EXHIBIT 7

United States Patent [19]

Hol et al.

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[45] **Date of Patent: Feb. 28, 1989**

[54] **9-(PHOSPONYLMETHOXYALKYL) ADENINES, THE METHOD OF PREPARATION AND ITILIZATION THEREOF**

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[4] **C07D 9/65;** C07D 473/34

[52] **U.S. Cl.** **544/244;** 544/277

[58] **Field of Search** 544/244; 514/81

[56] **References Cited**

U.S. PATENT DOCUMENTS

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4,659,825	4/1987	Holy et al.	544/244

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3400278	7/1984	Fed. Rep. of Germany	544/244
2539132	7/1984	France .	
WO84/04748	12/1984	PCT Int'l Appl.	544/244

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Holy, et al., Collection Czechoslovak Chem. Commun., vol. 47, pp. 3447–3463, (1982).

Benes, et al., Chemical Abstracts, vol. 104, 220678h, (1986).

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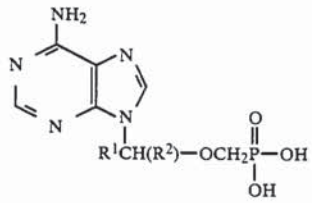
[57] **ABSTRACT**

The invention relates to 9-(phosphonylmethoxyalkyl-)adenines of the general formula I



(I)

wherein R^1 is a hydrogen atom, and alkyl group containing one to three carbon atoms, or a hydroxymethyl group, R^2 is a methylene, ethylene, propylene, ethylidene, methoxyethylene, benzyloxyethylene, tetrahydropyran-2-yloxyethylene, (1-ethoxyethoxy)ethylene or 1,2-O-isopropylidene-1,2-dihydroxypropylene group the method of their preparation and utilization.

Compounds of the general formula I exhibit biological effects (e.g. antiviral) or can be converted into compounds with such effects.

2 Claims, No Drawings

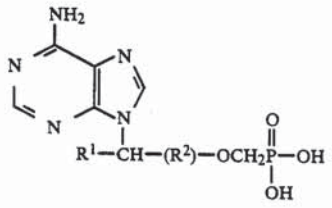
9-(PHOSPONYLMETHOXYALKYL) ADENINES, THE METHOD OF PREPARATION AND UTILIZATION THEREOF

This invention relates to new 9-(phosphonylmethoxyalkyl)adenines as well as their preparation and utilization.

Phosphonylmethyl ethers of alcohols (O-substituted hydroxymethanephosphonic acids) are analogues of esters of these alcohols with phosphoric acid, differing from the latter in having a chemically and enzymatically stable ether linkage. Since phosphoric acid esters, e.g. nucleotides, phosphoglyceric acid, sugar phosphates etc., are of great importance for metabolic processes in the living matter, such analogues may also be biologically active. The said compounds can be prepared e.g. by reaction of alcohols with chloromethanephosphonic acid or its esters (E. N. Walsh, T. M. Beck, A. D. F. Toy: J. Amer. Chem. Soc. 78, 4455 (1956)) or by reaction of formals with phosphorus trichloride (U.S. Pat. No. 2,500,022) or, in case of derivatives of 1,2-diols, by reaction of these diols with chloromethanephosphonyl dichloride and subsequent alkaline hydrolysis (PV 88-83). Another method, applicable also to monohydric alcohols, is reaction of a sodium alkoxide with an ester of p-toluenesulfonyloxymethanephosphonic acid; this reaction has been used in the preparation of 5'-O-phosphonylmethyl derivatives of nucleosides (A. Hol , I. Rosenberg: Collect. Czech. Chem. Commun. 47, 3447 (1982)).

9-Alkyladenines containing one or more hydroxy groups in the alkyl chain behave as analogues of the metabolite adenosine and exhibit various biological activities (e.g. antiviral, chemosterillzing etc., see Czech. Author's Certificate No. 199093, 199094, 199095, PV 377-83, PV, 7380-83, PV 970-84). Therefore, phosphonylmethyl ethers of these compounds can be regarded as so-called acyclic analogues of adenine nucleotides. Some of these compounds show also a chemosterilizing effect in insects (Czech. Author's Certificate No. 233 655).

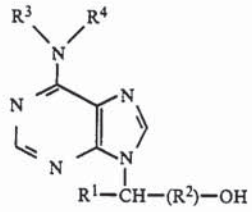
This invention relates to 9-(phosphonylmethoxyalkyl)adenines of the general formula I.



(I)

wherein R^1 is an atom of hydrogen, methyl or a hydroxymethyl group, R^2 is a methylene, ethylene, propylene, ethylidene, benzyloxyethylene, tetrahydropyran-2-yloxyethylene, 1-(ethoxyethoxy)ethylene or 1,2-O-isopropylidene-1,2-dihydroxypropylene group and the salts thereof with alkali metals, ammonia or amines.

Further, the invention relates to the method of preparing compounds of the general formula I, characterized in that 9-hydroxyalkyladenines of the general formula II

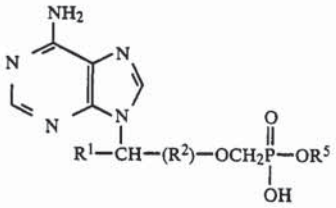


(II)

wherein R^1 and R^2 have the same signification as in the formula I, R^3 is a benzoyl group, R^4 is a hydrogen atom or a benzoyl group, or both R^3 and R^4 together are a dimethylaminomethylene group, are brought into a reaction with 1 to 2 equivalents (relative to compound II) of sodium hydride in a dipolar aprotic solvent, preferably dimethylformamide, and with 1 to 2 molar equivalents of an ester of p-toluenesulfonyloxymethanephosphonic acid of the general formula III,

(III)

wherein R^5 is a methyl or ethyl group, at temperatures 0° C. to 100° C., whereupon the mixture is worked up in an alkaline aqueous or aqueous-alcoholic medium and products of the general formula IV



(IV)

wherein R^1, R^2 and R^5 have the same signification as in the formula I and III, are isolated by chromatography, preferably on an ion-exchanging resin or hydrophobized silica gel, treated with a solution of trimethyliodosilane in dimethylformamide at temperatures 0° C. to 50° C., and the compounds of the general formula I are isolated by chromatography, preferably on an ion-exchanging resin or hydrophobized silica gel.

The starting compounds of the general formula II are accessible by reactions of suitably activated alcohols (e.g. tosyl or mesyl derivatives) or alkyl halides with salts of adenine, usually in dimethylformamide (see e.g. A. Hol : Collect. Czech. Chem. Commun. 43, 3444 (1978); 44, 593 (1979); 43, 3103 (1978); 43, 2054 (1978)).

The method of preparing the compounds according to this invention is based on formation of sodium salts of 9-hydroxyalkyladenine of the general formula II which contain an isolated hydroxy group. In order to prevent reaction of sodium hydride, used in the preparation of the salts, with other functionalities in the molecule, particularly those bonded to the heterocyclic adenine base, it is necessary to protect them with aroyl (benzoyl) groups or preferably with the N-dimethylaminomethylene group which can be easily introduced by reaction with the so-called dimethylformamide acetals (dialkoxymethyldimethylamines). The salts of thus-protected starting compounds of the formula II are prepared by addition of an equivalent amount or a

slight excess of sodium hydride to a solution of compounds II in a solvent which does not react with sodium hydride, preferably dimethylformamide.

These salts of compounds of the general formula II are then condensed with tosylates of the general formula III which are easily accessible from diesters or triesters of phosphoric acid (Czech. Author's Certificate No. 220713, 220714). The compounds of the formula III are used in a slight excess relative to compounds of the formula II in order to eliminate possible side reactions. The condensation is carried out at room or slightly elevated temperature under strictly anhydrous conditions.

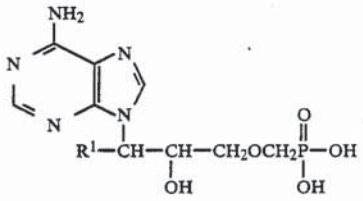
The reaction mixtures are worked up simply by dilution with water. The arising alkaline medium removes the protecting groups (aroyl or dimethylaminomethylene) together with one of the two groups bonded to the phosphonic acid by ester bonds. The arising monophosphonates of the general formula IV are not hydrolyzed further and can be easily isolated from the mixture, preferably by deionization of the adenine derivatives on strongly acidic ion-exchangers. Compounds of the general formula IV, obtained by desalting, are purified by chromatography, e.g. on an anion-exchanging resin or octadecyl-silica gel.

In the reaction with trimethyliodosilane, dried compounds of the formula IV are dissolved in dimethylformamide and mixed with the reagent (or its solution in dimethylformamide). The amount of the reagent taken is at least twice of that calculated for the number of equivalents of compound IV (taking into account all the hydroxy or amino groups present in its molecule). (Trimethyliodosilane can be also prepared in situ by reaction of trimethylchlorosilane with sodium, lithium or potassium iodidesin dimethylformamide.) The reaction of compounds of the formula IV with trimethyliodosilane is carried out under anhydrous conditions, the reaction time being usually 18–24 hours at room temperature. The reaction mixture is then decomposed by addition of a neutral or weakly alkaline buffer, e.g. the volatile triethylammonium hydrogen carbonate, and compounds of the general formula I are desalted, preferably using a medium acidic cation-exchanging resin from which, after removal of the salts, they are eluted with a volatile base such as aqueous ammonia. Compounds of the formula I are purified by chromatography on anion-exchanging resins in neutral or acidic medium, or on octadecyl-silica gel.

Compounds of the general formula I and V can be stored as free acids or their salts, prepared either by exact neutralization of the free acids or conversion of their ammonium salts into alkali metal salts using cation-exchanging resins in the appropriate form. The advantage of the last-mentioned salts (sodium and lithium salts) is their good solubility in water.

The method of preparing compounds of the formula I according to the invention can be used also for preparation of individual isomers of phosphonylmethoxyalkyladenines derived from di- or trihydroxyalkyladenines, i.e. when the mentioned preparation of these compounds by reaction with chloromethanephosphonyl chloride followed by alkaline hydrolysis (Czech Author's Certificate No. 233 655) leads to a mixture of isomers which have to be separated. In such cases the reaction is performed with a dihydroxy- or trihydroxyalkyladenine, protected on the adenine ring with a benzoyl or dimethylaminomethylene group, and with suitable alkali-stable groups, such as an acetal grouping or a benzyl group, on all the side-chain hydroxy groups except the one which shall react according to this invention. Isolated hydroxy groups can be protected preferably with tetrahydropyran-2-yl or 1-ethoxyethyl group, cis-diol groupings as isopropylidene or ethoxymethylene derivatives. Also other groups, resistant to sodium hydride, such as substituted silyl groups (tert-butyldimethylsilyl) or groups of the benzyl or trityl type, can be used. After the reaction with trimethyliodosilane, the crude compounds of the general formula I are stripped of the mentioned protected groups using a suitable procedure, such as acid hydrolysis, hydrogenolysis in an acid medium, or treatment with fluorides.

Some compounds of the general formula I which are the subject of this invention, are important active components of antiviral drugs. An example of such compound is 9-phosphonylmethoxyethyladenine which exhibits a specific activity against DNA-viruses and Moloney sarcoma (PV 3018-85). Other compounds of the general formula I can be easily converted into such biologically active compounds: e.g. 9-(3-phosphonylmethoxy-2-hydroxypropyl)adenine of the formula V (R^1 is H)



(V)

wherein R^1 denotes the same as in the formula I, is prepared from compounds of the formula I, where R^2 is a tetrahydropyran-2-yloxyethylene,(1-ethoxyethoxy)ethylene or benzyloxyethylene group by acid hydrolysis or hydrogenolysis.

The following Examples, together with the Table, illustrate the preparation and use of the new compounds of the general formula I according to this invention, without exhausting all the possibilities of the invention.

EXAMPLE 1

9-(2-Phosphonylmethoxyethyl)adenine

Sodium hydride (0.48 g; 20 mmol) is added to a solution of 9-(2-hydroxyethyl)-N^6-benzoyladenine (2.83 g; 10 mmol) is dimethylformamide and the mixture is stirred under exclusion of moisture (calcium chloride protecting tube) at room temperature for 20 minutes. After addition of dimethyl p-toluenesulfonyloxymethanephosphonate (2.95 g; 10 mmol) the mixture is stirred in a stoppered bottle for 48 hours at room temperature. Water (100 ml) is added and the mixture is set aside at room temperature for 15 hours. Dowex 50×8 (H^+ form) is added until the mixture has acid reaction and the suspension is applied on a column of the same ion-exchanging resin (200 ml). The column is washed with water until the eluate is no longer acidic and does not absorb at 260 nm, and then with dilute (1:10, vol/-vol) ammonia. Fractions, absorbing at 260 nm, are taken down at 40° C./2 kPa, and the residue is dissolved in water (10 ml) and adjusted to pH 9–10 with ammonia. This solution is applied on a column of Sephadex A-25 (HCO_3 form; 100 ml) and the column is washed with water until the eluate no longer absorbs at 260 nm: Then the material is eluted by a linear gradient of triethylam-

monium hydrogen carbonate (prepared from 1 liter of water and 1 liter of 0.2 mol l^{-1} of the mentioned buffer). The fractions, containing the principal UV-absorbing portion of the eluate, are pooled and taken down at 40° C./2 kPa. The residue is twice co-evaporated with ethanol (50 ml) and the obtained compound of the formula IV (triethylammonium salt) is dried over phosphorus pentoxide at room temperature and 13 Pa for 24 hours. Yield, 70%.

This material is dissolved in dimethylformamide (70 ml) and trimethyliodosilane (12 g; 60 mmol) is added at 0° C. with magnetic stirring. After stirring in a stoppered flask at room temperature overnight, 2 mol l^{-1} triethylammonium hydrogen carbonate (90 ml) is added and the mixture is heated to 60° C. for 3 hours. Water (700 ml) is added, the mixture is extracted three times with chloroform (100 ml), the aqueous phase is evaporated at 40° C./2 kPa and the residue is coevaporated with ethanol (3×100 ml). The residue is again deionized on a column of Dowex 50×8 (H^+ form; 200 ml) as described above. The crude compound I in water (20 ml) is adjusted to pH 9–10 with ammonia, and applied on a column of Dowex 1×2 (100 ml; acetate form). After washing with water, the column is eluted with a linear gradient of acetic acid (made from 1 liter of water and 1 liter of 1 mol l^{-1} acetic acid). The fractions of the main UV-absorbing portion of the eluate are combined, evaporated at 40° C./2 kPa, and the acetic acid is removed by repeated evaporation with water (3×50 ml). The residue is mixed with ethanol (5 ml) and then with ether (100 ml) and the crystalline product is filtered, washed with ether and dried in vacuo, affording 1.15 g (60% based on compound of the formula IV) of 9-(2-phosphonylmethoxyethyl)adenine, not melting up to 260° C. For $C_8H_{12}N_5O_4$ (273.3)

calculated: 35.16% C, 4.43% H, 25.63% N, 11.36% P; found: 34.84% C, 4.50% H, 25.33% N, 11.40% P.

The characteristics of this compound are given in Table 1 under No. 1. According to Example 1, also 9-(1-phosphonylmethoxy-3-hydroxy-2-propyl)adenine (No. 10) an 9-(3-phosphonylmethoxypropyl)adenine (No. 3) were prepared.

EXAMPLE 2

9-(3-Phosphonylmethoxy-2-methoxypropyl)adenine

Dimethylformamide dimethylacetal (15 ml) is added to a suspension of 9-(3-hydroxy-2-methoxypropyl)adenine (1.12 g; 5 mmol) in dimethylformamide (25 ml). The mixture is stirred at room temperature in a stoppered flask for 15 hours and then evaporated at 40° C./13 Pa. After addition of 50% aqueous pyridine (50 ml) and solid carbon dioxide (50 g), the mixture is stirred for 30 minutes, again evaporated at 40° C./13 Pa, dried by repeated coevaporation with pyridine (3×50 ml) and then with dimethylformamide (25 ml) under the same conditions. This crude N^6-dimethylaminomethylene derivative is dissolved in dimetylformamide (50 ml) and sodium hydride (0.24 g; 10 mmol) is added. The subsequent reaction and work-up procedure is the same as described in Example 1 and affords 0.80 g (50%) of free 9-(3-phosphonylmethoxy-2-methoxypropyl)adenine, not melting up to 260° C. For $C_{10}H_{16}N_5O_5P$ (317.3) calculated: 37.85% C, 5.08% H, 22.07% N, 9.78% P; found: 37.50% C, 5.24% H, 22.15% N, 9.54% P. The characteristics of this compound (No. 5) are given in Table 1.

According to Example 2 were prepared 9-(2-phosphonylmethoxypropyl)adenine (No. 2) and 9-(4-phosphonylmethoxybutyl)adenine (No. 4).

EXAMPLE 3

9-(2-Benzyloxy-3-phosphonylmethoxypropyl)adenine

Dimethylformamide dimethylacetal (15 ml) is added to a solution of 9-(2-benzyloxy-3-hydroxypropyl)adenine (1.5 g; 5 mmol) in dimethylformamide (25 ml) and the desired N^6-dimethylaminomethylene derivative is isolated as described in Example 2. Further reaction and processing are executed in the same manner as in Example 2 except that diethyl p-toluenesulfonyloxymethanephosphonate (1.60 g; 5 mmol) is used instead of dimethyl p-toluenesulfonyloxymethanephosphonate. After treatment of the reaction mixture with water and evaporation in vacuo, the residue is heated with concentrated aqueous ammonia (25 ml) to 50° C. for 5 hours, evaporated at 40° C./2 kPa and applied on a column of octadecyl-silica gel (30μ; 90 ml) in water. The material is eluted with a linear gradient of methanol using 1 liter of water and 1 liter of 20% (vol) aqueous methanol. The principal UV-absorbing fractions are combined, taken down at 40° C./2 kPa and the thus-obtained ammonium salt of compound of the formula IV (4 mmol; 80%) is further treated with trimethyliodosilane as described in Example 1. After treatment of the reaction mixture with buffer and extraction with chloroform, the residue after evaporation of the main portion is again chromatographed on a column of octadecyl-silica gel (90 ml) under the above-described conditions. The remaining triethylammonium salt of the compound of the formula I is dissolved in water (5 ml), applied on a column of Dowex 50×8 (Li^+ form; 20 ml) and eluted with water. The UV-absorbing fractions are taken down at 40° C./2 kPa, the residue is coevaporated with ethanol and mixed with ethanol (5 ml). Upon addition of ether (100 ml), the precipitate is filtered, washed with ether and dried at 13 Pa, affording 1.14 g (70% based on compound of the formula IV) of lithium salt of 9-(2-benzyloxy-3-phosphonylmethoxypropyl)adenine whose characteristics are given in Table 1 (No. 8).

EXAMPLE 4

2',3'-O-Isopropylidene-(L-threo)-9-(4-phosphonylmethoxy-2,3-dihydroxybutyl)adenine

2',3'-O-Isoproylidene-L-threo-9-(2,3,4-trihydroxybutyl)adenine (1.4 g; 5 mmol) is converted to the N^6-dimethylaminomethylene derivative according to Example 3 and the reaction is carried out with 0.24 g (10 mmol) of sodium hydride and 1.5 g (5 mmol) of dimethyl p-toluenesulfonyloxymethanephosphonate as described in Example 1. The isolation of the compound of the formula IV, its reaction with trimethyliodosilane and the subsequent isolation of compound of the formula I are performed as described in Example 3, affording 3.6 mmol (72%) of lithium salt of compound I whose characteristics are given in Table 1 (No. 9).

According to Example 4 were prepared 9-(3-phosphonylmethoxy-2-tetrahydropyranyloxypropyl)adenine (lithium salt, No. 6) and 9-(3-phosphonylmethoxy-2-(1-ethoxyethyl)oxypropyl)adenine (lithium salt, No. 7).

EXAMPLE 5

9-(3-Phosphonylmethoxy-2-hydroxypropyl)adenine

A solution of lithium salt of 9-(3-phosphonyloxymethoxy-2-tetrahydropyranyloxypropyl)adenine (1 mmol) in 0.25 mol l^{-1} sulfuric acid (20 ml) was kept at 40° C. for 18–24 hours, diluted with water (100 ml) and neutralized with saturated solution of barium hydroxide. The suspension was heated to 80° C. for 30 min and filtered through Celite. The filtrate was concentrated at 40° C./2 kPa to about 20 ml, this solution was applied on a column of Dowex 50×8 (Na^+ form; 20 ml) and eluted with water. The UV-absorbing eluate was evaporated at 40° C./2 kPa, the residue was dried by coevaporation with ethanol (2×20 ml), mixed with ethanol (3 ml) and the product was precipitated with ether (100 ml). Filtration, washing with ether and drying at 13 Pa gave 80% of sodium salt of 9-(3-phosphonylmethoxy-2-hydroxypropyl)adenine, whose characteristics are given in Table 1 (No. 11).

9-(3-Phosphonylmethoxy-2-hydroxypropyl)adenine (No. 11) was prepared according to Example 5 also from lithium salt of 9-(3-phosphonylmethoxy-2-(1-ethoxyethyl)oxypropyl)adenine (No. 7). The procedure was also applied to the preparation of 9-(L-threo)-(4-phosphonylmethoxy-2,3-dihydroxybutyl)adenine (No. 12) from the 2′,3′-O-isopropylidene derivative (No. 9).

EXAMPLE 6

9-(3-Phosphonylmethoxy-2-hydroxypropyl)adenine

To a solution of lithium salt of 9-(3-phosphonyloxymethoxy-2-benzyloxypropyl)adenine (No. 8; 1 mmol) in methanol (50 ml) were added subsequently 10% palladium on charcoal (0.50 g), 30% palladium chloride (0.5 ml) and hydrochloric acid (0.3 ml). After flushing the hydrogenation vessel three times with hydrogen, the mixture is stirred in a hydrogen atmosphere (0.1 MPa overpressure) at room temperature for 16–24 hours. The mixture is filtered through Celite, made alkaline with ammonia and evaporated to dryness. The residue, dissolved in water (5 ml), is applied on a column of Dowex 50×8 (H^+ form; 50 ml). After washing with water (300 ml), the product is eluted with 2.5% ammonia solution. The UV-absorbing fractions are evaporated to dryness at 40° C./2 kPa and the residue is converted into the lithium salt as described in Example 3, affording 75–80% of product identical with the lithium salt prepared according to Example 5.

EXAMPLE 7

Primary rabbit kidney cells grown in Eagle's essential medium are infected for 1 hour with $10^{4.5}$ PFU/0.5 ml (PFU denotes a plaque formation unit) of herpes simplex virus, type 1 (KOS strain). Then the medium is replaced by a solution of compound of the formula I, where R^1 is an hydrogen atom and R^2 is a methylene group (compound No. 1 in Table 1), in Eagle's essential medium (concentration, 100 μg I/ml medium). After incubation for 48 hours at 37° C., the yield of the virus is determined by plaque formation in the PRK cells. A control experiment is carried out in the same manner but the culture is incubated only in Eagle's essential medium. Under these conditions the virus titre decreases 14,500 times (Δ log PFU/ml=3.16).

EXAMPLE 8

Primary rabbit kidney cells in Petri dishes are infected with herpes simplex virus, type 2 (G-strain), in a dose hundred times larger than that necessary for inducing 50% of the cytopathic effect of the virus. After 1 hour the cells are incubated with increasingly concentrated solutions of the compounds in Eagle's essential medium for 24 hours at 37° C. The cytopathic effect of the virus is determined as described in "Tissue culture", Pergamon Press, New York 1973, p. 510. Under these conditions, compounds of the formula I, No. 1 and 12 in Table 1, show a 50% inhibition of the cytopathic effect of HSV-2 virus in concentration 7 μg/ml.

TABLE 1

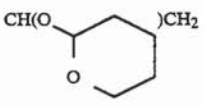
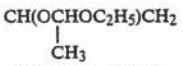
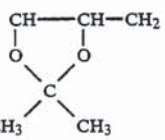
			Characteristics of the compounds according to the invention					
			IV			I		
No.	R^1	R^2	Yield %	R_F[a]	R_{Up}[b]	Yield %	R_F[a]	R_{Up}[b]
1	H	CH_3	70	0.45	0.45	60	0.11	0.82
2	H	$CH(CH_3)$	75	0.50	0.42	80	0.18	0.80
3	H	CH_2CH_2	72	0.50	0.42	67	0.18	0.80
4	H	$CH_2CH_2CH_2$	75	0.54	0.40	70	0.24	0.81
5	H	$CH(OCH_3)CH_2$	78	0.55	0.40	64	0.25	0.78
6	H		80	0.57	0.40	67	0.35	0.78
7	H		70	0.57	0.38	70	0.35	0.76
8	H	$CH(OCH_2C_6H_5)CH_2$	80	0.70	0.35	70	0.42	0.72
9	H		80	0.60	0.40	90	—	0.75
10	CH_3	CH_2	75	0.52	0.40	70	0.18	0.78
11	$HOCH_2$	CH_2	70	0.47	0.40	60	0.12	0.80
12	H	$CH(OH)CH_2$[c]	—	—	—	80	0.10	0.82

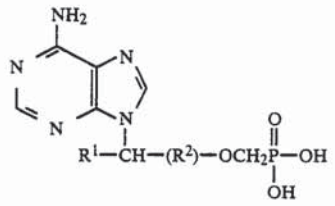
TABLE 1-continued

			Characteristics of the compounds according to the invention					
			IV			I		
No.	R^1	R^2	Yield %	R_F[a]	R_{Up}[b]	Yield %	R_F[a]	R_{Up}[b]
13	H	$CH(OH)CH(OH)CH_2$	—	—	—	85	0.10	0.82

[a]Paper chromatography in the system 2-propanol - conc. aqueous ammonia - water (7:1:2);
[b]paper electrophoresis (20 V/cm) in 0.1 mol l^{-1} triethylammonium hydrogen carbonate;
[c]compound of the formula V.

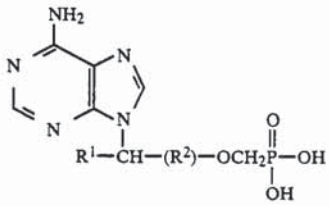
What we claim is:

1. A 9-(phosphonylmethoxyalkyl)adenine having the formula I



wherein R^1 is hydrogen and R^2 is selected from the group consisting of methylene, ethylene, propylene, ethylidene, and 1,2-O-isopropylidene-1,2-di-hydroxypropylene; and the salts thereof with alkali metals or ammonia.

2. A 9-(phosphonylmethoxyalkyl)adenine of the formula



wherein R^1 is selected from the group consisting of methyl and hydroxymethyl and R^2 is selected from the group consisting of methylene, ethylene, propylene, ethylidene, methoxyethylene, benzyloxyethylene, tetrahydropyranyl-2-oxyethylene, (1-ethoxyethoxy)ethylene and 1,2-O-isopropylidene-1,2-dihydroxypropylene; and the salts thereof with alkali metals or ammonia.

* * * * *

EXHIBIT 8

US005814639A

United States Patent [19]

Liotta et al.

[11] Patent Number: 5,814,639

[45] Date of Patent: Sep. 29, 1998

[54] **METHOD FOR THE SYNTHESIS, COMPOSITIONS AND USE OF 2'-DEOXY-5-FLUORO-3'-THIACYTIDINE AND RELATED COMPOUNDS**

[75] Inventors: **Dennis C. Liotta**, Stone Mountain; **Raymond F. Schinazi**, Decatur, both of Ga.; **Woo-Baeg Choi**, North Brunswick, N.J.

[73] Assignee: **Emory University**, Atlanta, Ga.

[21] Appl. No.: **17,820**

[22] Filed: **Feb. 16, 1993**

Related U.S. Application Data

[60] Division of Ser. No. 659,760, Feb. 22, 1991, Pat. No. 5,210,085, which is a continuation-in-part of Ser. No. 473,318, Feb. 1, 1990, Pat. No. 5,204,466.

[51] **Int. Cl.**[6] **A61K 31/505**; C07D 239/02

[52] **U.S. Cl.** **514/274**; 544/317

[58] **Field of Search** 544/317; 514/274

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9117159	11/1991	WIPO .
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(List continued on next page.)

Primary Examiner—James O. Wilson

Attorney, Agent, or Firm—Sherry M. Knowles; Jacqueline Haley; King & Spalding

[57] **ABSTRACT**

The present invention relates to a method of preparing the antiviral compounds 2'-deoxy-5-fluoro-3'thiacytidine (FTC) and various prodrug analogues of FTC from inexpensive precursors with the option of introducing functionality as needed; methods of using these compounds, particularly in the prevention and treatment of AIDS; and the compounds themselves. This synthetic route allows the stereoselective preparation of the biologically active isomer of these compounds and related compounds.

2 Claims, 7 Drawing Sheets

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FIG. 1

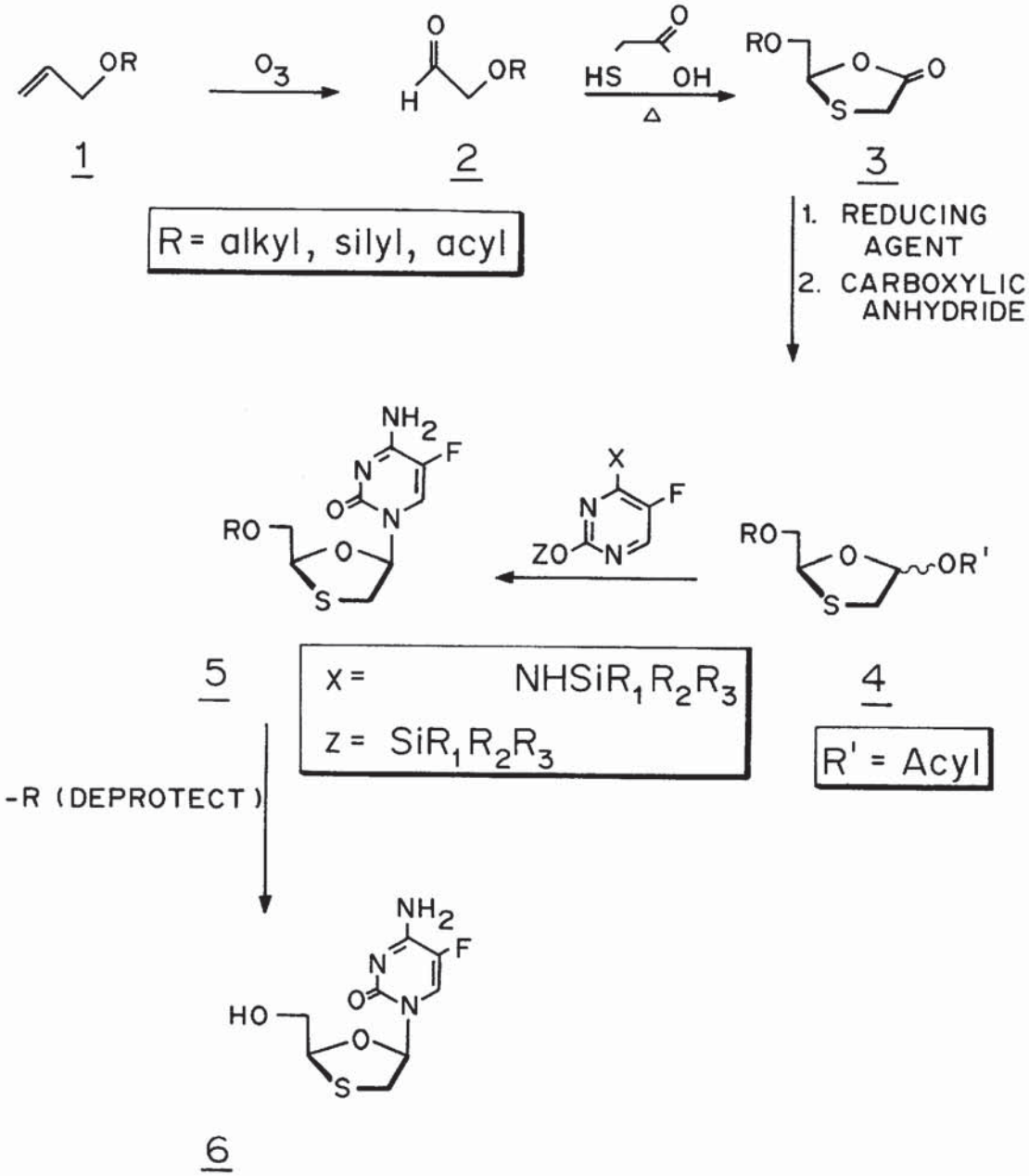

OR
O_3
O
H
OR
HS
OH
Δ
RO
O
O
S
1
2
3
R = alkyl, silyl, acyl
1. REDUCING AGENT
2. CARBOXYLIC ANHYDRIDE
NH_2
F
N
O
RO
S
X
ZO
RO
OR'
5
X = $NHSiR_1R_2R_3$
Z = $SiR_1R_2R_3$
4
R' = Acyl
-R (DEPROTECT)
HO
6

FIG. 2

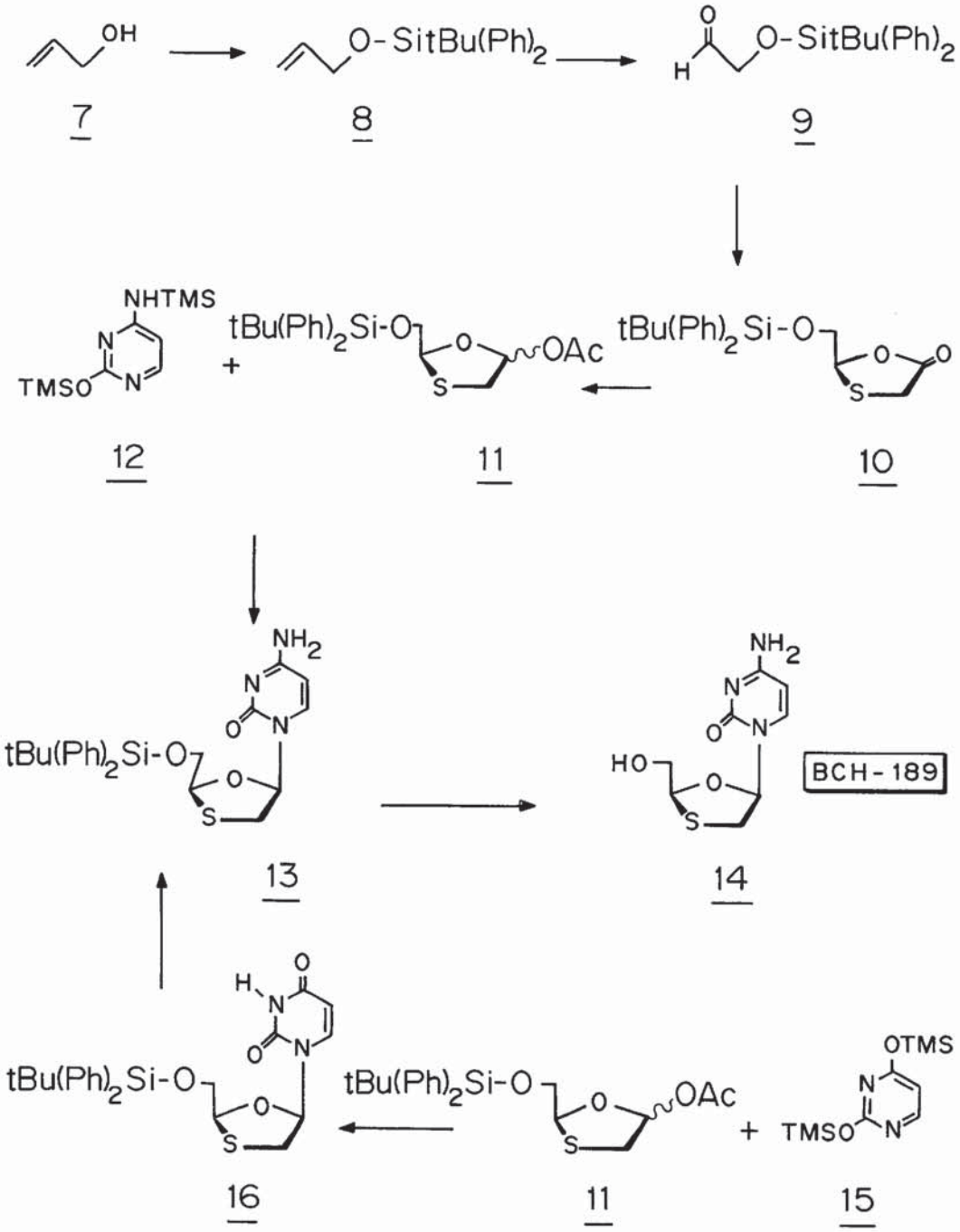

OH
O-SitBu(Ph)2
O-SitBu(Ph)2
7
8
9
NHTMS
TMSO
tBu(Ph)2Si-O
OAc
tBu(Ph)2Si-O
12
11
10
NH2
tBu(Ph)2Si-O
HO
BCH-189
13
14
tBu(Ph)2Si-O
tBu(Ph)2Si-O
OAc
OTMS
TMSO
16
11
15

FIG. 3

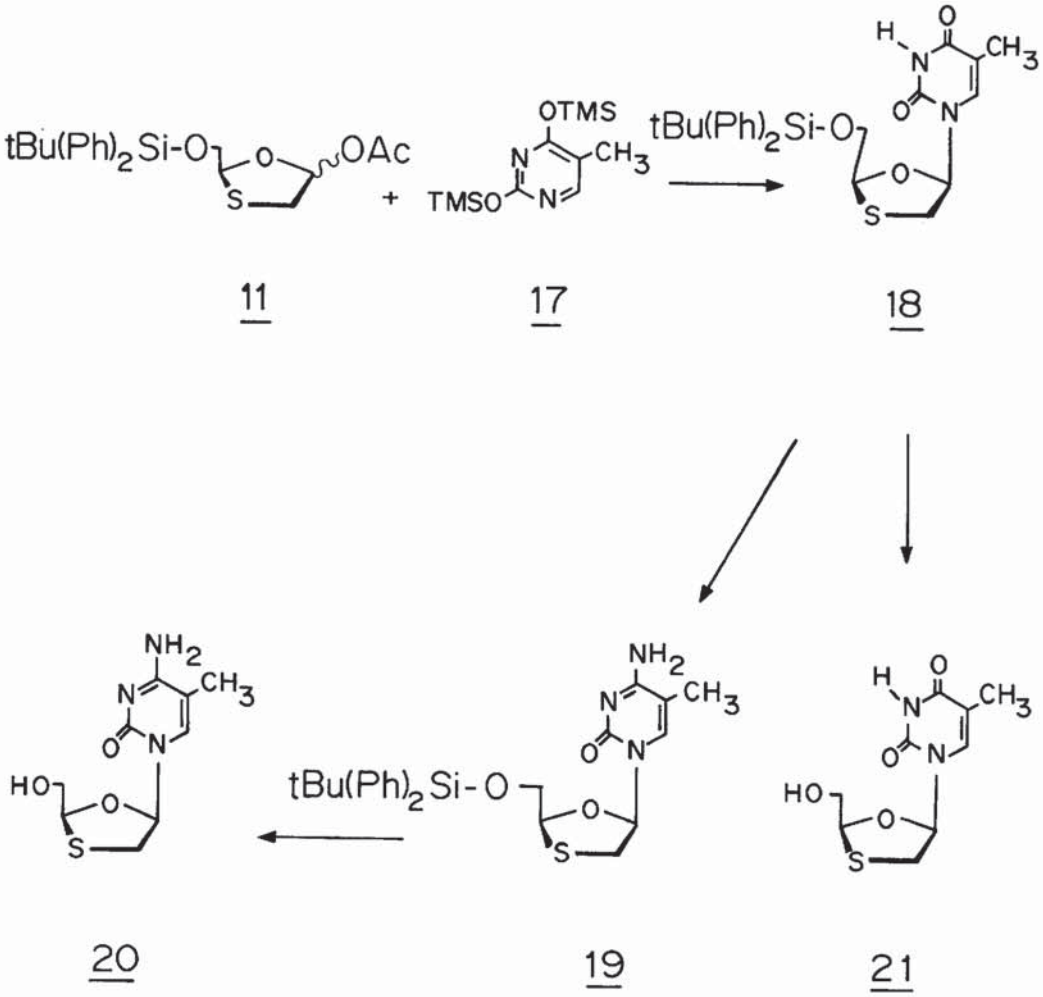

tBu(Ph)2Si-O
OAc
+
OTMS
TMSO
CH3
tBu(Ph)2Si-O
H
O
N
CH3
11
17
18
NH2
HO
tBu(Ph)2Si-O
20
19
21

FIG. 4

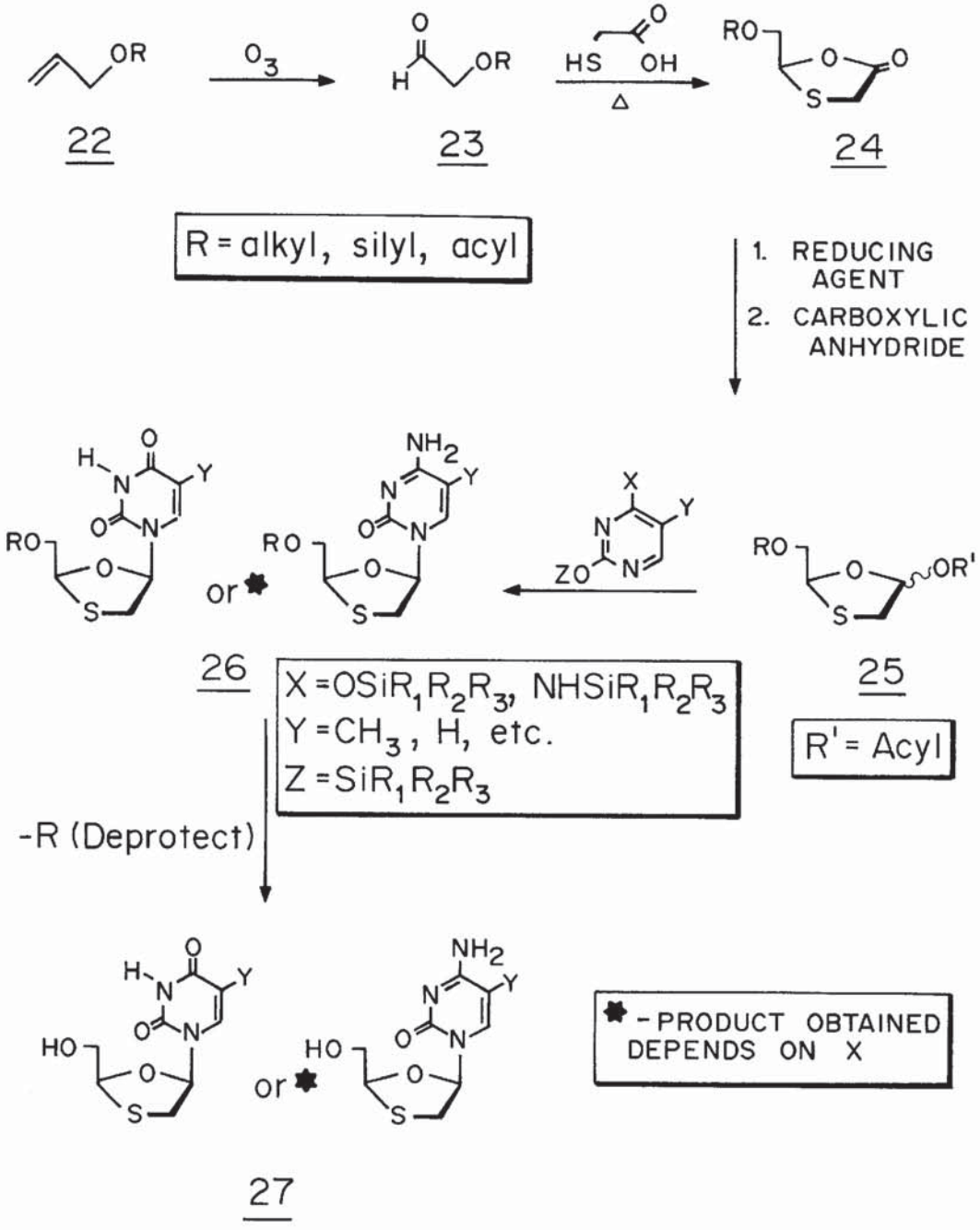
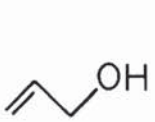

OR
O_3
HS OH
Δ
RO
22
23
24
R = alkyl, silyl, acyl
1. REDUCING AGENT
2. CARBOXYLIC ANHYDRIDE
or
ZO
OR'
26
25
X = $OSiR_1R_2R_3$, $NHSiR_1R_2R_3$
Y = CH_3, H, etc.
Z = $SiR_1R_2R_3$
R' = Acyl
-R (Deprotect)
HO
27
- PRODUCT OBTAINED DEPENDS ON X

FIG. 5



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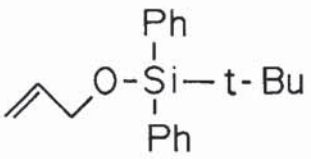
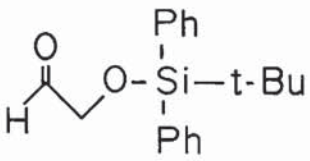
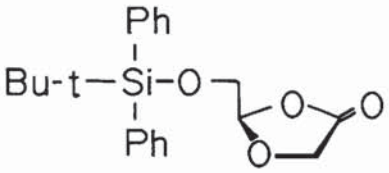


8



9



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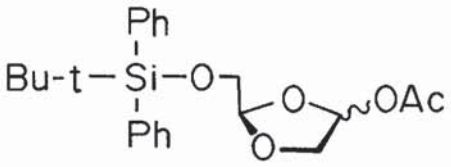

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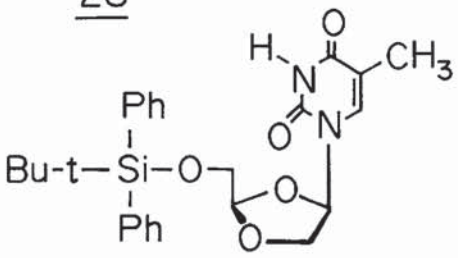

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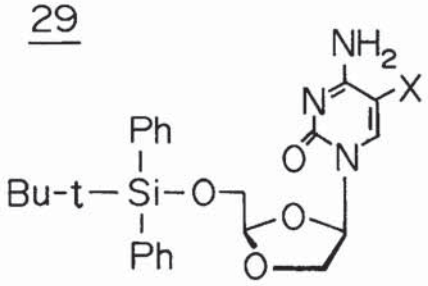
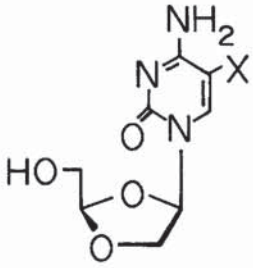
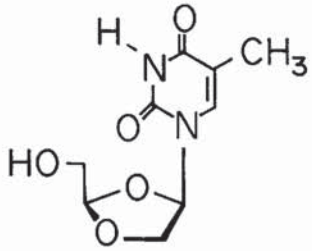


32 (X = H)
36 (X = F)



33 (X = H)
37 (X = F)



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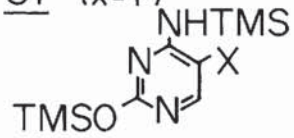
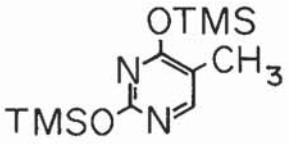


30 (X = H OR F)



31

FIG. 6

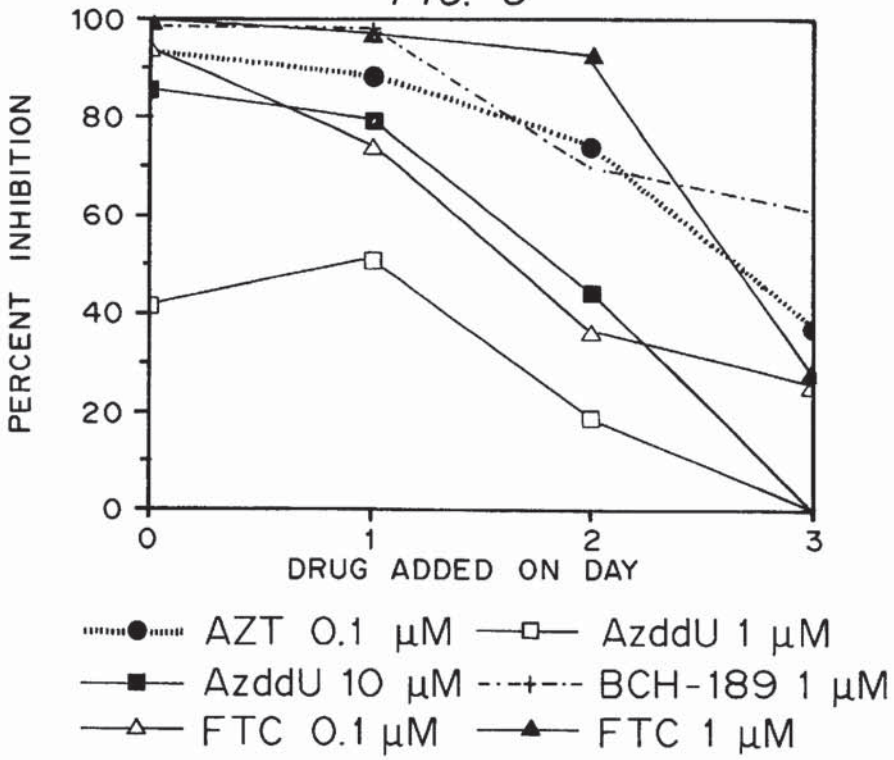

PERCENT INHIBITION
100
80
60
40
20
0
0
1
2
3
DRUG ADDED ON DAY
AZT 0.1 μM
AzddU 1 μM
AzddU 10 μM
BCH-189 1 μM
FTC 0.1 μM
FTC 1 μM

FIG. 7

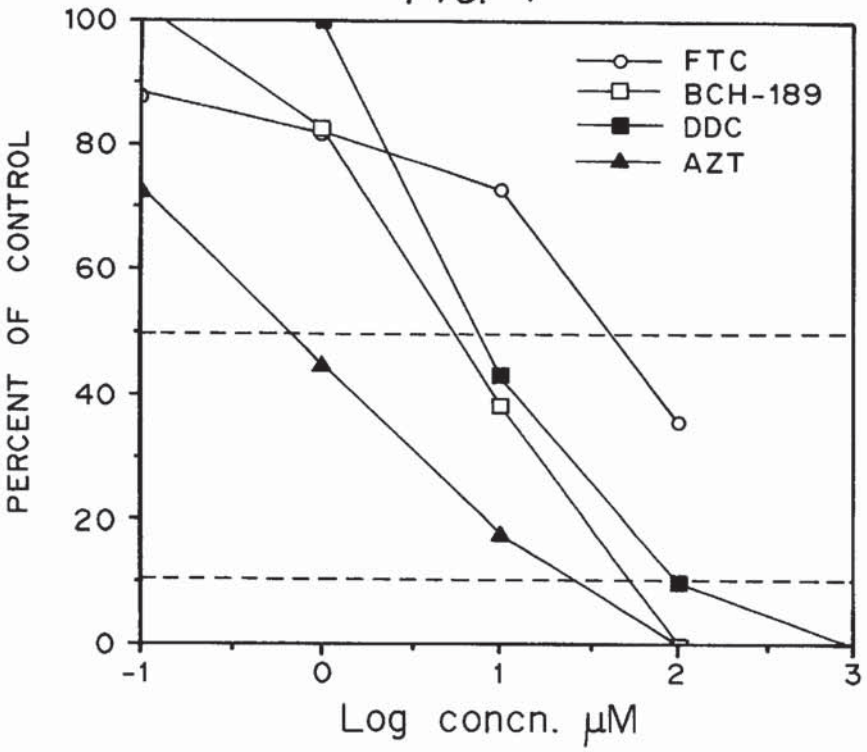
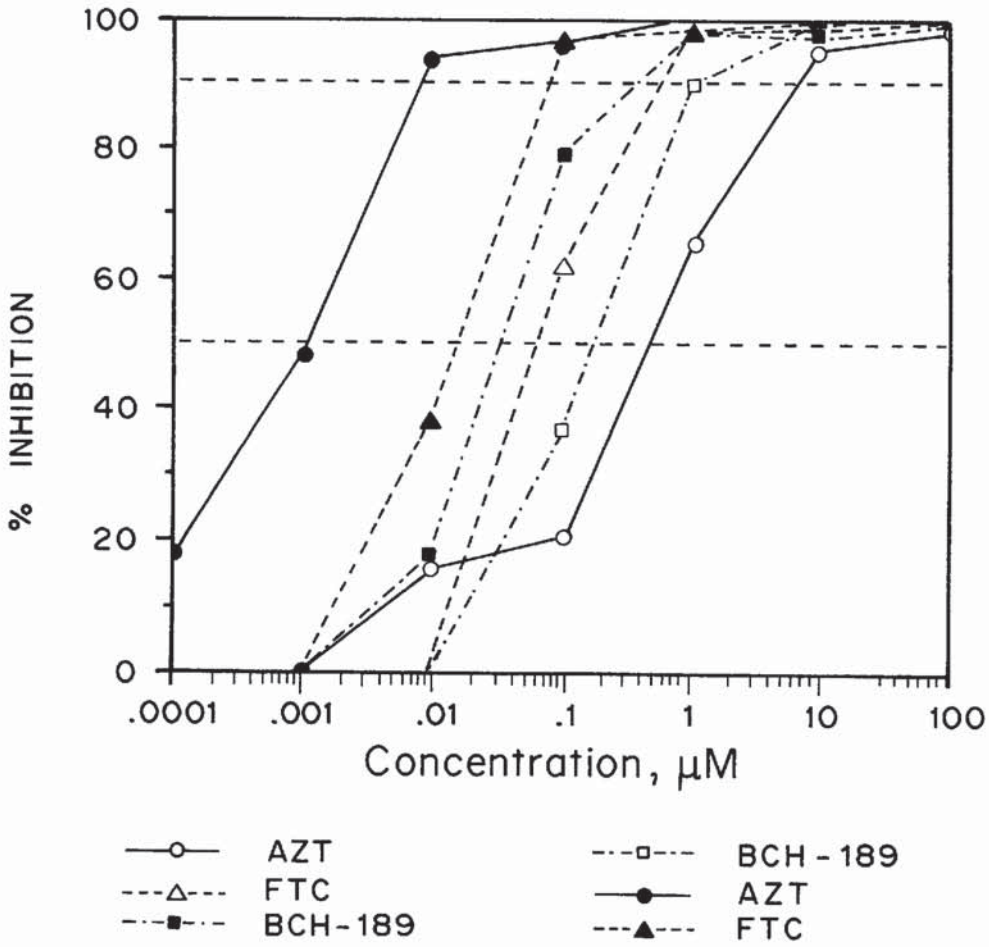

PERCENT OF CONTROL
100
80
60
40
20
0
-1
0
1
2
3
Log concn. μM
FTC
BCH-189
DDC
AZT

FIG. 8


100
80
60
40
20
0
% INHIBITION
.0001
.001
.01
.1
1
10
100
Concentration, μM
AZT
FTC
BCH-189
BCH-189
AZT
FTC

METHOD FOR THE SYNTHESIS, COMPOSITIONS AND USE OF 2'-DEOXY-5-FLUORO-3'-THIACYTIDINE AND RELATED COMPOUNDS

REFERENCE TO CO-PENDING APPLICATION

This application is a divisional application of U.S. Ser. No. 07/659,760, filed on Feb. 22, 1991, now U.S. Pat. No. 5,210,085; which is a continuation-in-part of U.S. Ser. No. 07/473,318, filed on Feb. 1, 1990, now U.S. Pat. No. 5,204,466.

The invention described herein was made with Government support under grants no. AI-28731 and no. AI-26055 awarded by the National Institutes of Health. The Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

The present invention relates to the use of and methods and compositions for preparing antiviral nucleoside analogues, particularly FTC (2'-deoxy-5-fluoro-3'-thiacytidine) and prodrug analogues of FTC. More particularly, the invention relates to the β-isomers of these compounds and their selective synthesis and use as antiviral agents.

In 1981, documentation began on the disease that became known as Acquired Immune Deficiency Syndrome (AIDS), as well as its forerunner AIDS Related Complex (ARC). Since that time, the World Health Organization (WHO) has confirmed that 300,000 people have been reported to have developed AIDS. Of these, over 150,000 are in the United States.

In 1983, the cause of the disease AIDS was established as a virus named the human immunodeficiency virus type 1 (HIV-1). As of December, 1990, the WHO estimates that the number of people who are infected with the virus is between 8 and 10 million worldwide and of that number, between 1,000,000 and 1,400,000 are in the U.S. Usually, a person infected with the virus will eventually develop AIDS; in all known cases of AIDS the final outcome has always been death.

The disease AIDS is the end result of HIV infection. The virion replication cycle begins with the virion attaching itself to the host human T-4 lymphocyte immune cell through the bonding of a receptor on the surface of the virion's protective coat (gp 120) with a glycoprotein on the lymphocyte cell (CD4). Once attached, the virion fuses with the cell membrane, penetrates into the host cell, and uncoats its RNA. The virion enzyme, reverse transcriptase, directs the process of transcribing the RNA into single stranded DNA. The viral RNA is degraded and a second DNA strand is created. The now double-stranded DNA is integrated into the T-cell genome.

The host cell uses its own RNA polymerase to transcribe the integrated DNA into viral RNA and the viral RNA directs the production of glycoproteins, structural proteins and viral enzymes for the new virion, which assemble with the viral RNA intact. Once all the components are assembled, the virus buds out of the cell. Thus, the number of HIV-1 virions grows while the number of T-4 lymphocytes declines.

There are at least three critical points in the virion's replication cycle which have been identified as targets for antiviral drugs: (1) the initial attachment of the virion to the T-4 lymphocyte (CD4 glycoprotein), (2) the transcription of viral RNA to viral DNA, and (3) the assemblage of the new virions during replication.

It is the inhibition of the virus at the second critical point, the viral RNA to viral DNA transcription process, that has provided the bulk of the therapies used in treating AIDS. This transcription must occur for the virion to replicate because the virion's genes are encoded in RNA. By introducing drugs that block the enzyme, reverse transcriptase, from transcribing viral RNA to viral DNA successfully, HIV-1 replication can be stopped.

After phosphorylation, nucleoside analogues, such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (DDC), 2',3'-didehydro-3'-deoxythymidine (D4T), 2',3'-dideoxyinosine (DDI), and various 2'-fluoro-derivatives of these nucleosides are relatively effective in halting HIV replication by inhibiting reverse transcription. Another promising anti-AIDS drug is 2'-deoxy-3'-thiacytidine (BCH-189), which contains an oxathiolane ring instead of the sugar moiety in the nucleoside. This invention provides the new antiviral nucleosides, 2'-deoxy-5-fluoro-3'-thiacytidine (FTC) and various prodrug analogues of FTC, which are unexpectedly potent and nontoxic.

AZT is a successful anti-HIV drug because it prevents the nucleotide chain-linking reaction that elongates viral DNA inside the host T-4 lymphocyte cells or other immune system cells such as macrophages. When AZT enters the cell, cellular kinases activate AZT by phosphorylation to AZT triphosphate. AZT triphosphate then competes with natural thymidine nucleotides for the receptor site of HIV reverse transcriptase enzyme. The natural nucleotide possesses two reactive ends, the 5'-triphosphate end which reacts with the growing nucleotide polymer and the 3'-OH group for linking to the next nucleotide. The AZT molecule only contains the first of these. Once associated with the HIV enzyme active site, the AZT azide group terminates viral DNA formation because the azide cannot make the 3',5'-phosphodiester bond with the ribose moiety of the following nucleoside.

AZT's clinical benefits include increased longevity, reduced frequency and severity of opportunistic infections, and increased peripheral CD4 lymphocyte count. Immunosorbent assays for viral p24, an antigen used to track HIV-1 activity, show a significant decrease with use of AZT. However, AZT's benefits must be weighed against the adverse reactions of bone marrow suppression (neutropenia), nausea, myalgia, insomnia, severe headaches, anemia, and seizures. Furthermore, these adverse side effects occur immediately after treatment begins whereas a minimum of six weeks of therapy is necessary to realize AZT's benefits.

Several other nucleotides inhibit HIV reverse transcription as does AZT triphosphate. Initial tests on 3'-deoxy-3'-fluorothymidine show that its antiviral activity is comparable to that of AZT. DDC and D4T have been tested in vitro against AZT in a delayed drug administration study; both were found to be potent inhibitors of HIV replication with activities comparable (D4T) or superior (DDC) to AZT. Both DDC and D4T are in clinical trials. Although DDC is converted to its 5'-triphosphate less efficiently than its natural analogue, 2'-deoxycytidine, the phosphorylated derivative is resistant to both deaminases and phosphorylases. If dosage and side-effect issues can be resolved, these drugs show potential for becoming effective anti-AIDS drugs.

Currently, DDI is used alone or in conjunction with AZT to treat AIDS. However, DDI's side effects include sporadic pancreatitis and peripheral neuropathy. Owing to its toxicity, reduced doses are necessary and this may limit its usefulness as an antiviral therapeutic treatment. In addition, the drug is susceptible to cleavage under acidic conditions.

Recent cell culture tests on BCH-189 have shown that it possesses anti-HIV activity similar to AZT and DDC, but without as much cellular toxicity. However, BCH-189, like DDC, is toxic at a concentration of ≦10 μM in intact CEM cells as measured by cell growth and by determining the extent of mitochondrial DNA synthesis, thus suggesting that one of the side effects of BCH-189 might be clinical peripheral neuropathy. Furthermore, although BCH-189 is less toxic to bone-marrow cells than AZT, another side effect of BCH-189, like AZT, might be anemia. Thus, there is a need for superior therapeutic agents such as FTC and FTC prodrug analogues that are provided herein. These agents combine high antiviral activity with minimum toxicity for use as inhibitors of replication and infectivity of HIV in vivo.

The commonly-used chemical approaches for synthesizing nucleosides or nucleoside analogues can be classified into two broad categories: (1) those which modify intact nucleosides by altering the carbohydrate, the base, or both and (2) those which modify carbohydrates and incorporate the base, or its synthetic precursor, at a suitable stage in the synthesis. Because FTC substitutes a sulfur for a carbon atom in the carbohydrate ring, only the second approach is applicable. The most important factor in this latter strategy involves delivering the base from the β-face of the carbohydrate ring in the glycosylation reaction because only the β-isomers exhibit useful biological activity.

It is well known in the art that the stereoselective introduction of bases to the anomeric centers of carbohydrates can be controlled by capitalizing on the neighboring group participation of a 2-substituent on the carbohydrate ring [*Chem. Ber.* 114:1234 (1981)]. However, FTC and its analogues do not possess an exocyclic 2-substituent and, therefore, cannot utilize this procedure unless additional steps to introduce a functional group that is both directing and disposable are incorporated into the synthesis. These added steps would lower the overall efficiency of the synthesis.

It is also well known in the art that "considerable amounts of the undesired α-nucleosides are always formed during the synthesis of 2'-deoxyribosides" [*Chem. Ber.* 114:1234, 1244 (1981)]. Furthermore, this reference teaches that the use of simple Friedel-Crafts catalysts like $SnCl_4$ in nucleoside syntheses produces undesirable emulsions upon the workup of the reaction mixture, generates complex mixtures of the α and β-isomers, and leads to stable σ-complexes between the $SnCl_4$ and the more basic silyated heterocycles such as silyated cytosine. These complexes lead to longer reaction times, lower yields, and production of the undesired unnatural N-3-nucleosides. Thus, the prior art teaches the use of trimethysilyl triflate or trimethylsilyl perchlorate as a catalyst during the coupling of pyrimidine bases with a carbohydrate ring to achieve the highest yields of the biologically active β-isomers. However, the use of these catalysts to synthesize FTC or FTC analogues exhibit little preference for the desired β-isomer; these reactions typically result in mixtures containing nearly equal amounts of both isomers. Thus, there exists a need for an efficient synthetic route to FTC and FTC prodrug analogues.

SUMMARY OF THE INVENTION

The present invention relates to the discovery of a surprisingly efficient synthetic route to 2'-deoxy-5-fluoro-3'-thiacytidine (FTC) and various FTC prodrug analogues from inexpensive precursors with the option of introducing functionality as needed. This synthetic route allows the stereoselective preparation of the biologically active β isomer of these compounds. This invention further relates to the discovery that FTC and FTC prodrug analogues possess surprisingly superior HIV inhibition and cell toxicity effects compared to BCH-189 and other analogues of BCH-189, including other 5-halo derivatives of BCH-189, or other 5-fluoro substituted nucleoside analogues such as 2'-deoxy-5-fluoro-3'-oxacytidine (FDOC). Thus, this invention provides for the therapeutic use of these compounds and pharmaceutical formulations containing these compounds as antiviral agents.

As used herein, the term "FTC prodrug analogue" refers to a 5'-oxyacyl or H substituted and/or 4-N alkyl, substituted alkyl, cycloalkyl or acyl substituted 2'-deoxy-5-fluoro-3'-thiacytidine that metabolizes to the same active component or components as FTC. The term "BCH-189 analogues" is meant to refer to nucleosides that are formed from pyrimidine bases substituted at the 5 position that are coupled to substituted 1,3-oxathiolanes.

The synthesis of the present invention includes ozonizing either an allyl ether or ester having the formula CH_2═CH—CH_2—OR or a diether or diester of 2-butene-1,3-diol having the formula ROCH_2—CH═CH—CH_2OR, in which R is a protecting group, such as an alkyl, silyl, or acyl group, to form a glycoaldehyde having the formula OHC—CH_2—OR; adding thioglycolic acid to the glycoaldehyde to form a lactone of the formula 2-(R-oxy)-methyl-5-oxo-1,3-oxathiolane; reducing the lactone to various compounds containing a leaving group at the 5 position of the oxathiolane ring; coupling these compounds with a silyated pyrimidine base fluoro-substituted at the 5 position of the base in the presence of $SnCl_4$ to form the β-isomer of a 2'-deoxy-5-fluoro-5'-(R-oxy)-3'-thia-nucleoside analogue; and replacing the R protecting group with a hydrogen or acyl to form FTC or a prodrug analogue of FTC.

Accordingly, one of the objectives of this invention is to provide the antiviral nucleoside β-2'-deoxy-5-fluoro-3'-thiacytidine (FTC), prodrug analogues of FTC that are 5'-oxyacyl substituted and pharmaceutically acceptable formulations containing these compounds. Furthermore, it is an object of this invention to provide an efficient and direct method for preparing the β-isomer of FTC and prodrug analogues of FTC in high yields. In addition, this invention provides for the use of these compounds, or pharmaceutically acceptable formulations containing these compounds, as effective and nontoxic antiviral agents.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** illustrates one embodiment of a synthesis of FTC and FTC prodrug analogues according to the present invention;

FIG. **2** illustrates one embodiment of the synthesis of BCH-189 according to the present invention;

FIG. **3** illustrates one embodiment of the synthesis of 5-methylcytidine and thymidine derivatives of BCH-189 according to the present invention;

FIG. **4** illustrates one embodiment of the synthesis of BCH-189 and BCH-189 analogues according to the present invention;

FIG. **5** illustrates one embodiment of the synthesis of FDOC, DOC and DOT according to the present invention;

FIG. **6** illustrates the effect of delayed treatment on the anti-HIV-1 activity of AZT, FTC and other nucleoside analogues in PBM cells;

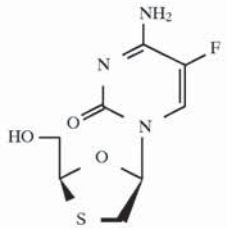
FIG. **7** illustrates the effect of FTC, BCH-189, DDC and AZT on colony formation of granulocyte-macrophage precursor cells; and

FIG. **8** illustrates the effect of FTC, AZT and BCH-189 on AZT-resistant and AZT-sensitive HIV-1 in human PBM cells.

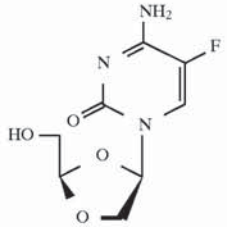
DETAILED DESCRIPTION OF TEE INVENTION

A. Synthesis of FTC or FTC Prodrug Analogues

FTC is a compound of the formula:



FDOC is a compound of the formula:



Because only the β-isomers of these nucleoside analogues generally exhibit useful biological activity, the synthesis for β-FTC is provided for by the instant invention, using a stereoselective base coupling reaction that is operative through "in situ" complexation of a suitable cyclic precursor and Lewis acid. The crucial step in the stereoselectivity of the FTC synthesis is the coupling of a 2-(R-oxy)-methyl-5-carboxy-1,3-oxathiolane with a silylated pyrimidine base at ambient temperature using the Lewis acid, $SnCl_4$. Deprotection of the silyl group gives the free nucleoside β-FTC, or its analogues. The initial NMR stereochemical assignments have been reconfirmed by X-ray structures, both confirming the β selectivity. Correspondingly, the crucial step in the stereoselectivity of the FDOC synthesis is the coupling of a 2-(R-oxy)-methyl-4-carboxy-1,3-dioxolane with a silylated pyrimidine base at ambient temperature using the Lewis acid, $TiCl_4$.

Other data regarding these coupling reactions also indicate a metal dependent selectivity. Use of $TiCl_4$ rather than $SnCl_4$ in the FTC synthesis, or $SnCl_4$ rather than $TiCl_4$ in the FDOC synthesis, results in a loss in stereoselectivity caused by a Lewis acid-heteroatom mismatch. Furthermore, reactions employing trimethysilyl triflate in both syntheses result in non-stereoselective reactions as well.

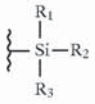
All of the above results can be rationalized through a heteroatom-Lewis acid interaction. Upon exposure of the carboxylate to the Lewis acid and silylated base, an intermediate oxonium ion is formed. In the presence of a complexing Lewis acid, an intermediate could be formed in which the metal would complex to the heteroatom in the ring; one of it's ligands, such as chloride or acetate, would be associated with a carbon bearing a partial positive charge. The result of this complexation would be blockage of the α-face opposite to the bulky (t-butyldiphenyl) hydroxymethyl substituent and β attack of the silylated base. Use of trimethysilyl triflate or a non-interacting Lewis acid would generate an oxonium ion that has no facial bias.

A process of the p resent invention for preparing FTC and FTC prodrug analogues is set forth in FIG. **1**. An allyl ether or ester 1 is ozonized to give an aldehyde 2, which reacts with thioglycolic acid to give a lactone 3. The lactone 3 is treated with a reducing agent, followed by a carboxylic anhydride, to produce the carboxylate 4. This carboxylate is coupled with a silylated 5-fluoro substituted pyrimidine base in the presence of a Lewis acid that can catalyze stereoselective coupling, such as $SnCl_4$, to yield the β-isomer of the substituted nucleoside 5 in essentially a 100:0 ratio of β:α isomers. The substituted nucleoside 5 is deprotected to produce FTC 6 or modified at the 5'-position to form a FTC prodrug analogue.

The process for preparing FDOC is set forth in FIG. **5**. Glycolic acid reacts with glycoaldehyde 9 to form the lactone 28, which is reduced to form the carboxylate 29. 29 is coupled with a silylated 5-fluoro substituted pyrimidine base in the presence of a Lewis acid that can catalyze stereoselective coupling, such as $TiCl_4$, $TiCl_3(OiPr)$ or $TiCl_2(OiPr)_2$, to yield the β-isomer of the substituted nucleoside 36. The substituted nucleoside 36 is deprotected to produce FDOC 37.

The protecting group R in 1 can be selected to provide protection for the corresponding alcohol until the final step in the synthesis is carried out (deprotection of 5 to form 6). Any group that functions in this manner may be used. For instance, alkyl, silyl, and acyl protecting groups or groups that possess substantially the same properties as these groups can be used.

An alkyl protecting group, as used herein, means triphenylmethyl or an alkyl group that possesses substantially the same protecting properties as triphenylmethyl. A silyl protecting group, as used herein, means a trialkylsilyl group having the formula:

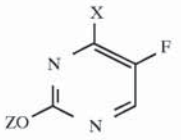


wherein R_1, R_2, and R_3 may be lower-alkyl, e.g., methyl, ethyl, butyl, and alkyl possessing 5 carbon atoms or less; or phenyl. Furthermore, R_1 may be identical to R_2; R_1, R_2, and R_3 may all be identical. Examples of silyl protecting groups include, but are not limited to, trimethylsilyl and t-butyldiphenylsilyl.

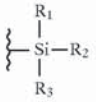
An acyl group, as used herein to describe an acyl protecting group (as in 1) or to describe a carboxylate (as in 4), is a group having the formula:

wherein R' is a lower alkyl, e.g., methyl, ethyl, butyl, and alkyl possessing 5 carbon atoms or less; substituted lower alkyl wherein the alkyl bears one, two, or more simple substituents, including, but not limited to, alkyl, amino, carboxyl, pavoloyl, hydroxy, phenyl, lower-alkoxy, e.g., methoxy and ethoxy; phenyl; substituted phenyl wherein the phenyl bears one, two, or more simple substituents, including, but not limited to, lower alkyl, halo, e.g., chloro and bromo, sulfato, sulfonyloxy, carboxyl, carbo-lower-alkoxy, e.g., carbomethoxy and carbethoxy, amino, mono- and di-lower alkylamino, e.g., methylamino, amido, hydroxy, lower alkoxy, e.g., methoxy and ethoxy, lower-alkanoyloxy, e.g., acetoxy.

A 5-fluoro substituted silyated pyrimidine base, as used herein, means a compound having the formula:



wherein X is either a trialkylsilyloxy or a trialkylsilylamino group and Z is a trialkylsilyl group. A trialkylsilyl group, as used herein, means a group having the formula:



wherein R_1, R_2, and R_3 may be lower-alkyl, e.g., methyl, ethyl, butyl, and alkyl possessing 5 carbon atoms or less, or phenyl. Furthermore, R_1 may be identical to R_2; R_1, R_2, and R_3 may all be identical. Examples of trialkylsilyl groups include, but are not limited to, trimethylsilyl and t-butyldiphenylsilyl.

As used herein, a leaving group means a functional group that forms an incipient carbocation when it leaves.

Illustrative examples of the synthesis of FTC or FTC prodrug analogues, BCH-189 or BCH-189 analogues and FDOC according to the present invention are given in FIGS. **1–5** and Examples 1–6.

EXAMPLE 1

SYNTHESIS OF BCH-189

FIG. **2** shows the synthesis of BCH-189 starting with allyl alcohol 7. A NaH oil suspension (4.5 g, 60%, 110 mmol) was washed with THF twice (100 ml×2) and the resulting solid suspended in THF (300 ml). The suspension was cooled to 0° C., allyl alcohol 7 (6.8 ml, 100 mmol) was added dropwise, and the mixture was stirred for 30 minutes at 0° C. t-Butyl-diphenylsilyl chloride (25.8 ml, 100.8 mmol) was added dropwise at 0° C. and the reaction mixture was stirred for 1 hour at 0° C. The solution was quenched with water (100 ml), and extracted with diethyl ether (200 ml×2). The combined extracts were washed with water, dried over $MgSO_4$, filtered, concentrated, and the residue distilled under vacuum (90°–100° C. at 0.5–0.6 mm Hg) to give a colorless liquid 8 (28 g., 94 mmol, 94%). ^1H NMR: ($CDCl_3$, 300 MHz) 7.70–7.35 (10H, m, aromatic-H); 5.93 (1H, m, H_2); 5.37 (1H, dt, H_1) J=1.4 and 14.4 Hz; 5.07 (1H, dt, H_1) J=1.4 and 8.7 Hz; 4.21 (2H, m, H_3); 1.07 (9H, s, t-Bu))

The silyl allyl ether 8 (15.5 g, 52.3 mmol) was dissolved in CH_2Cl_2 (400 ml), and ozonized at −78° C. Upon completion of ozonolysis, DMS (15 ml, 204 mmol, 3.9 eq) was added at −78° C. and the mixture was warmed to room temperature and stirred overnight. The solution was washed with water (100 ml×2), dried over $MgSO_4$, filtered, concentrated, and distilled under vacuum (100°–110° C. at 0.5–0.6 mm Hg) to give a colorless liquid 9 (15.0 g, 50.3 mmol, 96%). (^1H NMR: ($CDCl_3$, 300 MHz) 9.74 (1H, s, H—CO); 7.70–7.35 (10H, m, aromatic-H); 4.21 (2H, s, —CH_2); 1.22 (9H, s, t-Bu))

Silylated glycoaldehyde 9 (15.0 g, 50.3 mmol) was dissolved in toluene (200 ml) and thioglycolic acid (3.50 ml, 50.3 mmol) was added all at once. The solution was refluxed for 2 hours while the resulting water was removed with a Dean-Stark trap. The solution was cooled to room temperature and washed with saturated $NaHCO_3$ solution and the aqueous washings were extracted with diethyl ether (200 ml×2). The combined extracts were washed with water (100 ml×2), dried over $MgSO_4$, filtered, and concentrated to give a colorless oil 10 (16.5 g, 44.3 mmol, 88%), which gradually solidified under vacuum. Recrystallization from hexane afforded a white solid 10 (15.8 g, 84%). (^1H NMR: 7.72–7.38 (10H, m, aromatic-H); 5.53 (1H, t, H_2) J=2.7 Hz; 3.93 (1H, dd, —CH_2O) J=9.3 Hz; 3.81 (1H, d, $1H_4$) J=13.8 Hz; 3.79 (1H, dd, —CH_2O); 3.58 (1H, d, $1H_4$); 1.02 (9H, s, t-Bu))

2-(t-Butyl-diphenylsilyloxy)-methyl-5-oxo-1,2-oxathiolane 10 (5.0 g, 13.42 mmol) was dissolved in toluene (150 ml) and the solution was cooled to −78° C. Dibal-H solution (14 ml, 1.0M in hexanes, 14 mmol) was added dropwise, while the inside temperature was kept below −70° C. all the time. After the completion of the addition, the mixture was stirred for 30 minutes at −78° C. Acetic anhydride (5 ml, 53 mmol) was added and the mixture was warmed to room temperature and stirred overnight. Water (5 ml) was added to the mixture and the resulting mixture was stirred for 1 hour at room temperature. The mixture was diluted with diethyl ether (300 ml), $MgSO_4$ (40 g) was added, and the mixture was stirred vigorously for 1 hour at room temperature. The mixture was filtered, concentrated, and the residue flash chromatographed with 20% EtOAc in hexanes to give a colorless liquid 11 (3.60 g, 8.64 mmol, 64%), which was a 6:1 mixture of anomers. (^1H NMR of the major isomer: 7.70–7.35 (10H, m, aromatic-H); 6.63 (1H, d, H_5) J=4.4 Hz; 5.47 (1H, t, H_2); 4.20–3.60 (2H, m, —CH_2O); 3.27 (1H, dd, $1H_4$) J=4.4 and 11.4 Hz; 3.09 (1H, d, $1H_4$) J=11.4 Hz; 2.02 (3H, s, CH_3CO); 1.05 (9H, s, t-Bu); ^1H NMR of the minor isomer: 7.70–7.35 (10H, m, aromatic-H); 6.55 (1H, d, H_5) J=3.9 Hz; 5.45 (1H, t, H_2); 4.20–3.60 (2H, m, —CH_2O); 3.25 (1H, dd, $1H_4$) J=3.9 and 11.4 Hz; 3.11 (1H, d, $1H_4$) J=11.4 Hz; 2.04 (3H, s, CH_3CO); 1.04 (9H, s, t-Bu))

Alternatively, 50 g (0.134 mol, 1.0 eq) of 2-(t-Butyl-diphenylsilyloxy)-methyl-5-oxo-1,2-oxathiolane 10 in 500 ml of anhydrous tetrahydrofuran was transferred into a flame-dried, argon-charged 3,000 ml three-necked round-bottomed flask, equipped with an addition funnel and thermometer. The clear solution was cooled to −10° C. (ice/acetone bath) and treated with 147 ml (0.147 mol. 1.1 equiv) of a 1M solution of lithium tri-t-butoxy aluminum hydride in THF (prepared solution of the solid obtained from Aldrich). The reaction was qualitatively monitored for the disappearance of the lactone (R_f=0.38) and the appearance of a second UV-active component at R_f=0.09 (SiO_2, eluting with 90% hexanes in ethyl acetate). In addition, the reaction was quantitatively monitored by GC. The lactol formed was allowed to react at room temperature with 126 ml (1.34 mol, 10.0 equiv) of acetic anhydride (freshly distilled from calcium hydride). The reaction was monitored by the appearance of UV-active component at R_f=0.34 (SiO_2, eluting with 90% hexanes in ethyl acetate) and GC until no lactol was detected. The reaction was quenched with saturated sodium bicarbonate solution and stirred overnight. Anhydrous magnesium sulfate was added and the resulting mixture filtered, concentrated and placed under vacuum to give 49.3 g of crude material 11 as a light red oil.

2-(t-Butyl-diphenylsilyloxy)-methyl-5-acetoxy-1,3-oxathiolane 11 (0.28 g, 0.67 mmol) was dissolved in 1,2-dichloroethane (20 ml), and silylated cytosine 12 (0.20 g, 0.78 mmol) was added at once at room temperature. The mixture was stirred for 10 minutes and to it was added $SnCl_4$

solution (0.80 ml, 1.0M solution in CH_2Cl_2, 0.80 mmol) dropwise at room temperature. Additional cytosine 12 (0.10 g, 0.39 mmol) and $SnCl_4$ solution (0.60 ml) were added in a same manner 1 hour later. After completion of the reaction in 2 hours, the solution was concentrated, and the residue was triturated with triethylamine (2 ml) and subjected to flash chromatography (first with neat EtOAc and then 20% ethanol in EtOAc) to give a tan solid 13 (100% β configuration) (0.25 g, 0.54 mmol, 80%). (^{1}H NMR (DMSO-d^6): 7.75 (1H, d, H_6) J=7.5 Hz; 7.65–7.35 (10H, m, aromatic-H); 7.21 and 7.14 (2H, broad, —NH_2); 6.19 (1H, t, $H_{5'}$); 5.57 (1H, d, H_5); 5.25 (1H, t, $H_{2'}$); 3.97 (1H, dd, —CH_2O) J=3.9 and 11.1 Hz; 3.87 (1H, dd, —CH_2O); 3.41 (1H, dd, $1H_{4'}$) J=4.5 and 11.7 Hz; 3.03 (1H, dd, $1H_{4'}$) J=?; 0.97 (9H, s, t-Bu))

Silyether 13 (0.23 g, 0.49 mmol) was dissolved in THF (30 ml), and to it was added n-Bu_4NF solution (0.50 ml, 1.0M solution in THF, 0.50 mmol) dropwise at room temperature. The mixture was stirred for 1 hour and concentrated under vacuum. The residue was taken up with ethanol/triethylamine (2 ml/1 ml), and subjected to flash chromatography (first with EtOAc, then 20% ethanol in EtOAc) to afford a white solid 14 in 100% anomeric purity (BCH-189; 0.11 g, 0.48 mmol, 98%), which was further recrystallized from ethanol/$CHCl_3$/Hexanes mixture. (^{1}H NMR (DMSO-d_6): 7.91 (1H, d, H_6) J=7.6 Hz; 7.76 and 7.45 (2H, broad, —NH_2); 6.19 (1H, t, $H_{5'}$); 5.80 (1H, d, H_5) J=7.6 Hz; 5.34 (1H, broad, —OH); 5.17 (1H, t, $H_{2'}$); 3.74 (2H, m, —CH_2O); 3.42 (1H, dd, $1H_{4'}$) J=5.6 and 11.5 Hz; 3.09 (1H, dd, $1H_{4'}$) J=4.5 and 11.5 Hz)

EXAMPLE 2

SYNTHESIS OF BCH-189 FROM A URACIL DERIVATIVE

BCH-189 and its analogues can also be synthesized by coupling a silylated uracil derivative with 11. Silylated uracil derivative 15 (1.80 g, 7.02 mmol) was coupled with 11 (1.72 g, 4.13 mmol) in 1,2-dichloroethane (50 ml) in the presence of $SnCl_4$ (5.0 ml) as described above in the preparation of the cytosine derivative 13. The reaction was complete after 5 hours. Flash chromatography, first with 40% EtOAc in hexane and then EtOAc, afforded a white foam 16 (1.60 g, 3.43 mmol, 83%). (^{1}H NMR: 9.39 (1H, broad, —NH) 7.90 (1H, d, H_6) J=7.9 Hz; 7.75–7.35 (10H, m, aromatic-H); 6.33 (1H, dd, $H_{5'}$); 5.51 (1H, d, H_5) J=7.9 Hz; 5.23 (1H, t, $H_{2'}$); 4.11 (1H, dd, —CH_2O) J=3.2 and 11.7 Hz; 3.93 (1H, dd, —CH_2O); 3.48 (1H, dd, $1H_{4'}$) J=5.4 and 12.2 Hz; 3.13 (1H, dd, $1H_{4'}$) J=3.2 and 12.2 Hz)

The uracil derivative 16 can be converted to the cytosine derivative 13. The uracil derivative 16 (0.20 g, 0.43 mmol) was dissolved in a mixture of pyridine/dichloroethane (2 ml/10 ml), and the solution cooled to 0° C. Triflic anhydride (72 μl, 0.43 mmol) was added dropwise at 0° C. and the mixture was warmed to room temperature and stirred for 1 hour. Additional triflic anhydride (0.50 μl, 0.30 mmol) was added and the mixture stirred for 1 hour. TLC showed no mobility with EtOAc. The reaction mixture was then decannulated into a NH_3-saturated methanol solution (30 ml) and the mixture was stirred for 12 hours at room temperature. The solution was concentrated, and the residue subjected to flash chromatography to give a tanned foam 13 (0.18 g, 0.39 mmol, 91%), which was identical with the compound obtained from the cytosine coupling reaction.

EXAMPLE 3

SYNTHESIS OF 5-METHYLCYTIDINE AND TRYMIDINE BCH-189 DERIVATIVES

FIG. **3** illustrates the synthesis of 5-methylcytidine and thymidine derivatives of BCH-189. The acetate 11 (0.93 g, 2.23 mmol) in 1,2-dichloroethane (50 ml), was reacted with the silylated thymine derivative 17 (1.0 g, 3.70 mmol), and $SnCl_4$ solution (4.0 ml) in a manner similar to that described for the preparation of cytosine derivative 13. (^{1}H NMR: 8.10 (1H, broad, NH); 7.75–7.30 (11H, m, 10 Aromatic H's and $1H_6$); 6.32 (1H, t, $H_{1'}$) J=5.4 Hz; 5.25 (1H, t, $H_{4'}$) J=4.2 Hz; 4.01 (1H, dd, $1H_{5'}$) J=3.9 and 11.4 Hz; 3.93 (1H, dd, $1H_{5'}$) J=4.5 and 11.4 Hz; 3.41 (1H, dd, $1H_{2'}$) J=5.4 and 11.7 Hz; 3.04 (1H, dd, $1H_{2'}$) J=5.7 and 11.7 Hz; 1.75 (3H, s, CH_3); 1.07 (9H, s, t-Bu))

The thymine derivative 18 (0.20 g, 0.42 mmol) was dissolved in a mixture of pyridine/dichloroethane (2 ml/10 ml), and the solution cooled to 0° C. To it was added triflic anhydride (100 μl, 0.60 mmol) dropwise at 0° C., and the mixture was allowed, with continuous stirring, to warm to room temperature. After reaching room temperature, it was stirred for 1 hour. TLC showed no mobility with EtOAc. The reaction mixture was then decannulated into the NH_3-saturated methanol solution (20 ml), and the mixture stirred for 12 hours at room temperature. The solution was concentrated, and the residue was subjected to flash chromatography to give a tanned foam 19 (0.18 g, 0.38 mmol, 90%). (^{1}H NMR: 7.70–7.30 (12H, m, 10 Aromatic H's, 1NH and H_6); 6.60 (1H, broad, 1NH); 6.34 (1H, t, $H_{1'}$) J=4.5 Hz; 5.25 (1H, t, $H_{4'}$) J=3.6 Hz; 4.08 (1H, dd, $1H_{5'}$) J=3.6 and 11.4 Hz; 3.96 (1H, dd, $1H_{5'}$) J=3.6 and 11.4 Hz; 3.52 (1H, dd, $1H_{2'}$) J=5.4 and 12.3 Hz; 3.09 (1H, dd, $1H_{2'}$) J=3.9 and 12.3 Hz; 1.72 (3H, s, CH_3); 1.07 (9H, s, t-Bu))

Silylether 19 (0.18 g, 0.38 mmol) was dissolved in THF (20 ml), and an n-Bu_4NF solution (0.50 ml, 1.0M solution in THF, 0.50 mmol) was added, dropwise, at room temperature. The mixture was stirred for 1 hour and concentrated under vacuum. The residue was taken up with ethanol/triethylamine (2 ml/1 ml), and subjected to flash chromatography (first with EtOAc, then 20% ethanol in EtOAc) to afford a white solid 20 (0.09 g, 0.37 mmol, 97%), which was further recrystallized from ethanol/$CHCl_3$/Hexanes mixture to afford 82 mg of pure compound (89%). (^{1}H NMR: (in d^6-DMSO): 7.70 (1H, s, H_6); 7.48 and 7.10 (2H, broad, NH_2); 6.19 (1H, t, $H_{1'}$) J=6.5 Hz; 5.31 (1H, t, OH); 5.16 (1H, t, $1H_{4'}$) J=5.4 Hz; 3.72 (2H, m, $2H_{5'}$) 3.36 (1H, dd, $1H_{2'}$) J=6.5 and 14.0 Hz; 3.05 (1H, dd, $1H_{2'}$) J=6.5 and 14.0 Hz; 1.85 (3H, s, CH_3))

Silylether 18 (0.70 g, 1.46 mmol) was dissolved in THF (50 ml), and an n-Bu_4NF solution (2 ml, 1.0M solution in THF, 2 mmol) was added, dropwise, at room temperature. The mixture was stirred for 1 hour and concentrated under vacuum. The residue was taken up with ethanol/triethylamine (2 ml/1 ml), and subjected to flash chromatography to afford a white solid 21 (0.33 g, 1.35 mmol, 92%). (^{1}H NMR: (in d^6-Acetone): 9.98 (1H, broad, NH); 7.76 (1H, d, H_6) J=1.2 Hz; 6.25 (1H, t, $H_{4'}$) J=5.7 Hz; 5.24 (1H, t, $H_{1'}$) J=4.2 Hz; 4.39 (1H, t, OH) J=5.7 Hz; 3.85 (1H, dd, $2H_{5'}$) J=4.2 and 5.7 Hz; 3.41 (1H, dd, $1H_{2'}$) J=5.7 and 12.0 Hz; 3.19 (1H, dd, $1H_{2'}$) J=5.4 and 12.0 Hz; 1.80 (3H, s, CH_3))

EXAMPLE 4

SYNTHESIS OF FTC

Acetate 11 (1.70 g, 4.08 mmol) was dissolved in dichloromethane (100 ml). Silylated 5-fluorocytosine (1.22 g, 4.5 mmol) was mixed with tin (IV) chloride solution (8.6 ml, 1.0M in dichloromethane, 8.6 mmol) in dichloromethane (20 ml). The pre-mixed solution was decannulated in the acetate solution over 20 minutes. The mixture was stirred for

3 hours at room temperature, then pyridine (3 ml) was added to the mixture in one portion. The mixture was concentrated under vacuum, and the residue taken up with ethanol (10 ml) and subjected to flash chromatography to give a tan solid (1.80 g, 3.71 mmol, 91%), which was further recrystallized from ethanol to give a total of 1.75 g of a crystalline compound (5'-O-t-Butyldiphenysilyl-3'-thia-2',3'-dideoxy-5-fluorocytidine, 100% β configuration). (^{1}HNMR: (DMSO-d^6) 7.96 (1H, d, H_6, J=6.8 Hz), 7.87 & 7.61 (2H, broad, NH_2), 7.64 & 7.43 (10H, m, Aromatic H's), 6.19 (1H, t, $H_{1'}$, J=5.4 Hz), 5.28 (1H, t, $H_{4'}$, J=4.0 Hz), 4.01 (H, dd, $1H_{5'}$, J=3.6 & 11.5 Hz), 3.90 (1H, dd, $1H_{5'}$, J=4.3 & 11.5 Hz), 3.45 (1H, dd, $1H_{2'}$, J=5.4 & 11.5 Hz), 3.16 (1H, dd, $1H_{2'}$, J=5.4 & 11.5 Hz); mp 214°–215° C.; Anal. Calc. for $C_{24}H_{28}O_3N_3FSSi$: C, 59.36; H, 5.81; N, 8.65; S, 6.60. Found: C, 59.44; H, 5.81; N, 8.60; S, 6.64.

The silylether (5'-O-t-Butyldiphenysilyl-3'-thia-2',3'-dideoxy-5-fluorocytidine, 100% β configuration)(1.12 g, 2.31 mmol) was dissolved in THF (80 ml), and to it was added n-Bu_4NF solution (2.50 ml, 1.0M solution in THF, 2.50 mmol) dropwise at room temperature. The mixture was stirred for 0.5 hours and concentrated under vacuum. The residue was taken up with EtOH/pyridine (3 ml/1 ml), and subjected to flash chromatography to afford a white solid (0.75 g), which was further recrystallized from EtOH to give a total of 0.56 g of the crystalline compound 2'-Deoxy-5-fluoro-3'-thiacytidine (FTC; 100% β isomer; 2.26 mmol; 98%). (^{1}H NMR: (DMSO-d^6) 8.18 (1H, d, H_6, J=8.4 Hz), 7.81 & 7.57 (2H, broad, NH_2), 6.12 (1H, dd, $H_{1'}$, J=5.7 & 4.2 Hz), 5.40 (1H, t, OH, J=5.7 Hz), 5.17 (1H, t, $H_{4'}$, J=3.6 Hz), 3.74 (2H, m, $2H_{5'}$), 3.41 (1H, dd, $1H_{2'}$, J=5.7 & 11.7 Hz), 3.11 (1H, dd, $1H_{2'}$, J=4.2 & 11.7 Hz); ^{13}C NMR: (DMSO-d^6) 157.85 (d, J=13.4 Hz), 153.28, 136.12 (d, J=241 Hz), 126.01 (d, J=32.6 Hz), 86.90, 86.84, 62.48, 37.07; mp 195°–196° C.; Anal. Calc. for $C_8H_{10}O_3N_3SF$: C, 38.86; H, 4.08; N, 17.00; S, 12.97. Found: C, 38.97; H, 4.07; N, 16.93; S, 12.89.)

EXPERIMENT 5

SYNTHESIS OF 5-HALO DERIVATIVES OF β-BCH-189

The coupling of the acetate 11 with various bases was done as shown in FIG. **4**. This coupling could be done, in general, in two ways to obtain the cytidine analogues, either by direct coupling of the acetate with a corresponding bis-silylated cytosines in the presence of tin(IV) chloride or by ammonolysis of the triflate derived from the corresponding uridine analogues. The typical experimental procedure is outlined below.

The acetate 25 (0.28 g, 0.67 mmol) was dissolved in 1,2-dichloroethane (20 ml), and to it the silylated cytosine (0.20 g, 0.78 mmol) was added in one portion at room temperature. The mixture was stirred for 10 minutes and to it a $SnCl_4$ solution (1.34 ml, 1.0M solution in CH_2Cl_2, 1.34 mmol) was added, dropwise, at room temperature. Upon completion, the solution was concentrated, the residue was triturated with Et_3N (2 ml) and subjected to flash chromatography to give a tan solid 26 (0.25 g, 0.54 mmol, 80%).

Silylether 26 (0.23 g, 0.49 mmol) was dissolved in THF (30 ml), and an n-Bu_4NF solution (0.50 ml, 1.0M solution in THF, 0.50 mmol) was added, dropwise, at room temperature. The mixture was stirred for 1 hour and concentrated under vacuum. The residue was taken up with EtOH/Et_3N (2 ml/1 ml), and subjected to flash chromatography to afford a white solid 27 (100% β isomer; 0.11 g, 0.48 mmol, 98%), which was further recrystallized from EtOH/$CHCl_3$/Hexanes mixture.

The procedure for coupling a silylated uracil with acetate 25 is as follows: The acetate 25 (1.72 g, 4.13 mmol), in 1,2-dichloroethane (50 ml), was reacted with the silylated uracil derivative (1.80 g, 7.02 mmol) and $SnCl_4$ solution (5.0 ml) for 5 hours to complete the reaction. Flash chromatography with 40% EtOAc in hexane and then EtOAc afforded a white foam 26 (1.60 g, 3.43 mmol, 83%).

The uracil derivative 26 (0.20 g, 0.43 mmol) was dissolved in a mixture of pyridine/dichloroethane (2 ml/10 ml), and the solution cooled to 0° C. To the solution was added Tf_2O (72 μl, 0.43 mmol) dropwise at 0° C. and the mixture was allowed, with continuous stirring, to warm to room temperature. After reaching room temperature, it was stirred for 1 hour. Additional Tf_2O (0.50 μl, 0.30 mmol) was added and the mixture was stirred for 1 hour. TLC showed no mobility with EtOAc. The reaction mixture was then decannulated into the NH_3-saturated methanol solution (30 ml), and the mixture stirred for 12 hours at room temperature. The solution was concentrated and the residue was subjected to flash chromatography to give a tanned foam 27 (100% β isomer; 0.18 g, 0.39 mmol, 91%), which was identical with the compound obtained from the cytosine coupling reaction.

The compounds synthesized include:

2'-Deoxy-5-methyl-3'-thiacytidine

^{1}H NMR (DMSO-d^6) 7.70 (1H, s, H_6), 7.48 and 7.10 (2H, broad, NH_2), 6.19 (1H, t, $H_{1'}$, J=5.4 Hz), 5.31 (1H, t, OH, J=4.5 Hz), 5.16 (1H, t, $H_{4'}$, J=4.5 Hz), 3.72 (2H, m, $2H_{5'}$), 3.36 (1H, dd, $1H_{2'}$, J=5.4 & 11.7 Hz), 3.05 (1H, dd, $1H_{2'}$, J=5.4 & 11.7 Hz), 1.85 (3H, d, CH_3, $J_{allylic}$=0.6 Hz); mp 183°–185° C.

2'-Deoxy-5-fluoro-3'-thiacytidine

^{1}H NMR (DMSO-d^6) 8.18 (1H, d, H_6, J=8.4 Hz), 7.81 & 7.57 (2H, broad, NH_2), 6.12 (1H, dd, $H_{1'}$, J=5.7 & 4.2 Hz), 5.40 (1H, t, OH, J=5.7 Hz), 5.17 (1H, t, $H_{4'}$, J=3.6 Hz), 3.74 (2H, m, $2H_{5'}$), 3.41 (1H, dd, $1H_{2'}$, J=5.7 & 11.7 Hz), 3.11 (1H, dd, $1H_{2'}$, J=4.2 & 11.7 Hz); mp 195°–196° C.; Anal. Calc. for $C_8H_{10}O_3N_3SF$: C, 38.86; H, 4.08; N, 17.00; S, 12.97. Found: C, 38.97; H, 4.07; N, 16.93; S, 12.89.

2'-Deoxy-5-chloro-3'-thiacytidine

^{1}H NMR (DMSO-d^6) 8.30 (1H, s, H_6), 7.89 & 7.26 (2H, broad, NH_2), 6.13 (1H, t, $H_{1'}$, J=4.5 Hz), 5.45 (1H, t, OH, J=5.7 Hz), 5.19 (1H, t, $H_{4'}$, J=3.6 Hz), 3.76 (2H, m, $2H_{5'}$), 3.44 (1H, dd, $1H_{2'}$, J=5.4 & 12.0 Hz), 3.16 (1H, dd, $1H_{2'}$, J=3.9 & 12.0 Hz); mp 212°–212.5° C.; Anal. Calc. for $C_8H_{10}O_3N_3SCl$: C, 36.44; H, 3.82; N, 15.93; S, 12.16; Cl, 13.44. Found: C, 36.53; H, 3.86; N, 15.90; S, 12.08; Cl, 13.50.

2'-Deoxy-5-bromo-3'-thiacytidine

^{1}H NMR (DMSO-d^6) 8.37 (1H, s, H_6), 7.90 & 7.05 (2H, broad, NH_2), 6.14 (1H, t, $H_{1'}$, J=4.5 Hz), 5.46 (1H, t, OH, J=5.4 Hz), 5.19 (1H, t, $H_{4'}$, J=3.6 Hz), 3.76 (2H, m, $2H_{5'}$), 3.41 (1H, dd, $1H_{2'}$, J=5.4 & 12.0 Hz), 3.16 (1H, dd, $1H_{2'}$, J=3.6 & 12.0 Hz); mp 197°–198° C.; Anal. Calc. for $C_8H_{10}O_3N_3SBr$: C, 331.18; H, 3.27; N, 13.64; S, 10.40; Br, 25.93. Found: C, 31.29; H, 3.29; N, 13.54; S, 10.49; Br, 25.98.

2'-Deoxy-5-iodo-3'-thiacytidine

^{1}H NMR (DMSO-d^6) 8.36 (1H, s, H_6), 7.87 & 6.66 (2H, broad, NH_2), 6.13 (1H, t, $H_{1'}$, J=4.5 Hz), 5.44 (1H, t, OH,

J=5.7 Hz), 5.18 (1H, t, $H_{4'}$, J=3.6 Hz), 3.73 (2H, m, $2H_{5'}$), 3.42 (1H, dd, $1H_{2'}$, J=5.7 & 12.0 Hz), 3.14 (1H, dd, $1H_{2'}$, J=3.6 & 12.0 Hz); mp 188°–189° C.

2'-Deoxy-5-fluoro-3'-thiauridine

^{1}H NMR (DMSO-d^6) 11.89 (1H, broad, NH), 8.33 (1H, d, H_6, J=7.5 Hz), 6.15 (1H, t, $H_{1'}$, J=3.9 Hz), 5.44 (1H, t, OH, J=5.7 Hz), 5.19 (1H, t, $H_{4'}$, J=3.6 Hz), 3.75 (2H, m, $2H_{5'}$), 3.43 (1H, dd, $1H_{2'}$, J=5.7 & 12.0 Hz), 3.25 (1H, dd, $1H_{2'}$, J=4.2 & 12.0 Hz); mp 158°–159° C.; Anal. Calc. for $C_8H_9O_4N_2SF$: C, 38.71; H, 3.65; N, 11.29; S, 12.92. Found: C, 38.79; H, 3.68; N, 11.23; S, 12.82.

2'-Deoxy-5-chloro-3'-thiauridine

^{1}H NMR (DMSO-d^6) 11.95 (1H, broad, NH), 8.11 (1H, s, H_6), 6.18 (1H, t, $H_{1'}$, J=4.8 Hz), 5.38 (1H, t, OH, J=3.6 Hz), 4.47 (1H, dd, $1H_{5'}$, J=4.5 & 12.3 Hz), 4.37 (1H, dd, $1H_{5'}$, J=3.0 & 12.3 Hz), 3.49 (1H, dd, $1H_{2'}$, J=5.4 & 12.0 Hz), 3.38 (1H, dd, $1H_{2'}$, J=4.2 & 12.0 Hz).

2'-Deoxy-5-iodo-3'-thiauridine

^{1}H NMR (DMSO-d^6) 11.73 (1H, broad, NH), 8.48 (1H, s, H_6), 6.15 (1H, dd, $H_{1'}$, J=4.0 & 5.0 Hz), 5.46 (1H, t, OH, J=5.4 Hz), 5.19 (1H, t, $H_{4'}$, J=3.6 Hz), 3.76 (2H, m, $2H_{5'}$), 3.44 (1H, dd, $1H_{2'}$, J=5.4 & 12.0 Hz), 3.30 (1H, dd, $1H_{2'}$, J=4.7 & 12.0 Hz); mp 177°–179° C.

EXAMPLE 6

SYNTHESIS OF DOC, DOT, and FDOC

FIG. **5** shows the synthesis of 2'-deoxy-3'-oxacytidine (DOC), 2'-deoxy-3'-oxathymidine (DOT), and 2'-deoxy-5-fluoro-3'-oxacytidine (FDOC) according to the present invention. The silyated glycoaldehyde 9 was prepared as in Example 1. (4.0 g, 13.40 mmol) of 9 was dissolved in 1,2-dichloroethane (50 ml) and to it was added glycolic acid (1.10 g, 14.46 mmol) in one portion and p-toluenesulfonic acid (0.1 g). The mixture was refluxed for 1 hour. The volume of the solution was then reduced to about half by distilling off the solvent with a Dean-Stark trap. Another 50 ml of dichloroethane was added and the solution refluxed for 30 minutes again. The solution was cooled to room temperature and concentrated under vacuum. The residue was dissolved in ether (200 ml) and the solution washed with $NaHCO_3$ solution (50 ml) and water (50 ml). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to give a colorless oil which gradually solidified under vacuum. Recrystallization from hexane afforded a waxy white solid 28 (2-(t-Butyl-diphenylsilyloxy)-methyl-4-oxo-1,3-dioxolane) (4.2 g, 11.78 mmol, 88%). (^{1}H NMR: ($CDCl_3$, 300 MHz) 7.66 & 7.42 (10H, m, aromatic-H), 5.72 (1H, broad, H_2), 4.46 (1H, d, $1H_5$, J=14.4 Hz), 4.28 (1H, d, $1H_5$, J=14.4 Hz), 3.81 (2H, d, $2CH_2O$, J=1.8 Hz), 1.04 (9H, s, t-Bu); mp 94°–95° C.; MS (FAB) 357 (M+H), 299, 241, 197, 163, 135, 91; Anal. Calc'd for $C_{20}H_{24}O_4Si$: C, 67.38; H, 6.79; Found: C, 67.32; H, 6.77.)

4-Acetoxy-2-(t-Butyldiphenylsilyloxymethyl)-1,3-dioxolane 29 was prepared using either of the following procedures A or B.

Procedure A: (DIBAL-H) The lactone 28 (1.0 g, 2.81 mmol) was dissolved in toluene (100 ml), and the solution cooled to −78° C. Dibal-H solution (3.0 ml, 1.0M in hexanes, 3 mmol) was added dropwise, while the inside temperature was kept below −70° C. throughout the addition. After the addition was completed, the mixture was stirred for 0.5 hours at −78° C. To it was added Ac_2O (5 ml, 53 mmol) and the mixture, with continuous stirring, was allowed to reach room temperature overnight. Water (5 ml) was added to it and the mixture was stirred for 1 h, $MgSO_4$ (40 g) was then added, and the mixture was stirred vigorously for 1 hour at room temperature. The mixture was filtered, concentrated, and the residue flash chromatographed with 20% EtOAc in hexanes to give a colorless liquid 29 (0.70 g) which was a mixture of the desired acetates and the aldehyde 9 derived from the ring opening reaction.

Procedure B: ($LiAlH(OtBu)_3$) Lactone 28 (1.426 g, 4 mmol) was dissolved in 20 ml of THF, cooled to 0° C., and to this was added 5 ml (5 mmol, 1.25 eq) of a $LiAlH(OtBu)_3$ solution (1M in THF; Aldrich) over a 40 minute period. After addition was completed, the mixture was stirred for 6 hours at 0° C. After this time, 3.8 ml (40 mmol, 10 eq) of dry acetic anhydride was added, and the mixture was warmed to room temperature. The reaction was then stirred for another 40 hours and then was quenched by adding 50 ml of ether and 50 ml of saturated $NaHCO_3$ solution. The layers were separated after 2 hours of stirring, and the organic layer was washed successively with saturated $NaHCO_3$ and NaCl solutions. The aqueous layers were combined and then re-extracted with 75 ml of ether (3 times). The organic layers were combined, dried over $MgSO_4$, filtered, and the solvent was removed. Column chromatography (Hexanes/EtOAc, 6/1) gave 1.09 g, which was 69% (753 mg, 47% yield) of the desired acetates 29 (3.6:1 ratio at the glycosidic center) by ^{1}H NMR analysis (the rest of the mixture was composed of the aldehyde 9 and the lactone 28, which were difficult to separate).

(^{1}H NMR: ($CDCl_3$, 300 MHz) 1.02 (s, 9H, major isomer), 1.04 (s, 9H, minor isomer), 1.96 (s, 3H, minor), 2.12 (s, 3H, major), 3.7 (m, 2H), 4.07 (m, 2H), 5.24 (t, 1H, minor, J=4.2 Hz), 5.37 (t, 1H, major, J=3 Hz), 6.3 (t, 1H, minor, J=3.9 Hz), 6.37 (dd, 1H, major, J=1.5 Hz, J=4.5 Hz), 7.39 (m, 6H), 7.67 (m, 4H). IR (neat): cm^{-1} 3090, 2980, 2880, 1760, 1475, 1435, 1375, 1240, 1120, 1000. MS (FAB, Li^+): 407(M+Li), 312, 282, 241, 197, 162, 125. Anal. Calc. for $C_{22}H_{28}O_5Si$: C, 65.97%, H, 7.05%; Found: C, 66.60%, H, 7.27%.)

The crude acetate 29 (0.25 g, 0.62 mmol, quantity assumed with 0.50 g of the previous mixture) was dissolved in methylene chloride (50 ml), and to it the silylated cytosine 30 (X═H) (0.10 g, 0.63 mmol) was added in one portion. The mixture was stirred for 10 minutes, and to it a $TiCl_4$ solution (1.30 ml, 1.0M solution in CH_2Cl_2, 1.30 mmol) was added, dropwise, at room temperature. It took 2 hours to complete the reaction. Upon completion, the solution was concentrated, the residue was triturated with pyridine (2 ml) and subjected to flash chromatography (first with neat EtoAc then 20% EtOH in EtOAc) to give a tan solid, which was further recrystallized to give a white crystalline solid 32 (0.25 g, 0.55 mmol, 89%). (^{1}HNMR ($CDCl_3$, 300 MHz) 7.97 (1H, d, H_6, J=7.8 Hz), 7.67 & 7.40 (10H, m, aromatic-H), 6.24 (1H, d, $H_{1'}$), 5.62 (1H, d, H_5, J=7.6 Hz), 5.03 (1H, t, $H_{4'}$), 4.20 (1H, dd, $1H_{2'}$, J=1.2 and 9.0 Hz), 4.15 (1H, dd, $1H_{2'}$, J=4.8 & 9.0 Hz), 3.96 (1H, dd, $1H_{5'}$, J=2.1 and 8.7 Hz), 3.93 (1H, dd, $1H_{5'}$, J=2.1 and 8.7 Hz), 1.08 (9H, s, t-Bu).)

Silylether 32 (0.12 g, 0.27 mmol) was dissolved in THF (20 ml), and an n-Bu_4NF solution (0.30 ml, 1.0M solution in THF, 0.30 mmol) was added, dropwise, at room temperature. The mixture was stirred for 1 hour and concentrated under vacuum. The residue was taken up with EtOH/pyridine (2 ml/1 ml), and subjected to flash chromatography (first with EtOAc, then 20% EtOH in EtOAc) to afford a white solid, which was further recrystallized from EtOH to

give a white crystalline solid 33 (DOC) (55 mg, 0.26 mmol, 96%). (^{1}H NMR: (DMSO-d^6, 300 MHz) 7.79 (1H, d, H_6, J=7.5 Hz), 7.18 and 7.11 (2H, broad, NH_2), 6.16 (1H, dd, $H_{1'}$, J=3.0 & 4.2 Hz), 5.70 (1H, d, $H_{3'}$, J=7.5 Hz), 5.16 (1H, t, OH, J=6.0 Hz), 4.91 (1H, t, $H_{4'}$, J=2.7 Hz), 4.05 (2H, m, $H_{2'}$), 3.62 (2H, m, $2H_{5'}$); mp 183°–184° C.)

The coupling reaction of acetate 29 with silylated thymine 31 showed a titanium species dependent selectivity in accordance with the following observations (ratios were determined by ^{1}H NMR of the crude reaction mixtures):

Titanium Species	β:α Ratio
$TiCl_4$	7:1
$TiCl_3(OiPr)$	10:1
$TiCl_2(OiPr)_2$	>98:2

In the coupling reaction using $TiCl_3(OiPr)$, the impure acetate 29 from the procedure B reduction above (assumed 69% of the mixture, 185.4 mg, 0.4653 mmol) was dissolved in 8 ml of dry dichloromethane along with 144 mg (1.15 eq) of silylated thymine 31, and this mixture was stirred under argon at room temperature. Next 0.57 ml (1.15 eq) of a freshly prepared solution of $TiCl_3(OiPr)$ in dichloromethane (1M solution prepared from 2 eq of $TiCl_4$ and 1 eq of $TiCl(OiPr)_3$) was added dropwise over a 25 minute period. After 2.5 hours, 0.07 ml (0.15 eq) of a $TiCl_4$/dichloromethane solution (1M, Aldrich) was added and the reaction was stirred for an additional hour. Then 3 ml of ethanol and 5 ml of $NaHCO_3$ solution were added, stirred for 10 minutes, followed by extraction with additional $NaHCO_3$ solution. The aqueous layer was separated, washed twice with 100 ml of dichloromethane, and the organic layers were combined and dried over $MgSO_4$. Filtration, solvent removal, column chromatography (1/2: Hexanes/EtOAc), and then recrystallization (1/1: Hexanes/Et_2O) gave 160 mg (74%) of compound 34 as a white powder. (^{1}H NMR: ($CDCl_3$, 300 MHz) 1.06 (s, 9H), 1.68 (s, 3H), 3.91 (t, 2H, J=3.3 Hz), 4.14 (d, 2H, J=3.9 Hz), 5.06 (t, 1H, J=3.3 Hz), 6.34 (t, 1H, J=3.9 Hz), 7.4 (m, 6H), 7.7 (m, 4H), 8.62 (bs, 1H). MS (FAB, Li^+): 473 (M+Li), 409, 307, 241, 197, 154, 127. Anal. Calc. for $C_{25}H_{30}O_5N_2Si$: C, 64.35%; H, 6.48%; N, 6.00%; Found: C, 64.42%; H, 6.52%; N, 5.97%.)

In the coupling reaction using $TiCl_2(OiPr)_2$, impure acetate from the procedure B reduction (assumed 50% of the mixture, 444 mg, 1.11 mmol) was dissolved in 18 ml of dry dichloromethane along with 654.1 mg of silylated thymine 31 and stirred at room temperature under argon. Next, 1.3 ml of a 2M $TiCl_2(OiPr)_2/CH_2Cl_2$ solution was added over a 20 minute period. After 14 h, 1 ml of a 1M $TiCl_4/CH_2Cl_2$ solution was added and the reaction was stirred for an additional 3 hours. Then 4 ml of concentrated NH_4OH was added, along with 10 ml of dichloromethane. Ten minutes of stirring followed by filtration over 1 inch of silica gel with EtOAc, solvent removal and then column chromatography of the resulting oil gave 164.9 mg (32%) of compound 34.

The silyl ether 34 (60.9 mg, 0.131 mmol) was dissolved in 2 ml of THF and 0.14 ml of a BU_4NF/THF solution (1M, Aldrich) was added. After stirring for 24 hours, the solvent was removed envaccuo and column chromatography (5/1: EtOAc/EtOH) of the resulting oil gave 22.6 mg (76%) of the desired nucleoside 35 (DOT) as a white powder. (^{1}H NMR: (HOD (4.8 ppm), 300 MHz) 1.83 (s, 3H), 3.82 (m, 2H), 4.18 (dd, 1H, J=10.5 Hz, J=6 Hz), 5.06 (s, 1H), 6.33 (d, 1H, J=5.7 Hz), 7.72 (s, 1H).)

The impure acetate 29 from the procedure B reduction above (assumed 80% by ^{1}H NMR analysis, 117.6 mg, 0.294 mmol) and 120.8 mg (1.5 eq) of silylated fluorocytosine 30 (X=F) were dissolved in 10 ml of dry dichloromethane. Then 0.59 ml (2 eq) of a $TiCl_4$/dichloromethane solution was added dropwise over 1 hour. After stirring for 30 additional minutes, 5 ml of dichloromethane and 1 ml of concentrated NH_4OH were added, the solvent was removed envaccuo, and column chromatography (EtOAc/EtOH: 1/1) gave 35 mg (25%) of compound 36 as a white solid. (^{1}H NMR: ($CDCl_3$, 300 MHz) 1.06 (s, 9H), 3.62 (dq, 2H, J=2.7 Hz, J=12.3 Hz), 3.9 (m, 2H), 5.01 (t, 1H, J=2.4 Hz), 6.2 (m, 1H), 7.41 (m, 6H), 7.7 (m, 4H), 7.92 (d, 1H, J=6 Hz).)

The silyl ether 36 (116.8 mg, 0.249 mmol) was dissolved in 3 ml of dry THF, and 0.3 ml of a Bu_4NF/THF solution (1M, Aldrich) was added. After 3 hours of stirring, the solvent was removed envaccuo and column chromatography (EtOAc/EtOH: 4/1) gave 48.1 mg (84%) of the nucleoside 37 (FDOC) as a white powder. (^{1}HNMR: (DMSO-d^6, 300 MHz) 3.63 (m, 2H), 4.01 (dd, 1H, J=5.1 Hz, J=9.6 Hz), 4.08 (d, 1H, J=9.6 Hz), 4.87 (s, 1H), 5.26 (t, 1H, J=6 Hz), 6.07 (m, 1H), 7.49 (bs, 1H), 7.73 (bs, 1H), 8.12 (d, 1H, J=7.2 Hz).)

B. Therapeutic Use of FTC and FTC Prodrug Analogues

As shown below, the compounds of this invention either possess antiretroviral activity, such as anti-HIV-1, anti-HIV-2 and anti-simian immunodeficiency virus (anti-SIV) activity, themselves and/or are metabolizable to species that possess antiretroviral activity. Thus, these compounds, pharmaceutically acceptable derivatives of these compounds or pharmaceutically acceptable formulations containing these compounds or their derivatives are useful in the prevention and treatment of viral infections in a host such as a human, preferably HIV infections and other AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological conditions, anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections. In addition, these compounds or formulations can be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

As used herein, a "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of FTC or a prodrug analogue of FTC which, upon administration to the recipient, is capable of providing, directly or indirectly, FTC or an antivirally active metabolite or residue of FTC, including, but not limited to, the mono-, di- and triphosphate esters of FTC or a prodrug analogue of FTC.

Thus, humans can be treated by administering to the patient a pharmaceutically effective amount of FTC or FTC prodrug analogues in the presence of a pharmaceutically acceptable carrier or diluent such as a liposomal suspension. A preferred carrier for oral administration is water, especially sterilized water. If administered intravenously, the preferred carriers are physiological saline or phosphate buffered saline. The compounds according to the present invention are included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful inhibitory effect on HIV in vivo without exhibiting adverse toxic effects on the patient treated. Pharmaceutically compatible binding agents and/or adjuvant materials may also be included as part of the composition. The active materials can also be mixed with other active materials that do not impair the desired action and/or supplement the desired action.

It will be appreciated by those skilled in the art that the effective amount of a compound or formulation containing

the compound required to treat an individual will vary depending on a number of factors, including whether FTC or a prodrug analogue of FTC is administered, the route of administration, the nature of the condition being treated and the age and condition of the patient. In general, however, an effective dose will range from about 1–50 mg per kg body weight of the patient per day, preferably 1–20 mg/kg/day. Preferably, a dose will produce peak blood levels of the active compound that range from about 1–10 μM, most preferably about 5 μM. The desired dose may be given in a single dose or as divided doses administered at appropriate intervals, such as two, three, four or more sub-doses per day.

Thus, FTC and FTC prodrug analogues or formulations containing these compounds or their pharmaceutically acceptable derivatives can be conveniently administered by any convenient route of administration, such as parenteral, including intramuscular, subcutaneous and intravenous; oral; rectal; nasal; vaginal or by inhalation. The compounds can be administered in unit dosage form, such as formulations containing 0.1 to 50 mg, preferably, 1 to 10 mg of active ingredient per unit dosage form.

A preferred mode of administration of the compounds of this invention is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds of this invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like.

Methodology for Testing Antiviral Activity

Antiviral compositions can be screened in vitro for inhibition of HIV by various experimental techniques. One such technique involves measuring the inhibition of viral replication in human peripheral blood mononuclear (PBM) cells. The amount of virus produced is determined by measuring the quantity of virus-coded reverse transcriptase (RT), an enzyme found in retroviruses, that is present in the cell culture medium.

PBM cells from healthy HIV-1 and hepatitis B virus seronegative donors were isolated by Ficoll-Hypaque discontinuous gradient centrifugation at 1,000×g for 30 minutes, washed twice in PBS and pelleted at 300×g for 10 minutes. Before infection, the cells were stimulated by phytohemagglutinin (PHA) at a concentration of 6 μg/ml for three days in RPMI 1640 medium supplemented with 15% heat-inactivated fetal calf serum, 1.5 mM L-glutamine, penicillin (100 U/ml), streptomycin (100 μg/ml), and sodium bicarbonate buffer. Most of the antiviral assays described below were performed with cells from at least two different donors.

HIV-1 (strain LAV-1) was obtained from the Centers for Disease Control, Atlanta, and propagated in PHA-stimulated human PBM cells using RPMI 1640 medium as above without PHA and supplemented with 7% interleukin-2 (Advanced Biotechnologies, Silver Spring, Md.), 7 μg/ml DEAE-dextran (Pharmacia, Uppsala, Sweden), and 370 U/ml anti-human leukocyte (alpha) interferon (ICN, Lisle, Ill.). Virus was obtained from the cell free culture supernatant and stored in aliquots at −70° C. until used.

Uninfected PHA-stimulated human PBM cells were uniformly distributed among 25 cm^3 flasks to give a 5 ml suspension containing about 2×10^6 cells/ml. Suitable dilutions of HIV were added to infect the cultures so that the mean reverse transcriptase (RT) activity of the inocula was 50,000 dpm/ml, which was equivalent to about 100 $TCID_{50}$, determined as described in *AIDS Res. Human Retro,* 3:71–85 (1987). The drugs, at twice their final concentrations in 5 ml of RPMI 1640 medium, supplemented as described above, were added to the cultures. Uninfected and treated PBM cells were grown in parallel as controls. The cultures were maintained in a humidified 5% CO_2–95% air incubators at 37° C. for five days after infection, at which point all cultures were sampled for supernatant RT activity. Previous studies indicate that the maximum RT levels are obtained at that time.

The RT assay was performed by a modification of the Spira et al., *J. Clin. Microbiol.* 25, 97–99 (1987) method in 96-well microtiter plates. The radioactive cocktail (180 μl), which contained 50 mM Tris-HCl pH 7.8, 9 mM $MgCl_2$, 5 mM dithiothreitol 4.7 μg/ml $(rA)_n\cdot(dT)_{12-18}$, 140 μM DATP and 0.22 μM [^{3}H]TTP (specific activity 78.0 Ci/mmol, equivalent to 17,300 cpm/pmol; NEN Research Products, Boston, Mass.), was added to each well. The sample (20 μl) was added to the reaction mixture and incubated at 37° C. for two hours. The reaction was terminated by the addition of 100 μl cold 10% trichloroacetic acid (TCA) containing 0.45 mM sodium pyrophosphate. The acid insoluble nucleic acid which precipitated was collected on glass filters using a Skatron semi-automatic harvester (setting 9). The filters were washed with 5% TCA and 70% ethanol, dried, and placed in scintillation vials. Four ml of scintillation fluid (Econofluor, NEN Research Products, Boston Mass.) was added and the amount of radioactivity in each sample determined using a Packard Tri-Carb liquid scintillation analyzer (model 2,000CA). The results were expressed in dpm/ml of original clarified supernatant. The antiviral activity, expressed as the micromolar concentration of compound that inhibits replication of the virus by 50% (EC_{50}), was calculated by determining the percent inhibition by the median effect method described in Chou and Talalay, *Adv. Enz. Regul.,* 22:27–55 (1984).

Methodology for Testing Toxicity and Inhibition of Cell Proliferation

The compounds were evaluated for their potential toxic effects on uninfected PHA-stimulated human PBM cells and also in CEM (T-lymphoblastoid cell line obtained from ATCC, Rockville, Md.) and Vero (African Green Monkey kidney) cells. PBM cells were obtained from whole blood of healthy HIV and hepatitis-B seronegative volunteers and collected by a single-step Ficoll-Hypaque discontinuous gradient centrifugation. The CEM cells were maintained in RPMI 1640 medium supplemented with 20% heat-inactivated fetal calf serum, penicillin (100 U/ml), and streptomycin (100 μg/ml). Flasks were seeded so that the final cell concentration was 3×10^5 cells/ml. The PBM and CEM cells were cultured with and without drug for 6 days at which time aliquots were counted for cell proliferation and viability using the trypan blue-exclusion method (Sommadossi et al, *Antimicrob. Agents Chemother.,* 32:997–1001 (1988). Only the effects on cell growth are reported because these correlated well with cell viability. The toxicity of the compounds in Vero cells was assessed after 3 days of treatment with a hemacytometer as described in Schinazi et al, *Antimicrob. Agents Chemother.,* 22:499–507 (1982). The toxicity, expressed as the micromolar concentration of compound that inhibits the growth of normal cells by 50% (IC_{50}), was determined, similarly to EC_{50}, by the method of Chou and Talalay.

In Vitro Assay is Predictive of In Vivo Activity

Using the antiviral activity PBM assay described above, a number of compounds have been tested for activity against HIV. While many of the compounds have been found to have little or no activity against the virus under the test

conditions, a number of the compounds have exhibited significant activity. For instance, DDI, DDC, D4T, AzddU (3'-Azido-2',3'-dideoxyuridine) and AZT were found to significantly inhibit HIV replication in vitro, and to have low cytotoxicity in PBM cells under the test conditions used. FTC also exhibits significant activity against HIV replication in the PBM cell line assay.

At least four of the compounds found active in the PBM cell line assay (DDI, DDC, DDA, and AzddU) are undergoing clinical testing in the U.S. Food and Drug Administration (FDA). All four compounds have been found to inhibit HIV in vivo. A fifth compound, AZT, is already approved by the FDA for treatment of HIV in humans. Based on the correlation of the results of the in vitro PBM assay with in vitro activity, it is clear that the activity of a compound against HIV in the PBM cell line in vitro is fairly predictive of its general activity in vivo in humans.

EXAMPLE 7

ANTIVIRAL AND CYTOTOXICITY ASSAYS OF FTC AND 3'-THIANUCLEOSIDE ANALOGUES OF FTC IN HUMAN PERIPHERAL BLOOD MONONUCLEAR (PBM) CELLS

Table 1 below lists the results of anti-HIV-1 activity and toxicity assays in human PBM Cells as described above for various 3'-thianucleoside analogues related to BCH-189. It appears that only the cytidine analogues are active in PBM cells, especially when the 5-position is substituted with H or F; FTC was more potent an inhibitor than any of the other tested compounds. Surprisingly, the 5-methyl derivative was inactive when tested up to 100 μM. These compounds were not cytotoxic to human PBM cells when tested up to 100 μM. Cells from at least two different donors were used in performing these antiviral assays. The margin of inter-assay variability error in EC_{50} values determined from a concentration-response curve can vary by as much as a factor of 10. However, using the above procedure and AZT as a positive control, a variance of 0.0008 to 0.006 μM with a mean value of 0.002 μM was determined.

TABLE 1

Anti-HIV Activity and Toxicity of Various Analogues of 2'-deoxy-3'-thiacytidine in Human PBM Cells

Antiviral Drug	EC_{50}, μM	IC_{50}, μM
2',3'-Dideoxy-3'-thiauridine	>100	>100
2'-Deoxy-5-methyl-3'-thiauridine	64.4	>100
2'-Deoxy-5-fluoro-3'-thiauridine	>100	>100
2'-Deoxy-5-chloro-3'-thiauridine	>60.8	>100
2'-Deoxy-5-bromo-3'-thiauridine	NA	NA
2'-Deoxy-5-iodo-3'-thiauridine	>100	>100
2'-Deoxy-3'-thiacytidine (BCH-189)	0.05	>100
2'-Deoxy-5-methyl-3'-thiacytidine	10	>100
2'-Deoxy-5-fluoro-3'-thiacytidine (FTC)	0.011	>100
2'-Deoxy-5-chloro-3'-thiacytidine	37.8	>100
2'-Deoxy-5-bromo-3'-thiacytidine	7.4	>100
2'-Deoxy-5-iodo-3'-thiacytidine	0.72	>100

Furthermore, as shown in FIG. **6**, FTC was highly effective in PBM cells even when the drug was added 3 days after virus infection. FIG. **6** shows a comparison of the effect of delaying treatment for up to three days on the anti-HIV-1 activity for FTC, BCH-189, AZT and AzddU. These results were determined by measuring the RT activity associated with virion produced in the presence and absence of drug to quantitate virus yield as described above. The control for this experiment had 232,154 dpm/ml of RT activity.

It is possible that BCH-189 analogues can be deaminated intracellularly to the inactive uracil analogue. Close to 6% of BCH-189 can be deaminated by Cyd/dCyd deaminase in a cell free system. However, the presence of fluorine in FTC would increase the lipophilicity of the drug, which should also increase its penetration into the CNS. In addition, FTC should be markedly less susceptible to deamination. Deamination of either BCH-189 or FTC would lead to the corresponding uracil analogues, which would cause them to lose their potent activity.

EXAMPLE 8

ANTIVIRAL AND CYTOTOXICITY ASSAYS OF FTC AND AZT IN HUMAN CEM CELLS

FTC was evaluated in vitro versus HIV-1, strain HTLV-III_B in CEM cells, a T-cell line, using AZT as the positive control. FTC was initially dissolved in sterile water at a concentration of 4 mM, and dilutions were prepared in RPMI-1640 medium containing 10% fetal bovine serum. The compound was tested at nine concentrations, ranging from 100 μM to 0.01 μM in half-log_{10} dilutions.

The assay was done in 96-well tissue culture plates using the CEM human T-lymphocyte cell line. CEM cells were treated with polybrene at a concentration of 2 μg/ml, and 1×10^4 cells were dispensed into each well. A 50 μl volume of each test article dilution, prepared as a 4×concentration, was added to 5 wells of cells, and the cells were incubated at 37° C. for 1 hour. A frozen culture of HIV-1, strain HTLV-III_B, was diluted in culture medium and 2×10^3 $TCID_{50}$ of virus were added to 3 of the wells for each test article concentration. This resulted in a multiplicity of infection of 0.2 for the HIV-1 infected samples. Normal culture medium was added to the remaining 2 wells of each test concentration to allow evaluation of cytotoxicity. Each assay plate contained 2 wells of untreated, uninfected, cell control samples and 3 wells of untreated, infected, virus control samples. The total volume in each well was 200 μl.

Assay plates were incubated at 37° C. in a humidified, 5% CO_2 atmosphere and observed microscopically for toxicity and/or cytopathogenic effect. On the 8th day post-infection, the cells in each well were resuspended and a 50 μl sample of each cell suspension was transferred to a new 96-well plate. A 100 μl volume of fresh RPMI-1640 medium and a 30 μl volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 50 μl cell suspension, and the cells were incubated at 37° C. for 4 hours. During this incubation, MTT is metabolically reduced by living cells, resulting in the production of a colored formazan product. A 50 μl volume of a solution of 20% sodium dodecyl sulfate in 0.02N hydrochloric acid was added to each sample, and the samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices V_{max} microplate reader. This assay detects drug-induced suppression of viral CPE, as well as drug cytotoxicity, by measuring the generation of MTT-formazan by surviving cells.

No cytotoxicity was noted for FTC from 0.01 to 100 μM and the EC_{50} was estimated to be 0.09 μM, giving a therapeutic index (IC_{50}/EC_{50}) in these cells of about 1000. In contrast, the EC_{50} for AZT in CEM cells was 0.01 μM and no cytotoxicity was noted up to 5 μM, the maximum concentration tested.

EXAMPLE 9

EFFECT OF FTC, BCH-189, AZT AND DDC ON COLONY FORMATION OF GRANULOCYTE-MACROPHAGE PRECURSOR CELLS

Because the limiting toxicity of compounds like AZT is bone-marrow toxicity, it was important to determine if FTC

was also toxic to these cells. The results of a bone-marrow toxicity assay may predict if anemia will occur in humans following treatment with a particular drug because these cell culture models are good prognosticators of what may happen in humans. Thus, FTC, BCH-189, DDC and AZT were tested for their effects on colony formation of granulocyte-macrophage precursor cells.

Human bone marrow cells were collected by aspiration from the posterior iliac crest of normal healthy volunteers, treated with heparin and the mononuclear population separated by Ficoll-Hypaque gradient centrifugation. Cells were washed twice in Hanks balanced salt solution, counted with a hemacytometer, and their viability was >98% as assessed by trypan blue exclusion. The culture assays were performed using a bilayer soft-agar or methyl cellulose method. McCoy 5A nutrient medium supplemented with 15% dialyzed fetal bovine serum (heat inactivated at 56° C. for 30 minutes, Gibco Laboratories, Grand Island, N.Y.) was used in all experiments. This medium was devoid of thymidine and uridine. Human recombinant GM-CSF (50 units/ml, Genzyme, Boston, Mass.) was used as colony-stimulating factors. After 14 days of incubation at 37° C. in a humidified atmosphere of 5% CO_2 in air, colonies (≧50 cells) were counted using an inverted microscope.

As shown in FIG. **7**, studies with human bone marrow cells indicate that FTC has an IC_{50} greater than 50 μM, whereas in the same assay BCH-189, DDC, and AZT are clearly more toxic. The IC_{50} for AZT is close to 1 μM.

Because both BCH-189, AZT and FTC do not seem to affect the proliferation of uninfected human PBM cells as shown above, it is important to calculate the therapeutic index of the drugs in terms of IC_{50} (toxicity) in human bone-marrow cells to EC_{50} (antiviral) against HIV in human PBM cells. The IC_{50} in human bone-marrow cells for BCH-189 is about 10 μM, whereas for FTC it is about 60 μM. Hence the therapeutic index for BCH-189 is 10/0.05= 200, while the index for FTC is 60/0.011=5,455. By these experiments, FTC is clearly a less toxic yet effective anti-HIV-1 agent compared to BCH-189.

EXAMPLE 10

ANTIVIRAL AND CYTOTOXICITY ASSAYS OF FTC IN MT-2 CELLS

Antiviral and cytotoxicity studies of FTC in human lymphocyte MT-2 cells were conducted. MT-2 cells (3×10^5/ml) were incubated with serial 10-fold dilutions of an HIV (IIIb) viral supernatant (stock), centrifuged, resuspended in fresh media, and plated into microculture wells (6×10^4 cell/well/ 0.2 ml). Because the assay can be performed with 0.2 ml of culture supernatant in a microtiter plate, HIV inoculation of target cell cultures can be monitored conveniently and endpoint titrations of infectious HIV can be performed. No manipulation of the culture is required during the seven day evaluation. The necessary multiple replicate numbers of cultures to generate statistically significant data were included in the $TCID_{50}$ assay. Since the MT-2 cell line is highly susceptible to virus infection and syncytia formation, it is easily observed and allows for a very sensitive assay system.

Quantitation of HIV infectivity was determined for serial 10-fold dilutions of the virus stock. Calculation of the highest dilution of virus which gave evidence of syncytia in 50% of the cultures, the endpoint determination, yielded a measure of the infectious particles in the stock. A $TCID_{50}$ titer is defined as the reciprocal of the dilution of HIV that when inoculated into the microcultures containing MT-2 cells resulted in syncytia in 50% of the cultures by the seventh day. The results of the HIV $TCID_{50}$ assay, as described in Table 2, correlates with the results using the reverse transcriptase results, immunofluorescent, cytoplasmic staining assay, p24 antigen capture assay, and cell cytopathic effects, thereby validating our assay system.

The MT-2 syncytium-forming assay has been applied for use in discovering antiviral drugs with potent anti-HIV activity. MT-2 cells are incubated in growth medium (DMEM, 20% heat inactivated fetal calf serum and 0.25 mg/ml L-glutamine with 1% penicillin and streptomycin) at 37° C. in a 5% CO_2 atmosphere. The MT-2 cell concentration that allows for the development of readily quantifiable syncytium formation in a microtiter plate is 3×10^5/ml (6×10^4 cell/0.2 ml).

HIV (IIIb) was obtained from the culture supernatant of H9 cells infected by multiple isolates of HIV concentrated to 10,000× by sucrose gradient centrifugation. A representative virus (IIIb) stock contained a total virus particle count of approximately 10^8/ml to 10^9/ml by electron microscopy. The $TCID_{50}$ was calculated as follows: Serial 10-fold dilutions of the H9 virus stock were performed and 1.0 ml used (in quadruplicate) to infect MT-2 cells. Endpoints were calculated by the method of Reed Muench from the highest dilution with detectable syncytium formation within seven days. The most recent virus stock, HIV (IIIb), that was evaluated contained an infectious viral titer of 6.23 $\log_{10}$ $TCID_{50}$/ml. The input dose of virus was adjusted to yield greater than 40 syncytia at the seventh day of culture. HIV stocks were aliquoted and stored at −85° C. until used. A frozen stock was thawed and an infectivity study was performed, in quadruplicate, to determine if >40 syncytia are formed at day seven. At the same time, the virus stock was subjected to antiviral inhibition with the use of AZT or DDA. These maneuvers, with the proper controls, ensure for reproducible input doses of virus for these studies.

TABLE 2

EFFECT OF BCR-189 AND FTC AGAINST HIV-1 (strain IIIb) IN MT-2 CELLS

Compound	Conc. (μM)	Mean # of Syncytia (per well)	% Inhib	EC_{50}, μM
Cells (no virus/no drug		0	0.00	
Virus (no drug)		62	0.00	
DDA (pos.	1	14	77.42	≈0.45
control	10	0.5	99.19	
BCH-189	0.1	61	1.61	0.88
	1	20.5	66.94	
	10	1	93.39	
	100	0	100.0	
FTC	0.1	63	−1.61	0.89
	1	23	62.90	
	10	0.5	99.19	
	100	0	100.00	

The MT-2 cells for the studies were expanded and treated with DEAE-dextran (25 μg/ml) for 20 minutes followed by three washings with PBS. Cell counts were performed and an appropriate number of cells that ultimately yielded a final cell concentration of 3×10^5 cells/ml (6×10^4 cells/0.2 ml) per well was chosen. The cells were infected in bulk (not in-well infection) at a multiplicity of infection of 10^{-3} and allowed to mix with the viral supernatant for one hour at 37° C. The

cells were subsequently resuspended in the wells containing the MT-2 media with drugs. The cultures were not manipulated until day seven when syncytium counts and cell viability studies were performed. The experimental controls for each experiment consisted of the following: 1) AZT or DDA; 2) uninfected MT-2 cells with drug; 3) infected MT-2 cells without drug, and 4) uninfected MT-2 cells without HIV or drugs.

The raw data was analyzed by the method of Chou and Talalay. The MT-2 cell lines were discarded at three month intervals with a new stock regrown to avoid the possibility of variations or contamination (mycoplasma) with long term growth. The original MT-2 cell frozen stock has been tested and is free of mycoplasma. EC_{50} and IC_{50} values were obtained by analysis of the data using the median-effect equation of Chou and Talalay. It is apparent from Table 2 that in this cell culture system, both BCH-189 and FTC are equally potent.

EXAMPLE 11

INHIBITION OF MITOCHONDRIAL DNA SYNTHESIS BY FTC IN CEM CELLS

In addition to bone-marrow toxicity, peripheral neuropathy has been observed with certain nucleoside antiviral drugs. There appears to be a good correlation between inhibition by nucleosides of mitochondrial DNA synthesis and clinical peripheral neuropathy. Therefore, studies were performed which indicated that FTC did not affect mitochondrial DNA synthesis in intact CEM cells when tested up to 100 μM. This result was determined by measuring the amount of mitochondrial DNA present in these lymphocytes after exposure using a mitochondrial DNA hybridization probe. However, BCH-189 and DDC are toxic in this system at a concentration $\leqq$10 μM.

EXAMPLE 12

EFFECT OF FTC, BCH-189 AND AZT ON AZT-RESISTANT AND AZT-SENSITIVE HIV-1 IN HUMAN PBM CELLS

We have also evaluated FTC and BCH-189) against AZT-resistant and sensitive HIV-1, as shown in FIG. **8** and Table 3. The paired AZT-resistant and sensitive viruses strain 9F (G910-6) and 10 (H112-2), respectively, were obtained through the NIH AIDS Research and Reference Program. All the viruses were propagated in PHA-stimulated human PBM cells using RPMI 1640 medium as described previously and supplemented with 7% interleukin-2 (Advanced Biotechnologies, Silver Spring, Md.), 7 μg/ml DEAE-dextran (Pharmacia, Uppsala, Sweden), and 370 U/ml anti-human leucocyte (alpha) interferon (ICN, Lisle, Ill.). Virus was obtained from cell-free culture supernatant and stored in aliquots at −70° C. until use. The antiviral assay in PBM cells was performed as described above.

TABLE 3

	EC_{50}, μM		
Compound	Strain 9F*	Strain 10	Fold Increase
AZT	0.298	0.00069	432
BCH-189	0.244	0.040	6.1
FTC	0.107	0.014	7.6

*AZT resistant HIV

At the same multiplicity of infection, a 7-fold increased resistance was noted at the EC_{50} level when the sensitivity of the pretherapy isolate was compared to the post-therapy AZT-resistant virus in PBM cells for FTC. This increase was not as great as that noted for AZT.

EXAMPLE 13

INHIBITORY EFFECT OF FTC AGAINST SIV_{251}

FTC was tested for its inhibitory effect against SIV_{251} in the human cell line AA-2 and C-8166, using AZT as a positive control. All tests were conducted in duplicate according to a standard protocol in 96 well tissue culture plates. Briefly, cells were exposed to the virus for 1 hour at 37° C. The cells were washed and the appropriate dilution of antiretroviral agent diluted in PBS was added with complete RPMI-1640 medium. After a 7-day incubation period at 37° C. and 5% CO_2, 95% air environment, cells were examined microscopically for cytopathic effects (syncytial cells) and cytotoxicity. The cells were counted and the percent of viable cells determined using the trypan blue exclusion method. Viral antigen expression in cell pellets was determined by an immunofluorescence (IF) assay. The percent of IF inhibition was based on the ratio of fluorescing cells in infected/treated cultures to fluorescing cells in infected control cultures.

FTC antiviral activity was observed versus SIV but less than that noted with AZT. As shown in Table 4, FTC was evaluated over a concentration range of 0 to 46 μM, and AZT was tested as the positive control.

TABLE 4

	Concentration	% IF Inhibition		Cell No. × 10^5	
	(μM)	AA-2	C-8166	AA-2	C-8166
FTC	0	0	0	6.0	3.9
	0.23	0	11	6.5	5.6
	0.46	17	5	6.5	6.0
	2.3	22	32	6.3	5.9
	4.6	36	47	7.3	6.1
	23	61	63	6.2	7.4
	46	70	79	9.9	9.9
AZT	0.0005	0	5	7.4	6.6
	0.005	30	16	7.4	8
	0.05	83	79	7.5	8
	0.5	100	100		

EXAMPLE 14

THYMIDYLATE SYNTHASE ASSAY OF FTC AND BCH-189

BCH-189 and FTC were also evaluated in an intact L1210 cellular thymidylate synthase (TS) assay. No evidence for any inhibition of TS by up to 1 mM of either compound as measured by the release of tritium from 5-^{3}H-dUrd was noted. Using 5-^{3}H-dCyd, inhibition of tritium release was observed at $>10^{-4}$M. At 1 mM, BCH-189 and FTC gave 63.2% and 74.7% inhibition of tritium release, respectively. Since the 5-^{3}H-dCyd concentration is 1 μM, it appears that the observed effects may be due to competitive inhibition of the phosphorylation of labeled dcyd by the analogue at high concentrations. The lack of TS inhibition by FTC is probably due to either of 2 alternatives: (1) its 5'-phosphate is not a substrate for dCMP deaminase; (2) if it is a substrate, the resulting 5-fluoro-3'-thia-dUMP cannot bind to TS or, if so, only very weakly.

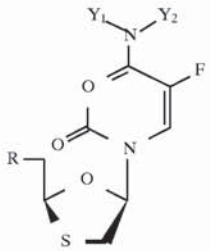
EXAMPLE 15

ANTIVIRAL ACTIVITY OF VARIOUS PRODRUGS OF FTC IN HUMAN PBM CELLS

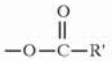
FTC may be modified at the 2-hydroxymethyl group of the oxathiolane ring by substituting the hydroxy group with

an oxyacyl group to produce 5'-oxyacyl or 5'-H substituted prodrug analogues of FTC. Furthermore, the 4-N position of FTC may be substituted with an alkyl, substituted alkyl, cycloalkyl or acyl group. These modifications at the 4-N and 5'-O positions affect the bioavailability and rate of metabolism of the active species, thus providing control over the delivery of the active species.

Preferred FTC prodrug analogues include compounds of the formula:



in which Y_1 and Y_2 are selected from H; lower straight or branched chain alkyl; substituted alkyl, preferably di-isopropylaminomethylene or alkoxyaminomethylene; cycloalkyl, preferably cyclopropyl; or acyl, wherein the term "acyl" corresponds to an acyl protecting group as given above and in which the 5'-R substituent is H or oxyacyl. As used herein, the term "oxyacyl" means a group of the formula



in which R' is selected from hydrogen, lower straight or branched chain alkyl (e.g., methyl, ethyl, n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl), substituted aryl (e.g., halogen, lower alkyl or lower alkoxy substituted phenyl); substituted dihydro pyridinyl (e.g., N-methyldihydro pyridinyl); sulphonate esters such as alkyl- or aralkylsulphonyl (e.g., methanesulphonyl); sulfate esters; amino acid esters (e.g., L-valyl or L-isoleucyl) and mono-, di- or tri-phosphate esters. Pharmaceutically accepted formulations of these compounds include liposome formulations.

TABLE 5

NY_1Y_2	5-position	5'-position	EC_{50}, μM
NHAc	H	CH_2OH	0.089
NH_2	H	$n\text{-}C_3H_7C(O)OCH_2$	0.037
NH_2	H	$CH_3C(O)OCH_2$	0.089
NHAc	H	$n\text{-}C_3H_7C(O)OCH_2$	0.11
NHAc	F	$n\text{-}C_3H_7C(O)OCH_2$	0.00576
NHAc	F	CH_2OH	0.0028
NH_2	F	$n\text{-}C_3H_7C(O)OCH_2$	0.00174

Using the method of determining anti-HIV-1 activity as described in Example 6 above, various prodrugs of FTC and BCH-189 were assayed in human PBM cells infected with HIV-1, as shown in Table 5. Relative to the BCH-189 prodrug analogues listed in Table 5, the FTC prodrug analogues showed superior anti-HIV activity.

EXAMPLE 16

ANTIVIRAL AND CYTOTOXICITY ASSAYS OF NUCLEOSIDES SIMILAR TO FTC

Table 6 below lists the results of anti-HIV-1 activity in human PBM cells and toxicity assays in human PBM cells, Vero (African Green Monkey kidney) cells, and CEM cells as described above for FTC, BCH-189, 2'-deoxy-3'-oxacytidine (DOC), 2'-deoxy-3'-oxathymidine (DOT), 2'-deoxy-5-fluoro-3'-oxacytidine (FDOC) and 2'-deoxy-5-fluoro-3'-oxauridine (FDOU) to show the effect of fluoro substitution at the 5-position and S→O substitution at the 3'-position in nucleosides that are similar to FTC.

Comparison of the data for FTC, FDOC and FDOU shows that 5-fluoro substitution leads to unpredictable results in these systems. For instance, fluoro substitution of BCH-189 at the 5-position to give FTC results in a compound that possesses better anti-HIV activity and is less toxic in CEM cells; both are nontoxic in PBM and Vero cells. However, fluoro substitution of DOC at the 5-position to give FDOC results in a compound that possesses inferior anti-HIV activity and is more toxic in Vero cells; both are nontoxic in PBM and toxic in CEM cells. FDOU is nontoxic in all three types of cells but does not possess anti-HIV activity.

Similarly, comparison of the data for FTC, BCH-189 versus DOC, DOT, FDOC and FDOU shows that 3'-substitution of an S for an O gives rise to unpredictable anti-HIV activity and toxicity behavior. For instance, substitution of BCH-189 to give DOC and FTC to give FDOC results in compounds that are toxic in the rapidly dividing Vero cells and CEM cells, thus most likely rendering them not viable as anti-HIV drugs because of associated side effects. However, the presence of the oxygen at the 3'-position in DOT does not render this compound toxic in Vero cells. Thus, discovery of the superior anti-HIV and toxicity properties of FTC was surprising and unexpected.

TABLE 6

Anti-HIV Activity and Toxicity of Various Nucleosides that are similar to FTC

Antiviral Drug	ANTI-HIV ACTIVITY EC_{50}, μM (PBM)	CYTOTOXICITY IC_{50}, μM (PBM)	IC_{50}, μM (Vero)	IC_{50}, μM (CEM)
FTC	0.011	>100	>100	>100
BCH-189	0.06	>100	>100	52.6
DOC	0.0047	>200	0.17	<1
DOT	0.09	>100	>100	
FDOC	0.0063	>200	<0.1	<1
FDOU	>10	>200	>100	>100

EXAMPLE 17

EFFECT OF FTC AND BCH-189 ON MITOGENIC STIMULATION

Peripheral blood mononuclear cells (PBM cells) were obtained by leukophoresis from a normal human donor and were further purified by density gradient centrifugation using Histopaque (Sigma; St. Louis, Mo.). Cells were washed twice in phosphate buffered saline, resuspended in complete media (RPMI supplemented with 10% fetal bovine serum, 2 μM L-glutamine, penicillin, and streptomycin), and adjusted to 2×10^6 cells/ml. Mitogens were added to separate aliquots of cell suspension to yield a final concentration of 1% phytohemagglutinin (PHA, a T-helper cell mitogen), 0.8 mg/ml concanavalin A (con A, a T-cytotoxic/suppressor cell mitogen), and 0.1% pokeweed mitogen (PWM, a B cell mitogen), respectively.

A cell suspension (100 μl) was dispensed into wells of 96-well flat-bottomed plates, followed by addition of 100 μl

of drug diluted in complete media. Control wells received 100 μl of complete media. Cells were incubated at 37° C. in 5% CO_2 for 54 hr, at which time 2 μCi ^{3}H-deoxyguanosine (Moravek Biochemicals, Brea, Calif.; diluted in 20 μl complete media) was added per well. After an additional 18 hour incubation, cells were harvested on filter paper using a Skatron cell harvester with 5% TCA and 70% ETOH. Filters were placed in scintillation vials with 4 ml Ecolite, and dpm were counted using a Beckman LS3801 beta counter.

At concentrations of 0.1, 1.0, and 10 μM, both BCH-189 and FTC increased the proliferation of PBM cells exposed to PHA, whereas they caused significant reduction in proliferation at 100 μM concentrations. Con A- and PWM-stimulated cells were suppressed by both drugs. In the absence of mitogen, BCH-189 has a mildly stimulatory effect, whereas FTC had a mildly inhibitory effect.

Modifications and variations of the present invention will be obvious to those skilled in the art from the foregoing detailed description of the invention. Such modifications and variations are intended to come within the scope of the appended claims. The references cited above are hereby incorporated by reference to more fully describe the invention.

What is claimed is:

1. β-2'-Deoxy-5-fluoro-3'-thiacytidine.

2. A pharmaceutical composition comprising an effective HIV treatment amount for humans of β-2'-deoxy-5-fluoro-3'-thiacytidine in a pharmaceutically acceptable carrier or diluent.

* * * * *

EXHIBIT 9

FDA NEWS RELEASE

FDA approves second drug to prevent HIV infection as part of ongoing efforts to end the HIV epidemic

For Immediate Release:

October 03, 2019

The U.S. Food and Drug Administration today approved Descovy (emtricitabine 200 mg and tenofovir alafenamide 25 mg) in at-risk adults and adolescents weighing at least 35kg for HIV-1 pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sex, excluding those who have receptive vaginal sex. Descovy is not indicated in individuals at risk of HIV-1 infection from receptive vaginal sex because the effectiveness in this population has not been evaluated.

“PrEP drugs are highly effective when taken as indicated in the drug labeling and can prevent HIV infection,” said Jeffrey Murray, M.D., M.P.H., deputy director of the Division of Antiviral Products in the FDA’s Center for Drug Evaluation and Research. “This approval provides more prevention options for certain patients at-risk for acquiring HIV and helps further efforts by the FDA and the U.S. Department of Health and Human Services to facilitate the development of HIV treatment and prevention options to reduce new HIV infections.”

According to the Centers for Disease Control and Prevention, 38,739 people received an HIV diagnosis in the U.S. in 2017. To confront this epidemic, President Trump announced an initiative, Ending the HIV Epidemic: A Plan for America (https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview), in his State of the Union address on February 5, 2019. This opportunity to eliminate new HIV infections in our nation seeks to provide our hardest-hit communities with additional expertise, technology and resources required to address the HIV epidemic. The aim is to reduce new infections by 75% in the next five years and by 90% in the next ten years, averting more than 250,000 HIV infections in that span.

PrEP, or pre-exposure prophylaxis, is an HIV prevention method in which people who do not have HIV take medicine on a daily basis to reduce their risk of getting HIV if they are exposed to the virus. Descovy for PrEP should be used as part of a comprehensive strategy, including adherence to daily administration and safer sex practices, including condoms, to reduce the risk of sexually acquired infections.

The safety and efficacy of Descovy for PrEP were evaluated in a randomized, double-blind multinational trial in 5,387 HIV-negative men and transgender women who have sex with men and were at risk of HIV-1 infection. The trial compared once daily Descovy to Truvada (emtricitabine, tenofovir disoproxil fumarate, 200 mg/300 mg), a daily fixed dose combination of two drugs approved in 2012 to prevent the sexual acquisition of HIV; participants were followed for 48 to 96 weeks. The primary endpoint was the rate of HIV-1 infection in each group. The trial showed that Descovy was similar to Truvada in reducing the risk of acquiring HIV-1 infection. The most common adverse reaction in individuals without HIV who were taking Descovy for PrEP was diarrhea.

There is a boxed warning for individuals who take Descovy who also have hepatitis B virus (HBV) to be aware of the risk of exacerbations of HBV in those who discontinue products with emtricitabine or tenofovir disproxil fumarate, and which may occur in individuals who discontinue Descovy. Descovy for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status and should only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every three months during use.

Descovy was FDA approved in 2016 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208215s000lbl.pdf) in combination with other antiretoviral drugs to treat HIV-1 infection in adults and pediatric patients. The FDA granted the approval of Descovy to Gilead Sciences Inc.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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240-402-0764

Consumer:

888-INFO-FDA

Related Information

- FDA – HIV (Human Immunodeficiency Virus) (/patients/get-illnesscondition-information/hiv-human-immunodeficiency-virus)
- FDA - HIV Prevention (/system/404)
- HIV.gov (https://www.hiv.gov/)

More Press Announcements (/news-events/newsroom/press-announcements)

EXHIBIT 10

HIV/AIDS

HIV Vaccines

Contents

What it is

Vaccines stimulate the body's immune system to provide protection against infection or disease. Vaccines against HIV are being developed, and they are in various stages of clinical trial but at present none have proven effective.

Why it is Important

It is important to conduct research to find an effective vaccine because:

- The availability of a safe, highly effective and accessible preventive HIV vaccine would be a valuable complement to other preventive interventions, significantly contributing to the interruption of the chain of transmission of HIV.
- Well conceived HIV immunization strategies could reach populations where other interventions are not sufficiently effective.
- Research on preventive HIV vaccines is providing new information on the possible use of vaccines as therapeutic interventions, to be used in association with antitretroviral therapies, which could lead to a lowering in the cost of the treatments and to an increase on their long-term efficacy.

How it is Done

Vaccine research is a long process that begins with basic laboratory research and product development, including animal experiments, mostly performed in academic laboratories and by the pharmaceutical industry.

The next step is to test these products (candidate vaccines) on healthy human volunteers through sequential phases. Phase I and II trials provide data on the safety of the candidate vaccines and on their ability to induce immune responses specific to HIV. These trials are done among small numbers of volunteers (50-200 per trial). Depending of the results obtained, candidate vaccines can proceed to large-scale Phase III trials, to obtain definitive information about their efficacy in inducing protection against HIV infection or AIDS. For scientific reasons, Phase III trials are done in populations with a high incidence of HIV infection, involving thousands of volunteers.

Since 1987, more than 30 HIV candidate vaccines have been tested in approximately 60 Phase I/II trails, involving more than 10,000 healthy volunteers. Most of these trials have been conducted in the United States and Europe, but several have also been conducted in developing countries (Brazil, China, Cuba, Haiti, Kenya, Peru, Thailand, Trinidad, and Uganda). The results have confirmed the safety of the vaccines, and have provided important scientific information to develop newer generations of candidate vaccines with better ability to induce anti-HIV specific immune responses.

At the present time, there are only two related candidate vaccines being evaluated in Phase III efficacy trials. The first trial started in 1998 in the United States (with sites in Canada and the Netherlands), enrolling 5,400 volunteers, mostly homosexual men. The trial is evaluating the efficacy of an envelope gp120 candidate vaccine based on the HIV subtype circulating in North America (subtype B), and the definitive results will be available early in 2003. The second Phase III trial started in 1999 in Thailand, and is testing the efficacy of a gp120 candidate vaccine based on the subtypes B and E prevalent in Thailand, enrolling a total of 2,500 volunteers, the majority of which are recovering intravenous drug users. Results from this trial will be available late in 2003.

The "simultaneous" development and evaluation of multiple vaccine concepts require that vaccine evaluation "sites" are identified and strengthened in multiple developing countries. This process requires intense national, regional and international coordination and collaboration. An example is the WHO-UNAIDS driven "African AIDS Vaccine Programme (AAVP)", a network of African experts working to facilitate the development and evaluation of AIDS vaccines for Africa through regional and international

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Cost Information

The global investment on HIV vaccine research, including industry and research agencies in industrialized countries has been estimated at approximately US$ 500 million per year. A very small fraction of that amount is dedicated to the activities aimed at developing vaccines for developing countries.

This level of investment is insufficient to carry on the simultaneous development of multiple vaccine products in parallel. Investments in HIV vaccines must be increased, including significantly higher budgets to build capacity in developing countries to conduct trials. As an example, initial budget estimates for the AAVP are in the order of US$ 25 to 35 million per year, just to complement other ongoing research efforts by other organizations.

In addition to its activities in Africa, the WHO-UNAIDS HIV Vaccine Initiative is also collaborating with national authorities and scientists working with HIV vaccine development and evaluation in other continents.

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EXHIBIT 11

RESOURCE TRACKING
FOR HIV PREVENTION
RESEARCH & DEVELOPMENT

2018

HIV Prevention Research & Development Investments

INVESTING TO END THE EPIDEMIC

HIV Prevention Research & Development Investments, 2018

INVESTING TO END THE EPIDEMIC

Resource Tracking for HIV Prevention Research & Development

JULY 2019

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Introduction

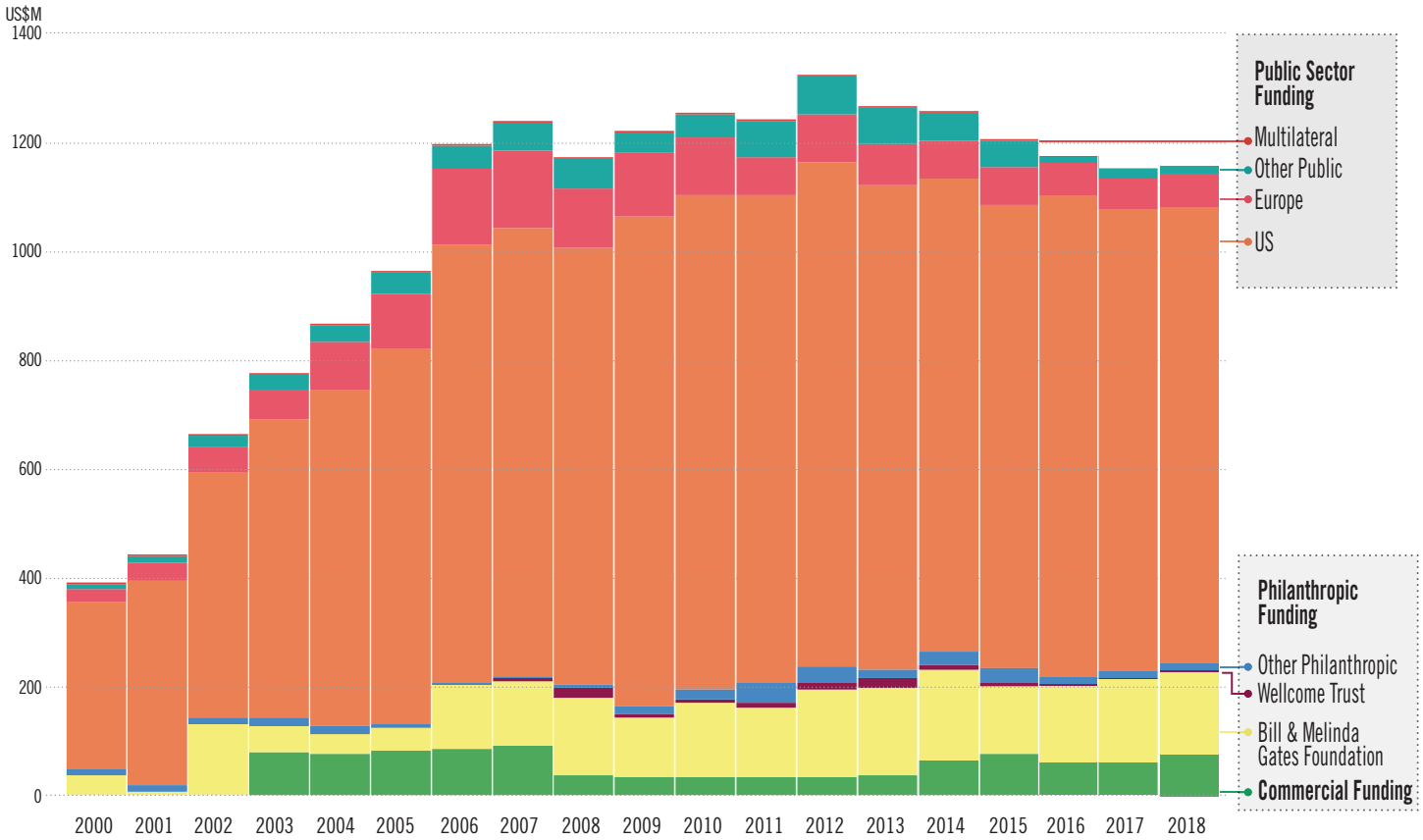
In its 15th annual report, the Resource Tracking for HIV Prevention Research & Development Working Group ("Working Group") documents research and development spending for the calendar year 2018 and analyzes funding trends spanning eighteen years.

The Working Group has employed a standardized methodology since 2004 to generate comprehensive statistics on investment in HIV prevention research and development (R&D[1]), including disaggregated trends for the following biomedical HIV prevention options: preventive AIDS vaccines, microbicides, pre-exposure prophylaxis (PrEP), treatment as prevention (TasP), voluntary medical male circumcision (VMMC), female condoms, prevention of vertical transmission (PMTCT) and multipurpose prevention technologies. As part of an ongoing collaboration with the International AIDS Society, the Working Group also tracks expenditures in HIV cure and therapeutic AIDS vaccine research[2].

The 2018 Resource Tracking report depicts the most up-to-date and comprehensive field-wide estimates for the *who's who* in financing HIV prevention research globally. Investment estimates that allow comparison across years, prevention options, sectors and countries engender greater transparency for funders and advocates alike, and help to assess the trajectory and impact of policies. These trends not only furnish vital facts for advocacy but also predict future funding scenarios that can impact the progress of this historic scientific agenda.

The Working Group's analysis for 2018 builds on the US$18 billion in funding tracked between 2000 and 2017 and underscores the importance of continued innovation in HIV prevention to bring a lasting end to the HIV/AIDS epidemic *(Figure 1)*.

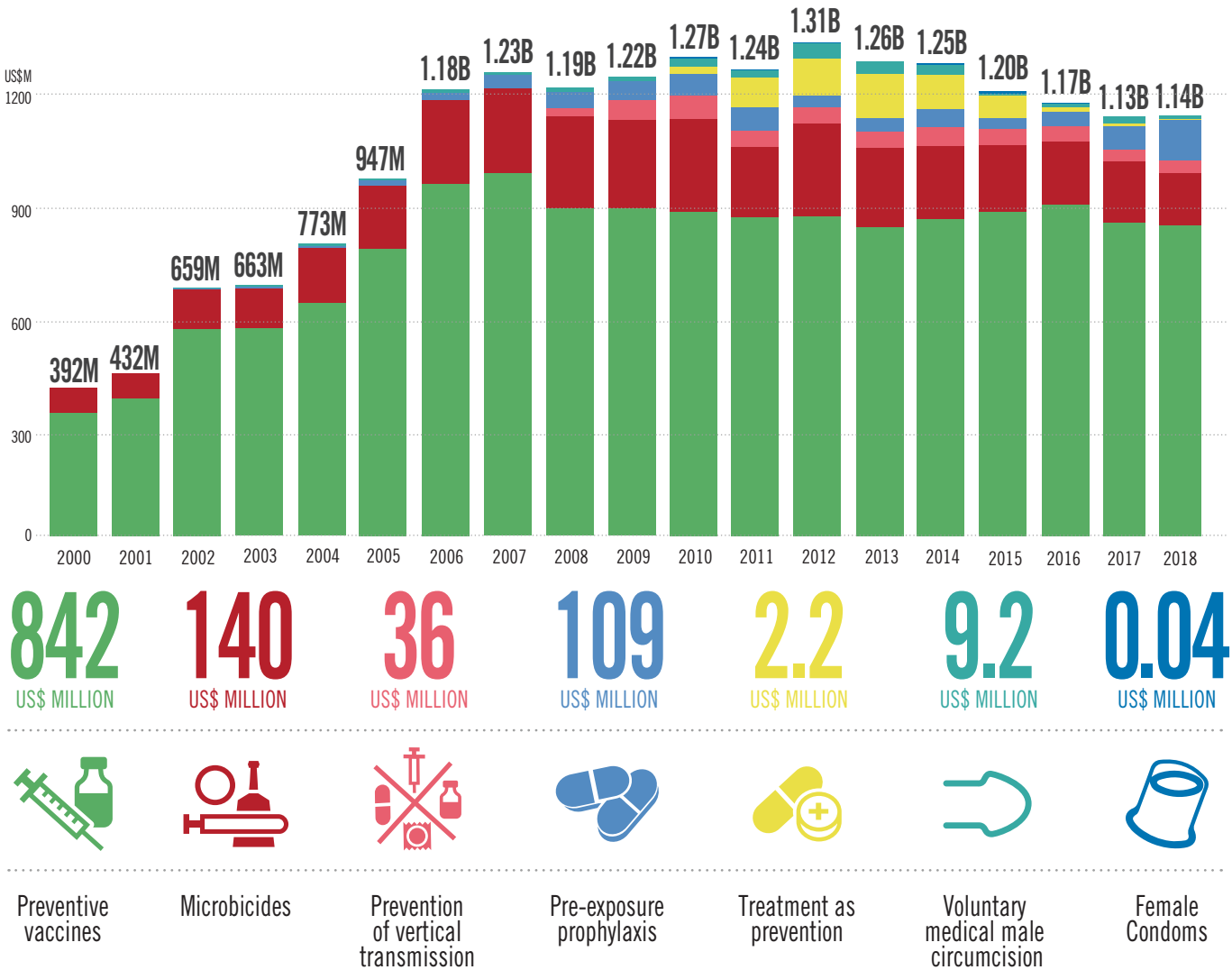
FIGURE 1 **Global Funding Sources for HIV Prevention R&D, 2000-2018** (US$ millions)



Trends in HIV Prevention R&D

- In 2018, reported funding for HIV prevention R&D increased by 1.2 percent (US$13 million) from the previous year, rising to US$1.14 billion. According to Working Group estimates, this is the first time in five years that the trend of declining funding has reversed. Significant variation existed in investment by technology category: R&D funding increased for PrEP, PMTCT and female condoms, while funding for preventive vaccines, microbicides, VMMC and TasP saw a decline from the previous year *(Figure 2)*. As the focus of three-fourths of total funding, preventive vaccines continued to make up the lion's share of overall HIV prevention funding, followed by microbicides and PrEP. The relative proportion of PrEP funding has been rising since 2016 and peaked at 9.6 percent, according to the most recent estimates *(Figure 3)*.

FIGURE 2 **Global HIV Prevention R&D Investment by Technology Category, 2000-2018**



[a] Tracking funding for female condom and treatment as prevention research began in 2010
[b] Tracking funding for prevention of vertical transmission began in 2008
[c] Tracking funding for pre-exposure prophylaxis began in 2002
[d] Tracking funding for medical male circumcision began in 2001

FIGURE 3 **Total Global HIV Prevention R&D Investment by Prevention Option, 2017-2018**

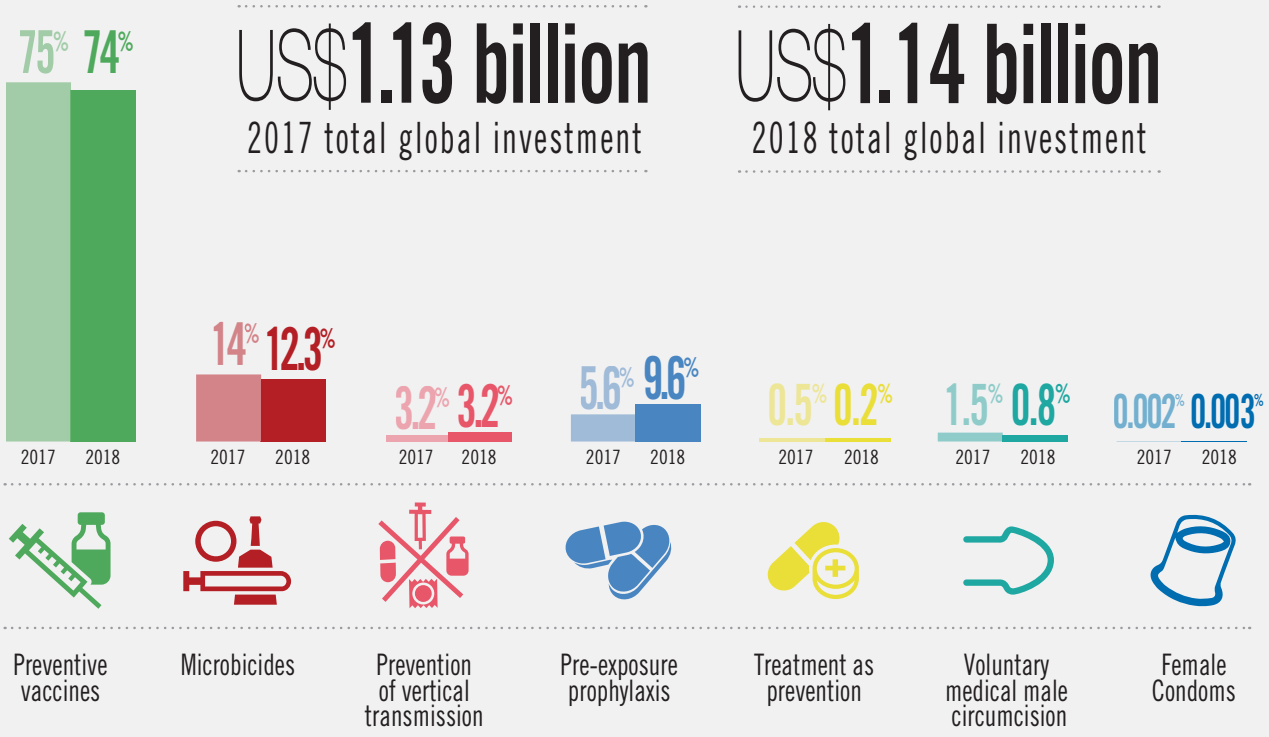
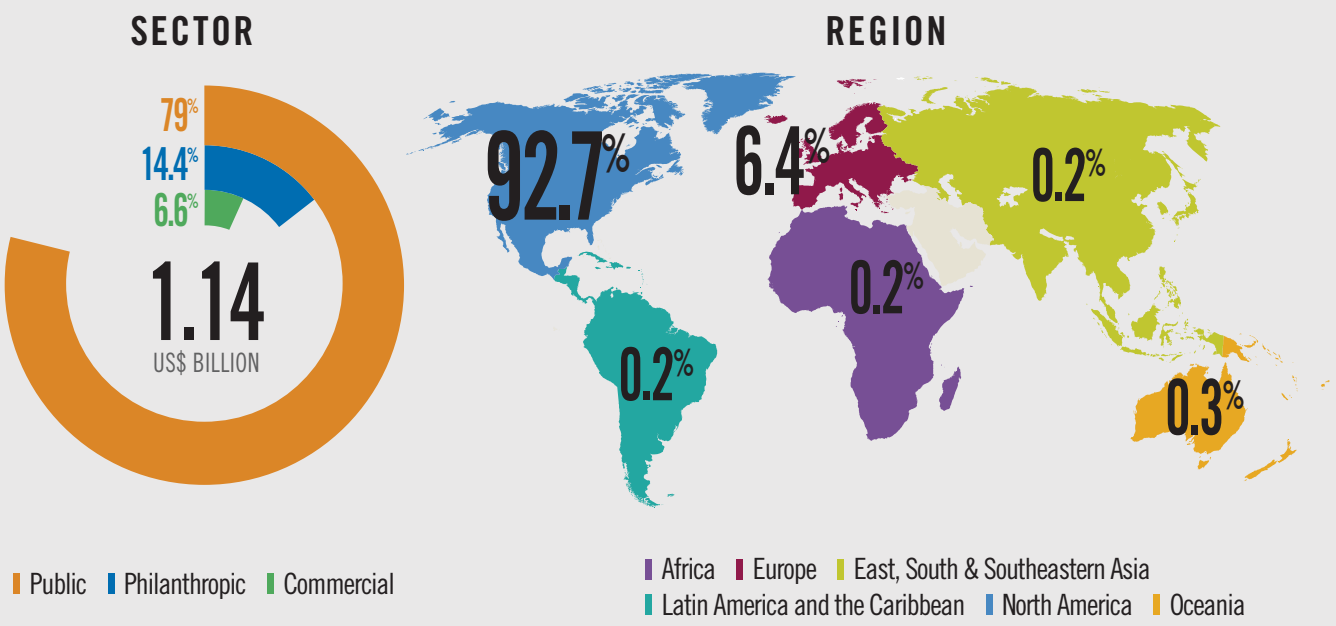


FIGURE 4 **Total Global HIV Prevention R&D Investment by Sector & Region, 2018**



- Compared to 2017 levels, a slight decrease in investment was observed in the public sector (0.5 percent), while philanthropic investment remained unchanged. Global private sector investment increased by 30.8 percent to US$74.7 million; however, this increase could be a factor of improved sector-wide reporting. The public sector continued to dominate, accounting for 79 percent of global investment (US$900 million), and the philanthropic and private sectors followed with 14.4 percent and 6.6 percent, respectively. North America, and specifically the US, made up the bulk of public sector funding at US$835 million (93 percent), while the European region came in second at US$57 million (6.4 percent). Other regions contributed US$8 million which which constituted one percent of the cumulative public sector funding *(Figure 4)*.

FIGURE 5a **US Public Sector Investments in HIV Prevention R&D Compared to All Other Funding, 2013-2018** (US$ billions)

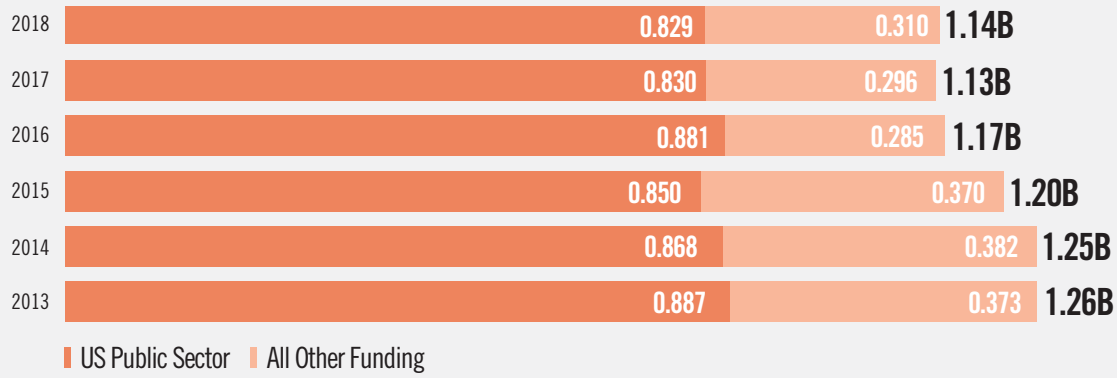
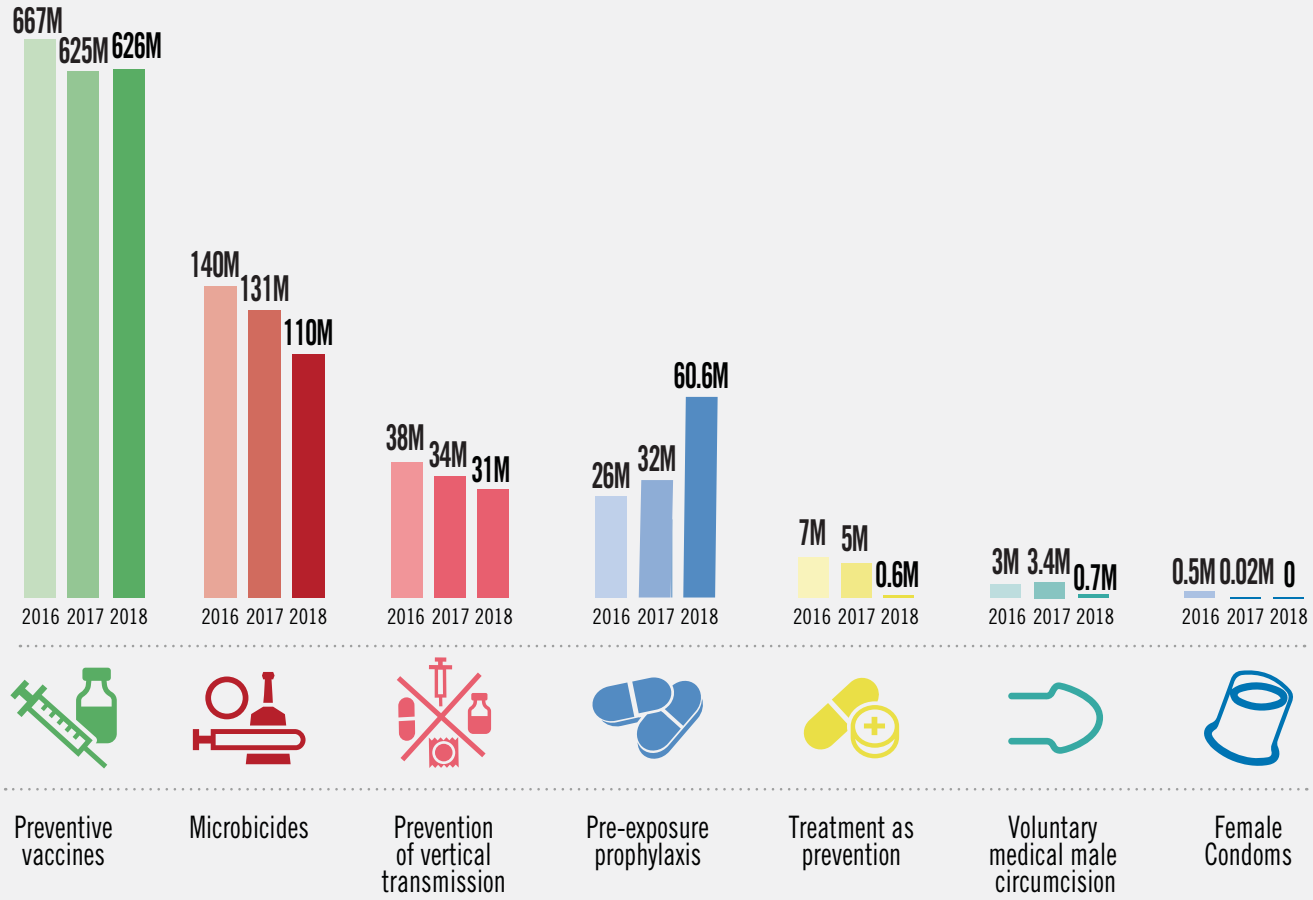


FIGURE 5b **US Public Sector Investments in HIV Prevention R&D by Technology, 2016-2018** (US$ millions)



US public sector investment remained unchanged in 2018, decreasing marginally from US$830 million in 2017 to US$829 million in 2018 *(Figure 5a)*. This negligible shift masked significant variation in donor trends. The Centers for Disease Control and Prevention (CDC) had a notable 84 percent decrease in investment, from US$9.9 million in 2017 to US$1.5 million in 2018. The Military HIV Research Program (MHRP) and the National Institutes of Health (NIH) were the two US public donors with increases of eight percent (US$35.6 million) and one percent (US$720 million), respectively.

While US investment for PrEP and preventive vaccines increased by 91.7 percent and 0.2 percent, respectively, contributions to all other prevention options declined *(Figure 5b)*.

FIGURE 6a **European Public Sector Investments in HIV Prevention R&D Compared to All Other Funding, 2013-2018** (US$ billions)

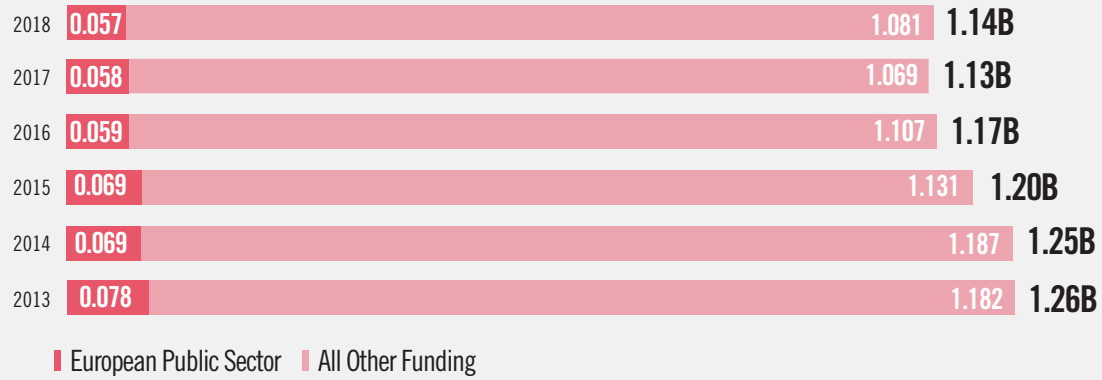
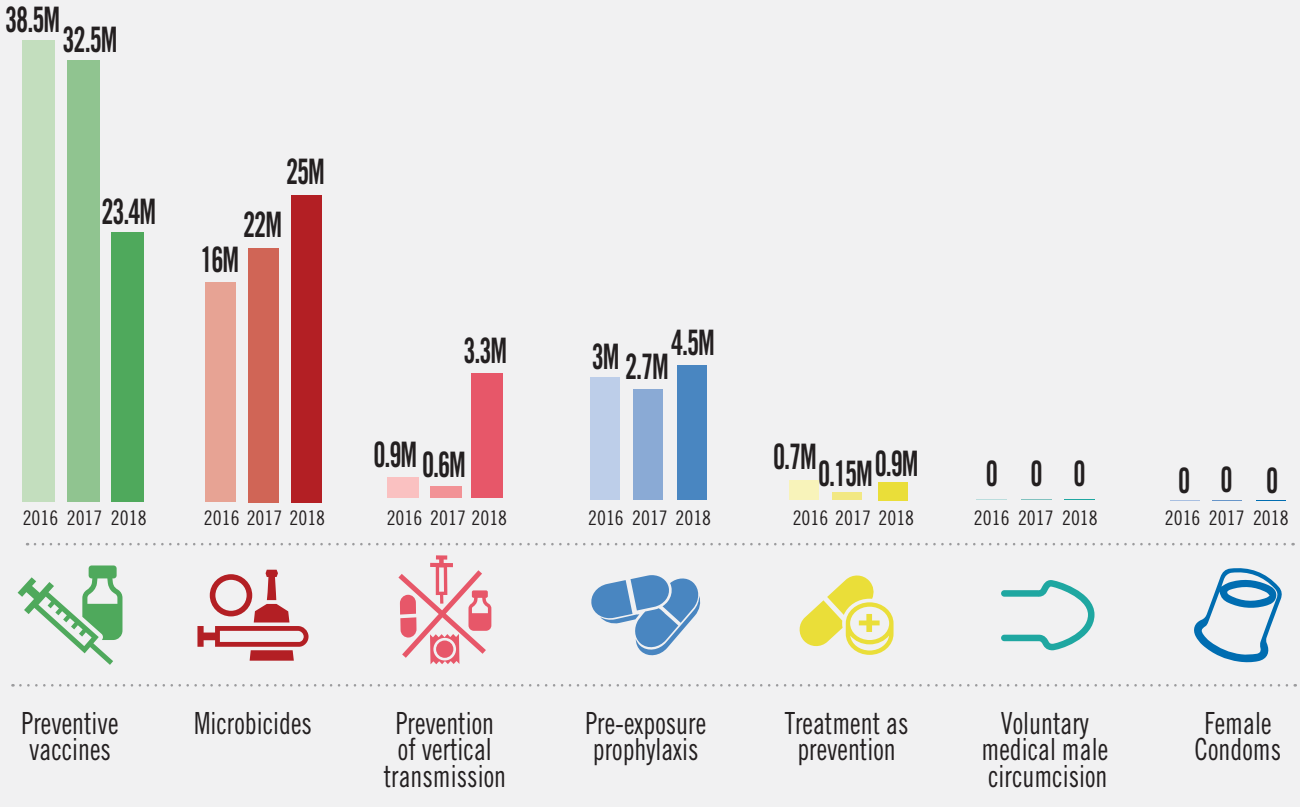


FIGURE 6b **European Public Sector Investments in HIV Prevention R&D by Technology, 2016-2018** (US$ millions)



- European public sector funding was also mostly unchanged at US$57.5 million, with a 0.7 percent dip from 2017 levels. Regardless, this is the lowest funding observed in over a decade for the region *(Figure 6a)*. Excluding preventive vaccines, European investment in all other prevention options increased in 2018 *(Figure 6b)*.
- Global philanthropic funding levels saw no change in 2018 and remained at US$164 million, or 14.4 percent of overall funding *(Figure 7a)*. The Bill and Melinda Gates Foundation remained the largest funder and decreased its contribution slightly by 0.3 percent to US$149.7 million. Wellcome Trust investment rose for the first time in five years to a total US$2.4 million *(Figure 7b)*. The majority of Gates Foundation investment was directed towards preventive vaccines (79 percent) and PrEP (14 percent), while Wellcome Trust funding was concentrated in preventive vaccine (44.8 percent) and microbicide (24.6 percent) research.

FIGURE 7a **Investment in HIV Prevention R&D by Top Philanthropic Funders, 2018** (US$ millions)

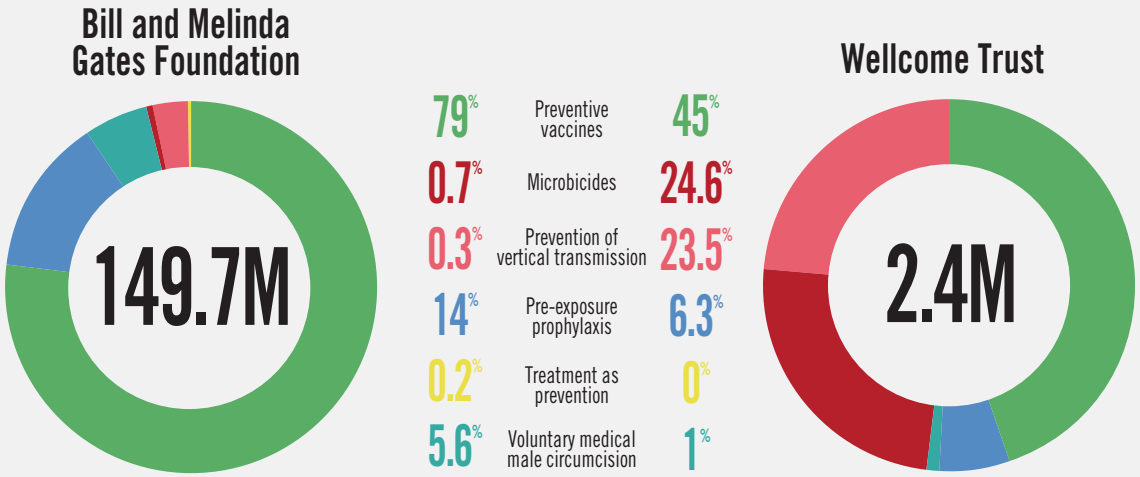
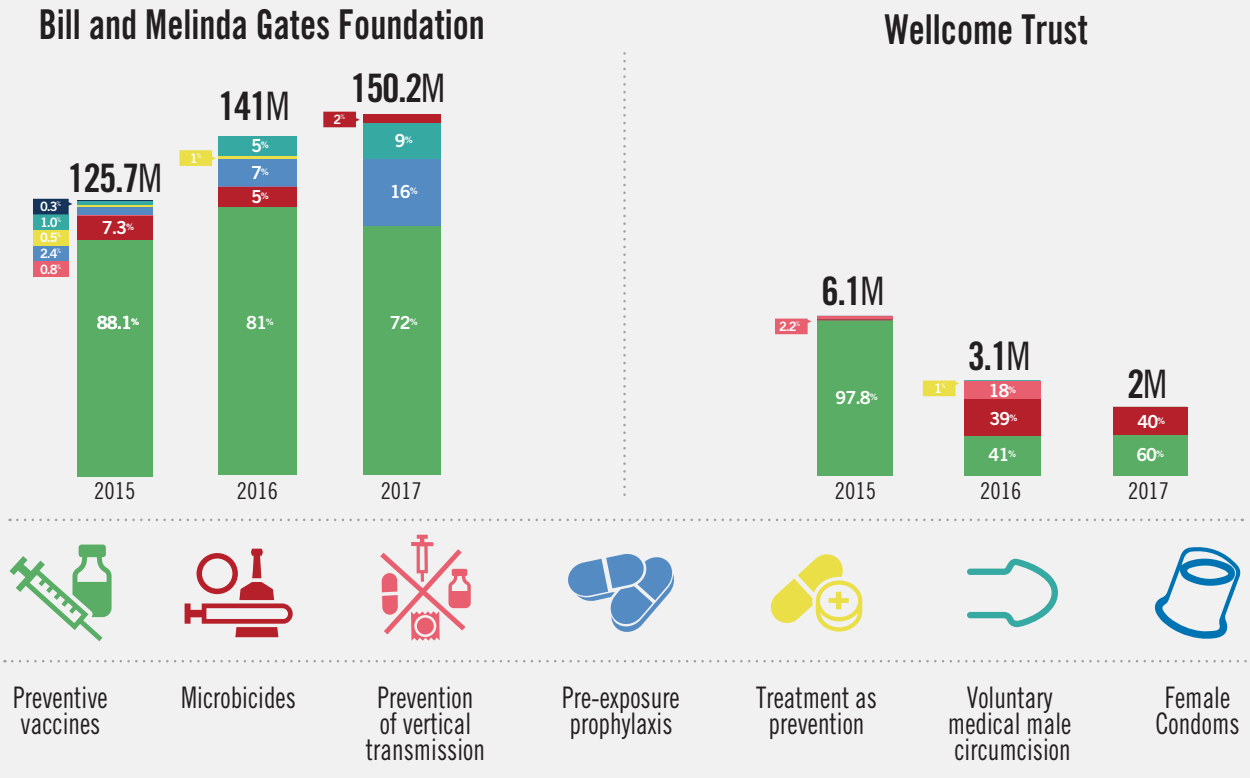


FIGURE 7b **Investments in HIV Prevention R&D by Top Philanthropic Funders, 2015-2017** (US$ millions)



Key Findings

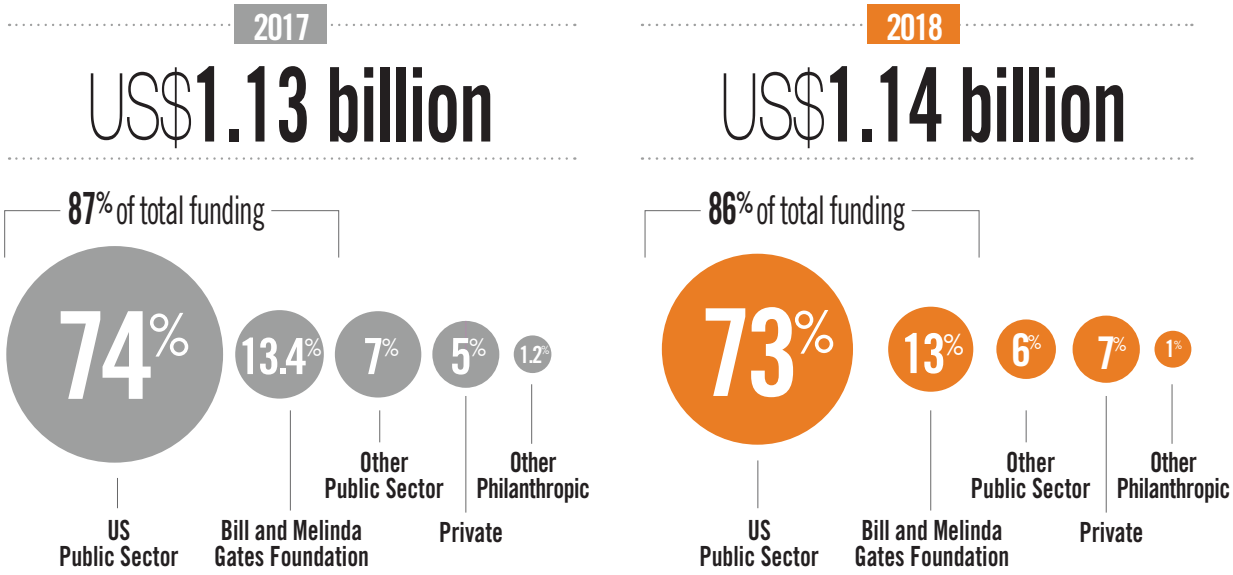
Dominant funders and their field-wide influence

Although past years' trend of a small number of large investors continued in 2018, the degree of funding imbalance has lessened slightly. The US public sector contributed almost three-fourths of all global funding (US$829 million out of US$1.14 billion), while the Bill and Melinda Gates Foundation remained the principal philanthropic donor, accounting for 91 percent (US$149.7 million out of US$164 million) of all sector investment. Investments by the two leading donors combined accounted for 86 percent of overall funding *(Figure 8a)*, or 86 cents of every dollar spent.

Whil the slight improvements in the funding imbalance are to be lauded, innovations in HIV prevention R&D are still vulnerable to shifting donor priorities and fluctuations in investment. Predictably, 68 percent of the US$8.2 million decrease in VMMC R&D in 2018 can be traced back to a reduction in investment from BMGF. Similarly, the 73 percent increase in PrEP funding in 2018 is due largely to enhanced investment from the US public sector, which increased PrEP investment by 91.7 percent, to US$60.6 million.

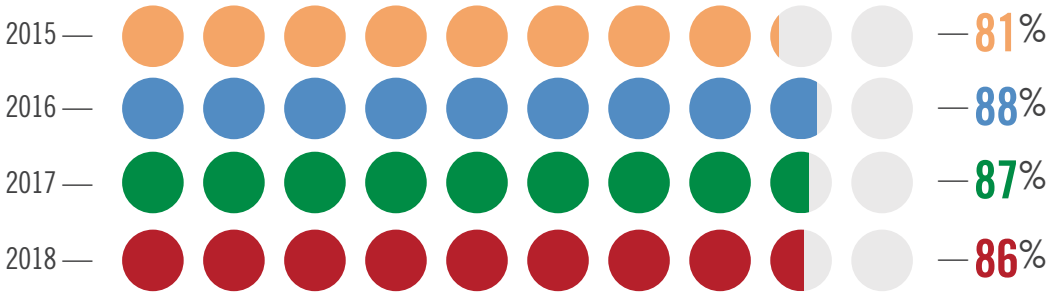
Diversifying the funding base is vital not only for the long-term sustainability of the field, but also to ensure that decades (and accompanying billions of dollars) of gains made in scientific innovation are not lost to mercurial policy shifts. The field has been moving toward greater proportionality for two years now but there is still much to be done to achieve parity in the funding landscape *(Figure 8b)*.

FIGURE 8a **Composition of the Global HIV Prevention R&D Investment Base, 2017-2018**



* *Other Public Sector* includes funding outside the US public sector; *Other Philanthropic* includes funding outside the Bill and Melinda Gates Foundation

FIGURE 8b **Contributions from the Two Largest Donors, 2015- 2018** (Percentage of overall funding)*



* *Refers to the US public sector and the Bill and Melinda Gates Foundation*

Emerging players outside of the US public sector

Funding outside the US public sector totaled US$74 million in 2017, with 15 countries accounting for seven percent of the overall funding for that calendar year. This number decreased slightly to US$71 million in 2018, and the 15 contributing countries represented six percent of overall funding. Prominent increases came from the UK (from US$11.2M to US$17.2M), Germany (from US$3.2M to US$7M), Canada (from US$5M to US$5.4M) and Australia (from US$1.5 million to US$1.6 million) *(Figure 9)*. The European Commission showed a 25 percent increase in funding, with levels rising from US$7.6 million in 2017 to US$9.5 million in 2018. Investment by Australia and Canada increased by 73.4 percent and 9 percent, respectively, in 2018, while funding from France decreased by 17 percent *(Figure 10)*.

FIGURE 9 **Top Countries Investing in HIV Prevention R&D, 2017-2018** (US$ millions)

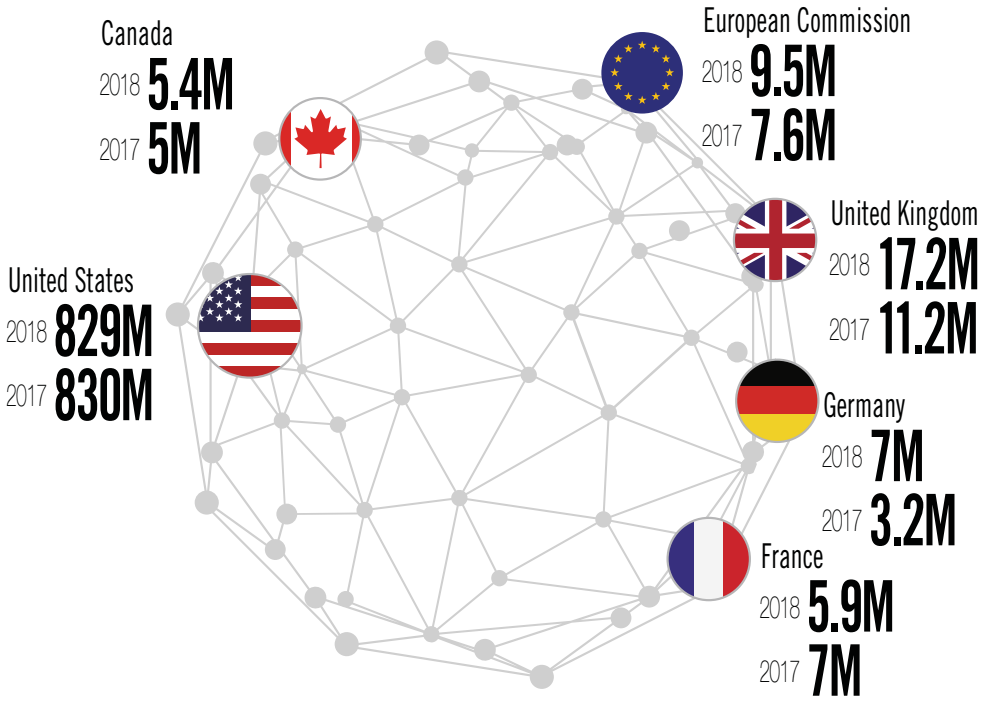
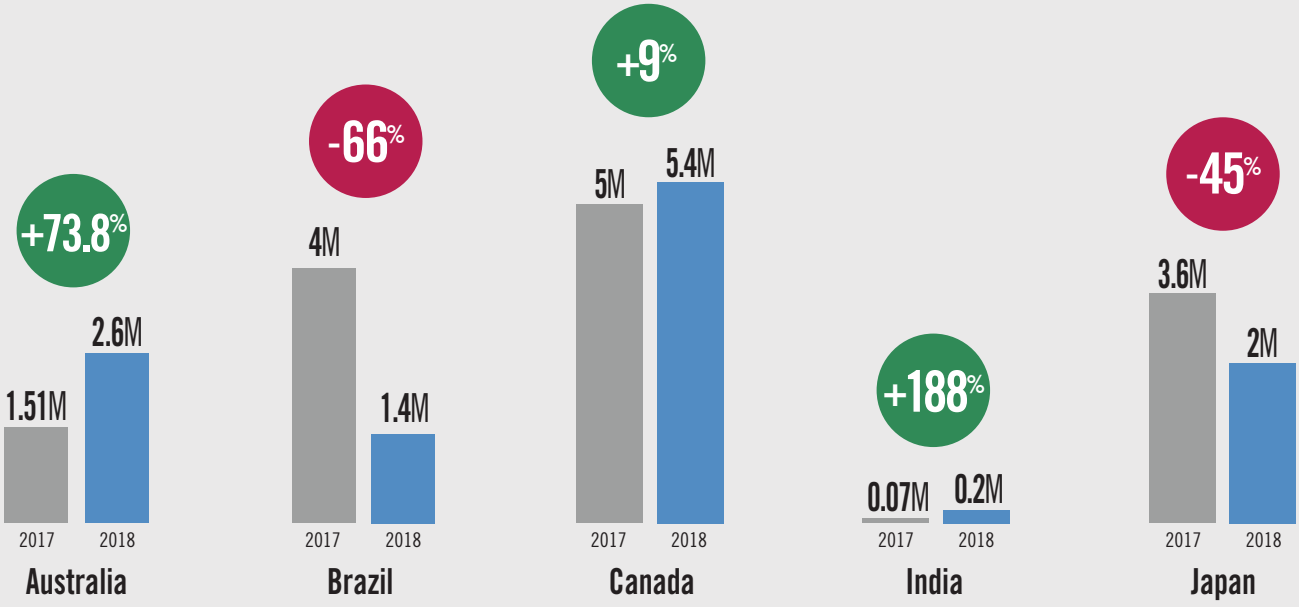


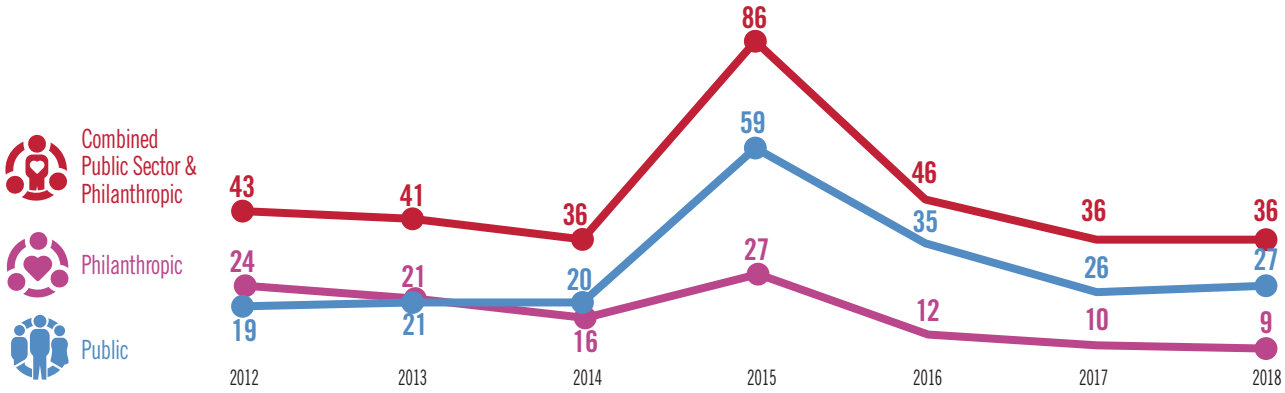
FIGURE 10 **Changes in Public Sector Investment Outside the US and Europe, 2017-2018** (US$ millions)



Decrease in the number of philanthropic funders engaged

Despite philanthropic funding levels remaining constant in 2018, the decline in the number of donors continued. In line with a trend observed since 2010 (which reversed briefly in 2015), the number of philanthropies engaged in HIV prevention research decreased to nine in 2018 *(Figure 11)*. For philanthropies that report funding to the Working Group, three reported no longer supporting HIV prevention research in 2018. Independent philanthropic donors are essential to a vibrant funding base and they would also improve the funding imbalance that currently afflicts the investment landscape

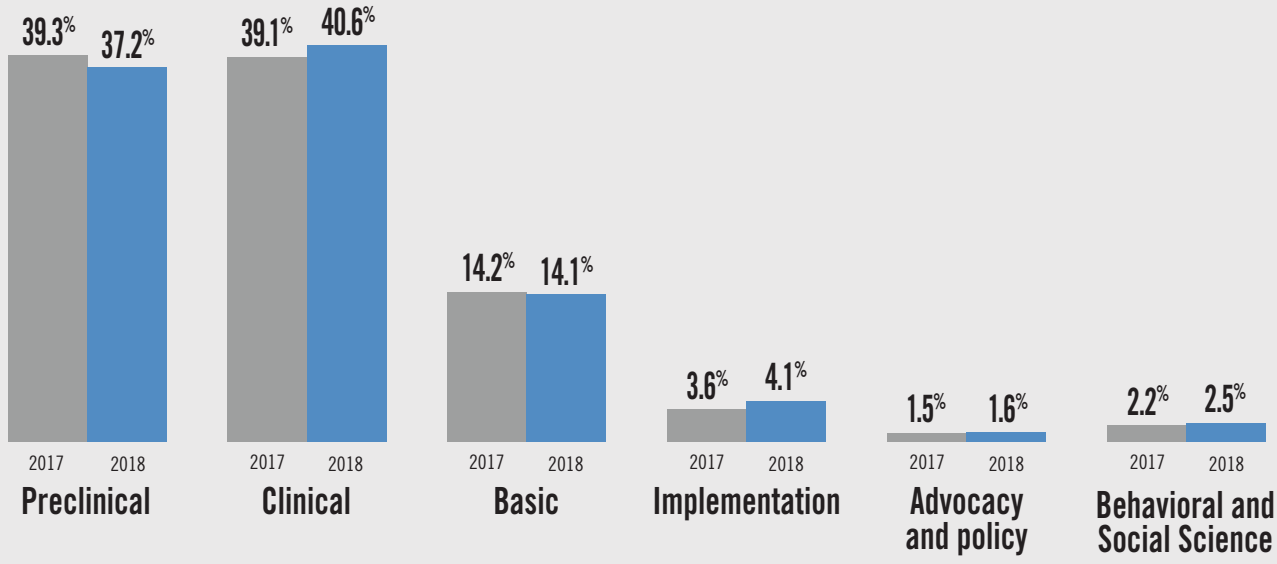
FIGURE 11 **Number of Public Sector and Philanthropic Funders Investing in HIV Prevention R&D, 2012-2018**



The unfinished agenda for social and behavioral research

As observed in previous years—and as is typical for R&D—clinical (40.6 percent) and preclinical research (37.2 percent) received more than three-fourths of overall funding in 2018. As for biomedical options with proven efficacy like VMMC and PMTCT, the emphasis remained on the "science of delivery'" or implementation science. Approximately US$28 million (50 percent) of PMTCT funding and US$16 million (47 percent) of VMMC funding was allocated to projects aimed at service delivery and roll-out. The trend of increased funding for behavioral and social science research endured in 2018: levels rose from US$25 million in 2017 to US$28 million in 2018. These are encouraging—albeit modest—findings when considering the US$1.14 billion invested in HIV prevention R&D overall *(Figure 12)*.

FIGURE 12 **Research to Rollout: Investment by Research Stage, 2017-2018**

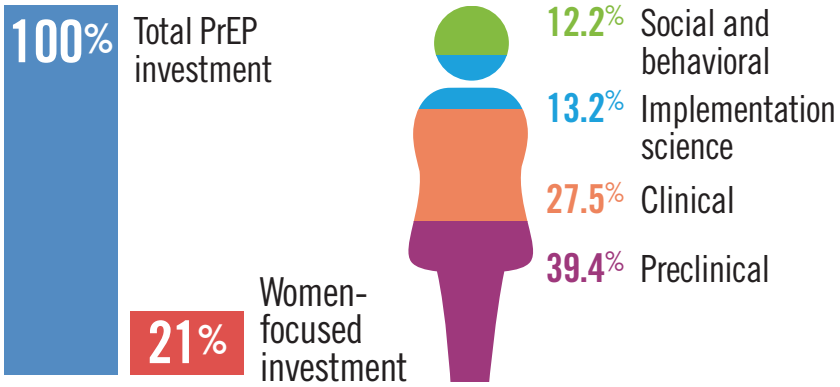


Women-focused PrEP research

The intersection of biological and structural factors confers a heightened risk of HIV acquisition in women and girls, and this is reflected in the disease's epidemiology: 7,000 new HIV infections are recorded weekly in adolescent girls and young women, and girls aged 15-19 years make up three out of every four new HIV cases in sub-Saharan Africa[3]. This disproportionate burden calls for the development of women-controlled and initiated HIV prevention products that have proven efficacy and are designed from bench to bedside with the unique intersecting needs of women in mind.

One such option is PrEP, both in oral form and in other long-acting delivery systems that would circumvent issues around daily adherence. Out of the US$109 million invested in PrEP overall, US$23 million, or 21 percent, was for research explicitly focused on women. Most of this research was preclinical, with an emphasis on long-acting products that conferred multipurpose protection against HIV and unintended pregnancy. Almost half (44 percent) of the implementation science budget focused on the uptake and adherence of oral PrEP in marginalized women, women with injecting drug use, and female sex workers *(Figure 13)*.

FIGURE 13 **Investment in Women-focused PrEP R&D, 2018**



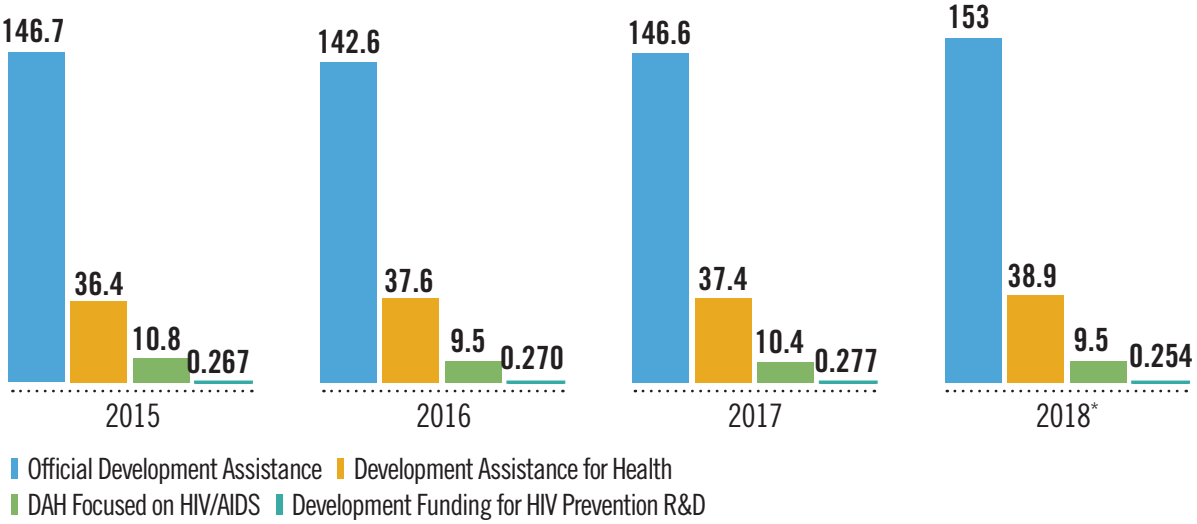
Over half of all preclinical funding was for multipurpose PrEP products that conferred protection against both HIV and unwanted pregnancy.

Of the total implementation science budget, **13%** and **12%** was dedicated to improving PrEP uptake and adherence in women with drug use and female sex workers, respectively. Research investigating attitudes and barriers to PrEP use in black women made up 20% of the total women-focused social behavioral science budget.

Spending on HIV/AIDS in the global context

Initiatives to end the HIV/AIDS epidemic have great support in the global health discourse and have been featured prominently in the Millennium Development Goals (MDG 6) and more recently, the Sustainable Development Agenda (SDG 3). Following an upswing in funding worth US$562 billion between 2000 and 2015, Development

FIGURE 14 **HIV Prevention R&D in the Context of Development Assistance for Health and Total Official Development Assistance, 2015-2018** (US$ billions)

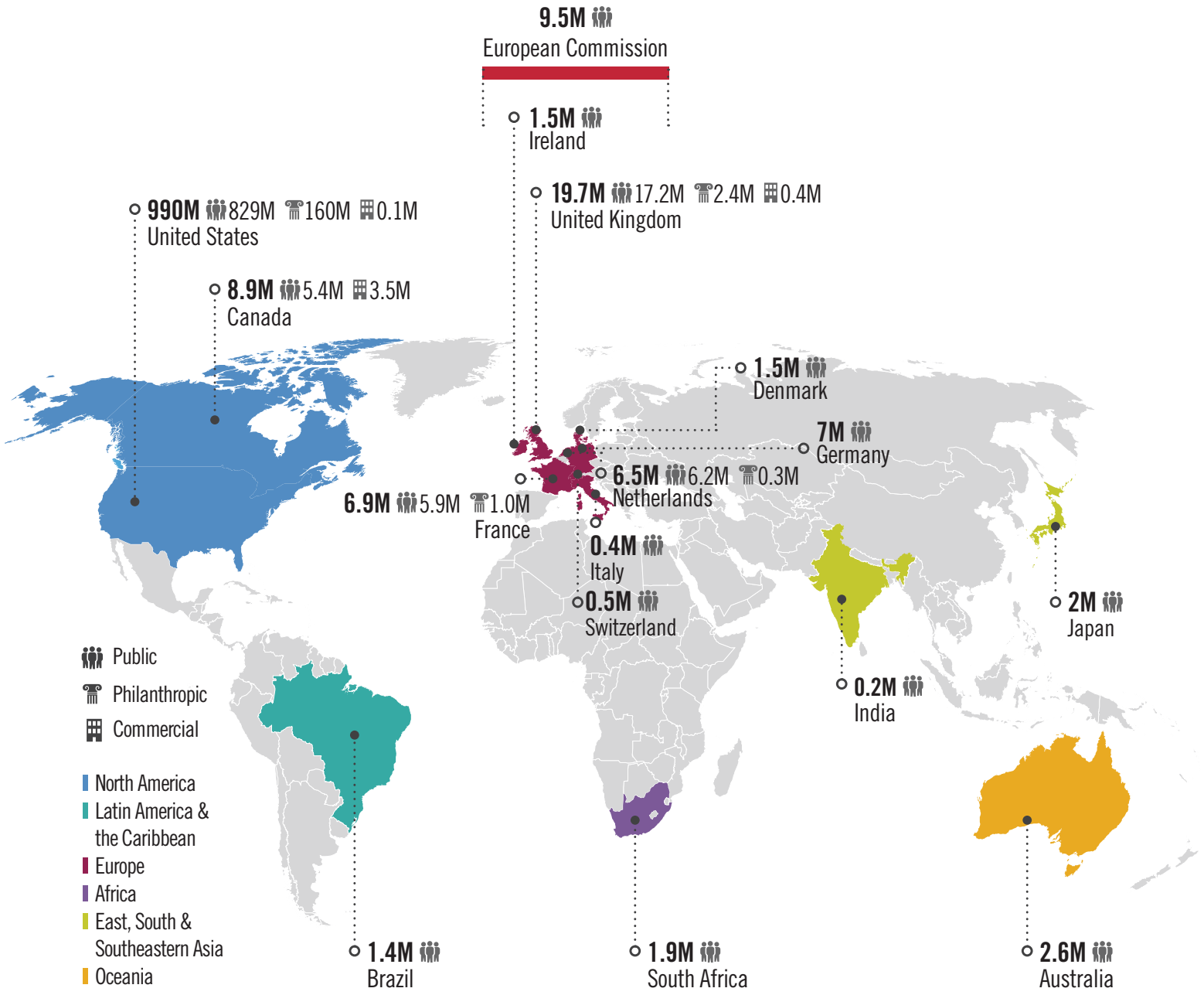


Assistance for Health (DAH) for HIV/AIDS has been declining annually at a rate of 1.4 percent since 2011[4]. DAH is defined as the financial or in-kind support from development agencies to low and middle-income countries in order to maintain or improve health.

In 2018, DAH focused on HIV/AIDS decreased from US$10.4 billion to US$9.5 billion. Development agency support for HIV prevention R&D amounted to US$254 million, or 2.7 percent of total DAH, decreasing from the 2017 level of US$277 million *(Figure 14)*.

* 2018 estimates are preliminary and subject to change

FIGURE 15 **Total Global Investment in HIV Prevention R&D by Country, 2018** (US$ millions)



* Information collected includes funding from those countries that responded to the Working Group's annual survey, or where public information on sources of funding was available. Totals include public, philanthropic and commercial sector funding from each country. Commercial-sector investments are allocated to a country based on the location of corporate headquarters and are underestimated due to a lack of reporting by companies. Not all commercial-sector estimates are able to be allocated by country.

Trial Participation

Participation of volunteers and the engagement of communities in which trials take place is essential to conducting HIV prevention research. In 2018, there were nearly 630,000 participants in HIV prevention research trials globally,mostly originating from sub-Saharan Africa, Asia, Europe and North America *(Figure 16a)*.

A majority of participants were enrolled in research investigating TasP and PrEP, and while there were trials enrolling groups like MSM, transgender people and PWID, most of the studies did not specify the inclusion of key populations (KPs) *(Figure 16b)*.

FIGURE 16a **HIV Prevention R&D Trial Participants by Region in 2018** (thousands)

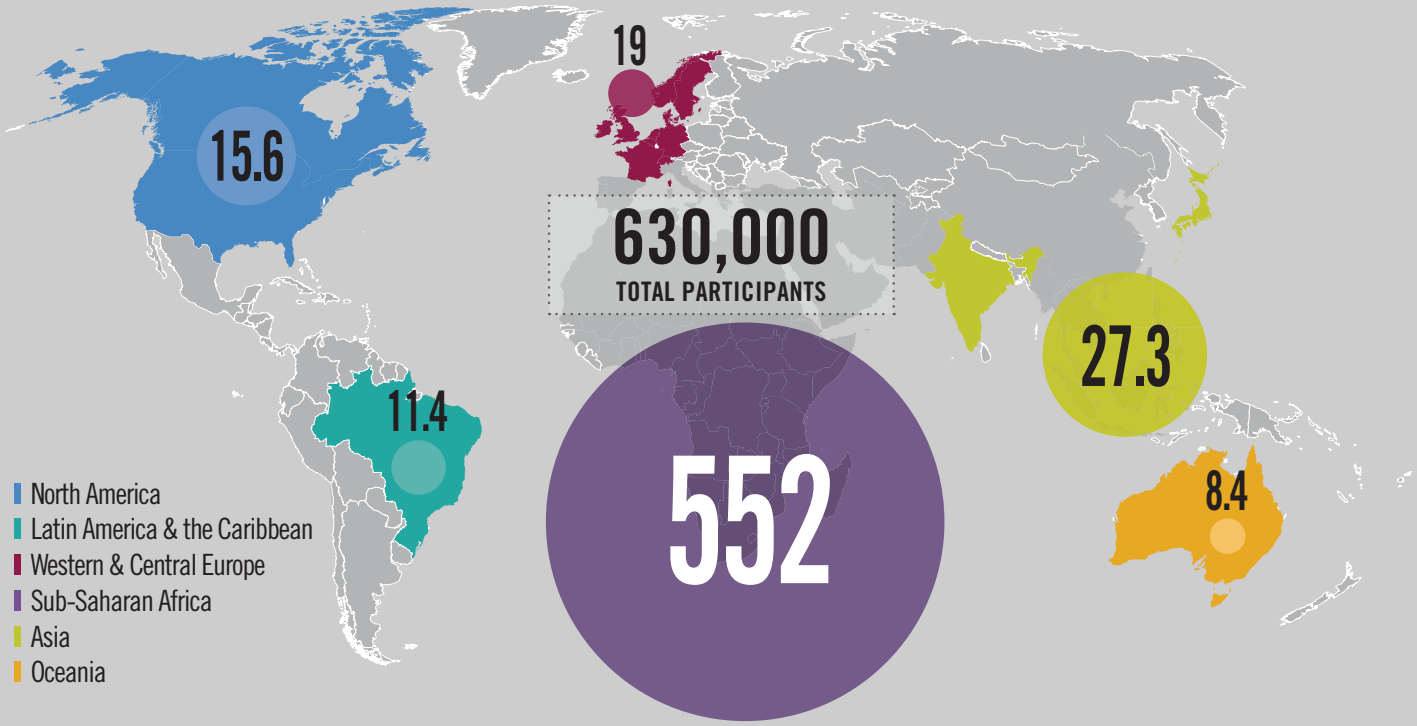
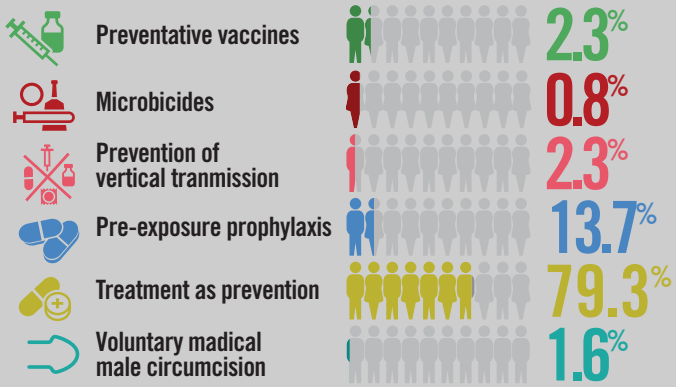
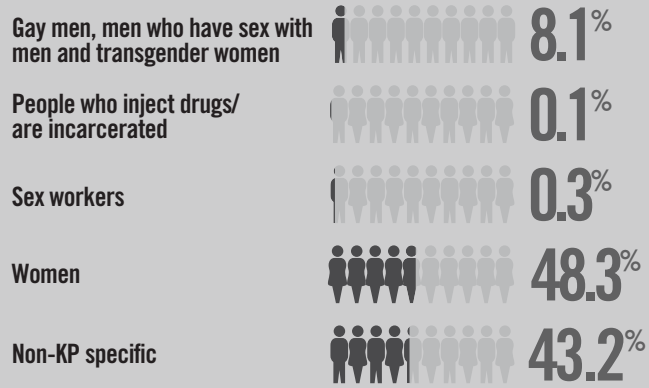


FIGURE 16b **Trial Participants, 2018**

TRIAL PARTICIPANTS BY PREVENTION RESEARCH AREA



KEY POPULATION REPRESENTATION IN CLINICAL TRIALS



Collection and Analysis Methodology

In order to generate investment estimates that can be compared from year to year, from one technology to another and across funding sources, a systematic approach to data collection and collation was developed at the establishment of this collaborative project in 2004. Its fundamental premise is that monitoring HIV prevention R&D investment trends permits the identification of investment needs, prioritization of research areas and assessment of the impact of public policies that increase or decrease investments. Investment data also provide the fact base for advocacy around spending levels, resource allocations, the value of sustained investments in research building on trial successes, attracting novel HIV prevention candidates to the pipeline and follow-on trials to assure the safety, immunogenicity, efficacy and acceptability of new HIV prevention products. The same methods were employed to generate the estimates of funding for R&D presented in this year's report.

R&D data were collected on annual disbursements by public, private and philanthropic funders for product development, clinical research, trial preparation, behavioral research and policy and advocacy efforts to estimate annual investments in HIV prevention R&D. Investment trends were assessed and compared by year, prevention type, research phase, funder category and geographic location. Comprehensive and consistent use of this methodology enables data comparisons across organizations, countries and years. The Working Group makes every effort to maintain a comparable data set, while allowing for the limitations inherent to global investment tracking styles and timing. Its primary limitation is that data collection largely depends on the response rate of public, private and philanthropic funders, and year-to-year variability is partly a reflection of this response rate. Funds were allocated to the year in which they were disbursed by the donor, irrespective of whether the funds were expended by the recipient in that year or in future years. Investment figures are rounded throughout the report. In order to minimize double-counting, the Working Group distinguishes between primary funders and intermediary organizations. "Intermediary" organizations receive resources from multiple funders and use these resources to fund their own work, as well as the work of others.

All figures in the report are given in current US dollars and have not been adjusted for inflation. Because of this, investments in later years may be overvalued relative to investments in earlier years due to inflation. From a total of 215 surveyed organizations, institutions and companies, 65 funders reported their investments. A total of 454 grants were allocated to HIV prevention research, with an average grant size of US$2.5 million.

TABLE 1 **Global Investments in HIV Prevention R&D: 2018 Funding Map**

Funding type	2017	2018	% Change 2017-2018	Funder	Total 2018	Total 2017	% Change	2018 totals in US$ millions *(2017 investments, percent change*)*																								
								Preventive AIDS vaccines			Microbicides			Prevention of vertical transmission			Pre-exposure prophylaxis			Treatment as prevention			Voluntary medical male circumcision			Female condoms							
								2018	2017	Change	2018	2017	Change	2018	2017	Change	2018	2017	Change	2018	2017	Change	2018	2017	Change	2018	2017	Change				
US Public Sector	$830 million	$829 million	-0.1%	NIH	$720	$713	1%	*$561.7*	*$561.8*	*-0.02%*	*$88.9*	*$95*	*-6.3%*	*$31.3*	*$34.3*	*-9%*	*$36.6*	*$20.1*	*82%*	*$0.6*	—	—	*$0.7*	*$1.7*	*-59.6%*	—	*$0.02*	—						
				USAID/PEPFAR*	$72.5	$74.7	-3%	*$28.7*	*$28.7*	—	*$19.9*	*$34.9*	*-42.8%*	—	—	—	*$23.8*	*$10*	*140%*	—	—	—	—	—	—	—	—	—						
				CDC	$1.5	$9.9	-84.2%	—	—	—	*$1.3*	*$1.6*	*-22.3%*	—	—	—	*$0.2*	*$1.7*	*-86.4%*	—	*$4.9*	—	—	*$1.6*	—	—	—	—						
				MHRP	$35.6	$33	8%	*$35.6*	*$33*	*8%*	—	—	—	—	—	—	—	—	—	—	—		—	—	—							
European Public Sector	$58 million	$57.5 million	-0.7%	Belgium	$0.2	—	—				*$0.2*	—	—	—	—	—	*$0.06*	—	—	—	—	—	—	—	—	—	—	—						
				Denmark	$1.5	$1.5	2%	*$0.7*	*$0.7*	*7.8%*	*$0.75*	*$0.77*	*-3.3%*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				EC	$9.5	$7.6	25%	*$9.4*	*$7.5*	*26%*	—	*$0.01*	—	*$0.1*	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				France	$5.9	$7.1	-17%	*$2.5*	*$5.8*	*-57%*	*$0.05*	*$0.2*	*-96.8%*	*$0.27*	*$0.55*	*-51%*	*$2.4*	*$2.7*	*-12%*	*$0.73*	*$0.14*	*416%*	—	—	—	—	—	—						
				Germany	$7.1	$3.2	122%	*$0.01*	—	—	*$6.9*	*$3.2*	*114%*	*$0.2*	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Ireland	$1.5	$2.1	-31%	—	*$0.6*	—	*$1.5*	*$1.6*	*-6.4%*		—	—	—	—	—	—	—	—	—	—	—	—	—						
				Italy	$0.4	$1.6	-73%	*$0.14*	*$1.6*	*-91%*	—	—	—	*$0.3*	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Netherlands	$6.2	$11.2	-45%	*$4.1*	*$3.7*	*10.2%*	*$2.1*	*$7.5*	*-72%*	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Norway	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Spain	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Sweden	—	$7.2	—	—	*$6.0*	—	—	*$1.1*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Switzerland	$0.5	$0.31	53.6%	*$0.32*	*$0.31*	*1%*	—	—	—	—	—	—	—	—	—	*$0.16*	—	—	—	—	—	—						
				UK	$17.2	$11.2	53.5%	*$3.1*	*$4.5*	*-30%*	*$13.5*	*$6.7*	*102%*	*$0.26*	*$0.02*	*1414%*	*$0.29*	—	—	—	—	—	—	—	—	—	—						
Other Countries	$16.4 million	$13.5 million	-17.5%	Australia	$2.6	$1.51	74%	*$1.9*	*$0.8*	*132%*	—	*$0.2*	—	*$0.07*	*$0.06*	*26%*	*$0.3*	*$0.03*	*998%*	*$0.1*	*$0.2*	*-42%*	*$0.19*	*$0.21*	*-5%*	—	—	—						
				Brazil	$1.4	$4.1	-66%	—	*$0.06*	—	—	—	—	—	*$0.4*	—	*$1.4*	*$4*	*-66%*	*$0.03*	—	—	—	—	—	—	—						
				Canada	$5.4	$5	9%	*$2.3*	*$3.8*	*-41%*	*$2.2*	*$0.8*	*174%*	*$0.3*	*$0.2*	*41%*	*$0.5*	—	—	*$0.086*	*$0.087*	*-1.7%*	*$0.01*	—	—	—	—						
				China	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Cuba	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				India	$0.2	$0.07	188%	*$0.2*	*$0.07*	*188%*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Israel	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Japan	$2	$3.6	-44%	*$2*	*$3.6*	*-45%*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Russia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				South Africa	—	$2.1	—	—	*$1.6*	—	—	*$0.2*	—	—	—	—	—	*$0.2*	—	—	—	—	—	—	—	—	—	—						
				Taiwan	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
				Thailand	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
Philanthropic	$164 million	$164 million	No change	BMGF	$149.7	$150.2	-0.3%	*$118*	*$108*	*9.5%*	*$1.1*	*$3.3*	*-67%*	*$0.42*	*$0.44*	*-4.5%*	*$21*	*$24*	*-12.5%*	*$0.23*	*$0.20*	*13%*	*$8.3*	*$13.9*	*-40%*	—	—	—						
				Wellcome Trust	$2.4	$2.1	18%	*$1.1*	*$1.2*	*-12%*	*$0.6*	*$0.8*	*-26.8%*	*$0.6*	—	—	*$0.15*	*$0.005*	*2669%*	—	—	—	*$0.02*	—	—	—	—	—						
				Other	$11.9	$11.8	1%	*$11.1*	*$11.2*	*-0.7%*	*$0.11*	*$0.14*	*-23%*	*$0.4*	—	—	*$0.41*	*$0.40*	*0.4%*	*$0.2*	*$0.1*	*107%*	—	—	—	—	—	—						
Industry	$57 million	$74.7 million	30.8%	Commercial Sector	$74.7 million	$57 million	30.8%	*$53.7*	*$57*	*-6%*	*$0.8*	*$0.2*	*303%*	—	—	—	*$20.2*	—	—	—	—	—	—	—	—	*0.04*	—	—						
Total	$1.13 billion	$1.14 billion	1.2%	HIV prevention option totals	$1.14 billion	$1.13 billion	1.2%	$842	$845	-0.3%	$140	$159	-12%	$36	$35.7	1%	$109	$63	73.4%	$2.2	$5.6	-61.5%	$9.2	$17.5	-47%	$0.04	$0.02	79%						
				% Change 2017–2018	1.2%			-0.3%			-12%			1%			73.4%			-61.5%			-47%			79%							

All figures are rounded. See Appendix for a detailed methodology section, including the limitations of data collection.

* The USAID Microbicide Program funding covers topical microbicide products as well as systemic and sustained-release HIV pre-exposure prophylaxes.

AIDS Vaccines

1.0 Global investment in preventive AIDS vaccines R&D

In 2018, funding for preventive AIDS vaccines R&D decreased by a marginal 0.3 percent or US$2.7 million from the previous year, to a total of US$842 million. The public sector made up 78 percent of overall investment, at US$657.8 million, with the philanthropic and commercial sectors contributing 15.5 percent and 6.4 percent, respectively. At US$626 million or 95 percent of all public sector funding, the US remained the largest donor of preventive vaccine research globally. US public sector funding increased by 0.2 percent from 2017 levels, to US$626 million, an uptick bolstered by the eight percent increase in funding from the MHRP *(Figure 17)*.

FIGURE 17 **AIDS Vaccine Funding, 2000 - 2018** (US$ millions)

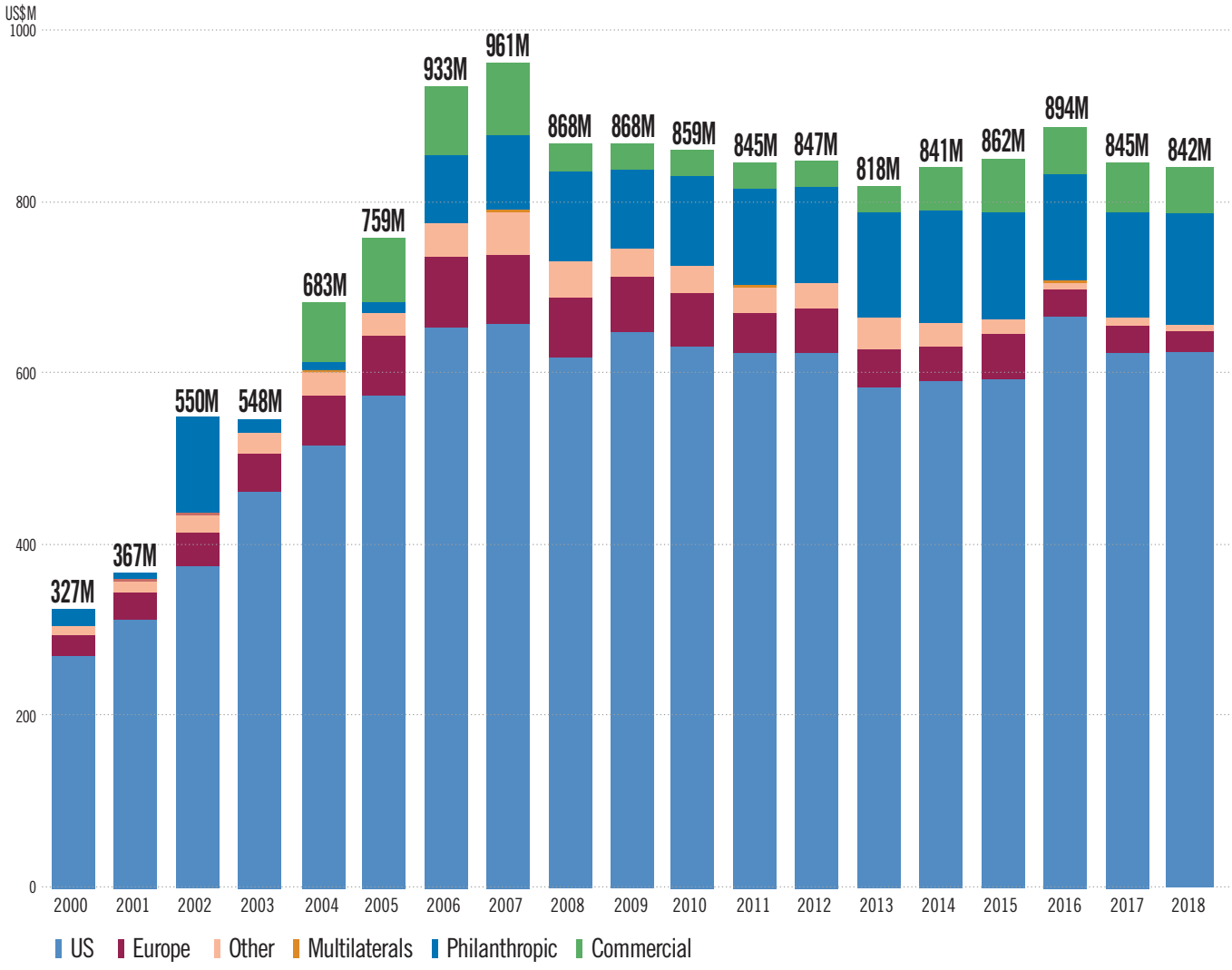
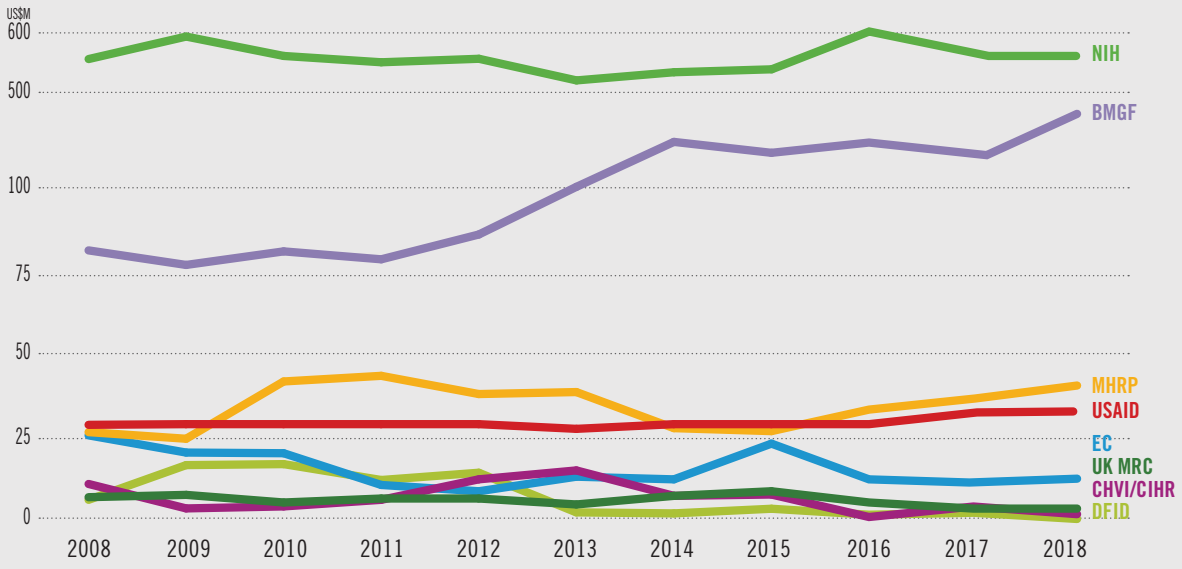


TABLE 2 **Annual Investment in AIDS vaccine R&D, 2000 – 2018** (US$ millions)

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
US	272	314	376	463	516	574	654	659	620	649	632	615	623	584	591	595	667	624.7	626
Europe	23	32	39	44	57	69	82	79	69	65	61	48.5	52	44	40	44	38.5	32.5	23.8
Other Countries	10	12	21	24	28	27	38	49	41	31	32	30	31	38	27	26	7.8	10.1	7.9
Multilaterals	2	2	2	2	2	2	2	2	1	1	1	0.5	0.5	0.5	0.5	0.5	0.5	0	0
Total Public	307	359	436	532	602	672	776	789	731	746	726	702	707	667	653	655	714	667	657.8
Total Philanthropic	20	7	112	15	12	12	78	88	104	92	103	113	110	120.5	131	132	126	120.7	130.7
Total Commercial	–	–	–	–	68	75	79	84	33	30	30	30	30	31	51	62	54	57	53.7
Total Global Investment	**327**	**366**	**548**	**547**	**682**	**759**	**933**	**961**	**868**	**868**	**859**	**845**	**847**	**818**	**840**	**859**	**894**	**845**	**842**

FIGURE 18 **Top AIDS Vaccine Funder Trends, 2008-2018** (US$ millions)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
NIH	556.1	596	561.6	550.4	556.6	518.2	532.7	537.9	605	561.8	561.7
BMGF	81.2	76.8	80.9	78.5	86	100.4	114	110.7	113.8	108	118.6
USAID	28.5	28.7	28.7	28.7	28.7	27.3	28.7	28.7	28.7	28.7	28.7
MHRP	26.3	24.3	41.6	43.3	37.8	38.4	27.5	26.6	33.1	33	35.6
EC	25.3	20.1	19.9	10.3	8.4	12.8	12	22.8	12	7.5	9.4
DFID	5.8	16.3	16.6	11.8	14	2	1.7	3.1	1.3	1.3	0
CHVI/CIHR	10.6	3.2	3.8	5.8	12	14.7	7	7.4	0.6	3.8	2.3
UK MRC	6.6	7.3	5	6.2	6.2	4.4	7	8.4	5	3.2	3.1



Overall European investment in preventive vaccine R&D decreased by 27 percent and amounted to US$23.8 million, the lowest levels observed since 2001. Philanthropic contributions increased by US$10 million, to US$130.7 million, in 2018. The aforementioned boost is due mostly to the 9.5 percent increase in BMGF funding, and BMGF remains the largest philanthropic funder of vaccine research, at US$118 million.

The commercial sector contributed US$53.7 million, representing a six percent decrease from the previous year.

Australia, Denmark, India, the Netherlands and Switzerland all increased their commitments in 2018, which helped cushion against the decrease in funding from Canada, France, Italy, Japan and the UK. The European Commission also stood out with an increase in investment from US$7.5 million to US$9.4 million in 2018.

TABLE 3 Philanthropic Investment in AIDS Vaccine R&D by Foundations and Commercial Philanthropy, 2018

Amount	Investors
US$118.6 million	Bill and Melinda Gates Foundation
US$1 million to US$10 million	Ragon Institute
US$250,000 to <US$1 million	Wellcome Trust, Institut Pasteur, Sidaction
<US$250,000	amfAR, Campbell Foundation

TABLE 4 **Top AIDS Vaccine Funders for 2012 - 2018** (US$ millions)[a,b]

	2012		2013		2014		2015		2016		2017		2018	
Rank	Funder	Amount	Funder	Amount	Funder	Amount	Funder	Amount	Funder	Amount	Funder	Amount	Funder	Amount
1	NIH	557	NIH	518.2	NIH	532.7	NIH	538	NIH	605	NIH	561.8	NIH	561.7
2	BMGF	86	BMGF	100.4	BMFG	114	BMFG	103	BMGF	114	BMGF	108	BMGF	118.6
3	MHRP	37.8	MHRP	38.4	USAID	28.7	USAID	28.7	MHRP	33	MHRP	33	MHRP	35.6
4	USAID	28.7	USAID	27.3	MHRP	27.5	MHRP	26.6	USAID	29	USAID	28.7	USAID	28.7
5	DFID	14	CHVI[c]	14.7	EC	12	EC	22.3	EC	12	Ragon Institute	10	Ragon Institute	10
6	CHVI	12	EC	12.8	Ragon Institute	10	Ragon Institute	10	Ragon Institute	10	EC	7.5	EC	9.4
7	Ragon Institute	10	Ragon Institute	10	CHVI	7	UK MRC	8.3	Swedish Research Council	6	EDCTP	5	Dutch PDP	4
8	EC	8.4	Wellcome Trust	7.7	China[d]	7	CHVI	7.2	ANRS	5.3	ANRS	4.3	UK MRC	3.1
9	Wellcome Trust	8.2	China[d]	7	UK MRC	7	China[d]	7	UK MRC	5	CIHR	3.8	Sumagen Canada, Inc.	3.5
10	China	7	NHMRC	6.8	Wellcome Trust	6.2	Wellcome Trust	6	Dutch PDP	3.6	Dutch PDP	3.7	EDCTP	3.4
11	MRC	6.2	ANRS	5.3	Nether-lands	5.1	Institut Pasteur	5.5	EDCTP	3	Sumagen Canada, Inc.	3.5	ANRS	2.5
12	Institute Pasteur	4.8	The Netherlands	4.9	Institute Pasteur	3.9	South Africa DST/ SAMRC	3.9	South Africa DST/ SAMRC	3.9	VIR Biotech-nology	3.4	CIHR	2.3
13	Netherlands	4.8	Institute Pasteur	4.8	Sumagen Canada Inc.	2.8	DFID	3.1	Sumagen Canada Inc.	1.4	UK MRC	3.2	World Bank (Japan)	2
14	NHMRC	4.4	UK MRC	4.4	ANRS	2.7	Japan AMED	2.4	DFID	1.3	World Bank (Japan)	2	NHMRC	1.8
15	ANRS	4	DANIDA	2.2	South Africa DST/ DOH	2.5	CIHR	2.4	Wellcome Trust	1.3	SAMRC	1.6	Wellcome Trust	1

[a] See appendix for list of acronyms.

[b] A portion of the significantly lower contribution to AIDS vaccine R&D by DfID in 2013 can be attributed to a difference in funding cycles: a £5m disbursement was recognized as 2012 funding due to Working Group Methodology.

[c] Participating CHVI Government of Canada departments and agencies are: the Canadian International Development Agency (CIDA), the Public Health Agency of Canada (PHAC), Industry Canada, the Canadian Institutes of Health Research (CIHR) and Health Canada. CIHR grants are reported separately.

[d] The Working Group could not obtain a response from China for investments made in 2012-2015; thus, an estimate was developed and sent to China's National Center for AIDS/STD Control and Prevention. The estimate was developed based on public information submitted by the National Center for AIDS/STD Control and Prevention and China's Center for Disease Control and Prevention on *clinicaltrials.gov*, regarding a Phase II preventive AIDS vaccine trial started in August 2012, as well as other basic research underway.

1.1 Developments in the field of preventive AIDS vaccine research

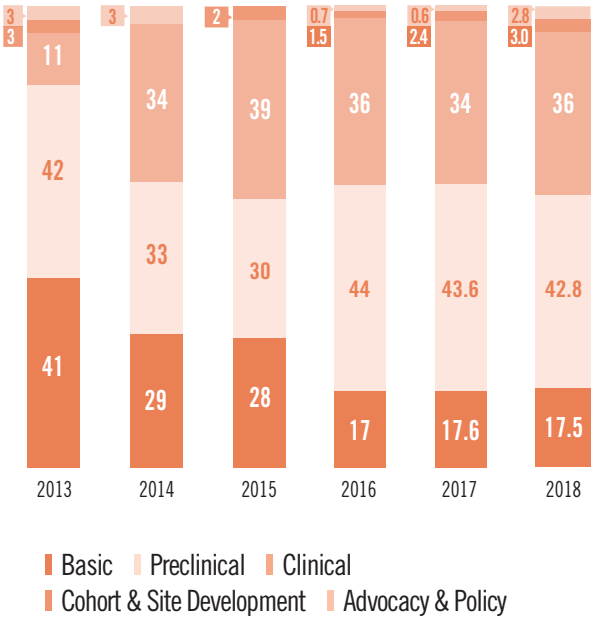
It is an unprecedented time for vaccine research with multiple late-stage vaccine efficacy trials underway. Some of these include:

- The AMP Study (HVTN 703/HPTN 081 and HVTN 704/HPTN 085)—which comprises two "sister" Phase II safety and efficacy trials—is currently active but no longer recruiting participants. These proof-of-concept trials are testing the administration of the VRC01 monoclonal antibody in HIV-negative women in several African countries[5], and in MSM and transgender men and women in North and South America[6]. Study results are expected in the latter half of 2020.
- The Phase IIb/III HVTN 702 study is ongoing and recruiting the target number of 5,400 men and women in South Africa. Driven by the Pox-Protein Public Private Partnership, or P5, HVTN702 is evaluating the efficacy, safety and tolerability of a clade C subtype vaccine candidate. Results of the study are expected in May 2022[7].
- HPX2008/HVTN 705 is the Phase IIb proof-of-concept study currently recruiting participants in five countries across sub-Saharan Africa. The trial will enroll 2600 women and is testing a mosaic immunogen designed to confer protection from more than one clade of HIV. Results are anticipated in the second quarter of 2022[8].

1.2 Funding allocations for preventive AIDS vaccine R&D

Funding for HIV vaccine R&D was allocated to the following areas in 2018: basic research (17.5 percent), preclinical (42.9 percent), clinical (36 percent), cohort and site development (2.8 percent) and advocacy and policy (2.8 percent). In an enduring trend since 2016, preclinical strategies out-funded clinical trials, which tend to be much more cyclical in nature. Further information about the categories used to define R&D can be found in Table 13 of the Methodology section of the Appendix.

FIGURE 19 **AIDS Vaccine Funding Allocations, 2013-2018**



BOX 1

Phase III Trial of the Mosaic Vaccine

Mosaico (HPX3002/HVTN 706) is the Phase III efficacy trial starting in 2019 among 3,800 MSM and transgender people across 55 trial sites in the following countries: Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain and the US[9]. Under investigation is the heterologous vaccine regimen using Ad26.Mos4.HIV and Clade C and Mosaic gp140. This is a slightly revised regimen—in that it has the added Mosaic gp140 to the boost doses—from the one being tested in the Phase IIb Imbokodo (HPX2008/HVTN 705) proof of concept trial in sub-Saharan Africa.

A mosaic-based vaccine regimen is designed to create immune responses to multiple clades and may offer one strategy for overcoming the constantly mutating HIV genes, as well as conferring broader geographic immunity. Mosaico is sponsored by Janssen Vaccines & Prevention B.V. and is estimated to end in June 2023[9].

Microbicides

2.0 Global investment in microbicide R&D

Investment in microbicide R&D totaled US$140 million in 2018, a 12 percent (US$19 million) decrease from 2017 funding levels. This is the sixth consecutive year of declining microbicide funding and the lowest investment levels recorded since 2003 *(Figure 19)*. The majority of funding originated from the public sector (98 percent), while philanthropic and commercial funding trailed at 1.3 percent and 0.6 percent, respectively. Public and philanthropic sector funding decreased by 11 and 57.8 percent, with a US$0.6 million increase in private funding.

FIGURE 20 **Microbicide Funding, 2000-2018** (US$ millions)

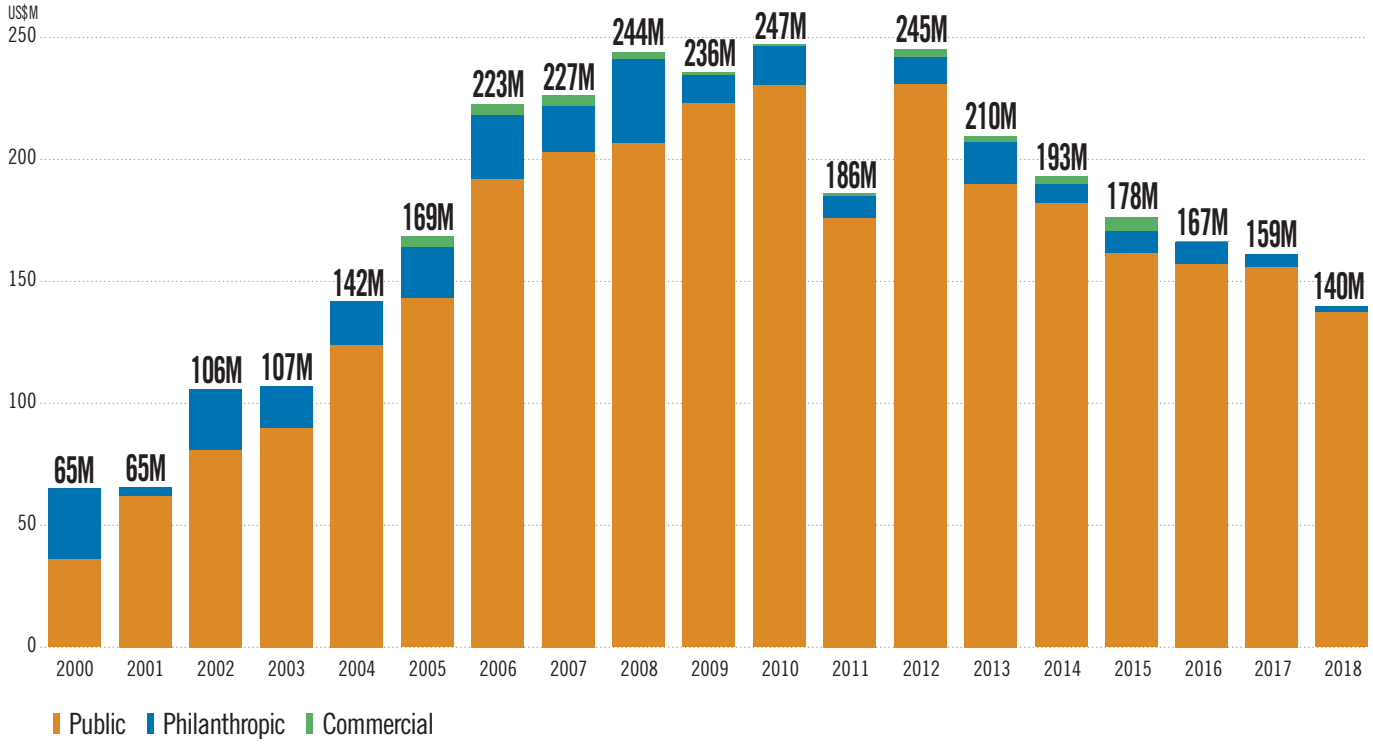
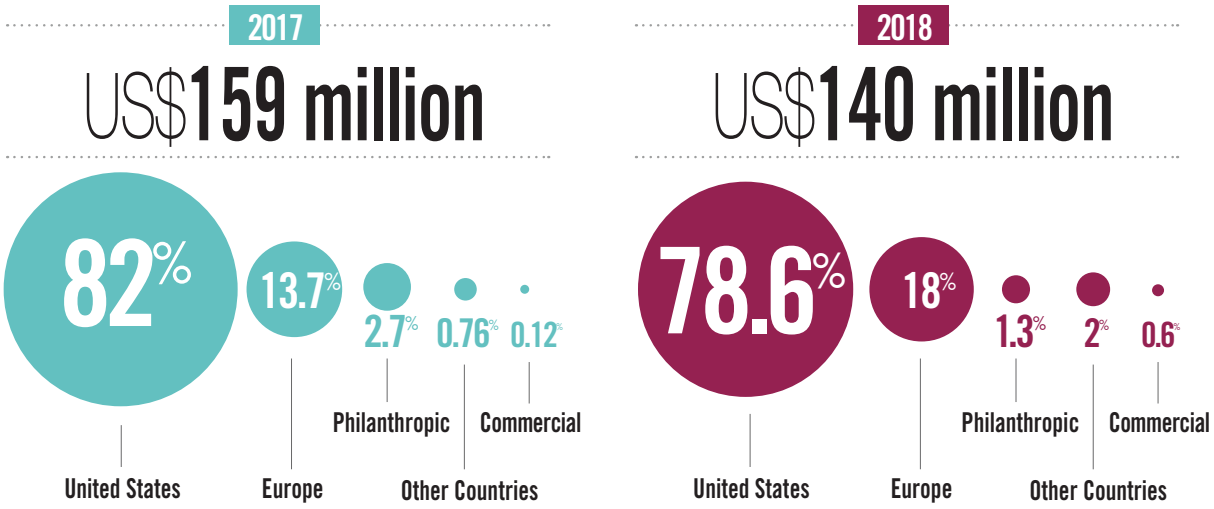


FIGURE 21 **The Funding Base for Microbicide R&D by Percentage, 2017-2018** (US$ millions)



Despite an 18 percent decrease in investment, the US public sector remained the predominant funder at US$110 million. European funding grew by nine percent, to US$25 million, boosted mostly by increased investments from the German Federal Ministry of Education and Research (BMBF, up 114 percent) and the UK Department of International Development (DFID, up 98 percent) *(Figure 21)*.

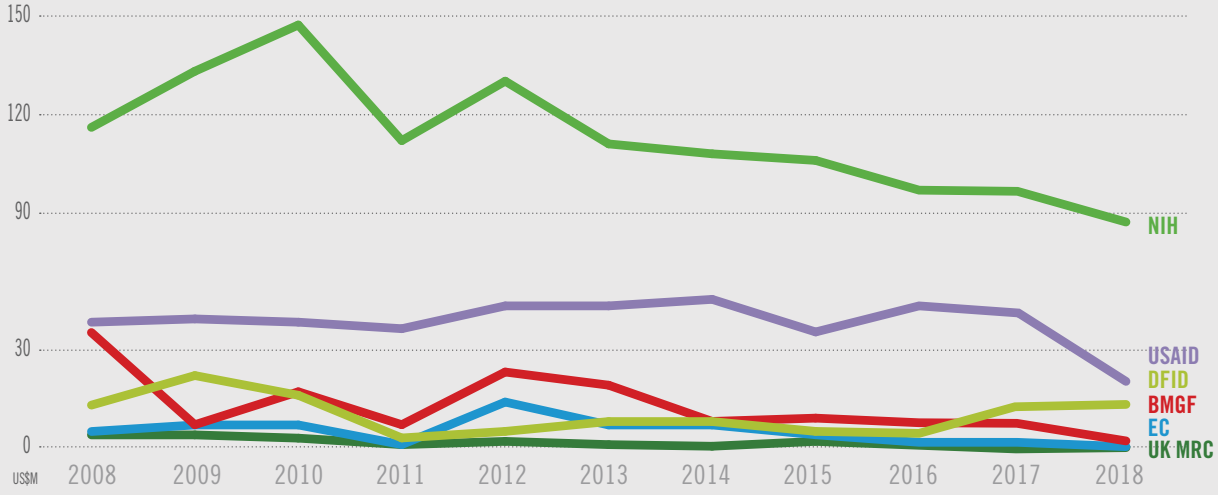
Investment from philanthropies decreased across the board, with the one exception of Sidaction (up 53 percent). The largest decline came from BMGF, with funding for microbicide R&D falling by 67 percent, from US$3.3 million to US$1.1 million. Investments totaling US$2.7 million were also made towards rectal microbicide research by the NIH, Wellcome Trust and Sidaction.

TABLE 5 **Annual Investment in Microbicide R&D by Sector, 2008-2018** (US$ millions)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
US	154	173	182	148	173	155	154	143	140	131	110
Europe	40	44	40	16	27	27	23	17	16	22	25
Other Countries	12	5.7	8.3	12	17	5	4.5	2.4	1.3	1.2	2.4
Multilaterals	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0	0
Total Public	207	223	230	176	217	187	182	162	157	154.7	137
Total Philanthropic	35	12	16	9	25	20	20	9.3	9	4.3	1.8
Total Commercial	2.5	1	1	1	3	3	3	6	0.4	0.2	0.8
Total Global Investment	**244**	**236**	**247**	**186**	**245**	**210**	**193**	**178**	**167**	**159**	**140**

FIGURE 22 **Top Microbicide Funder Trends, 2008-2018** (US$ millions)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
NIH	116	133	147	112	130	111	108	106	97	95	89
USAID*	38	39	38	36	43	43	45	35	43	34.9	20
BMGF	35	7	17	7	23	19	8	9	7.6	3.3	1.1
DFID	13	22	16	3	5	8	8	5.2	4.4	6.7	13.2
EC	5	7	7	1	14	7	7	4	1.7	0.12	0
UK MRC	4	4	3	1	2	1	0.5	1.2	0.8	0	0.3



* The USAID Microbicide Program funding covers topical microbicide products as well as systemic and sustained-release HIV pre-exposure prophylaxes.

TABLE 6 **Top Microbicide R&D Funders, 2012 - 2018** (US$ millions)

	2012		2013		2014		2015		2016		2017		2018	
Rank	Funder	Amount	Funder	Amount	Funder	Amount	Funder	Amount	Funder	Amount	Funder	Amount	Funder	Amount
1	NIH	129.9	NIH	111.2	NIH	107.8	NIH	106.3	NIH	97	NIH	95	NIH	89
2	USAID	43.2	USAID	42.8	USAID	45	USAID	45.2	USAID	43	USAID	34.9	USAID*	20
3	BMGF	22.9	BMGF	19.2	BMGF	7.6	BMGF	8.9	BMGF	7.6	Netherlands Ministry of Foreign Affairs	7.5	DFID	13.2
4	EC	13.6	DFID	8.4	DFID	7.4	DFID	5.2	Neth-erlands Ministry of Foreign Affairs	5	DFID	6.7	BMBF	6.9
5	CHVI[19]	9.2	EC	6.7	EC	5.7	EC	3.9	DFID	4.4	BMGF	3.3	Netherlands Ministry of Foreign Affairs	2.1
6	South Africa	7	Netherlands	3.6	Sweden	3.2	Sweden	2.9	EC	1.7	BMBF	3.2	IrishAid	1.5
7	DFID	4. 7	South Africa DST/DOH	2.3	Nether-lands	3	DANIDA	1.4	BMBF	1.4	CDC	1.6	CDC	1.3
8	UK MRC	2.2	Denmark	2.2	ICMR	2.3	UK MRC	1.2	Wellcome Trust	1.2	Irish Aid	1.6	Public Health Agency of Canada	1.2
9	Netherlands	1.7	EDCTP	2.2	Ireland	1.3	IrishAid	1.1	Swedish Research Council	1.2	Wellcome Trust	0.8	BMGF	1.1
10	Ireland	1.2	Norway	1.5	CDC	1.2	CDC	0.9	IrishAID	1.1	CIHR	0.8	CIHR	0.9
11	Norway	1	US CDC	1.5	NORAD	1	CIHR	0.8	UK MRC	0.8	DANIDA	0.8	DANIDA	0.7
12	OPEC	1	Ireland	1.3	DANIDA	0.8	NORAD	0.8	CIHR	0.7	SAMRC	0.2	Wellcome Trust	0.6
13	Denmark	0.9	UK MRC	0.8	CIHR	0.8	South Africa DST/ SAMRC	0.5	South Africa DST/ SAMRC	0.5	NHMRC	0.2	UK MRC	0.3
14	NHMRC	0.5	NHMRC	0.5	UK MRC	0.5	ANRS	0.2	CDC	0.4	MAPP Biophar-maceutical	0.2	Govern-ment of Flanders	0.2
15	Wellcome Trust	0.5	Wellcome Trust	0.3	South Africa DST/DOH	0.4	NHMRC	0.2	Osel Inc.	0.2	ANRS	0.2	EDCTP	0.1

* The USAID Microbicide Program funding covers topical microbicide products as well as systemic and sustained-release HIV pre-exposure prophylaxes.

2.1 Developments in the field of microbicide research

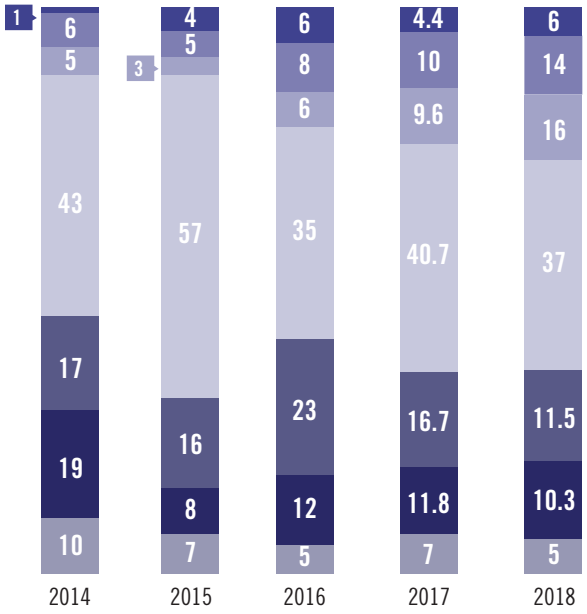
- While an opinion by the European Medicines Agency (EMA) on the dapivirine vaginal ring is expected in the latter half of 2019, the International Partnership for Microbicides (IPM) is moving forward with submissions to the US Food and Drug Administration (FDA) and the South African Health Products Regulatory Authority (SAHPRA). The intravaginal silicone ring is the first microbicide to be submitted for regulatory approval[10].
- A new Phase I study (MTN-038) launched in December 2018 is testing the pharmacokinetics and safety of a 90-day intravaginal ring containing tenofovir. The study is currently recruiting participants in three US trial sites and is designed to provide women with protection from both HIV and herpes simplex virus type 2 (HSV-2). MTN-038 is the first trial of its kind to recruit participants, and results are expected in the first quarter of 2020[11].

- The MTN-035 study, or DESIRE (Developing and Evaluating Short-acting Innovations for Rectal Use), began to enroll participants in April 2019 across sites in the US, Peru, Malawi, South Africa and Thailand. The study is the first to investigate the preferences of cis- and transgender men and transgender women regarding drug delivery methods to prevent HIV during receptive anal intercourse. The trial is employing three placebos in the form of a douche, a suppository and an insert for on-demand use. Results are expected in July 2020[12].

2.2 Funding allocations for microbicide R&D

Allocations for microbicide R&D in 2018 were as follows: basic mechanisms of mucosal transmission (six percent), preclinical research (14 percent), formulations and modes of delivery (16 percent), clinical trials (37 percent), behavioral and social science research (11.5 percent), research infrastructure (10 percent) and advocacy and policy (five percent) *(Figure 22)*. Investment in clinical trials decreased from 2017 levels but still made up the bulk of microbicide R&D at 40.7 percent. This is largely attributed to the topical microbicides, intravaginal rings (with active drugs tenofovir and tenofovir/levonorgestrel) and inserts that are currently in clinical testing. Investment in social and behavioral research also rose in 2018 (11.5 percent versus nine percent in 2017), and this may account for the improved acceptability and attitudes surrounding the dapivirine vaginal ring.

FIGURE 23 **Microbicide R&D Funding Allocations by Percentage, 2014-2018**



BOX 2

Results of the ECHO Study

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) study assessed the impact on women's HIV risk of three different contraceptive options, specifically, depot medroxyprogesterone acetate-intramuscular (DMPA-IM), or Depo-Provera, the copper intrauterine device and the levonorgestrel implant[13]. The results, released on June 13, 2019, are of major significance to women and girls—especially in East and Southern Africa—providers, policy makers, funders and advocates[12]. The ECHO study did not find any substantial difference in HIV risk among women using the aforementioned methods. All three contraceptive methods tested were safe, effective and acceptable. The majority of women stayed on the method that they were assigned to use and very few had unwanted pregnancies. High HIV incidence rates in all three arms of the trial highlight the importance of women-centered programs that offer a full range of contraceptive choices and HIV prevention strategies at the same site, and with an approach that is centered on women's informed choice.

Adapted from AVAC. *Understanding the Results of the ECHO Study.* June 2019[14].

Other HIV Prevention Options

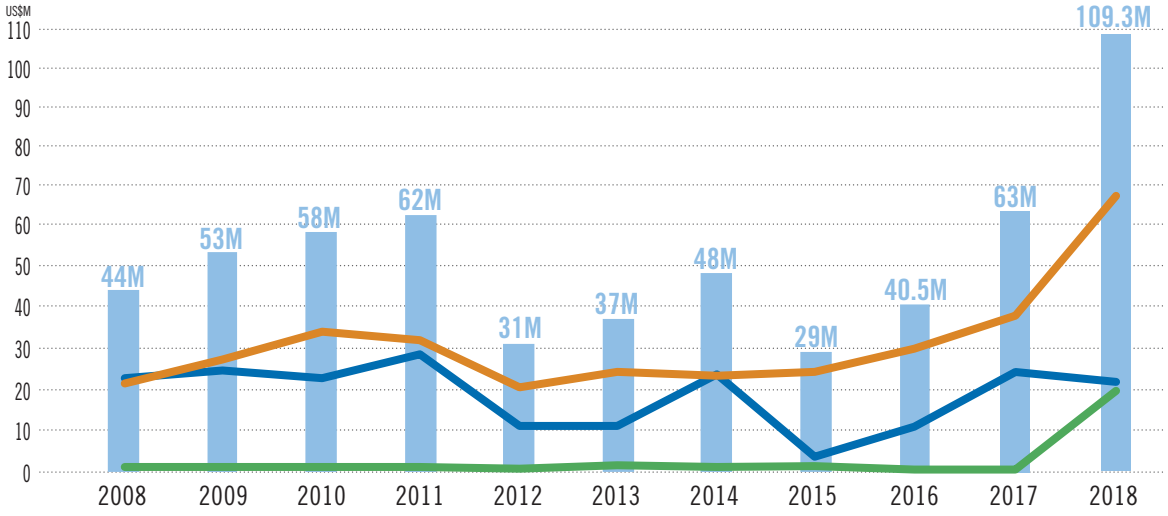
3.0 Global investment in R&D related to PrEP

In 2018, global investment in PrEP R&D amounted to US$109 million. This is a 73 percent increase from 2017 and the highest funding recorded in more than a decade *(Figure 23)*. The impetus behind this surge is the 75 percent increase in investment from the public sector, rising from US$38.6 million to US$67.5 million. The US NIH and USAID[e] were the two leading donors at US$36.6 million and US$23.8 million, respectively.

Commercial sector investment in PrEP totaled US$20.2 million; it must be noted, however, that a lack of reporting from the commercial sector explains the absence of investment in past years. Philanthropic investment decreased by 12 percent in 2018, a trend that is linked directly to the decline in BMGF funding from US$24 million to US$21 million.

FIGURE 24 **Investments in Pre-Exposure Prophylaxis by Sector, 2008-2018** (US$ millions)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Public	21	27	34	32	20	24	23	24	29.8	38.7	67.5
Philanthropic	23	25	23	29	11	11	24	3.2	10.7	24.4	21.6
Commercial	1.3	1.3	1.3	1.3	0.5	2	1.2	1.6	0	0	20.2
Total Funding	44	53	58	62	31	37	48	29	40.5	63	109.3



[e] The Working Group methodology defines systemic ARV prevention as PrEP, and accordingly, allocates microbicide funding in programs at USAID to PrEP notwithstanding their official designation as microbicide research funds by USAID.

3.1 Developments in the field of PrEP research

The global demand for oral PrEP is growing: Truvada and generic TDF/FTC have been approved for HIV prevention in 44 countries, while another nine have submitted applications for regulatory approval[15]. As PrEP rollout continues, the focus shifts towards improving uptake and adherence, as well as investigating alternative active drugs and delivery methods, e.g., long-acting injectables, implants etc. Relevant PrEP research that is currently underway includes:

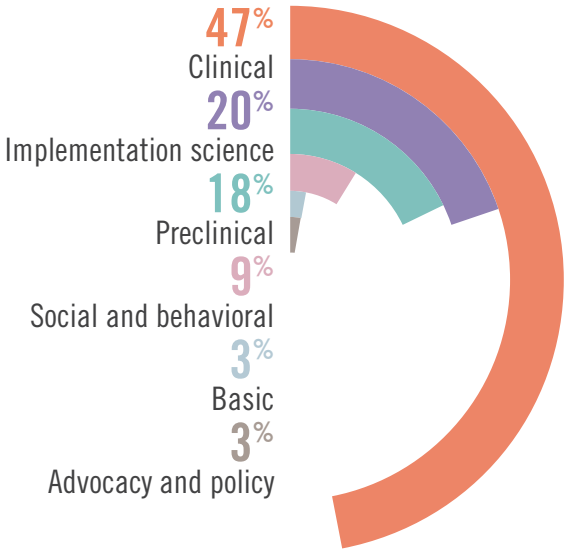
- Two Phase III trials investigating the safety and efficacy of the long-acting injectable drug cabotegravir as a PrEP agent are currently recruiting participants. HPTN 083 is ongoing in 4,500 HIV-negative cisgender men and transgender women who have sex with men (MSM and TGW) in the Americas, Asia and South Africa[16]. HPTN 084 is recruiting 3,200 women at high risk in sub-Saharan Africa[17].

- ImPrEP is a demonstration project sponsored by UNITAID and the Ministries of Peru, Mexico and Brazil for implementation across the three countries. Almost 7,500 high-risk MSM and transgender individuals will be enrolled and the impact of sociodemographic status on the uptake and adherence of oral PrEP will be assessed[18].
- NZ PrEP is sponsored by the New Zealand AIDS Foundation and other donors, and aims to assess the impact of providing PrEP at clinics in Auckland to individuals at high-risk of HIV (MSM, TGW and others). The demonstration project is also looking to assess any difference in risk behaviors while on PrEP and the sociodemographic factors impacting the acceptability and retention of PrEP[18].

3.2 Funding allocations for PrEP R&D

In 2018, PrEP R&D was allocated across the following six categories: basic (three percent), preclinical (18 percent), clinical (47 percent), implementation science (20 percent), behavioral and social science (nine percent) and advocacy and policy (three percent). Investments allocated for clinical research increased in 2018 and could be a result of the clinical studies investigating novel long-acting PrEP formulations and alternative active drugs for PrEP *(Figure 24)*.

FIGURE 25 **PrEP R&D Funding Allocations by Percentage in 2018**

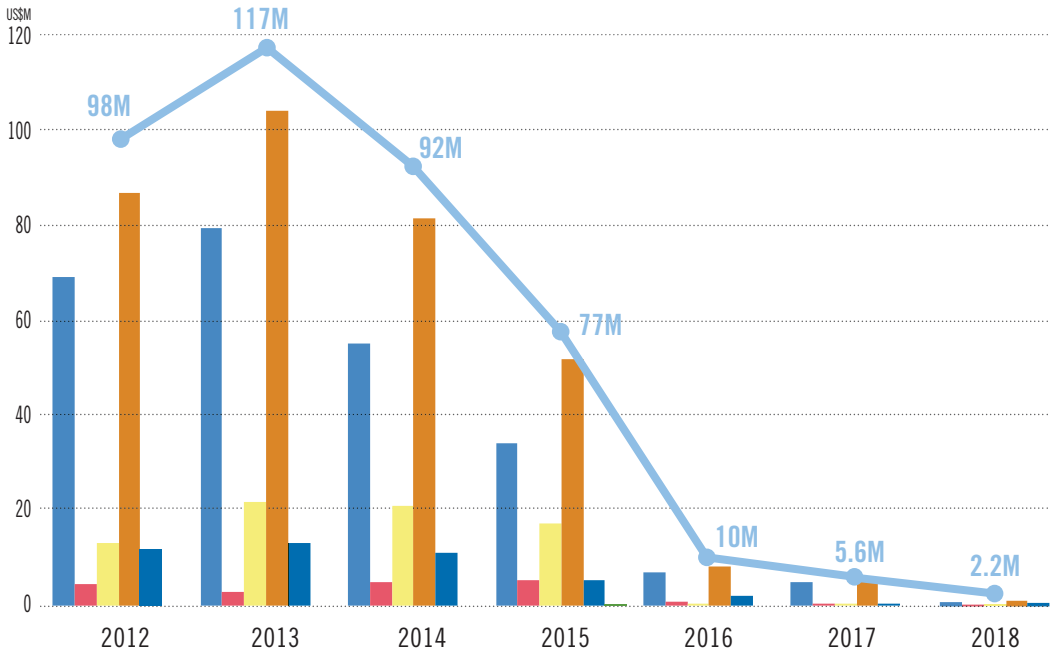


4.0 Global investment in R&D related to TasP

Following a 61 percent decrease from 2017 levels, funding for TasP totaled US$2.2 million in 2018. Philanthropic funding increased slightly but public sector investment decreased by 68 percent, from US$5.3 million in 2017 to US$1.7 million in 2018. This decrease is linked directly to the completion of the CDC-funded Botswana Combination Prevention project, which had been ongoing since 2013[19] (Figure 25). The efficacy of TasP as an HIV prevention strategy has been proven in multiple large-scale trials such as HPTN 052, PARTNER, Opposites Attract, and PARTNER 2[20]. This likely explains the sharp decline in R&D investment for TasP since 2015.

FIGURE 26 **Investment in Treatment as Prevention by Sector, 2012-2018** (US$ millions)

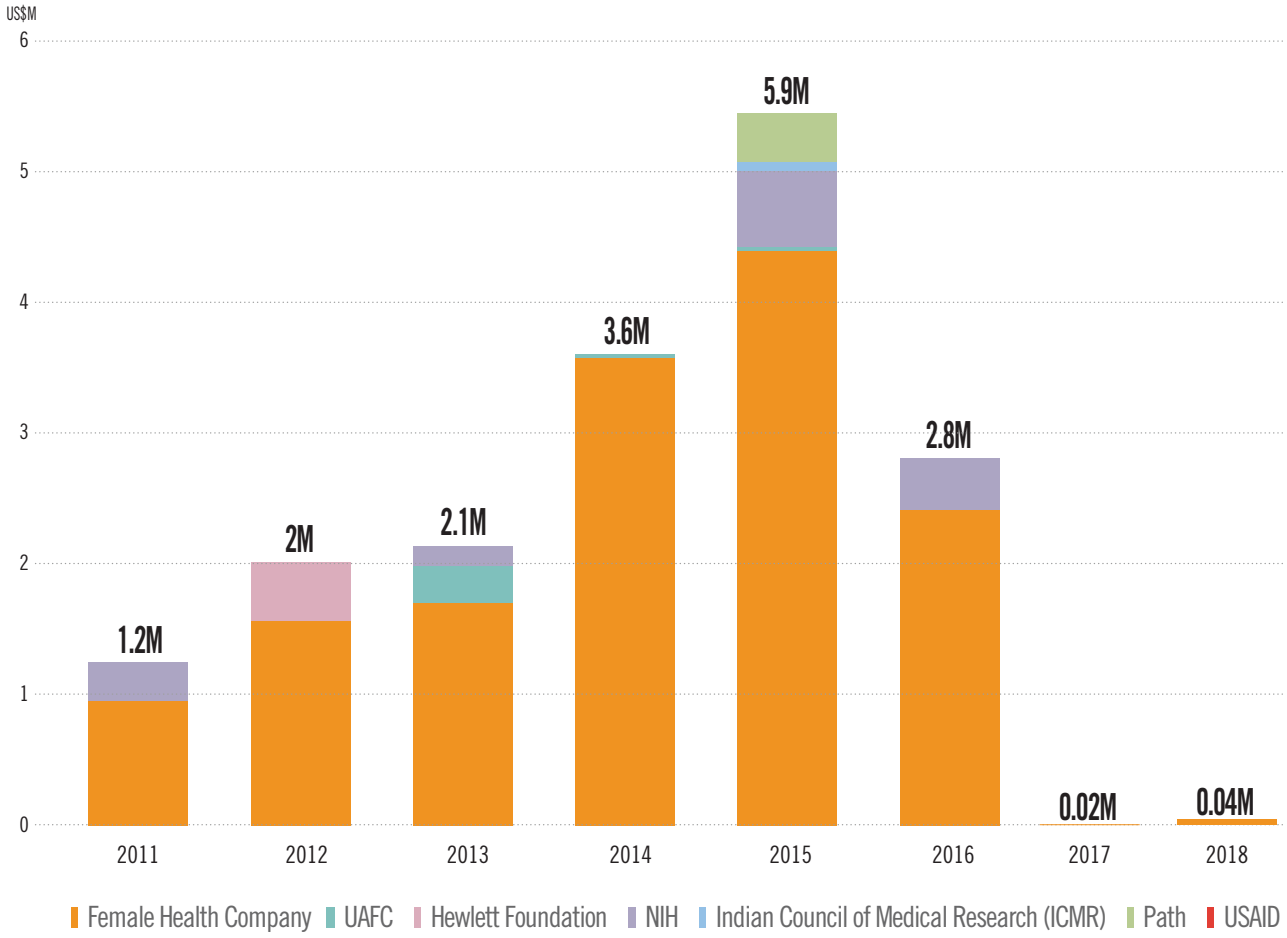
	2012	2013	2014	2015	2016	2017	2018
US	68.6	79	55	47	7	4.9	0.5
Europe	4.6	3	5	4.6	0.7	0.1	0.9
Other Countries	13	21.5	21	20	0.4	0.3	0.2
Total Public	86.2	103.5	81	71	8	5.3	1.7
Total Philanthropic	11.8	13.1	11	5.5	2	0.3	0.5
Total Commercial	–	–	–	<0.1	–	–	–
Total Global Investment	98	117	92	77	10	5.6	2.2



5.0 Global investment in female condom R&D

Investment in female condom research increased by 79 percent to US$0.004 million. Although an uptick from 2017, these levels are still a far cry from the millions invested between 2011 and 2016 *(Figure 26)*. The Female Health Company, traditionally the preeminent sponsor of female condom research, was the only donor internationally.

FIGURE 27 **Investments in the Female Condom, 2011-2018** (US$ millions)



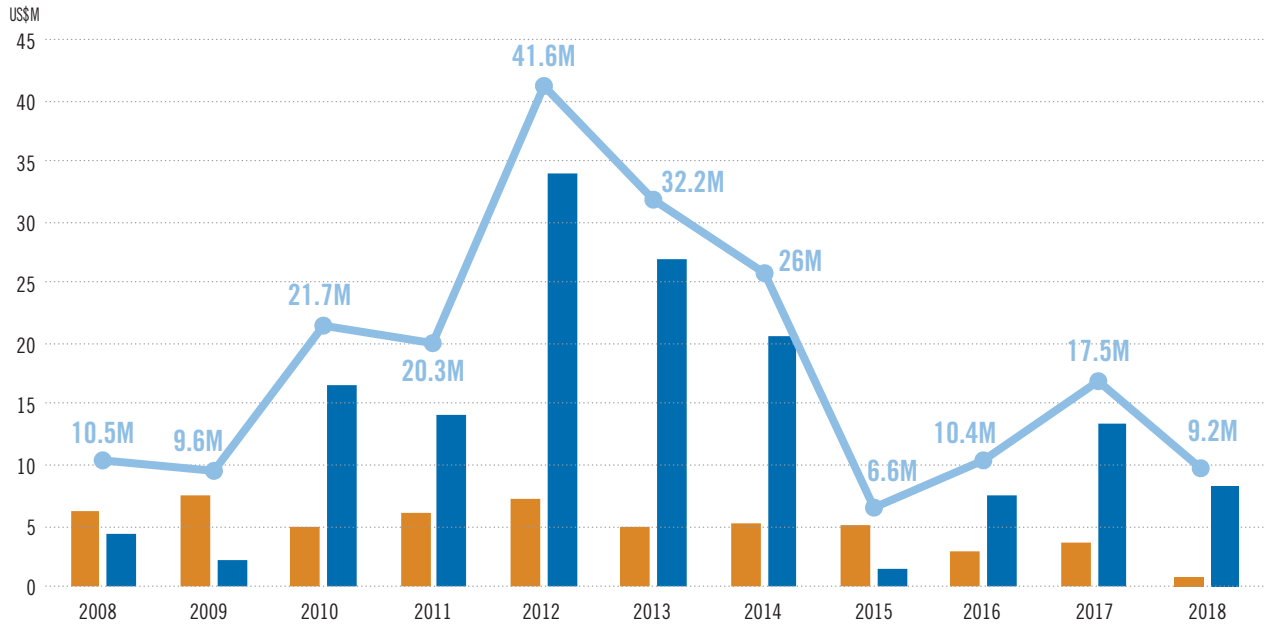
6.0 Global investment in the implementation of VMMC

The sharp 64 percent increase in VMMC observed last year reversed course in 2018. Overall funding decreased by 47 percent falling to US$9.2 million. This drop can be traced back to a 40 percent decline in investment from BMGF, the largest technology-specific donor. BMGF funding fell to US$8.3 million in 2018 but still constituted 90 percent of all investment. US public sector investment also declined from US$3.4 million to US$0.7 million, with the only contribution coming from the NIH.

Sufficient empirical studies have already affirmed the efficacy of VMMC as a prevention option, which is likely why 66 percent of the research is allocated to implementation science and the large-scale rollout of services in underserved populations. Other areas of focus include behavioral and social science research (19 percent), basic (2 percent) and advocacy and policy development (12 percent).

FIGURE 28 **Investment in Voluntary Medical Male Circumcision by Sector, 2008-2018** (US$ millions)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total Public	6.2	7.5	5	6.1	7.2	5	5.2	5.1	2.9	3.6	0.9
Total Philanthropic	4.3	2.1	16.7	14.2	34.4	27.2	20.8	1.4	7.5	13.9	8.3
Total Global Investment	10.5	9.6	21.7	20.3	41.6	32.2	26	6.6	10.4	17.5	9.2



7.0 Investments in research related to PMTCT

Funding for PMTCT increased by one percent, with levels rising from US$35.7 million to US$36 million in 2018 *(Table 7)*. The number of donors financing PMTCT research also increased from seven to 12 in 2018. Most PMTCT research (almost 97 percent) was funded by the public sector, with the US NIH remaining the largest donor, at US$31 million. European funding increased by 477%, which can be attributed largely to commitments from the EDCTP (US$2.1 million) and the European Commission (US$0.1 million). Philanthropic funding levels also rose to US$1.03 million, bolstered by funding from BMGF, Wellcome Trust and Aidsfonds.

TABLE 7 **Annual Investment in Prevention of Vertical Transmission by Sector, 2010-2018** (US$ millions)

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
US	44.6	56.9	36.2	34.6	42	44.9	39.1	37.7	34.3	31.3
Europe	5.9	1.5	1.1	1.7	0.1	1.2	2.1	0.9	0.5	2.9
Other Countries	–	1.3	5.1	6.7	0.2	–	0.8	–	0.3	0.4
Total Public	50.5	59.7	42.6	42.9	42.4	46.6	41.3	39	35.3	34.6
Total Philanthropic	0.9	0	0.5	0.8	1.7	2.5	2.3	1.7	0.4	1
Total Commercial	0	0	0	0	0	0.5	0.5	–	–	–
Total Global Investment	**51.4**	**59.7**	**43.1**	**43.7**	**44.1**	**49**	**44.1**	**41**	**35.7**	**35.7**

Endnotes

[1] For the purposes of this report, the terms "research and development, or "R&D" and "research" are used interchangeably and all refer to the entire spectrum of research activities.

[2] See Appendix for more information.

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Appendix: Methodology

This report was prepared by Fatima Riaz (AVAC), with contributions from Kevin Fisher (AVAC), Jennifer Maple (IAVI), UNAIDS staff and Mitchell Warren (AVAC) of the Resource Tracking for HIV Research and Development Working Group (herein referred to as "the Working Group"), with contributions from Emily Hayman. The Working Group developed and has utilized a systematic approach to data collection and collation since 2004. These methods were employed to generate the estimates of funding for R&D presented in this report. A detailed explanation of the methodology can be found on the Working Group website *(www.hivresourcetracking.org)*. Categories used to describe different R&D activities—one for AIDS vaccines and one for HIV microbicide—were derived from those developed by the US NIH and are shown in the following tables.

TABLE 8 Public, Philanthropic and Commercial Sector Primary Funders

Total responders: 65	
Sector	**Type of Responders**
Public	• National governments (including government research bodies, international development assistance agencies and other government funding agencies) • European Commission • Multilateral agencies
Philanthropic	• Private, not-for-profit organizations (e.g., foundations, trusts and non-governmental organizations) • Charities • Corporate donations
Commercial	• Pharmaceutical companies • Biotechnology companies

Data Collection Methods and Fluctuation in Investment Levels

HIV prevention R&D investment figures are collected annually by the Resource Tracking for HIV Prevention R&D Working Group through an email survey. For the present report, the Working Group reached out from February to June 2019 to 215 funders in the public, philanthropic and commercial sectors and collected information on investments that the Group then allocated to HIV prevention R&D.

Two different types of resource flows were tracked: investments, defined as annual disbursements by funders; and, when available, expenditures, defined as the level of resources directly spent on R&D activities by funding recipients in a particular year. The main reasons for differentiating between these two resource flows were: (1) some funders may forward fund (i.e., disburse funding in one year to be expended over multiple years); (2) research projects may be delayed and (3) entities such as the increasingly important product development public-private partnerships (PDPs) often receive funds in one year but expend them over a period of time or may hold funds to sustain multiyear contracts. Investment figures were based on estimates of the level of funds disbursed each year and generated from the perspective of the funder. As such, funds were allocated to the year in which they were disbursed by the donor, irrespective of whether the funds were expended by the recipient in that year or in future years.

In order to minimize double-counting, the Working Group distinguished between primary funders and intermediary organizations. "Intermediary" organizations receive resources from multiple funders and use these resources to fund their own work as well as the work of others. All identified primary funders were categorized as public, (such as government research bodies, international development agencies and multilaterals), philanthropic, (such as foundations, charities and corporate donors) or commercial, (pharmaceutical and biotechnology companies) sector funders.

While limitations exist in developing a method for breaking down funding allocations by type of activity or stage of product development, the Working Group allocates resources into categories based on NIH definitions. As the largest funder of HIV prevention R&D and thus, with the majority of grants toward HIV prevention research allocated based on NIH definitions, this allows for the most accurate possible analysis of the largest portion of grants. For grants received outside of NIH funding, the allocation of funding was based on the information provided by the intermediaries or funders. When this information was not available, the Working Group reviewed the descriptions of the projects funded and, based on the description of each project, allocated the funds across the expenditure categories.

All figures in the report are given in current US dollars and have not been adjusted for inflation. Funding information in other currencies was converted into US dollars using the appropriate International Monetary Fund (IMF) annual average exchange rate for July 1, 2018, except for those funds where we had access to the actual rate received.

Every effort was made to obtain a comprehensive set of data that was comparable across organizations and countries. However, the data presented in this report are subject to a number of limitations:

- Requests for information were directed to all public, philanthropic and commercial organizations identified as providing funding for HIV prevention R&D. However, not all entities contacted responded or provided financial information with their response. For the private sector, annual investments and funding estimates were extrapolated based on qualitative data collection on R&D programs and expert opinions.
- The Working Group provides R&D allocation definitions in the survey sent to funders. However, most funders and intermediary organizations do not break down their expenditures and investments by type of activity or stage of product development, and definitions often vary among funders.
- The Working Group attempted to reduce the potential for double-counting and to distinguish between funders and recipients of funding. However, all financial information is "self-reported" by organizations and not independently verified.

Data Collection Categories:

- Preventive AIDS vaccines
- Microbicides
- Multipurpose prevention technologies
- Pre-exposure prophylaxis (PrEP)
- Treatment as prevention
- Male circumcision
- Female condom
- Prevention of vertical transmission
- HIV cure
- Therapeutic AIDS vaccines

Preventive and therapeutic AIDS vaccine R&D	
Category	**Definition**
Basic research	Studies to increase scientific knowledge through research on protective immune responses and host defenses against HIV.
Preclinical research	Efforts to improve preventive AIDS vaccine design, development and animal testing.
Clinical research	Medical research involving human volunteers and encompassing clinical trials (Phases I, II, III and IV) as well as observational studies.
Cohort and site development	Support to identify trial sites, build capacity, ensure adequate performance of trials and address the prevention needs of the trial communities.
Advocacy and policy development	Education and mobilization of public and political support for preventive AIDS vaccines and the targeting of potential regulatory, financial, infrastructural or political barriers to their rapid development and use.

Microbicides R&D	
Category	**Definition**
Basic mechanisms of mucosal transmission	Elucidate basic mechanisms of HIV transmission at mucosal/epithelial surfaces.
Discovery, development and preclinical testing	Target R&D efforts at the discovery, development and pre-clinical evaluation of topical microbicides alone and or in combination.
Formulations and modes of delivery	Develop and assess acceptable formulations and modes of delivery for microbicides.
Clinical research	Medical research involving human volunteers and encompassing clinical trials (Phases I, II, III and IV) as well as observational studies.
Behavioral and social science research	Conduct applied behavioral and social science research to inform and optimize microbicide development, testing and acceptability and use.
Microbicide research infrastructure	Establish and maintain the appropriate infrastructure (including training) needed to conduct research.
Advocacy and policy development	Education and mobilization of public and political support for microbicides, and the targeting of potential regulatory, financial, infrastructural or political barriers to their rapid development.

Other prevention tools: male circumcision, treatment as prevention, treatment of herpes simplex virus type 2 (HSV-2), cervical barriers and pre-exposure prophylaxis (PrEP)	
Category	**Definition**
Basic research	Studies to increase scientific knowledge through research on protective immune responses and host defenses against HIV.
Preclinical research	Efforts to improve design, development and animal testing of experimental interventions.
Clinical trials	Support for Phase I, II and III trials (including the costs of candidate products).
Behavioral and social science research	Conduct applied behavioral and social science research to inform and optimize product development, acceptability and use.
Advocacy and policy development	Education and mobilization of public and political support for new HIV prevention tools and the targeting of potential regulatory, financial, infrastructural or political barriers to their rapid development and use.

Definitions	
Category	**Definition**
Treatment as prevention research	Research evaluating the impact of early/expanded ART (at any CD4 count), ART initiation strategies (e.g., Seek, Test, Treat and Retain) or ART adherence strategies on HIV incidence, HIV transmission risk, HIV risk behavior and/or community viral load; and impact of ART at CD4 count ≥ 350 cells/mm3 on HIV and/or TB-related morbidity and mortality or HIV transmission.
Multipurpose Prevention Technologies (MPTs)	Combine protection to prevent at least two sexual and reproductive health risks: unintended pregnancy and HIV and other sexually transmitted infections (STIs). Indications of interest include: • HIV • HSV • Pregnancy • Bacterial Vaginosis (BV) • Chlamydia • Gonorrhea • Hepatitis • HPV • Syphilis • Trichomoniasis • Urinary Tract Infections (UTI) • Other STIs
Cure research	Research conducted on viral latency, elimination of viral reservoirs, immune system and other biological approaches, as well as therapeutic strategies that may lead to either a functional (control of virus rather than elimination, without requirement for therapy) or sterilizing (permanent remission in absence of requirement for therapy) cure of HIV infection.

Toward a Cure Program Definition: US NIH eradication of viral reservoirs

Research conducted on viral latency, elimination of viral reservoirs, immune system and other biological approaches, as well as therapeutic strategies that may lead to either a functional (control of virus rather than elimination, without requirement for therapy) or sterilizing (permanent remission in absence of requirement for therapy) cure of HIV infection.

Pathogenesis studies

Basic research on viral reservoirs, viral latency and viral persistence, including studies on genetic factors associated with reactivation of the virus, and other barriers to HIV eradication.

Animal models

Identification and testing of various animal and cellular models to mimic the establishment and maintenance of viral reservoirs. These studies are critical for testing novel or unique strategies for HIV reactivation and eradication.

Drug development and preclinical testing

Programs to develop and preclinically test new and better antiretroviral compounds capable of entering viral reservoirs, including the central nervous system.

Clinical trials

Studies to evaluate lead compounds, drug regimens and immune-based strategies capable of a sustained response to HIV, including clinical studies of drugs and novel approaches capable of eradicating HIV-infected cells and tissues.

Therapeutic vaccines

Design and testing of vaccines thatwould be capable of suppressing viral replication and preventing disease progression.

Adherence/compliance

Development and testing of strategies to maintain adherence/compliance to treatment, in order to improve treatment outcomes and reduce the risk of developing HIV drug resistance.

Appendix: List of acronyms

amfAR	The Foundation for AIDS Research
ANRS	National Agency for Research on AIDS and Viral Hepatitis (France)
ARC	Australian Research Council
ART	Anti-retroviral therapy
ARV	Anti-retroviral
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
BMGF	Bill & Melinda Gates Foundation
BMS	Bristol-Meyers Squibb
bNAB	Broadly neutralizing antibody
BV	Bacterial vaginosis
CANFAR	Canadian Foundation for AIDS Research
CDC	US Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness
CHVI	Canadian HIV Vaccine Initiative
CIDA	Canadian International Development Agency
CIHR	Canadian Institutes of Health Research
COP	Country Operational Plan
CROI	Conference on Retroviruses and Opportunistic Infections
DAH	Development assistance for health
DANIDA	Danish International Development Agency
DBT	Department of Biotechnology at India's Ministry of Science and Technology
DFID	UK Department for International Development
DIB	Development Impact Bond
DOH	Department of Health
DREAMS	Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe women
DST	Department of Science and Technology, South Africa
EAVI2020	European AIDS Vaccine Initiative
EC	European Commission
ECHO	Evidence for Contraceptive Options and HIV Outcomes
EDCTP	European and Developing Countries Clinical Trials Partnership
EHVA	European HIV Vaccine Alliance
EIMC	Early infant male circumcision
FDA	US Food and Drug Administration
FRESH	Females Rising through Education, Support, and Health
FSW	Female sex workers
GIS	Geographic information systems
GSK	Glaxo SmithKline
HOPE	HIV Open-label Prevention extension trial
HPTN	HIV Prevention Trials Network
HPV	Human papillomavirus
HSV	Herpes simplex virus
HVTN	HIV Vaccine Trials Network
IAS	International AIDS Society
IAVI	International AIDS Vaccine Initiative
ICMR	Indian Council of Medical Research
IHME	Institute for Health Metrics and Evaluation
IMF	International Monetary Fund
IMPT	Initiative for Multipurpose Prevention Technologies
IPM	International Partnership for Microbicides
KP	Key population
LAI	Long-acting injectable
LMIC	Lower-middle-income country
MDG	Millennium Development Goal
MHRP	US Military HIV Research Program
MPT	Multipurpose prevention technology
MRC	UK Medical Research Council
MSM	Men who have sex with men
MTN	Microbicide Trials Network
NEMAPP	National Evaluation of Malawi's PMTCT programme
NHMRC	Australian National Health & Medical Research Council
NIAID	US National Institute of Allergy and Infectious Diseases
NIH	US National Institutes of Health
Norad	Norwegian Agency for Development Cooperation
OAR	US NIH Office of AIDS Research
ODA	Official Development Assistance
OECD	Organisation for Economic Co-operation and Development
OFID	OPEC Fund for International Development
OHTN	Ontario HIV Treatment Network
OPEC	Organization of the Petroleum Exporting Countries
P5	Pox-Protein Public-Private Partnership
PDP	Product development partnership
PEPFAR	US President's Emergency Plan for AIDS Relief
PHAC	Public Health Agency of Canada
PMTCT	Prevention of vertical transmission
POWER	Prevention Options for Women's Evaluation Research
PrEP	Pre-exposure prophylaxis
R&D	Research & development
SA DOH	South African Department of Health
SDG	Sustainable Development Goal
SIDA	Swedish Agency for International Cooperation Development
SIDACTION	Association de lutte contre le sida
SNSF	Swiss National Science Foundation
START	Strategic Timing of AntiRetroviral Treatment study
TasP	Treatment as prevention
TDF	Tenofovir
TDF/FTC	Tenofovir/Emtricitabine
TEMPRANO	A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa
TPP	Target Product Profiles
UAFC	Universal Access to Female Condoms Joint Programme
UK	United Kingdom
UMIC	Upper-middle-income country
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
USAID	US Agency for International Development
USD	United States dollar
UTI	Urinary tract infections
VMMC	Voluntary Medical Male Circumcision
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VRC	US Vaccine Research Center
WHO	World Health Organization

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Resource Tracking for HIV Prevention R&D Working Group

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International AIDS Vaccine Initiative (IAVI)
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Joint United Nations Programme on HIV/AIDS (UNAIDS)
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EXHIBIT 12

Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016

from the
Centers for Disease Control and Prevention,
U.S. Department of Health and Human Services

Update: Interim Statement Regarding Potential Fetal Harm from Exposure to Dolutegravir – Implications for HIV Post-exposure Prophylaxis (PEP). Please see attached file.

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This report describes use of certain drugs and tests for some indications that do not reflect labeling approved by the Food and Drug Administration at the time of publication. Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

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I. List of Tables and Figures

II. Abbreviations and Acronyms

3TC	lamivudine
Ab	antibody
Ag	antigen
Ag/Ab	antigen/antibody combination test
AIDS	acquired immunodeficiency syndrome
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
aOR	adjusted odds ratio
ATV	atazanavir
ATV/r	ritonavir-boosted atazanavir
CAI	condomless anal intercourse
CA-NSI	community-acquired needlestick injury
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
d4T	stavudine
DDI	didanosine
DNA	deoxyribonucleic acid
DRV	darunavir
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
DHHS	U.S. Department of Health and Human Services
ED	emergency department
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FTC	emtricitabine
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IDV	indinavir
IDV/r	ritonavir-boosted indinavir
IFA	indirect fluorescent antibody
LPV	lopinavir

LPV/r	ritonavir-boosted lopinavir
MSM	gay, bisexual, and other men who have sex with men
NAAT	nucleic acid amplification test
NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
nPEP	nonoccupational postexposure prophylaxis
oPEP	occupational postexposure prophylaxis
PCR	polymerase chain reaction
PI	protease inhibitor
PrEP	preexposure prophylaxis
PWID	persons who inject drugs
OR	odds ratio
PCR	polymerase chain reaction
PEP	postexposure prophylaxis
PrEP	preexposure prophylaxis
QALY	quality-adjusted life year
RAL	raltegravir
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir
SANE	Sexual Assault Nurse Examiner
SD	standard deviation
SIV	simian immunodeficiency virus
SHIV	simian human immunodeficiency virus
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
ZDV	zidovudine

III. Disclosure of Potential Competing Interest

nPEP Guidelines Consultants and Working Group Potential Competing Interest. The federal government employees who prepared this report have no competing interests with the manufacturers of the products discussed herein. See Appendixes 1A, 1B, and 1C for the definition of competing interests for persons involved in guidelines development and procedures for managing conflicts of interest, lists of names and affiliations of the nPEP guidelines development teams and consultants, and financial disclosures of potential competing interests.

IV. Summary

The purpose of these guidelines is to provide health care providers in the United States with updated guidelines to the 2005 U.S. Department of Health and Human Services nonoccupational postexposure prophylaxis (nPEP) recommendations[1] on the use of antiretroviral nPEP and other aspects of case management for persons with isolated exposure outside health care settings to blood, genital secretions, or other potentially infectious body fluids that might contain human immunodeficiency virus (HIV). The use of occupational PEP (oPEP) for case management for persons with possible HIV exposures occurring in health care settings are not addressed in this guideline; updated oPEP guidelines have been published separately.[2]

IV-A. What Is New in This Update

This update incorporates additional evidence regarding use of nonoccupational postexposure prophylaxis (nPEP) from animal studies, human observational studies, and consideration of new antiretroviral medications that were approved since the 2005 guidelines, some of which have improved tolerability. New features are inclusion of guidelines for the use of rapid antigen/antibody (Ag/Ab) combination HIV tests, for revised preferred and alternative 3-drug antiretroviral nPEP regimens, an updated schedule of laboratory evaluations of source and exposed persons, updated antimicrobial regimens for prophylaxis of sexually transmitted infections and hepatitis, and a suggested procedure for transitioning patients between nPEP and HIV preexposure prophylaxis (PrEP), as appropriate.

IV-B. Summary of Guidelines

- Health care providers should evaluate persons rapidly for nPEP when care is sought ≤72 hours after a potential nonoccupational exposure that presents a substantial risk for HIV acquisition.[a] [VI-A4] [VII-A2][b]
    - All persons considered for nPEP should have determination of their HIV infection status by HIV testing, preferably by using rapid combined Ag/Ab, or antibody blood tests. [VII-A1] [VII-B1]
    - If rapid HIV blood test results are unavailable, and nPEP is otherwise indicated, it should be initiated without delay and can be discontinued if the patient is later determined to have HIV infection already or the source is determined not to have HIV infection. [VII-A1]

[a] See Figure 1.

[b] Numbers in brackets refers readers to the section in these guidelines that provides the basis for the recommendation.

- nPEP is recommended when the source of the body fluids is known to be HIV-positive and the reported exposure presents a substantial risk for transmission. [VII-A]

- nPEP is not recommended when the reported exposure presents no substantial risk of HIV transmission. [VII-A]

- nPEP is not recommended when care is sought > 72 hours after potential exposure. [VI-A4] [VII-A] [VII-A2]

- A case-by-case determination about the nPEP is recommended when the HIV infection status of the source of the body fluids is unknown and the reported exposure presents a substantial risk for transmission if the source did have HIV infection. [VII-A]

- All persons offered nPEP should be prescribed a 28-day course of a 3-drug antiretroviral regimen.[a] [VII-B1] [VII-C]

    - The preferred regimen for otherwise healthy adults and adolescents
        - tenofovir disoproxil fumarate (tenofovir DF or TDF) (300 mg) with emtricitabine (200 mg) once daily ***plus***

          raltegravir (RAL) 400 mg twice daily or dolutegravir (DTG) 50 mg daily. [VI-A2ci] [VII-C]

    - Alternative regimen for otherwise healthy adults and adolescents is
        - tenofovir DF (300 mg) with emtricitabine (FTC) (200 mg) once daily ***plus***

          darunavir (DRV) (800 mg) and ritonavir[a] (RTV) (100 mg) once daily. [VII-C]

    - Regimens are also provided for children, persons with decreased renal function, and pregnant women (see Table 6). [VII-C]

    - Health care providers considering using antiretroviral regimens for nPEP other than those listed in these guidelines as preferred or alternative are encouraged to consult with other health care providers who have expertise in antiretroviral medication use for similar patients (e.g., children, pregnant women, or those with such comorbid conditions as impaired renal function). [VII-C] [VII-E2]

- All persons evaluated for possible nPEP should be provided any indicated prevention, treatment, or supportive care for other exposure-associated health risks and conditions (e.g., bacterial sexually transmitted infections, traumatic injuries, hepatitis B virus and hepatitis C virus infection, or pregnancy). [VII] [VII-B3] [VII-B4] [VII-B5] [VII-D]

- All persons who report behaviors or situations that place them at risk for frequently recurring HIV exposures (e.g., injection drug use, or sex without condoms) or who report receipt of ≥ 1 course of nPEP in the past year should be provided risk-reduction counseling and intervention services, including consideration of preexposure prophylaxis. [VII-E4] [VII-E5]

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[a] Ritonavir is used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration and prolong the half-life of darunavir and other protease inhibitors; it was not considered an additional drug when enumerating drugs in a regimen.

V. INTRODUCTION

The most effective methods for preventing human immunodeficiency virus (HIV) infection are those that protect against exposure. Antiretroviral therapy cannot replace behaviors that help avoid HIV exposure (e.g., sexual abstinence, sex only in a mutually monogamous relationship with an HIV-uninfected partner, consistent and correct condom use, abstinence from injection drug use, and consistent use of sterile equipment by those unable to cease injection drug use). Provision of antiretroviral medication after isolated sexual, injection drug use, or other nonoccupational HIV exposure, known as nonoccupational postexposure prophylaxis (nPEP), is less effective at preventing HIV infection than avoiding exposure.

In 2005, the U.S. Department of Health and Human Services (DHHS) released its first recommendations for nPEP use to reduce the risk for HIV infection after nonoccupational exposures to blood, genital secretions, and other body fluids that might contain HIV.[1] In 2012, updated guidelines on the use of occupational PEP (oPEP) for case management for persons with possible HIV exposures occurring in health care settings were published and are not addressed in this guideline.[2] Other organizations, including health departments, professional medical societies, and medical institutions, have developed guidelines, recommendations, and protocols for nPEP delivered to adults and children.[3-10]

This document updates the 2005 DHHS nPEP recommendations in response to new information regarding clinical experience for delivering nPEP, including using newer antiretroviral regimens and their side-effect profiles and cost-effectiveness of nPEP to prevent HIV infection for different exposure types. We describe in more detail the goals for the new guidelines, funding source of the guidelines, persons involved in guidelines development, definition of competing interest for persons involved in guidelines development and procedures for managing competing interest (Appendix 1A).

CDC scientists selected nPEP subject matter experts from the Food and Drug Administration (FDA), the National Institutes of Health (NIH), hospitals, clinics, health departments, and professional medical societies to participate as panelists to discuss recent developments in nPEP practice by CDC teleconferences in December 2011, and April 2012 (Appendix 1B). Any potential conflicts of interests reported by persons involved in developing the guidelines and the determination made for each of those potential conflicts are listed in Appendix 1C.

A working group of CDC HIV prevention scientists and other CDC scientists with expertise pertinent to the nPEP guidelines conducted nPEP-related systematic literature reviews. Appendix 2 summarizes the methods used to conduct that review, including databases queried, topics addressed, search terms, search dates, and any limitations placed on the searches (i.e., language, country, population, and study type). All studies identified through the literature search were reviewed and included in the body of evidence. Appendix 3 includes a summary of the key observational and case studies among humans that comprise the main body of evidence.

These nPEP guidelines are not applicable for occupational exposures to HIV; however, we attempted to standardize the selection of preferred drugs for nPEP and occupational postexposure prophylaxis (oPEP).[2] These guidelines also do not apply to continuous daily oral antiretroviral prophylaxis that is initiated before potential exposures to HIV as a means of reducing the risk for HIV infection among persons at high risk for its sexual acquisition (preexposure prophylaxis or PrEP[11]).

Among the limitations of these guidelines is that they are based on a historical case-control study related to occupational PEP among hospital workers, observational and case studies examining nPEP's effectiveness among humans, animal studies related to PEP's efficacy among primates, and expert opinion on clinical practice among humans related to nPEP. Because of concerns about the ethics and feasibility of conducting large-scale prospective randomized placebo-controlled nPEP clinical trials, no such studies have been

conducted. Additionally, although nPEP failures were rare in the observational studies we reviewed, those studies often have inadequate follow-up testing rates for HIV infection; therefore, nPEP failures might be underestimated. Because these guidelines represent an update of previous guidelines about a now established clinical practice, we elected not to use a formal grading scheme to indicate the strength of supporting evidence.

VI. Evidence Review

VI-A. Possible Effectiveness of nPEP

No randomized, placebo-controlled clinical trial of nPEP has been conducted. However, data relevant to nPEP guidelines are available from animal transmission models, perinatal clinical trials, observational studies of health care workers receiving prophylaxis after occupational exposures, and observational and case studies of nPEP use. Although the working group mainly systematically reviewed studies conducted after 2005 through July 2015, we also include findings from seminal studies published before 2005 that help define key aspects of nPEP guidelines. Newer data reviewed in this document continue to support the assertion that nPEP initiated soon after exposure and continued for 28 days with sufficient medication adherence can reduce the risk for acquiring HIV infection after nonoccupational exposures.

V1-A1. oPEP Studies

A case-control study demonstrating an 81% (95% confidence interval [CI] = 48%–94%) reduction in the odds of HIV transmission among health care workers with percutaneous exposure to HIV who received zidovudine (ZDV) prophylaxis was the first to describe the efficacy of oPEP.[12] Because of the ethical and operational challenges, no randomized controlled trials have been conducted to test the efficacy of nPEP directly. In the absence of a randomized controlled trial for nPEP, this case-control study reports the strongest evidence of benefit of antiretroviral prophylaxis initiated after HIV exposure among humans.

V1-A2. Observational and Case Studies of nPEP

The following is a synopsis of domestic and international observational studies and case reports that have been published since the 2005 U.S. nPEP guidelines were issued. In the majority of studies, failure of nPEP, defined as HIV seroconversion despite taking nPEP as recommended, was typically confirmed by a seronegative HIV enzyme-linked immunosorbent assay (ELISA) at baseline visit, followed by a positive ELISA and Western blot or indirect fluorescent antibody (IFA) during a follow-up visit.

VI-A2a. Men Who Have Sex with Men

Based on 1 case report[13] and 6 studies[14-19] reporting results exclusively or separately among men who have sex with men (MSM), 49 seroconversions were reported after nPEP use. The case report from Italy described an nPEP failure in an MSM despite self-reported 100% adherence to his 3-drug medication regimen consisting of ZDV, lamivudine (3TC), and indinavir (IDV) and denial of ongoing HIV risk transmission behaviors after completing nPEP; concomitant hepatitis C virus (HCV) seroconversion was also diagnosed.[13] In the 6 studies, 48 of 1,535 (31.3 seroconverions/1,000 persons) MSM participants became HIV infected despite nPEP use. At least 40 of the 48 seroconversions likely resulted from ongoing risk behavior after completing nPEP. Thirty-five of these 40 seroconversions occurred ≥ 180 days subsequent to nPEP initiation and are unlikely to constitute nPEP failures.[16,18] The remaining 8 seroconverters among 1,535 MSM participants (5.2 seroconverions/1,000 persons) may be classified as potential nPEP failures. This included 1 recipient with an indeterminate HIV test result and isolation of an M184 mutation resistant virus on the last day of his 28-day regimen despite initiating

nPEP ≤ 48 hours after exposure,[20] indicating that seroconversion was occurring during the 28-day period of nPEP administration. Another 4 patients seroconverted at 91 days, 133 days, 160 days, and 168 days after nPEP initiation, including 3 who reported completing the 28-day regimen; however, there was no description of the presence or lack of ongoing sexual risk behaviors after nPEP completion.[18] Among the remaining 3 men who seroconverted after taking nPEP, taking nPEP was not associated with any suggestion of change in seroconversion risk, although no information was reported regarding the nPEP regimen prescribed, adherence to nPEP, delay in nPEP initiation or timing of HIV-positive results.[15]

In a 2-year prospective study in Brazil, investigators provided 200 seronegative MSM at high risk with education regarding nPEP and a 4-day starter pack with instructions to initiate its use for a suspected eligible exposure.[16] A follow-up 24-day pack (to complete a 28-day course) was provided only for those men with eligible exposures. Sixty-eight of 200 MSM initiated nPEP. Adherence to nPEP medications was estimated on the basis of questions at the 28-day visit and remaining pill counts. The entire 28-day nPEP regimen was completed by 89% of men with eligible exposures including 1 participant who seroconverted. Ten of 11 seroconversions occurred among men who did not initiate nPEP.[16]

VI-A2b. Sexual Assault

VI-A2bi. General Population (all ages). Globally, 3 systematic reviews[20-22] and 1 prospective *cohort* study[23] spanning childhood through adulthood reported wide-ranging proportions of participants being eligible for nPEP (range, 6%–94%), being offered nPEP (range, 5%–94%), accepting nPEP (range, 4%–100%), or completing nPEP (range, 9%–65%). Among the 3 systematic reviews, none reported HIV screening results or the number of nPEP failures.[20-22]

VI-A2bii. Adults and Adolescents. Although nPEP use for sexual assault survivors has been widely encouraged both in the United States and elsewhere,[24-27] documented cases of HIV infection resulting from sexual assault of women or men rarely have been published.[25,28,29] Of 5 individual retrospective studies of nPEP limited to adult and/or adolescent sexual assault survivors that the working group reviewed, 3 reported no seroconversions at baseline or at follow-up among those sexual assault survivors who completed nPEP,[30-32] and 2 did not report any information about HIV screening results or the number of nPEP failures.[33,34]

VI-A2biii. Children and Adolescents. Studies of nPEP also have focused on children or adolescents evaluated for sexual assault. In a pooled analysis based on 10 studies of 8,336 children or adolescents evaluated for sexual assault or abuse, at least 1,362 were determined to be nPEP eligible. Twenty-four of the remaining 6,974 (3.4 seroconversions/1,000 persons) children or adolescents who were not eligible for nPEP were found to be HIV infected at baseline testing.[35-44] Among 672 children or adolescents reported to have been offered nPEP, 472 were known to have initiated nPEP, and 126 were reported to have completed a 28-day nPEP course. No new HIV infections were documented among these 472 (0.0 seroconversions/1,000 persons) children/adolescents in the pooled analysis who initiated nPEP. New HIV infections might have been underestimated as return rates for children or adolescents attending at least 1 follow-up visit during which an HIV test might have been conducted after initiating nPEP ranged from 10%[40] to 76%.[44]

VI-A2c. Mixed or Other Populations

VI-A2ci. Mixed populations. Eighteen studies, including 9 international studies[45-54] and 9 domestic studies[55-63] examined multiple routes of HIV risk exposure among adults, adolescents, and children with sexual and nonsexual exposures, including consensual sexual relations, sexual assault, injection drug use, and needlestick exposures.

Fifteen of the 19 studies reported both the number of participants who completed 28 days of nPEP and the number of participants who HIV seroconverted after initiating nPEP.[46-58,62,63] In these 15 studies, 2,209 participants completed 28 days of nPEP, of whom, at least 19 individuals HIV seroconverted,[45-48,52,54,56,62,63] but

only 1 seroconversion[47] (8.6/1,000) was attributed to nPEP failure. This seroconversion occurred 6 weeks after nPEP initiation in a sexually assaulted female who presented ≤ 4 hours after assault and completed nPEP.[47] She had a positive HIV RNA polymerase chain reaction (PCR) test but no confirmatory HIV ELISA test documented during the 5–6 week follow-up HIV testing period after initiating nPEP. Among the other 18 seroconversions that occurred during follow-up HIV testing among participants who completed 28 days of nPEP, 5 occurred ≥6 months after nPEP completion and were likely associated with ongoing sexual risk behavior after nPEP completion.[45,54] One seroconversion occurred after a participant reported poor adherence to nPEP, ongoing sexual risk behavior, and multiple nPEP courses after the initial course of nPEP, however, the timing of seroconversion was not clearly specified.[63] One seroconversion occurred in an MSM presenting with acute retroviral syndrome 3 weeks after condomless anal sex with an anonymous partner and no receipt of nPEP.[48] One seroconversion occurred in a woman during the 6-month follow-up period after completing nPEP and it was attributed to ongoing sharing of injection drug use equipment.[48] One seroconversion occurred in a patient who started nPEP > 72 hours after a high-risk exposure.[46] Additional seroconversions occurred at various time periods after initiation of nPEP without detailed information about ongoing sexual exposure or adherence to nPEP (2 and 5 months [n=2 participants][62]; 3 and 6 months [n=2 participants][52]; 5 months [n=1 participant][62]; and 12 months [n=1 participant]).[62] Among 3 participants who seroconverted while taking or shortly after taking ZDV-containing nPEP regimens, there was a lack of information about ongoing sexual exposure or detailed information about strict adherence to the full 28-day nPEP regimen.[56] However, only 33.8%–42.1% of all patients who were administered ZDV-containing nPEP regimens in this study completed their regimens as prescribed.[56]

In the remaining 4 of 19 studies, 2 studies did not report rates of HIVseroconversion[59,60] and 2 studies did not report rates of completion of the 28-day nPEP regimen,[45,61] including a study that reported 7 seroconversions that occurred at unspecified time periods during the 6 months after nPEP initiation among 649 users of nPEP.[61]Of all nPEP clients in this study, 18.5% had previously used nPEP between 1 and 5 times.[61]

In 3 domestic studies, participants who were administered tenofovir (TDF)-containing nPEP regimens were substantially more likely than historical control subjects in studies consisting of ZDV-containing regimens to complete their prophylaxis as prescribed and less likely to experience common side effects.[49,56,57,60] In two studies, the highest completion rates were observed for the TDF-3TC (87.5%) and TDF-emtricitabine (FTC) (72.7%) arms followed by the TDF-FTC-raltegravir (RAL) (57%) and ZDV-3TC-3rd drug arms (the 3rd drug was mainly a protease inhibitor [PI]) (38.8 %).[57] In addition to the 57% of patients who completed all 3 drugs of the TDF-FTC-RAL arm, 27% of patients took their TDF-FTC and first RAL dose daily, but sometimes missed the second dose of RAL.[57] In another study, the completion rates were highest in the TDF-FTC-ritonavir (RTV)-boosted lopinavir (LPV/r) arm (88.3%) compared with the TDF-3TC-RTV-boosted atazanavir (ATV/r) arm (79%), ZDV-3TC-LPV/r arm (77.5%), or ZDV-3TC-nelfinavir (NFV) arm (65.5%).[49] In the last domestic study, TDF-containing compared with ZDV-containing regimens were associated with significantly higher completion rates in the bivariate analysis (OR 2.80 [95% CI = 1.69–1.18]) but not in the multivariate analysis (OR 1.96 [95% CI = 0.73–5.28]).[60]

VI-A2cii. Other Populations. Data for 438 persons with unintentional nonoccupational needlestick or other sharps exposures described in 7 published reports were reviewed, including data for 417 children and 21 adults.[64-70] Childhood and adolescent exposures were characterized as community-acquired exposures occurring in public outdoor places (e.g., playgrounds, parks, or beaches) or by reaching into needle disposal boxes at home or in a hospital. Adult exposures were often similar to occupational exposures occurring while handling needles or disposing of needles in a sharps container. In all cases, the HIV status of the source person was unknown except in 1 report[64] involving multiple percutaneous exposures with lancets among 21 children while playing with discarded needles in a playground. Some of the lancets had been used multiple times to stick different children. One of the children stuck with a lancet was known to be HIV infected before the incident, not receiving antiretroviral therapy, and documented to have an HIV-1 plasma viral load of 5,250,000 copies/mL; the other 20 children were considered potentially exposed to HIV.[64] Additionally, in 1 of the studies, 2 children

were hepatitis B surface antigen (HBsAg)-positive at baseline before starting prophylaxis.[66] Among 155 children offered nPEP, 149 accepted and initiated nPEP, and 93 completed their 28-day nPEP course.[64-70] Antiretroviral prophylaxis with either ZDV and 3TC or ZDV, 3TC plus a PI (IDV, NFV, LPV/r) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (nevirapine [NVP]) was used for those 149 children or adults accepting and initiating nPEP. No seroconversions for HIV, hepatitis B virus (HBV), or HCV were reported among those receiving or not receiving nPEP.[64-70]

In the case report of a 12-year old girl in Saudi Arabia with sickle-cell disease who was inadvertently transfused with a large volume of packed red blood cells, the use of a 13-week, 4-drug nPEP regimen of TDF, FTC, ritonavir-boosted darunavir (DRV/r) (later changed to LPV) and RAL resulted in loss of presence of detectable HIV-1 antibodies.[71] No HIV-1 DNA or plasma HIV-1 RNA was detected by PCR testing during the 8-month follow-up period.

VI-A3. Postnatal Prophylaxis of Infants Born to HIV-infected Mothers

Data regarding the efficacy of infant PEP to prevent mother-to-child HIV transmission provides only limited, indirect information about the efficacy of antiretroviral medications for nPEP. Postpartum antiretroviral prophylaxis is designed to prevent infection after contact of mucosal surfaces (ocular, oral, rectal, or urethral) or broken skin in the infant with maternal blood or other fluids that are present at time of labor and delivery, especially during vaginal births. Trials in which the infant was provided postpartum prophylaxis but the mother received neither prepartum or intrapartum antiretroviral prophylaxis provide the most relevant indirect data regarding nPEP after exposure to a source who did not have suppressed viral load secondary to antiretroviral therapy. Although a combination of prophylaxis during the prenatal, intrapartum, and postpartum periods offers the most effective reduction of perinatal transmission, postpartum prophylaxis alone also offers reduction.[72-75]

A randomized open-label clinical trial of antiretrovirals provided to infants born to breastfeeding HIV-infected women demonstrated an overall reduction in postnatal HIV infection at 14 weeks (the end of the period of prophylaxis) by approximately 70% (95% CI unreported). The trial compared a control group receiving a short-arm postnatal prophylaxis regimen and 2 comparison groups, each receiving different extended-arm postnatal prophylaxis regimens.[76] The control group received the short-arm regimen consisting of single-dose NVP plus 1-week ZDV and the 2 comparison groups received the control regimen and either 1) extended daily NVP for 14 weeks or 2) extended daily NVP and ZDV for 14 weeks. The corresponding HIV infection rates at 14 weeks were 8.5% in the control group, and 2.6% and 2.5% in the 2 extended arms comparison groups, respectively.

An observational study documented a potential effect of ZDV prophylaxis initially started postnatally compared with the prepartum and intrapartum periods. A review of 939 medical records of HIV-exposed infants in New York State indicated that the later the prophylaxis was started after the prepartum period, the higher the likelihood of perinatal transmission and that a benefit existed to postnatal prophylaxis alone (without maternal intrapartum or prepartum medication). Perinatal prophylaxis started during the prepartum, intrapartum, early postpartum (≤48 hours after birth), and late postpartum (3 days–42 days) periods resulted in corresponding transmission rates of 6.1%, 10.0%, 9.3%, and 18.4%, respectively.[77] A perinatal transmission rate of 31.6% was observed when no perinatal prophylaxis was provided; the study included data from patients who had pregnancies early in the epidemic when HIV perinatal prophylaxis was first being implemented, and it was uncertain whether using intrapartum and/or postnatal prophylaxis alone was beneficial among mothers without prenatal care.

VI-A4. Animal Studies

Macaque models have been used to assess potential PEP efficacy. These studies examined artificial exposures to simian immunodeficiency virus (SIV) which varied by modes of exposure, virus innocula, and drug

regimens. The parameters imposed by those animal studies might not reflect human viral exposures and drug exposures, and those differences should be considered when interpreting their findings. Nevertheless, macaque models have provided important proof-of-concept data regarding PEP efficacy. More recent animal studies have tested the effectiveness of newer antiretrovirals and alternate routes of PEP administration. Subcutaneous tenofovir was reported to block SIV infection after intravenous challenge among long-tailed macaques if initiated ≤ 24 hours after exposure and continued for 28 days.[78] All 10 macaques initiated on PEP at 4 or 24 hours post inoculation were documented to be SIV-uninfected at 36–56 weeks post inoculation compared with all 10 macaques that failed to receive any prophylaxis and became SIV infected within 20–36 weeks post-inoculation. In a study of 24 macaques, TDF was less effective if initiated 48 or 72 hours post-exposure or if continued for only 3 or 10 days.[79] In contrast, all 11 macaques became SIV infected in a study involving 3 control macaques receiving no prophylaxis and 8 macaques receiving a combination of ZDV, 3TC, and IDV administered orally through nasogastric catheter after intravenous virus inoculation at 4 or 72 hours post-SIV inoculation.[80] High virus innocula and drug exposures that are lower than those achieved among humans as a result of inadequate interspecies adjustment of drug dosing might have contributed to the lack of protection reported for that study. However, a macaque study designed to model nPEP for vaginal HIV exposure demonstrated that a combination of ZDV, 3TC and a high dose of IDV protected 4 of 6 animals from vaginal SIV infection when initiated ≤ 4 hours after vaginal exposure and continued for 28 days, whereas 6 of 6 animals in the control group receiving a placebo became SIV infected.[81] In another study, after 20 vaginal simian/human immunodeficiency virus infection (SHIV) challenges and a 10-week follow-up period, 5 of 6 macaques were protected when treated with topically applied gel containing 1% RAL 3 hours after each virus exposure compared with none of four macaques treated with placebo gel.[82] Likewise, macaques administered subcutaneous TDF for 28 days, beginning 12 hours (4 animals) or 36 hours (4 animals) after vaginal HIV-2 exposure, were protected from infection. Three of 4 animals treated 72 hours after exposure were also protected.[83] Three of 4 untreated animals in the control group became infected with HIV-2. Overall, data from these macaque studies demonstrate that PEP might be effective among humans if initiated ≤ 72 hours and continued daily for 28 days. In a systematic review and meta-analysis of 25 nonhuman primate studies, including rhesus macaques in10 studies and cynomolgus monkeys in 5 studies, use of PEP was associated with an 89% lower risk of seroconversion compared with nonhuman primates who did not use PEP. Also, use of tenofovir compared with other drugs was associated with lower seroconversion.[84]

VI-B. Possible Risks Associated with nPEP

Concerns regarding potential risks associated with nPEP as a clinical HIV prevention intervention include the occurrence of serious adverse effects from the short-term use of antiretroviral medications by otherwise healthy persons without HIV infection, and potential selection for drug-resistant strains of virus among those who become HIV infected despite nPEP use (particularly if medication adherence is inconsistent during the 28-day course or if the source transmits resistant virus). An additional concern is that persons engaging in consensual sex or nonsterile injection drug use may rely solely on PEP instead of adopting more long-term risk-reduction behaviors such as safer sexual and drug-injecting behaviors.

VI-B1. Antiretroviral Side Effects and Toxicity

In a meta-analysis[20] of 24 nPEP-related studies, including 23 cohort studies and 1 randomized clinical trial (behavioral intervention to improve nPEP adherence), of 2,166 sexually assaulted persons, clinicians prescribed 2-drug regimens,[36,38,40,42,85-88] 3-drug regimens,[23,31,58,89-92] 2- and 3-drug regimens,[30,32,50,93,94] or an unknown number of drugs.[46,95-97] ZDV was a part of all the regimens and all 2-drug regimens contained ZDV and 3TC, except 1 study in which ZDV and zalcitabine were prescribed.[88] Antiretrovirals provided as a part of 3-drug regimens included ZDV, 3TC, NFV, IDV, LPV/r, NVP, efavirenz (EFV), or co-formulated FTC/TDF with co-formulated LPV/r. Nausea, vomiting, diarrhea, and fatigue were the most commonly reported side effects.[20]

Serious side effects have been reported occasionally (e.g., nephrolithiasis and hepatitis) in the literature.[98-100] Rarely, severe hepatotoxicity has been observed among patients administered NVP-containing regimens for both oPEP and nPEP, including a female health care worker who required a liver transplantation after taking oPEP[101]; therefore, CDC advises against use of NVP forPEP.[1,99] Also, since January 2001, product labeling for NVP states that using it as part of a PEP regimen is contraindicated.[102]

A retrospective study in western Kenya involved 296 patients who were eligible for and initiated nPEP, including 104 who completed a 28-day course of nPEP; patients received either stavudine (d4T), 3TC and NVP or ZDV, 3TC, and LPV/r.[47] Neither the proportion of patients reporting side effects (14% [LPV-containing arm] and 21% [NVP-containing arm]) nor antiretroviral therapy completion rates differed substantially between the 2 arms. The most commonly reported side effects included epigastric pain, skin rash, and nausea among patients receiving NVP-containing regimens and diarrhea, dizziness, and epigastric pain among those receiving LPV/r-containing regimens. However, 1 hepatitis-related death of a sexual assault survivor taking a NVP-containing regimen prompted investigators to change to a new PEP regimen containing ZDV, 3TC, and LPV/r. Inclusion of NVP and d4T were initially included in nPEP regimens because of availability and cost but were discontinued in 2005 as a result of adverse events and toxicities among healthy patients. This change was also influenced by a black box warning in the drug labeling for NVP describing increased toxicity among patients on NVP with higher CD4 T lymphocyte (CD4) cell counts.

Commonly used medications in the observational studies of nPEP published after 2005 included ZDV, 3TC, LPV/r, TDF, FTC, and RAL. The majority of regimens involved using 3 drugs (range, 2–4 drugs) with a daily 2-pill burden (range, 1–3 pills). The side-effect profile that included fatigue, nausea, headache, diarrhea, and other gastrointestinal complaints was similar across studies of MSM having mainly consensual sex and studies of sexual assault survivors, including mainly women, children, and a limited proportion of men.[20,23,31,44,55-57,103]

Two trials, including a total of 602 participants, compared TDF- versus ZDV-containing nPEP regimens; both reported better medication tolerability among participants taking TDF-containing regimens.[49,56] Another study reported fewer side effects among 100 adult participants prescribed a 3-drug nPEP regimen that included RAL, TDF, and TDF compared to historical controls using a 3-drug PEP regimen including ZDV, 3TC, and a RTV-boosted PI.[57]

In an open-label, nonrandomized, prospective cohort study comparing RAL-FTC-TDF in 86 MSM and FTC-TDF in 34 MSM, 92% and 91% of participants completed 28 days of treatment, respectively, with mean adherences of 89% and 90%, respectively.[17] Use of RAL rather than a PI was associated with the avoidance of 8 prescribed drug, and 37 potential illicit drug, interactions. However, in the RAL arm, 8 recipients (9%) developed mild myalgias, and 4 recipients developed grade 4 elevations in creatinine kinase. Both the myalgias and creatinine kinase elevations improved to grade 2 or less by week 4 without RAL discontinuation.

Among 100 MSM in an open-label, single-arm study at 2 public health clinics and 2 hospital EDs in urban areas in Australia, a once daily 28-day nPEP single-pill combination regimen of FTC-rilpivirine (RPV)-TDF was well tolerated with 98.5% adherence by self-report and 92% completion of the 28-day regimen.[19] However, within 1 week of completing nPEP, 1 patient developed acute abdominal pain, vomiting, and grade 4 laboratory evidence of acute pancreatitis (lipase 872 IU/L). The pancreatitis resolved ≤ 21 days without need for hospitalization.[19]

In a 2-arm open label randomized multicenter clinical trial in EDs in 6 urban hospitals in Barcelona, Spain, comparing ZDV/3TC + LPV/r with ZDV/3TC + atazanavir (ATV), 64% of nPEP recipients in both arms completed the 28-day course and 92% of patients reported taking > 90% of scheduled doses (without difference between arms).[53] Adverse events were reported in 46% of patients overall (49%, LPV/r arm; 43%, ATV arm). Gastrointestinal problems were more common in the LPV/r arm.

A pooled series of case reports revealed that 142 (67%; range, 0%–99%) of 213 children and adolescents who initiated nPEP and who had ≥1 follow-up visit, reported adverse effects and 139 of 465 (30%; range, 0%–64.7%) children and adolescents who initiated nPEP, completed their course of nPEP.[32,35-44] Most commonly reported nPEP regimens included ZDV + 3TC or ZDV + 3TC + (NFV or IDV or LPV/r). Most common adverse events among the 213 participants included nausea (n = 83; 39%), fatigue (n = 58; 27%), vomiting (n = 38; 18%), headache (n = 26; 12%), diarrhea (n = 25; 12%), and abdominal pain (n = 15; 7%).

V1-B2. Selection of Resistant Virus

In instances where nPEP fails to prevent infection, selection of resistant virus by the antiretroviral drugs is theoretically possible. However, because of the paucity of resistance testing in documented nPEP failures, the likelihood of resistance occurring is unknown.

A case report from Brazil documented a 3TC-resistance mutation on day 28 of therapy in a man treated with ZDV and 3TC who subsequently underwent HIV seroconversion.[16] Although the patient was noted to have taken nPEP, detailed information regarding adherence was unreported. Because the source-person could not be tested, whether the mutation was present at the time of transmission or whether it emerged during nPEP use is unknown.

Rationale for the concern regarding acquiring resistant virus from the exposure that leads to nPEP prescription includes data from an international meta-analysis of 287 published studies of transmitted HIV-1 drug resistance among 50,870 individuals during March 1, 2000–December 31, 2013, including 27 studies and 9,283 individuals from North America.[104] The study-level estimate of transmitted drug resistance in North America was 11.5% (resistance to any antiretroviral drug class), 5.8% (resistance to NRTIs), 4.5% (resistance to NNRTIs, and 3.0% (resistance to PIs).

VI-B3. Effects of nPEP on Risk Behaviors

The majority of studies examining the association between use and availability of nPEP and sexual risk behaviors during or after its use have been conducted in developed countries, primarily among MSM; no studies related to risk compensation were conducted among persons with injection-related risk factors.[14,16,105-111] The majority of these studies did not report increases in high-risk sexual behaviors after receipt of nPEP[14,16,106,110,111] and participants sometimes reported a decrease in sexual risk-taking behavior.[16,106] However, in 3 studies, nPEP users were more likely than persons who did not use nPEP to report having multiple partners and engaging in condomless receptive or insertive anal sex with HIV-infected partners or partners with unknown serostatus after completing nPEP.[14,108,110] In 2 of these studies, nPEP users were also more likely to subsequently become HIV infected than patients who did not use nPEP.[108,110] During 2000–2009 in the Amsterdam Cohort Study, MSM who were prescribed nPEP, compared with a reference cohort of MSM, had an incidence of HIV infection approximately 4 times as high (6.4 versus 1.6/100 person-years).[108] During 2001–2007, MSM in a community cohort study in Sydney, Australia reported continued, but not increased, high-risk sexual behaviors among nPEP users; more specifically, no change in sexual behavior was reported at 6 months after 154 incident nPEP uses and after ≥18 months for 89 incident nPEP uses. Among those MSM who received nPEP, the hazard ratio of subsequent HIV infection was 2.67 (95% CI = 1.40, 5.08).[110] The authors did not attribute this elevated risk for HIV seroconversion among users of nPEP to nPEP failure but rather to a documented higher prevalence of condomless anal intercourse (CAI) with HIV-infected partners among users of nPEP, compared with persons who did not use nPEP. In summary, users of nPEP, compared with participants who did not use nPEP had a continued higher prevalence of ongoing CAI with HIV-infected persons resulting in a greater likelihood of HIV seroconversion during all periods, especially after completing nPEP. In another study, repeated courses of nPEP were unassociated with risk for subsequent HIV infection.[45] In a study of 99 patients who attended a clinic in Toronto to be evaluated for nPEP during January 1, 2013–September 30, 2014, 31 (31%) met CDC criteria for

PrEP initiation.[112] PrEP candidacy in this study was associated with sexual exposure to HIV, prior nPEP use, and lack of drug insurance. Those studies[14,108,110,112] demonstrate that certain nPEP users with ongoing high-risk sexual behaviors might need additional behavioral and biomedical prevention interventions, including PrEP, instead of nPEP.[11,113]

One U.S.-based study among 89 MSM that examined risk behavior during the 28-day course of nPEP reported that among participants, 21% reported having insertive or receptive CAI, and 43% reported engaging with ≥ 1 partner known to be HIV-positive or of unknown serostatus (i.e., a high-risk partner).[105] Ninety-four percent of participants reporting having high-risk partners also reported having insertive or receptive anal intercourse. Of participants with high-risk partners and who practiced insertive or receptive anal intercourse, 26% reported CAI with their high-risk partner while receiving nPEP. The strongest predictor of CAI during nPEP in that study was HIV engagement, defined as receiving services from an HIV-related organization, donating money to or volunteering for an HIV-related cause, or reading HIV-related magazines and online sites. A nearly 5-fold chance of reporting condomless sex with a high-risk partner during nPEP was associated with each standard deviation increase in HIV engagement (OR 4.7 [95% CI = 1.3–17.04]). Investigators hypothesized that persons who are more involved with HIV-related services or organizations might be more informed about the effectiveness of nPEP and more likely to perceive themselves to be at less risk for HIV transmission while receiving nPEP and therefore more likely to have CAI.[105]

Awareness of nPEP availability, defined as general knowledge of availability of nPEP as a tool for preventing HIV infection after a potential HIV exposure[107] or nPEP use more than once in 5 years,[103] was associated with condomless sex among MSM.[103,107] Additionally, a longitudinal study of MSM in the Netherlands reported no associations existed between any nPEP-related beliefs (e.g., perceiving less HIV or acquired immunodeficiency syndrome (AIDS) threat, given the availability of nPEP, or perceiving high effectiveness of nPEP in preventing HIV) and the incidence of sexually transmitted infections (STIs) or new HIV infection.[109]

VI-C. Antiretroviral Use During Pregnancy

No trials have been conducted to evaluate use or the maternal or fetal health effects of short-term (i.e., 28-day) antiretroviral use as nPEP among pregnant women without HIV infection. However, clinical trials have been conducted and extensive observational data exist regarding use of specific antiretrovirals during pregnancy among HIV-infected women both when initiated as treatment for health benefits to the women and when initiated to reduce mother-to-child HIV transmission. Although duration of antiretroviral use during pregnancy has varied in these trials, it often spans months of pregnancy. Only ZDV is specifically approved for use in pregnancy, but as a result of data from clinical trials, other antiretroviral drugs have been reported to have short-term safety for pregnant women and their fetuses, and therefore can be considered for nPEP in women who are or who might become pregnant. See *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States* for information regarding use of specific antiretrovirals during pregnancy.[114] Additionally, results from ongoing surveillance of major teratogenic effects related to antiretroviral use during pregnancy are described in the Antiretroviral Pregnancy Registry International Interim Report every 6 months.[115]

Certain antiretrovirals have been associated with severe side effects, toxicity, potential for teratogenicity, or other untoward effects among pregnant and non-pregnant women with HIV infection[114] and therefore are not recommended for nPEP use (see section VII-F2b. Pregnant Women and Women of Childbearing Potential for a list of antiretroviral medications that should not be used for nPEP in pregnant women). These include EFV, NVP, and d4T plus didanosine (DDI).[114] Using IDV without RTV-boosting demonstrated altered drug metabolism during pregnancy.[116,117] No severe side effects, toxicity, or adverse pregnancy outcomes have been reported to occur among HIV-uninfected women taking antiretrovirals for oPEP or nPEP.

Reports are conflicting regarding whether an association exists of substantial malformations with use of EFV during the first trimester among humans. Studies using cynomolgus monkeys reported a potential association between neurologic congenital malformations and first-trimester use of EFV.[118] Although case reports exist of neurologic defects among infants of women receiving EFV,[119,120] no elevated risk for overall congenital malformations associated with first-trimester EFV exposure have been reported in either prospectively reported pregnancies from the Antiretroviral Pregnancy Registry[115] or from a meta-analysis of 23 studies with birth outcomes from 2,026 live births among women receiving EFV during the first trimester.[121]

HIV-infected pregnant women receiving combination antiretroviral regimens that included NVP have been reported to suffer severe hepatic adverse events, including death. However, whether pregnancy increases the risk for hepatotoxic events associated with NVP therapy is unknown. Use of NVP in HIV-infected women (regardless of pregnancy status) with high CD4 counts > 250 cells/mm^3[102] or elevated transaminase levels at baseline[122] has been associated with potentially life-threatening rash and hepatotoxicity. NVP use in 3 HIV-infected women with CD4 counts <100 cells/mm^3 at baseline has been associated with death among those also taking anti-tuberculosis therapy.[122]

Among antiretroviral medication combinations no longer recommended, regimens containing d4T with DDI have been associated with severe maternal lactic acidosis among pregnant HIV-infected women,[123,124] including severe necrotic pancreatic and hepatic steatosis and necrotic cellulitis of the abdominal wall in 1 woman,[123] 1 fetal demise (normal for gestational age) at 38 weeks gestation,[124] and 1 postnatal death at age 2 weeks in a 1,000 gram infant with trisomy 18.[123] Additionally, using IDV without RTV-boosting during pregnancy results in substantially lower antepartum exposures of IDV, compared with use of RTV-boosted IDV.[116,117]

VI-D. Behavioral Intervention to Support Risk Reduction During nPEP Use

Study findings from 2 randomized control trials underscore the importance of combining nPEP with behavioral interventions[125] to support continuing risk reduction. In a randomized controlled counseling intervention trial among nPEP recipients at a single U.S. site, investigators compared behavioral effects among those who received 2 (standard) versus 5 (enhanced) risk-reduction counseling sessions. Both interventions were based on social cognitive theory, motivational interviewing, and coping effectiveness. Compared with baseline, a reduction occurred at 12 months in the reported number of condomless sex acts for both intervention arms. The group reporting ≤ 4 condomless sex acts during the previous 6 months at baseline benefitted more from the 2-session intervention, while persons reporting ≥ 5 condomless sex acts during the previous 6 months at baseline revealed a greater reduction of condomless sex acts after receiving the 5-session intervention.[126] These findings demonstrate that more counseling sessions might be necessary for persons reporting higher levels of sexual risk behavior when initiating nPEP. In another randomized control trial, MSM who received contingency management, a substance abuse intervention providing voucher-based incentives for stimulant-use abstinence, had greater nPEP completion rates, greater reductions in stimulant use, and fewer acts of condomless anal intercourse compared with control participants who received incentives that were not contingent on their substance abstinence.[127]

VI-E. Adherence to nPEP Regimens and Follow-up Visits

Difficulties in adherence have been noted in both maintaining adherence to daily doses of antiretroviral medication for 28 days among the majority of populations and adherence to follow-up clinical visits for HIV testing and other care. Such adherence difficulties appear particularly severe in studies of nPEP for sexually assaulted persons. Methods for measuring completion of nPEP medication regimen differed across studies, and loss to follow-up was a major hindrance to assessing medication adherence for the majority of studies.

In a systematic review and meta-analysis of 34 nPEP studies not including sexual assault and 26 nPEP studies including only sexual assault, nPEP completion rates were lowest among persons who experienced sexual assault (40.2% [95% CI = 31.2%, 49.2%]) and highest among persons who had other nonoccupational exposures (65.6% [95% CI = 55.6%, 75.6%]).[128] In a separate meta-analysis of 24 nPEP-related studies, including 23 cohort studies and 1 randomized behavioral intervention to improve nPEP adherence, of 2,166 sexually assaulted persons receiving nPEP and pooled across the 24 studies, 40.3% (95% CI = 32.5%–48.1%; range, 11.8%–73.9%) adhered to a 28-day course of nPEP, and 41.2% (95% CI = 31.1%–51.4%; range, 2.9%–79.7%) did not return to pick up their prescribed medication or did not return for follow-up appointments.[20] Medication adherence was measured in 24 studies by using varying methodology, including pill count, volume of syrup remaining, self-report, counts of number of pharmacy visits, recall of number of doses taken by notation on a calendar, number of prescriptions filled, and number of weekly clinic appointments kept. Reported medication adherence was lower in developed countries (n=15 studies, 5 countries)[23,30-32,36,38,46,50,58,88-92,94,97] compared with developing countries (n=8 studies, three countries)[40,42,85-87,93,95,96] (33.3% versus 53.2%, respectively; *P*=0.007), possibly due to higher awareness of HIV transmission risk in countries with a high HIV prevalence.[20] Eight of the 24 (33%) studies[30,32,46,86-89,97] provided nPEP medications at time of initiation of prophylaxis as starter packs including 4–7 days of medication, and 1 study provided either a starter pack of medications or a full 28-day supply of nPEP at initiation.[96] In this latter study, the proportion who adhered to the 28 days of nPEP was 29% for patients initially receiving the starter pack and 71% for patients receiving a full 28-day supply.[96]

Although sexually assaulted persons are sometimes at risk for HIV transmission, they often decline nPEP, and many who do take it do not complete the 28-day course. This pattern has been reported in multiple countries and in programs in North America. In Ontario, for example, 798 of 900 eligible sexually assaulted persons were offered nPEP, including 69 and 729 at high or unknown risk for HIV transmission due to the factors associated with their sexual assault, respectively.[23] Forty-six (67%) of 69 persons at high risk for HIV transmission and 301 (41%) of 729 persons with unknown risk accepted and initiated nPEP. Twenty-four percent of patients at high risk and 33% of patients with unknown risk completed the 28-day course. Reasons for discontinuing treatment were documented in 96 cases and included adverse effects (81%), interference with routine (42%), inability to take time away from work or school (22%), and reconsideration of HIV risk (19%).

Of the observational studies of sexually assaulted persons provided nPEP, the majority identified similar challenges. Studies have demonstrated that early discontinuation of medication and a lack of follow-up pose challenges to providing nPEP to sexually assaulted persons.[31,33,47,50]

Four international studies examined adherence among both men and women with non-assault sexual and injection drug use risk exposures.[46,48,49,51] Full medication adherence in these studies ranged from 60%–88%; 60%[48] and 79%[51] completed therapy (without specifying how completion was defined) and 67%[48] and 88%[49] completed 28 days or 4 weeks of nPEP. The proportion of MSM who adhered to nPEP medication for 28 days reported in those studies ranged from 42%–91%.

Studies that used a fixed dose combination of ZDV/3TC and LPV/r as primary components in the nPEP drug regimen reported low medication adherence for 28 days (24%–44%).[23,44,47] A study among MSM compared use of a fixed-dose combination regimen containing TDF/FTC with or without RAL (an integrase inhibitor) with ZDV/3TC and a RTV-boosted PI; adherence rates were superior for the TDF-containing regimens (57% [with RAL]–72.7% [without RAL]) compared with the PI-containing regimen (46%). Although 57% of the TDF/FTC/RAL arm reported taking their medications as directed, an additional 27% took their once daily medication, but sometimes missed their second daily dose of RAL.[57]

VI-F. nPEP Cost-effectiveness

Estimates of cost-effectiveness of nPEP as an HIV prevention method reported in the literature vary by HIV exposure route and estimated prevalence of infection among source persons. A study using data from the San Francisco nPEP program estimated the cost-effectiveness of hypothetical nPEP programs in each of the 96 metropolitan statistical areas in the United States.[129] It included 3 different data sources, including data from clinical care and drug cost data from the San Francisco Department of Public Health nPEP program,[130] estimates of the per-act probability of HIV transmission associated with different modes of sexual and parenteral HIV exposure,[131-133] and HIV prevalence data from 96 U.S. metropolitan statistical areas.[134] Investigators estimated the cost-effectiveness of hypothetical nPEP programs as an HIV prevention method in each area compared with no intervention. By defining cost-effective programs as those costing <$60,000/quality-adjusted life year (QALY), that study found nPEP programs were cost-effective across the combined metropolitan statistical areas with a cost utility ratio of $12,567/QALY saved (range, $4,147–$39,101). nPEP was most cost-effective for MSM ($4,907/QALY). It was not cost-effective for needle-sharing persons who inject drugs (PWID) ($97,867/QALY), persons sustaining nonoccupational needlesticks ($159,687/QALY), and receptive female partners ($380,891/QALY) or insertive male partners ($650,792/QALY) in penile-vaginal sex. The hypothetical nPEP program would be cost-saving (cost-utility ratio, <$0) only for men and women presenting with receptive anal intercourse or if nPEP use was limited to clients with known HIV-infected partners.[129] In another study limited to San Francisco, the overall cost-utility ratio for the existing nPEP program was $14,449/QALY saved and for men experiencing receptive anal sex, the nPEP program was cost-saving.[130]

Studies in Australia and France reported similar results. For example, in Australia, using a threshold for cost-effectiveness of $50,000/QALY, nPEP was cost-effective among persons having CAI with an HIV-infected source ($40,673/QALY).[135] In France, using thresholds for cost-saving and cost-effectiveness of €0/QALY saved and <€50,000/QALY saved, respectively, nPEP was cost-saving among men and women who had receptive anal intercourse with an HIV-infected man (-€22,141/QALY saved [men]; and -€22,031/QALY saved [women]) and cost-saving among PWID having shared needles with an HIV-infected person (-€1,141/QALY saved).[136]

Additionally, these same French and Australian studies, and a Swiss study, reported that HIV testing to determine the status of the source person (when possible) was determined to reduce costs associated with nPEP programs by avoiding unnecessary prophylaxis.[48,135,136]

VI-G. Attitudes, Policies, and Knowledge About nPEP Use Among Health Care Providers and Candidates for nPEP

Since 1997, certain health care providers, health policy makers, and scientific investigators of nPEP have recommended wider availability and/or use of nPEP,[24,131,137-144] while others have been more cautious about implementing it in the absence of definitive evidence of efficacy or effectiveness.[145,146] Multiple public health jurisdictions in the U.S., including the New York State AIDS Institute, the San Francisco County Health Department, the Massachusetts Department of Public Health, the Rhode Island Department of Health, and the California State Office of AIDS, have issued policies or advisories for nPEP use.[3,4,147,148]

Surveys of health care providers and facilities indicate a low level of awareness and capacity to provide nPEP as well as a lack of access for nPEP for those for whom it is recommended need for more widespread dissemination and implementation of guidelines and protocols for nPEP use and a need for improved access. In a study of 181 patients presenting to the emergency department (ED) who had been sexually assaulted, lack of insurance, older patient age, and acquaintance rape were factors associated with not being offered nPEP.[30] A study evaluating access to nPEP services in 117 health care sites in Los Angeles County through use of Internet

searches and telephone surveys, determined that only 14% offered nPEP to clients regardless of insurance status, and an even lower percentage, 8%, offered nPEP to uninsured clients, indicating the need to improve access to such services.[149] A survey in New York State (NYS) reported that among 184 EDs, 88% reported evaluating patients with possible nonoccupational exposures to HIV in accordance with NYS guidelines, however, full implementation of NYS nPEP guidelines was incomplete with 4% neither supplying nor prescribing antiretroviral drugs in the ED and only 22% confirming whether linkage to follow-up care was successful.[150] Screening of STIs, risk-reduction counseling, and education about symptoms of acute HIV seroconversion were not consistently performed according to the NYS guidelines.[150] Additionally, in a survey of 142 HIV health care providers in Miami and the District of Columbia, prescribing nPEP was associated with having patients request nPEP, or having a written nPEP protocol, although most providers reported not having a written nPEP protocol and that patients rarely or never requested nPEP.[151] Lack of prescribing nPEP was associated with believing that nPEP would lead to antiretroviral resistance.[151] More health care providers in the District of Columbia compared with those in Miami, prescribed nPEP (59.7% versus 39.5%, respectively $P < 0.048$).[152] In a cross-sectional study describing program practices related to HIV testing and nPEP among 174 sexual assault nurse examiner (SANE)/forensic nurse examiner (FNE) programs in the U.S. and Canada, 75% had nPEP policies, 31% provided HIV testing, and 63% offered nPEP routinely or based on patient request.[153] Medication cost was the most important barrier to providing nPEP in these programs.

Awareness, knowledge, and use of nPEP has been described among MSM.[14,15,106,108,110,154] Evidence indicates awareness of nPEP and interest in its use among potential patients. When nPEP studies were established in San Francisco, approximately 400 persons sought treatment during December 1997–March 1999.[106,154] In an HIV prevention trial of 4,295 MSM in 6 U.S. cities during 1999–2003, a total of 2,037 (47%) had heard of nPEP at baseline and 315 (7%) reported using nPEP on ≥1 occasion.[14] Predictors of nPEP use included having multiple partners, engagement in condomless sex with a known HIV-infected partner or with a partner of unknown HIV status, and use of illicit drugs. Among 1,427 MSM in a community cohort of HIV-negative men in Sydney, Australia, during 2001–2007, knowledge of nPEP increased from 78.5% at baseline to 97.4% by the fifth annual interview, and nPEP use increased from 2.9/100 person-years in 2002 to 7.1/100 person-years in 2007.[110] During 2006–2009, knowledge of nPEP among MSM from urban areas in the Netherlands increased from 46% to 73%.[108] Also, the annual number of PEP prescriptions to MSM in Amsterdam increased 3-fold, from 19 in 2000 to 69 in 2007.[15]

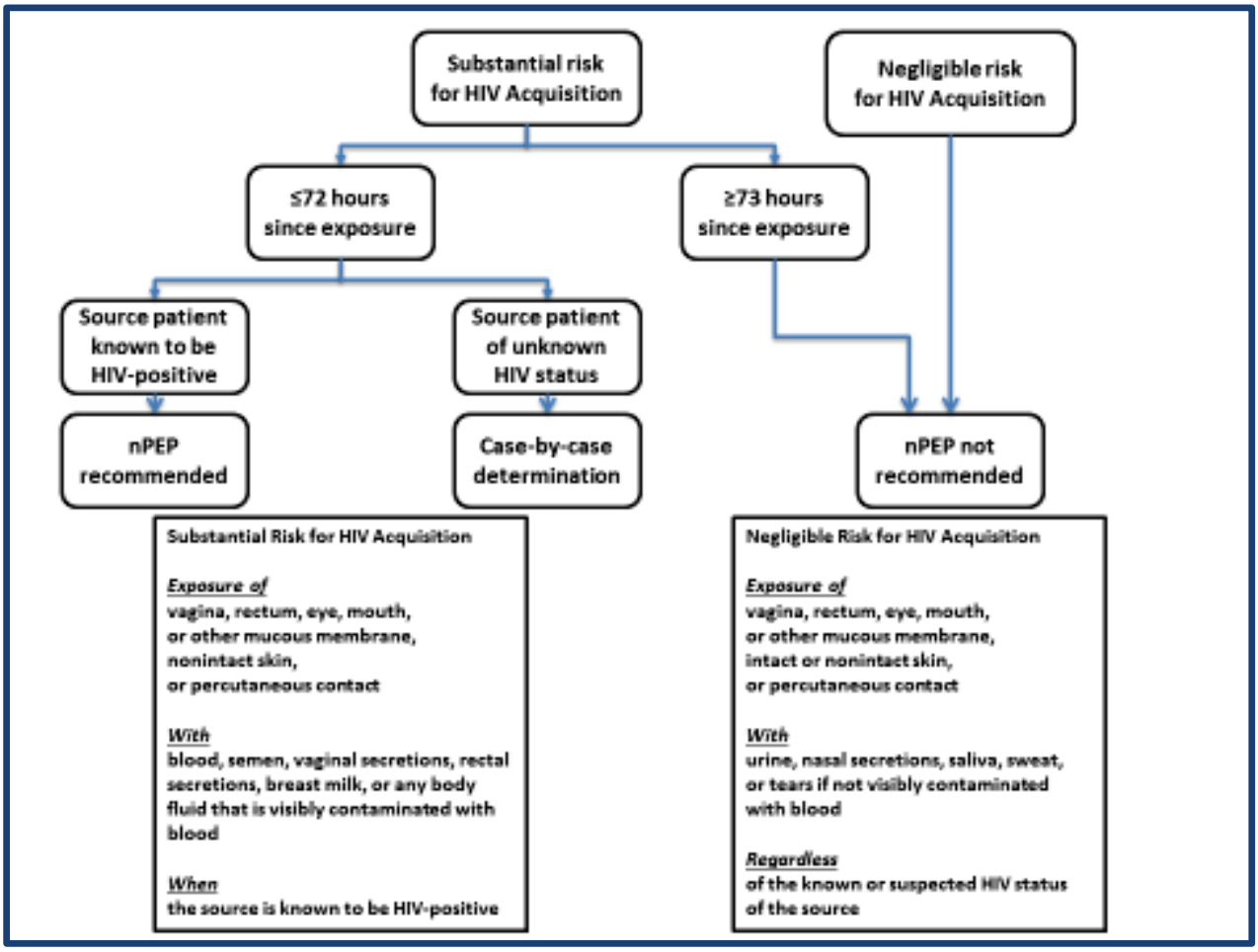
In a study of 227 pediatric and adolescent patients aged 9 months–18 years who were evaluated for sexual assault in Atlanta, Georgia, 40% of patients were examined ≤ 72 hours after the sexual assault, of whom 81% reported a history of genital or anal trauma.[41] In that study, patients aged 13–18 years and those who reported sexual assault by a stranger were more likely to present to the ED ≤ 72 hours after the sexual assault. Health care providers in the hospital's ED where this nPEP study was conducted expressed reluctance to prescribe nPEP to pre-pubertal children. For example, of 87 children and adolescents seen in the ED ≤ 72 hours after the assault, 23 had anogenital trauma or bleeding, and 5 were offered nPEP.

VII. Patient Management Guidelines

VII-A. Initial Evaluation of Persons Seeking Care After Potential Nonoccupational Exposure to HIV

Effective delivery of nPEP after exposures that carry a substantial risk for HIV infection requires prompt evaluation of patients and consideration of biomedical and behavioral interventions to address current and ongoing health risks. The initial evaluation provides the information necessary for determining if nPEP is indicated (Figure 1).

Figure 1. Algorithm for evaluation and treatment of possible nonoccupational HIV exposures



Procedures at the evaluation visit include determining the HIV infection status of the potentially exposed person and the source person (if available), the timing and characteristics of the exposure for which care is being sought, and the frequency of possible HIV exposures. Additionally, to determine whether other treatment or prophylaxis is indicated, health care providers should assess the likelihood of STIs, infections efficiently transmitted by injection practices or needlesticks (e.g., hepatitis B or hepatitis C virus), and pregnancy for women.

VII-A1. HIV Status of the Potentially Exposed Person

nPEP is only indicated for potentially exposed persons without HIV infection. Because potentially exposed persons might have acquired HIV infection already and be unaware of it, routine HIV antibody testing should

be performed on all persons seeking evaluation for potential nonoccupational HIV exposure. If possible, this should be done with an FDA-approved rapid antibody or Ag/Ab blood test kit with results available within an hour. If HIV blood test results will be unavailable during the initial evaluation visit, a decision whether nPEP is indicated should be made based on the initial assumption that the potentially exposed patient is not infected. If medication of HIV prophylaxis is indicated by the initial evaluation and started, it can be discontinued if the patient is later determined to already have HIV infection.

VII-A2. Timing and Frequency of Exposure

Available data from animal studies indicate that nPEP is most effective when initiated as soon as possible after HIV exposure; it is unlikely to be effective when instituted > 72 hours after exposure.[83] Therefore, persons should seek nPEP as soon as possible after an exposure that might confer substantial risk and health care providers should evaluate such patients rapidly and initiate nPEP promptly when indicated.

nPEP should be provided only for infrequent exposures. Persons who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of antiretroviral medications (e.g., HIV-discordant sex partners who inconsistently use condoms or PWID who often share injection equipment) should not be prescribed frequent, repeated courses of nPEP. Instead, health care providers should provide persons with repeated HIV exposure events (or coordinate referrals for) intensive sexual or injection risk-reduction interventions, and consider the prescription of daily oral doses of the fixed-dose combination of TDF and FTC (Truvada, Gilead Sciences, Inc., Foster City, California) for PrEP.[11] However, if the most recent recurring exposure is within the 72 hours prior to an evaluation, nPEP may be indicated with transition of the patient to PrEP after completion of 28 days of nPEP medication.

In the special case of children with evidence of chronic sexual abuse who come to the attention of a health care provider ≤ 72 hours after their most recent exposure, nPEP can be considered on a case-by-case basis. In addition, child protective services should be engaged for consideration of removal of the child from exposure to the perpetrator of the sexual abuse.

VII-A3. HIV Acquisition Risk from the Exposure

In addition to determining when the potential exposure occurred, determining whether nPEP is indicated requires assessing if the reported sexual, injection drug use, or other nonoccupational exposure presents a substantial risk for HIV acquisition. Health care providers should consider 3 main factors in making that determination: (1) whether the exposure source is known to have HIV infection, (2) to which potentially infected body fluid(s) the patient was exposed, and (3) the exposure site or surface.

The highest level of risk is associated with exposure of susceptible tissues to potentially infected body fluid(s) from persons known to have HIV infection, particularly those who are not on antiretroviral treatment. Persons with exposures to potentially infectious fluids from persons of unknown HIV status are at unknown risk for acquiring HIV infection. When the source of exposure is known to be from a group with a high prevalence of HIV infection (e.g., a man who has sex with men or a PWID who shares needles or other injection equipment), the risk for unrecognized HIV infection in the source is increased.

The estimated per-act transmission risk, when exposed to infectious fluid(s) from a person with HIV infection, varies considerably by exposure route (Table 1).[155] The highest estimated per-act risks for HIV transmission are associated with blood transfusion, needle sharing during injection drug use, receptive anal intercourse, and percutaneous needlestick injuries. Insertive anal intercourse, insertive penile-vaginal intercourse, and oral sex represent substantially lower per-act transmission risk.

Table 1. Estimated per-act risk for acquiring human immunodeficiency virus (HIV) from an infected source, by exposure act[a]

Exposure type	Rate for HIV acquisition per 10,000 exposures
Parenteral	
Blood transfusion	9,250
Needle sharing during injection drug use	63
Percutaneous (needlestick)	23
Sexual	
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other[b]	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

Source: http://www.cdc.gov/hiv/policies/law/risk.html

[a] Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and preexposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

[b] HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

A history should be taken of the specific sexual, injection drug use, or other exposure events that can lead to acquiring HIV infection. Eliciting a complete description of the exposure and information about the HIV status of the partner(s) can substantially lower (e.g., if the patient was exclusively the insertive partner or a condom was used) or increase (e.g., if the partner is known to be HIV-positive) the estimate of risk for HIV transmission resulting from a specific exposure.

Percutaneous injuries from needles discarded in public settings (e.g., parks and buses) sometimes result in requests for nPEP. Although no HIV infections from such injuries have been documented, concern exists that syringes discarded by PWID might pose a substantial risk. However, such injuries typically involve small-bore needles that contain only limited amounts of blood, and the infectiousness of any virus present might be low.[156,157] Saliva that is not contaminated with blood contains HIV in much lower titers and constitutes a negligible exposure risk,[158] but saliva that is contaminated with HIV-infected blood poses a substantial exposure risk. HIV transmission by this route has been reported in ≥ 4 cases.[159-162]

VII-A4. HIV Status of the Exposure Source

When the exposure source's HIV status is unknown, that person's availability for HIV testing should be determined. When the source person is available and consents to HIV testing, a clinical evaluation visit should be arranged that includes HIV testing by using a fourth-generation combined Ag/Ab test. The risk for transmission might be especially great if the source person has been infected recently because the viral burden in blood and semen might be particularly high.[163,164] However, ascertaining this in the short time available for the initial nPEP evaluation might not be possible. If the risk associated with the exposure is high, starting nPEP and then making a decision whether to continue nPEP after the source's HIV status is determined is recommended.

If the exposure source is known to have HIV infection at the time of the nPEP evaluation visit and consents, the health care provider should attempt to interview that person or that source person's health care provider to determine the history of antiretroviral use and most recent viral load. That information might help guide the choice of nPEP medications to avoid prescribing antiretroviral medications to which the source-virus is likely to be resistant. If the person with HIV infection is willing, the clinician might consider drawing blood for viral load and resistance testing, the results of which might be useful in modifying the initial nPEP medications if the results can be obtained promptly.[165]

VII-B. Laboratory Testing

Laboratory testing is required to (1) document the HIV infection status of the person presenting for nPEP evaluation (and the exposure source when available and consent has been granted), (2) identify and clinically manage any other conditions potentially resulting from sexual- or injection-related exposure to potentially infected body fluids, (3) identify any conditions that would affect the nPEP medication regimen, and (4) monitor for safety or toxicities related to the regimen prescribed (Table 2).

Table 2. Recommended schedule of laboratory evaluations of source and exposed persons for providing nPEP with preferred regimens

Test	Source	Exposed persons			
	Baseline	Baseline	4–6 weeks after exposure	3 months after exposure	6 months after exposure
		For all persons considered for or prescribed nPEP for any exposure			
HIV Ag/Ab testing[a] (or antibody testing if Ag/Ab test unavailable)	✓	✓	✓	✓	✓[b]
Hepatitis B serology, including: hepatitis B surface antigen hepatitis B surface antibody hepatitis B core antibody	✓	✓	—	—	✓[c]
Hepatitis C antibody test	✓	✓	—	—	✓[d]
		For all persons considered for or prescribed nPEP for sexual exposure			
Syphilis serology[e]	✓	✓	✓	—	✓
Gonorrhea[f]	✓	✓	✓[g]	—	—
Chlamydia[f]	✓	✓	✓[g]	—	—
Pregnancy[h]	—	✓	✓	—	—
		For persons prescribed tenofovir DF+ emtricitabine + raltegravir or tenofovir DF+ emtricitabine + dolutegravir			
Serum creatinine (for calculating estimated creatinine clearance[i])		✓	✓	—	—
Alanine transaminase, aspartate aminotranferase		✓	✓	—	—
	For all persons with HIV infection confirmed at any visit				
HIV viral load	✓	✓[j]			
HIV genotypic resistance	✓	✓[j]			

Abbreviations: Ag/Ab, antigen/antibody combination test; HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis; tenofovir DF, tenofovir disoproxil fumarate.

[a] Any positive or indeterminate HIV antibody test should undergo confirmatory testing of HIV infection status.

[b] Only if hepatitis C infection was acquired during the original exposure; delayed HIV seroconversion has been seen in persons who simultaneously acquire HIV and hepatitis C infection.

[c] If exposed person susceptible to hepatitis B at baseline.

[d] If exposed person susceptible to hepatitis C at baseline.

[e] If determined to be infected with syphilis and treated, should undergo serologic syphilis testing 6 months after treatment

[f] Testing for chlamydia and gonorrhea should be performed using nucleic acid amplification tests. For patients diagnosed with a chlamydia or gonorrhea infection, retesting 3 months after treatment is recommended.

- For men reporting insertive vaginal, anal, or oral sex, a urine specimen should be tested for chlamydia and gonorrhea.
- For women reporting receptive vaginal sex, a vaginal (preferred) or endocervical swab or urine specimen should be tested for chlamydia and gonorrhea.
- For men and women reporting receptive anal sex, a rectal swab specimen should be tested for chlamydia and gonorrhea.
- For men and women reporting receptive oral sex, an oropharyngeal swab should be tested for gonorrhea. (http://www.cdc.gov/std/tg2015/tg-2015-print.pdf)

[g] If not provided presumptive treatment at baseline, or if symptomatic at follow-up visit.

[h] If woman of reproductive age, not using effective contraception, and with vaginal exposure to semen.

[i] eCrCl = estimated creatinine clearance calculated by the Cockcroft-Gault formula; eCrClCG = [(140 − age) x ideal body weight] ÷ (serum creatinine x 72) (x 0.85 for females).

[j] At first visit where determined to have HIV infection.

VII-B1. HIV Testing

All patients initiating nPEP after potential HIV exposure should be tested for the presence of HIV-1 and HIV-2 antigens and antibodies in a blood specimen at baseline (before nPEP initiation), preferably using a rapid test. Patients with baseline rapid tests indicating existing HIV infection should not be started on nPEP. Patients for whom baseline HIV rapid test results indicate no HIV infection or rapid HIV test results are not available should be offered nPEP. There should be no delay in initiation of nPEP while awaiting baseline HIV test results. Repeat HIV testing should occur at 4–6 weeks and 3 months after exposure to determine if HIV infection has occurred. See http://www.cdc.gov/hiv/testing/laboratorytests.html regarding information on approved HIV tests. Oral HIV tests are not recommended for use among persons being evaluated for nPEP.

Additionally, persons whose sexual or injection-related exposures results in concurrent acquisition of HCV and HIV infection might have delayed HIV seroconversion. This has been documented among MSM with sexual exposure[13] and health care personnel receiving oPEP for needlestick exposures.[166,167] Therefore, for any person whose HCV antibody test is negative at baseline but positive at 4–6 weeks after the exposure, HIV antibody tests should be conducted at 3 and 6 months to rule out delayed seroconversion (see Table 2).

VII-B2. Recognizing Acute HIV Infection at Time of HIV Seroconversion

Persons initiating nPEP, if it fails, may experience signs and symptoms of acute HIV infection while on nPEP. At the initial visit, patients should be instructed about the signs and symptoms associated with acute (primary) HIV infection (Table 3), especially fever and rash,[168] and asked to return for evaluation if these occur during the 28 days of prophylaxis or anytime within a month after nPEP concludes.

Table 3. Clinical signs and symptoms of acute (primary) human immunodeficiency virus infection[169,170]

		Sex		Mode of HIV acquisition	
Features	**Overall (n = 375), %**	**Male (n = 355), %**	**Female (n = 23), %**	**Sexual (n = 324), %**	**Injection drug use (n = 34), %**
Fever	75	74	83	77	50
Fatigue	68	67	78	71	50
Myalgia	49	50	26	52	29
Skin rash	48	48	48	51	21
Headache	45	45	44	47	30
Pharyngitis	40	40	48	43	18
Cervical adenopathy	39	39	39	41	27
Arthralgia	30	30	26	28	26
Night sweats	28	28	22	30	27
Diarrhea	27	27	21	28	23

Acute HIV infection is associated with high viral load. However, health care providers should be aware that available assays might yield low viral-load results (e.g., <3,000 copies/ml) among persons without HIV infection (i.e., false-positives). Without confirmatory tests, such false-positive results can lead to misdiagnoses of HIV infection.[171] Transient, low-grade viremia has been observed among persons exposed to HIV who were

administered antiretroviral nPEP[172] and did not become infected. In certain cases, this outcome might represent aborted infection rather than false-positive test results, but this can be determined only through further testing.

All patients who have begun taking nPEP and for whom laboratory evidence later confirms acute HIV infection at baseline or whose follow-up antibody testing indicates HIV infection, should be transferred rapidly to the care of an HIV treatment specialist (if nPEP was provided by another type of health care provider). If the patient is taking a 3-drug antiretroviral regimen for nPEP at the time of HIV infection diagnosis, the 3-drug regimen should not be discontinued by the nPEP provider until the patient has been evaluated and a treatment plan initiated by an experienced HIV care provider.[173]

VII-B3. STI Testing

Any sexual exposure that presents a risk for HIV infection might also place a person at risk for acquiring other STIs.[174] For all persons evaluated for nPEP because of exposure during sexual encounters, STI-specific nucleic acid amplification (NAAT) testing is recommended for gonorrhea and chlamydia,[174] by testing first-catch urine or with swabs collected from each mucosal site exposed to potentially infected body fluids (oral, vaginal, cervical, urethral, rectal).[174,175] Additionally, blood tests for syphilis should be conducted for all persons evaluated for nPEP.

VII-B4. HBV Testing

HBV infection is of specific concern when considering nPEP for 2 reasons. First, multiple medications used for nPEP, including 2 in the preferred regimen (TDF and FTC) are active against HBV infection. For safety reasons, health care providers need to know if a patient has active HBV infection (positive hepatitis B surface antigen [HBsAg]) so that the patient can be closely monitored for reactivation "flare ups" when nPEP is stopped, and treatment for HBV infection is discontinued. Although this is rare, it can result in substantial hepatic dysfunction if not detected and treated early. Additionally, obtaining hepatitis serology (HBsAg, hepatitis B surface antibody [anti-HBs], and hepatitis B core antibody [anti-HBc]) will identify nonimmune persons who should be provided hepatitis B vaccination Table 4).[176]

Table 4. Hepatitis B virus screening serology[177]

HBsAg	Anti-HBc	Anti-HBs	IgM Anti-HBc	Interpretation	Action
Negative	Negative	Negative	—	Susceptible	Vaccinate
Negative	Positive	Positive	—	Immune (natural infection)	Document
Negative	Negative	Positive	—	Immune (prior vaccination)	Document
Positive	Positive	Negative	Negative	Chronic hepatitis B virus infection	Evaluate for treatment
Positive	Positive	Negative	Positive	Acute hepatitis B virus infection	Follow and evaluate for treatment
Negative	Positive	Negative	—	Unclear—might be: • resolved infection (most common) • false-positive anti-HBc; susceptible • "low level" chronic infection • resolving acute infection	Case-by-case evaluation
Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody.					

VII-B5. Pregnancy Testing

nPEP is not contraindicated for pregnant women. Moreover, because pregnancy has been demonstrated to increase susceptibility to sexual HIV acquisition,[178] nPEP can be especially important for women who are pregnant at the time of sexual HIV exposure.

For women of reproductive capacity who have had genital exposure to semen and a negative pregnancy test when evaluated for possible nPEP, current contraception use should be assessed, and if a risk for pregnancy exists, emergency contraception should be discussed with the patient.

VII-B6. Baseline and Follow-up Testing to Assess Safety of Antiretroviral Use for nPEP

All patients who will be prescribed nPEP should have serum creatinine measured and an estimated creatinine clearance calculated at baseline to guide selection of a safe and appropriate antiretroviral regimen for nPEP. Also, health care providers treating patients with nPEP should monitor liver function, renal function, and hematologic parameters when indicated by the prescribing information for the antiretrovirals prescribed. Drug-specific recommendations are available at the online AIDS*Info* Drugs Database at: http://aidsinfo.nih.gov/drugs or the antiretroviral treatment guidelines.[114,173,179]

Unusual or severe toxicities from antiretroviral drugs should be reported to the manufacturer or FDA (http://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or 1-800-FDA-1088 [1-800-332-1088]).

If nPEP is prescribed to a woman who is pregnant at the time of exposure or becomes pregnant while on nPEP, health care providers should enter the patient's information (anonymously) into the Antiretroviral Pregnancy Registry (http://www.apregistry.com).

VII-C. Recommended Antiretroviral nPEP Regimens

A 28-day course of nPEP is recommended for HIV-uninfected persons who seek care ≤ 72 hours after a nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of persons known to be HIV infected or of unknown HIV status when that exposure represents a substantial risk for HIV acquisition. Since adherence is critical for nPEP efficacy, it is preferable to select regimens that minimize side effects, number of doses per day and the number of pills per dose.

No strong evidence exists, based on randomized clinical trials, that any specific combination of antiretroviral medication is optimal for nPEP use. Although a limited number of studies have evaluated the penetration of antiretroviral medications into genital tract secretions and tissues,[180-182] evidence is insufficient for recommending a specific antiretroviral medication as most effective for nPEP for sexual exposures. Therefore, the recommended regimens for nPEP in these guidelines are based on expert opinion from the accumulated experience with antiretroviral combinations that effectively suppress viral replication among HIV-infected persons for the purpose of HIV treatment and mainly observational studies of the medication tolerance and adherence when these same drugs are taken for nPEP.

The recommendation for a 3-drug antiretroviral regimen is based on extrapolation of data demonstrating that the maximal suppression of viral replication occurs among persons with HIV infection when combination antiretroviral therapy with ≥3 drugs is provided. Also, the likelihood of protection against acquiring resistant virus would be greater with a 3-drug regimen compared with a 2-drug regimen. Recommending a 3-drug regimen for all patients who receive nPEP will increase the likelihood of successful prophylaxis in light of potential exposure to virus with resistance mutation(s) and will provide consistency across PEP guidelines for

both nPEP and oPEP.[2] Additionally, if infection occurs despite nPEP, a 3-drug regimen will more likely limit emergence of resistance than a 2-drug regimen.

Table 5. Preferred and alternative antiretroviral medication 28-day regimens for nPEP[a,b]

Age group	Preferred/ alternative	Medication
Adults and adolescents aged ≥ 13 years, including pregnant women, with normal renal function (creatinine clearance ≥ 60 mL/min)	**Preferred**	A 3-drug regimen consisting of tenofovir DF 300 mg ***and*** fixed dose combination emtricitabine 200 mg (Truvada[c]) once daily ***with*** raltegravir 400 mg twice daily ***or*** dolutegravir 50 mg once daily
	Alternative	A 3-drug regimen consisting of tenofovir DF 300 mg ***and*** fixed dose combination emtricitabine 200 mg (Truvada) once daily ***with*** darunavir 800 mg (as 2, 400-mg tablets) once daily ***and*** ritonavir[b] 100 mg once daily
Adults and adolescents aged ≥ 13 years with renal dysfunction (creatinine clearance ≤59 mL/min)	**Preferred**	A 3-drug regimen consisting of zidovudine ***and*** lamivudine, with both doses adjusted to degree of renal function ***with*** raltegravir 400 mg twice daily ***or*** dolutegravir 50 mg once daily
	Alternative	A 3-drug regimen consisting of zidovudine ***and*** lamivudine, with both doses adjusted to degree of renal function ***with*** darunavir 800 mg (as 2, 400-mg tablets) once daily ***and*** ritonavir[b] 100 mg once daily
Children aged 2–12 years	**Preferred**	A 3-drug regimen consisting of tenofovir DF, emtricitabine, and raltegravir, with each drug dosed to age and weight[d]
	Alternative	A 3-drug regimen consisting of zidovudine ***and*** lamivudine ***with*** raltegravir ***or*** lopinavir/ritonavir[b], with raltegravir and lopinavir/ritonavir dosed to age and weight[d]
	Alternative	A 3-drug regimen consisting of tenofovir DF ***and*** emtricitabine ***and*** lopinavir/ritonavir[b], with each drug dosed to age and weight[d]

Age group	Preferred/ alternative	Medication
Children aged 3–12 years	Alternative	A 3-drug regimen consisting of tenofovir DF **and** emtricitabine **and** darunavir[e]/ritonavir[b], with each drug dosed to age and weight[d]
Children aged 4 weeks[f]–< 2 years	**Preferred**	A 3-drug regimen consisting of zidovudine oral solution ***and*** lamivudine oral solution ***with*** raltegravir ***or*** lopinavir/ritonavir[b] oral solution (Kaletra[g]), with each drug dosed to age and weight[d]
Children aged 4 weeks[f]–< 2 years	Alternative	A 3-drug regimen consisting of zidovudine oral solution ***and*** emtricitabine oral solution ***with*** raltegravir ***or*** lopinavir/ritonavir[b] oral solution (Kaletra), with each drug adjusted to age and weight[d]
Children aged birth–27 days	Consult a pediatric HIV-specialist	

Abbreviations: HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis; tenofovir DF, tenofovir disoproxil fumarate.

[a] These recommendations do not reflect current Food and Drug Administration-approved labeling for antiretroviral medications listed in this table.

[b] Ritonavir is used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration and prolong the half-life of darunavir, lopinavir, and other protease inhibitors. Ritonavir is not counted as a drug directly active against HIV in the above "3-drug" regimens.

[c] Gilead Sciences, Inc., Foster City, California.

[d] See also Table 6.

[e] Darunavir only FDA-approved for use among children aged ≥ 3 years.

[f] Children should have attained a postnatal age of ≥ 28 days and a postmenstrual age (i.e., first day of the mother's last menstrual period to birth plus the time elapsed after birth) of ≥ 42 weeks.

[g] AbbVie, Inc., North Chicago, Illinois.

Table 6. Formulations, cautions, and dose adjustments for antiretroviral medications in preferred and alternative nPEP regimens[a]

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Tenofovir disoproxil fumarate (TDF) (Viread, Gilead Sciences, Inc., Foster City, California) Also available as component of fixed-dose combination, Truvada (Gilead Sciences, Inc., Foster City, California) (emtricitabine + TDF)	150-mg tablet 200-mg tablet 250-mg tablet 300-mg tablet 40-mg/gm powder	**Side effects:** Asthenia, headache, diarrhea, nausea, vomiting **Contraindications:** Nephrotoxicity; for nPEP, should not be administered to persons with acute or chronic kidney injury or those with eCrCl < 60 mL/min **Cautions:** TDF can be used in nPEP regimens for patients with chronic hepatitis B infection, but hepatic function tests should be closely monitored when regimen is stopped because withdrawal of this drug may cause an acute hepatitis exacerbation.	**Children aged 2–11 years (powder)** • 8 mg/kg body weight • Not to exceed adult dose (300 mg qd) **Children aged 2–11 years (tablet), per body weight** • 17 to < 22 kg, 150 mg-tablet once daily • 22 to < 28 kg, 200 mg-tablet once daily • 28 to < 35 kg, 250-mg tablet once daily • ≥ 35 kg, 300-mg tablet once daily • Not to exceed adult dose (300 mg once daily)
Emtricitabine (FTC) (Emtriva, Gilead Sciences, Inc., Foster City, California) Also available as component of fixed-dose combination, Truvada (FTC + TDF)	200-mg capsule 10-mg/mL oral solution	**Side effects:** Hyperpigmented rash or skin discoloration **Cautions:** FTC can be used in nPEP regimens for patients with chronic hepatitis B infection, but hepatic function tests should be closely monitored when regimen is stopped because withdrawal of this drug might cause an acute hepatitis exacerbation. **Contraindications:** Do not administer with lamivudine	**Children aged 0–3 months (oral solution)** • 3 mg/kg once daily • Not to exceed 240 mg once daily **Children aged 3 months–17 years, per body weight** • 6 mg/kg once daily (oral solution) • ≥ 33 kg 200-mg tablet once daily • Not to exceed 240 mg once daily
Raltegravir (RAL) (Isentress, Merck & Co., Inc., Kenilworth, New Jersey)	400-mg tablet 100-mg chewable, scored tablet 25-mg chewable tablet	**Side effects:** Insomnia, nausea, fatigue, headache; severe skin and hypersensitivity reactions have been reported **Cautions:** Dosage adjustment required if co-administered with rifampin (800 mg twice daily for adults). Co-administration with antacids, laxatives, or other products containing polyvalent cations (Mg, Al, Fe, Ca, Zn), including iron, calcium, or magnesium supplements; sucralfate; buffered medications; and certain oral multivitamins can reduce absorption of RAL. RAL should be administered ≥ 2 hours before or ≥ 6 hours after administration of cation-containing medications or products, however, RAL can be co-administered with calcium carbonate-containing antacids.[154] **Contraindications:** None	**Children aged 6–12 years and weighing > 25 kg** • 400 mg-tablet twice daily **Or** • Chewable tablets twice daily. See table below for chewable tablet dose. **Children aged 2–12 years (chewable tablets), per body weight** • 11 to < 14 kg, 75-mg twice daily • 14 to < 20 kg, 100-mg twice daily • 20 to < 28 kg, 150-mg twice daily • 28 to < 40 kg, 200-mg twice daily • ≥ 40 kg, 300-mg twice daily

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Dolutegravir (DTG) (Tivicay, ViiV Healthcare, Brentford, Middlesex, United Kingdom)	50-mg tablet	**Side effects:** Insomnia, headache **Cautions:** Dosage adjustment required if co-administered with rifampin, fosamprenavir/ritonavir, tipranvir/ritonavir, or efavirenz (50 mg twice daily for adults). Co-administration with antacids, laxatives, or other products containing polyvalent cations (Mg, Al, Fe, Ca, Zn), including iron, calcium, or magnesium supplements; sucralfate; buffered medications; and some oral multivitamins can reduce absorption of DTG. DTG should be administered ≥2 hours before or at ≥6 hours after administration of cation-containing medications or products.[151] **Contraindications:** Do not administer with dofetilide.	**Children aged 12 years old and older and weighing ≥40 kg** • 50-mg tablet once daily
Darunavir (DRV)/ritonavir(RTV) (Prezista, Janssen Therapeutics, Titusville, New Jersey)	75-mg tablet 150-mg tablet 400-mg tablet 600-mg tablet 100-mg/mL oral suspension	**Side effects:** Rash (sulfonamide allergy), diarrhea, nausea, headache **Cautions:** Must be administered with food; must be co-administered with ritonavir; can cause hepatotoxicity. Use with caution with persons with known allergy to sulfonamide medications **Contraindications:** Co-administration of ritonavir with certain sedative hypnotics, antiarrhythmics, sildenafil, or ergot alkaloid preparations is contraindicated and might result in potentially life-threatening adverse events.	**Children aged 3 to <18 years and weight >10 kg** WEIGHT (KG) — DOSE (TWICE DAILY WITH FOOD) 10 to <11 kg* — darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL†) 11 to <12 kg* — darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL†) 12 to <13 kg* — darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL†) 13 to <14 kg* — darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL†) 14 to <15 kg* — darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL†) 15 to <30 kg — darunavir 375 mg (combination of tablets or 3.8 mL‡) plus ritonavir 48 mg (0.6 mL†) 30 to <40 kg — darunavir 450 mg (combination of tablets or 4.6 mL‡) plus ritonavir 100 mg (tablet or 1.25 mL†) ≥40 kg — darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL†) * The dose in children weighing 10–15 kg is 20 mg/kg darunavir and 3 mg/kg ritonavir per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight. † Ritonavir 80 g/mL oral solution ‡ The 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Lopinavir (LPV)/ritonavir (RTV) (Kaletra, AbbVie Inc., North Chicago, Illinois)	200/50-mg tablets 100/25-mg tablets 80/20-mg/mL oral solution	**Side effects:** Nausea, vomiting, diarrhea **Cautions:** PR and QT interval prolongation have been reported. Use with caution with patients at risk for cardiac conduction abnormalities or receiving other drugs with similar effect. Do not administer to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of ≥ 42 weeks and a postnatal age of ≥ 14 days. **Contraindications:** Co-administration of ritonavir with certain sedative hypnotics, antiarrhythmics, sildenafil, or ergot alkaloid preparations is contraindicated and might result in potentially life-threatening adverse events.	**Children aged 14 days–12 months, per body weight** Suspension (lopinavir/ritonavir) • 16/4 mg/kg or 300/75 mg/m^2 twice daily **Children aged > 12 months–18 years, per body weight** Suspension (lopinavir/ritonavir) • < 15 kg, 12/3 mg/kg twice daily • ≥ 15 kg to 40 kg, 10/2.5 mg/kg twice daily • > 40 kg, 400/100 mg twice daily • not to exceed the recommended adult dose (400/100 mg [5 mL] twice daily **Children aged > 12 months–18 years** Tablet, weight-based dosing (lopinavir/ritonavir) • 15 to 25 kg, 2 100/25-mg tablets twice daily • > 25 to 35 kg, 3 100/25-mg tablets twice daily • > 35 kg, 4 100/25-mg tablets twice daily or 2 200/50-mg tablets twice daily
Ritonavir[b](RTV) (Norvir, AbbVie, Inc., North Chicago, Illinois)	100-mg tablets 100-mg soft gelatin capsules 80-mg/mL oral solution	**Side effects:** Abdominal pain, asthenia, headache, malaise, anorexia, diarrhea, dyspepsia, nausea, vomiting, circumoral paresthesia, peripheral paresthesia, dizziness, and taste perversion. **Cautions:** PR and QT interval prolongation have been reported. Use with caution with patients at risk for cardiac conduction abnormalities or receiving other drugs with similar effect. Can cause hepatotoxicity, pancreatitis, or hyperglycemia **Contraindications:** Co-administration of ritonavir with certain sedative hypnotics, antiarrhythmics, sildenafil, or ergot alkaloid preparations is contraindicated and might result in potentially life-threatening adverse events.	• See pediatric dosage for use as a boosting agent with darunavir or lopinavir in respective darunavir and lopinavir sections of this table.

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Zidovudine (ZDV; AZT) (Retrovir, ViiV Healthcare, Brentford, Middlesex, United Kingdom)	100-mg capsule 300-mg tablet 10-mg/mL oral syrup 10-mg/mL intravenous infusion	**Side effects:** Nausea, vomiting, headache, insomnia, and fatigue **Cautions:** Can cause anemia and neutropenia	**Infants aged birth–41 days** **Full term (aged ≥35 weeks gestation at birth), per body weight** Syrup • 4 mg/kg orally twice daily Intravenous[c] • 3.0 mg/kg, infused over 30 minutes, every 12 hours **Premature (aged ≥30 to 35 weeks gestation at birth; from birth through day 14 of life; switch to full term infant dose at 15 days of life), per body weight** Syrup • 2 mg/kg orally twice daily Intravenous[c] • 1.5 mg/kg, infused over 30 minutes, every 12 hours **Premature (aged <30 weeks gestation at birth; day 14–28 of life; switch to full term infant dose at 29 days* of life), per body weight** Syrup • 2 mg/kg orally twice daily Intravenous[c] • 1.5 mg/kg, infused over 30 minutes, every 12 hours **Infants and children aged ≥35 weeks post-conception and at least 4 weeks post-delivery, per body weight** Syrup or Capsules • 4 to <9 kg, 12 mg/kg twice daily • 9 to <30 kg, 9 mg/kg twice daily Tablet • ≥30 kg, 300-mg tablet twice daily * Note: Premature infants exposed to HIV after day 1 of life are switched to full-term infant dose at 29 days of life.

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Lamivudine (3TC) (Epivir, ViiV Healthcare, Brentford Middlesex, United Kingdom)	150-mg scored tablet 100-mg tablet 300-mg tablet 10-mg/mL oral solution	**Side effects:** Headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough **Cautions:** 3TC may be used in nPEP regimens for patients with chronic hepatitis B infection, but hepatic function tests should be closely monitored when regimen is stopped since withdrawal of this drug may cause an acute hepatitis exacerbation. **Contraindications:** Do not administer with emtricitabine	**Neonates and infants, aged ≤ 27 days** Oral solution • 2 mg/kg twice daily **Children, aged ≥ 4 weeks** Oral solution • 4 mg/kg (maximum dose 150 mg) twice daily **Children aged < 16 years and weighing ≥ 14 kg** Scored 150-mg tablet • 14 to < 20 kg, 75 mg (1/2 tablet) AM + 75 mg (1/2 tablet) PM • 20 to < 25 kg, 75 mg (1/2 tablet) AM + 150 mg (1 tablet) PM • ≥ 25 kg, 150 mg tablet twice daily **Adolescents (aged ≥ 16 years) and adults, per body weight** • < 50 kg, 4 mg/kg (up to 150 mg) twice daily • ≥ 50 kg, 150 mg twice daily or 300 mg once daily

Abbreviations: eCrCl = estimated creatinine clearance calculated by the Cockcroft-Gault formula; eCrClCG = [(140 − age) x ideal body weight] ÷ (serum creatinine x 72) (x 0.85 for females); nPEP, nonoccupational postexposure prophylaxis.

[a] For most current dosing regimens for treatment naïve children, see 1) AIDSInfo Drugs Database at http://aidsinfo.nih.gov/drugs, 2) Drugs@FDA (FDA approved drug products index) at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, 3) Pediatric ARV treatment guidelines at http://aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0#, and 4) Perinatal guidelines at http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0

[b] Ritonavir is used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration and prolong the half-life of darunavir, lopinavir, and other protease inhibitors

[c] Infants unable to receive oral dosing may receive intravenous dosing

Health care providers might consider using antiretroviral regimens for nPEP other than those listed as preferred or alternative because of patient-specific information (e.g., an HIV-infected exposure source with known drug-resistance or contraindications to ≥1of the antiretrovirals in a preferred regimen). In those cases, health care providers are encouraged to seek consultation with other health care providers knowledgeable in using antiretroviral medications for similar patients (e.g., children, pregnant women, those with comorbid conditions) (Appendix 4).

> Providers should be aware that abacavir sulfate (Ziagen, ViiV Healthcare, Brentford, Middlesex, United Kingdom) should not be prescribed in any nPEP regimen. Prompt initiation of nPEP does not allow time for determining if a patient has the *HLA-B*5701* allele, the presence of which is strongly associated with a hypersensitivity syndrome that can be fatal.[183]

Health care providers and patients who are concerned about potential adherence and toxicity or the additional cost associated with a 3-drug antiretroviral regimen might consider using a 2-drug regimen (i.e., a combination of 2 NRTIs or a combination of a PI and a NNRTI). However, this DHHS guideline recommends a 3-drug regimen in all cases when nPEP is indicated.

VII-D. Prophylaxis for STIs and Hepatitis

All adults and adolescents with exposures by sexual assault should be provided with prophylaxis routinely for STIs and HBV,[174] as follows:

- For gonorrhea, (male and female adults and adolescents),
  - ceftriaxone 250 mg intermuscular, single dose;
  - ***plus*** azithromycin, 1 g, orally, single dose;
- For chlamydia (male and female adults and adolescents),
  - azithromycin, 1 g, orally, single dose
  - ***or*** doxycycline, 100 mg, orally, twice a day for 7 days.
- For trichomonas (female adults and adolescents),
  - metronidazole, 2 g, orally, single dose
  - ***or*** tinidazole, 2 g, orally, single dose

All persons not known to be previously vaccinated against HBV, should receive hepatitis B vaccination (without hepatitis B immune globulin),[174] with the first dose administered during the initial examination. If the exposure source is available for testing and is HBsAg-positive, unvaccinated nPEP patients should receive both hepatitis B vaccine and hepatitis B immune globulin during the initial evaluation. Follow-up vaccine doses should be administered during 1–2 months and at 4–6 months after the first nPEP dose. Previously vaccinated sexually assaulted persons who did not receive postvaccination testing should receive a single vaccine booster dose.

HPV vaccination is recommended for female survivors aged 9–26 years and male survivors aged 9–21 years. For MSM with who have not received HPV vaccine or who have been incompletely vaccinated, vaccine can be

administered through age 26 years. The vaccine should be administered to sexual assault survivors at the time of the initial examination, and follow-up dose administered at 1–2 months and 6 months after the first dose.[174]

Routine use of STI prophylaxis is not recommended for sexually abused or assaulted children.[174]

VII-E. Considerations for All Patients Treated with Antiretroviral nPEP

The patient prescribed nPEP should be counseled regarding potential associated side effects and adverse events specific to the regimen prescribed. Any side effects or adverse events requiring immediate medical attention should be emphasized.

VII-E1. Provision of nPEP Starter Packs or a 28-day Supply at Initiation

Patients might be under considerable emotional stress when seeking care after a potential HIV exposure and might not be attentive to, or remember, all the information presented to them before making a decision regarding nPEP. Health care providers should consider giving an initial prescription for 3–7 days of medication (i.e., a starter pack) or an entire 28-day course and scheduling an early follow-up visit. Provision of the entire 28-day nPEP medication supply at the initial visit rather than a starter pack of 3–7 days has been reported to increase likelihood of adherence, especially when patients find returning for multiple follow-up visits difficult.[96,184] Routinely providing starter packs or the entire 28-day course requires that health care providers stock nPEP drugs in their practice setting or have an established agreement with a pharmacy to stock, package and urgently dispense nPEP drugs with required administration instructions. At the patient's second visit, health care providers can discuss the results of baseline HIV blood testing (if rapid tests were not used), provide additional counseling and support, assess medication side effects and adherence, or provide an altered nPEP medication regimen if indicated by side effects or laboratory test results. nPEP starter packs or 28-day supplies might also include such medications as antiemetics to alleviate recognized side effects of the specific medications prescribed, if they occur. Health care providers should counsel patients regarding which side effects might occur (Table 6), how to manage them, and when to contact the provider if they do not resolve.[173]

VII-E2. Expert Consultation

When health care providers are inexperienced with prescribing or managing patients on antiretroviral medications or when information from persons who were the exposure source indicates the possibility of antiretroviral resistance, consultation with infectious disease or other HIV-care specialists, if available immediately, is warranted before prescribing nPEP to determine the correct regimen. Similarly, consulting with specialists with experience using antiretroviral drugs is advisable when considering prescribing nPEP for certain persons—pregnant women (infectious disease specialist or obstetrician), children (pediatrician), or persons with renal dysfunction (infectious disease specialist or nephrologist). However, if such consultation is not available immediately, nPEP should be initiated promptly and, if necessary, revised after consultation is obtained. Expert consultation can be obtained by calling the PEPline at the National Clinician's Consultation Center at 888-448-4911 (additional information is available at http://nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/).

VII-E3. Facilitating Adherence

Observational studies have reported that adherence to nPEP regimens is often inadequate and has been especially so among sexual assault survivors. Medication adherence can be facilitated by (1) prescribing medications with fewer side effects, fewer doses per day, and fewer pills per dose; (2) educating the patient

regarding potential side effects of the specific medications prescribed and providing medications to assist if side effects occur (e.g., antiemetics); (3) recommending medication adherence aids (e.g., pill boxes); (4) helping patients incorporate doses into their daily schedules; and (5) providing a flexible and proactive means for patient–health care provider contact during the nPEP period.[185,186] Also, establishing a trusting relationship and maintaining good communication about adherence can help to improve completion of the nPEP course. Adherence to the nPEP medications prescribed to children will depend on the involvement of and support provided to parents and guardians.

VII-E4. HIV Prevention Counseling

The majority of persons who seek care after a possible HIV exposure do so because of failure to initiate or maintain effective risk-reduction behaviors. Notable exceptions are sexual assault survivors and persons with community-acquired needlestick injuries.

Although nPEP can reduce the risk for HIV infection, it is not always effective. Therefore, patients should practice protective behaviors with sex partners (e.g., consistent condom use) or drug-use partners (e.g., avoidance of shared injection equipment) throughout the nPEP course to avoid transmission to others if they become infected and after nPEP to avoid future HIV exposures.

At follow-up visits, when indicated, health care providers should assess their patients' needs for behavioral intervention, education, and services. This assessment should include frank, nonjudgmental questions about sexual behaviors, alcohol use, and illicit drug use. Health care providers should help patients identify ongoing risk concerns and develop plans for improving their use of protective behaviors.[187]

To help patients obtain indicated interventions and services, health care providers should be aware of local resources for high-quality HIV education and ongoing behavioral risk reduction, counseling and support, inpatient and outpatient alcohol and drug-treatment services, family and mental health counseling services, and support programs for HIV-infected persons. Information regarding publicly funded HIV prevention programs can be obtained from state or local health departments.

VII-E5. Providing PrEP After nPEP Course Completion

Persons who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of nPEP should be offered PrEP[11] at the conclusion of their 28-day nPEP medication course. Because no evidence exists that prophylactic antiretroviral use delays seroconversion and nPEP is highly effective when taken as prescribed, a gap is unnecessary between ending nPEP and beginning PrEP. Upon documenting HIV-negative status, preferably by using an Ag/Ab test, daily use of the fixed dose combination of TDF (300mg) and FTC (200 mg) can begin immediately for patients for whom PrEP is indicated. Clinicians with questions about prescribing PrEP, are encouraged to call the PrEPline 855-448-7737 at the National Clinician Consultation Center or go to their website (http://nccc.ucsf.edu/clinician-consultation/prep-pre-exposure-prophylaxis/).

VII.E6. Providing nPEP in the Context of PrEP

Patients fully adhering to a daily PrEP regimen as recommended by their health care practitioner are not in need of nPEP if they experience a potential HIV exposure while on PrEP. PrEP is highly effective when taken daily or near daily.[11,188] For patients who report that they take their PrEP medication sporadically and those who did not take it within the week before the recent exposure, initiating a 28-day course of nPEP might be indicated. In

that instance, all nPEP baseline and follow-up laboratory evaluations should be conducted. After the 28-day nPEP regimen is completed, if confirmed to be HIV uninfected, the daily PrEP regimen can be reinitiated.

VII-E7. Management of Source Persons with HIV Infection

When persons who were the exposure source are present during the course of evaluating a patient for potential HIV exposure, health care providers should also assess that person's access to relevant medical care, behavioral intervention, and social support services. If needed care cannot be provided directly, health care providers should help HIV-infected source persons obtain care in the community (http://locator.aids.gov/).

VII-F. Additional Considerations

VII-F1. Reporting and Confidentiality

As with all clinical care, health care providers should handle nPEP evaluations with confidentiality. Confidential reporting of STIs and newly diagnosed HIV infections to health departments should occur as indicated by that jurisdiction's local laws and regulations.

For cases of sexual assault, health care providers should document their findings and assist patients with notifying local authorities.[174] How health care providers should document and report their findings is beyond the scope of these guidelines. Laws in all 50 states strictly limit the evidentiary use of a survivor's previous sexual history, including evidence of previously acquired STIs, to avoid efforts to undermine the credibility of the survivor's testimony. Evidentiary privilege against revealing any aspect of the survivor's examination or medical treatment also is enforced in the majority of most states.

Certain states and localities have special programs that provide reimbursement for medical therapy, including antiretroviral medication after sexual assault, and those areas might have specific reporting requirements. In all states, sexually assaulted persons are eligible for reimbursement of medical expenses through the U.S. Department of Justice Victim's Compensation Program in cases where the sexual assault is reported to the police (http://www.ojp.usdoj.gov/ovc/map.html).When the sexual abuse of a child is suspected or documented, the clinician should report it in compliance with that jurisdiction's laws and regulations.

VII-F2. Special Populations

VII-F2a. Sexually Assaulted Persons

Eighteen percent of a national sample of adult women in the United States reported having ever been raped, and approximately 1 in 10 women (9.4%) has been raped by an intimate partner during her lifetime.[189] Sexual assault also occurs among men. Approximately 1 in 71 men (1.4%) in the United States has been raped at some time in his life.[189] In 1 series from an ED, 5% of reported rapes involved men sexually assaulted by men.[190]

Sexual assault typically has multiple characteristics that increase the risk for HIV transmission if the assailant is infected. In 1 prospective study of 1,076 sexually assaulted person, 20% had been attacked by multiple assailants, 39% had been assaulted by strangers, 17% had had anal penetration, and 83% of females had been penetrated vaginally. Genital trauma was documented among 53% of those assaulted, and sperm or semen was detected in 48%.[191] Often, in both stranger and intimate-partner rape, condoms are not used[192,193] and STIs are frequently contracted.[194-197] In the largest study[198] examining prevalence of HIV infection among sexual assailants, 1% of men convicted of sexual assault in Rhode Island were HIV infected when they entered prison, compared with 3% of all prisoners and 0.3% of the general male population.

Persons provided nPEP after sexual assault or child sexual abuse should be examined and co-managed by professionals specifically trained in assessing and counseling patients and families during these circumstances (e.g., Sexual Assault Nurse Examiner [SANE] program staff). Local SANE programs can be located at http://www.sane-sart.com/. Patients who have been sexually assaulted will benefit from supportive services to improve adherence to nPEP if it is prescribed, and from crisis, advocacy, and counseling services provided by sexual assault crisis centers.

VII-F2b. Pregnant Women and Women with Childbearing Potential

Information is being collected regarding safe use of antiretroviral drugs for pregnant and breastfeeding women who do not have HIV infection, particularly those whose male partners have HIV infection and who use antiretrovirals as PrEP.[114] Because considerable experience has been gained in recent years in the safe and recommended use of antiretroviral medications during pregnancy and breastfeeding among women with HIV infection—either for the benefit of the HIV-infected woman's health or to prevent transmission to newborns—and because of the lack of similar experience in HIV-uninfected pregnant women, nPEP drug recommendations (Table 5) rely on those used for HIV-infected women during pregnancy and breastfeeding.

Health care providers should be aware that certain medications are contraindicated for use as nPEP among potentially or actually pregnant women as follows (Table 7):

- Efavirenz (EFV) is classified as FDA pregnancy Category D because of its potential teratogenicity when used during the first 5–6 weeks of pregnancy.[199] It should be avoided in nPEP regimens for HIV-uninfected women during the first trimester and should not be used for women of childbearing age who might become pregnant during an antiretroviral prophylaxis course. For all women with childbearing potential, pregnancy testing must be done before the EFV initiation, and women should be counseled regarding potential risks to the fetus and the importance of avoiding pregnancy while on an EFV-containing regimen.[114]

- Prolonged use of stavudine (d4T) in combination with didanosine (DDI) for HIV-infected pregnant women has been associated with maternal and fetal morbidity attributed to lactic acidosis; therefore, this combination is not recommended for use in an nPEP regimen during pregnancy.[123,124]

- Because using indinavir (IDV) is associated with increased risk for nephrolithiasis among pregnant women and its use without co-administration of a ritonavir as a boosting agent can result in substantially decreased plasma levels of IDV (the active agent) among pregnant women, IDV should not be used as nPEP for pregnant women.

- Severe hepatotoxicity has been observed among patients administered nevirapine (NVP)-containing nPEP regimens (regardless of pregnancy status); therefore, NVP is contraindicated for nPEP, including for pregnant women.[83]

Table 7. Antiretroviral medications that should not be used for nPEP among pregnant women

Antiretroviral	Risk in pregnancy	Concern
Efavirenz	Teratogenicity	Fetal safety
Nevirapine	Hepatotoxicity	Maternal safety
Stavudine and didanosine	Mitochondrial toxicity and lactic acidosis	Maternal safety
Indinavir (without co-administration with ritonavir) during second or third trimester	Substantially decreased plasma concentration; risk for nephrolithiasis	Efficacy and maternal safety
Abbreviation: nPEP, nonoccupational postexposure prophylaxis.		

If nPEP is prescribed to a woman who is pregnant at the time of exposure or becomes pregnant while on nPEP, health care providers should enter the patient's information (anonymously) into the Antiretroviral Pregnancy Registry (http://www.apregistry.com).

VII-F2c. Incarcerated Persons

Approximately 2 million persons are incarcerated in jails and prisons and can be at risk for HIV infection acquisition during incarceration. Studies have indicated that the risk for becoming infected while incarcerated is probably less than the risk outside a facility[200-202]; nevertheless, correctional facilities should develop protocols for nPEP to help reduce the legal, emotional and medical problems associated with an exposure event for this vulnerable population. As foundation for nPEP provision when it is indicated, correctional facilities should provide HIV education, voluntary HIV testing, systems to assist in identifying potential HIV exposures without repercussion for inmates, and provision of nPEP evaluation and medication. Sexual assaults in particular can put inmates at risk for HIV acquisition and inmates may engage in behaviors that put them at risk for HIV acquisition both prior to being incarcerated and upon reentry into the community. A 15-minute interactive educational program designed to educate inmates about nPEP resulted in a 40% increase in knowledge compared to baseline regardless of inmate-related demographics or HIV-risk characteristics.[203]

The federal Bureau of Prisons has published a clinical practice guideline that integrates guidance for nonoccupational and occupational HIV-related exposures.[204] Those guidelines specific to nPEP represent an adaptation of the 2005 CDC nPEP guidelines and outline HIV postexposure management recommendations for the different exposure types. The federal Bureau of Prisons nPEP recommendations can be modified for use in correctional facilities of varying sizes and resources. The Bureau of Prisons guidelines provide practical materials for both correctional health care providers and inmates and include worksheets to assist health care providers in systematically documenting HIV exposures and nPEP therapy management, and sample patient consent forms. They recommend that each correctional facility develop its own postexposure management protocol. The CDC recommends that health care providers should make every effort to use of current CDC guidelines related to selection of nPEP antiretrovirals.

VII-F2d. PWID

A history of injection drug use should not deter health care providers from prescribing nPEP if the exposure provides an opportunity to reduce the immediate risk for acquisition of HIV infection. A survey of health care providers who treat PWID determined a high degree of willingness to provide nPEP after different types of potential HIV exposure.[202]

When evaluating whether exposures are isolated, episodic, or ongoing, health care providers should assess whether persons who continue to engage in injecting or sexual HIV risk behaviors are practicing risk reduction (e.g., not sharing syringes, using a new sterile syringe for each injection, and using condoms with every partner or client). For certain persons, a high-risk exposure might be an exceptional occurrence and merit nPEP despite their ongoing general risk behavior. For other persons, the risk exposures might be frequent enough to merit consideration of PrEP either instead of nPEP or after a 28-day nPEP course.

PWID should be assessed for their interest in substance abuse treatment and their knowledge and use of safe injecting and sexual practices. Patients desiring substance abuse treatment should be referred for such treatment. Persons who continue to inject or who are at risk for relapse to injection drug use should be instructed regarding use of a new sterile syringe for each injection and the importance of avoiding sharing injection equipment. In areas where programs are available, health care providers should refer such patients to sources of sterile injection equipment. When sexual practices can result in ongoing risk for HIV acquisition, referral for sexual risk-reduction interventions is recommended.

None of the preferred or alternative antiretroviral drugs recommended for nPEP in Table 5 have substantial interactions with methadone or buprenorphine. However, other antiretrovirals might decrease or increase methadone levels; therefore, health care providers electing to use antiretrovirals not specifically recommended for nPEP should check for interactions before prescribing to persons on opiate substitution therapy. For example, RTV-boosted DRV can decrease methadone levels marginally (within acceptable clinical range), and careful monitoring for signs and symptoms of withdrawal is advised.[205]

VII-F3. Special Legal and Regulatory Concerns

VII-F3a. HIV Testing of Exposure Source Patients

When approaching persons who were the exposure source for patients being considered for nPEP, health care providers should be aware of potential legal concerns related to requesting them to undergo HIV testing. During 2011, a total of 33 states had ≥ 1 HIV-specific criminal exposure laws.[206] These laws focus explicitly on persons living with HIV. HIV-specific criminal laws criminalize or impose additional penalties on certain behaviors (e.g., sexual activity or needle-sharing without disclosure of HIV-positive status) and sex offenses. In jurisdictions where consent to HIV testing might invoke legal repercussions (see http://www.cdc.gov/hiv/policies/law/states/), the exposure source person should be made aware of possible legal jeopardies. Health care providers can opt instead to make nPEP treatment decisions without HIV testing of the source.

VII-F3b. Adolescents and Clinical Preventive Care

Health care providers should be aware of local laws and regulations that govern which clinical services adolescent minors can access with or without prior parental consent. In certain jurisdictions, minors of particular ages can access contraceptive services, STI diagnosis and treatment, or HIV testing without parental or guardian consent. In fewer settings, minors can access clinical preventive care (e.g. vaccines, nPEP, or PrEP).[207] To provide and coordinate care when a minor presents for possible nPEP, health care providers should understand their local regulations and institutional policies guiding provision of clinical preventive care to adolescent minors.

VII-F4. Potential Sources of Financial Assistance for nPEP Medication

Antiretroviral medications are expensive, and certain patients are unable to cover the out-of-pocket costs. When public, privately purchased, or employer-based insurance coverage is unavailable, health care providers can assist patients with obtaining antiretroviral medications through the medication assistance programs of the pharmaceutical companies that manufacture the prescribed medications. Applications are available online that can be faxed to the company or certain companies can be called on an established phone line. Requests for assistance often can be handled urgently so that accessing medication is not delayed. Information for specific medications and manufacturers is available at http://www.pparx.org/en/prescription_assistance_programs/list_of_participating_programs.

Additionally, persons being prescribed nPEP after sexual assault can be reimbursed for medications and clinical care costs through state Crime Victim's Compensation Programs funded by the U.S. Department of Justice. Contact information for each state is available at http;//www.ojp.usdoj.gov/ovc/map.html or http;//www.nacvcb.org/index.asp?bid=16.

VIII. CONCLUSION

Accumulated data from human clinical and observational studies, supported by data from animal studies, indicate that using antiretroviral medication initiated as soon as possible ≤72 hours after sexual, injection drug use, or other substantial nonoccupational HIV exposure and continued for 28 days might reduce the likelihood of HIV acquisition. Because of these findings, DHHS recommends prompt initiation of nPEP with a combination of antiretroviral medications when persons seek care ≤72 hours after exposure, the source is known to be HIV infected, and the exposure event presents a substantial risk for HIV acquisition by an exposed, uninfected person. When the HIV status of the source is unknown and the patient seeks care ≤72 hours after exposure, DHHS does not recommend for or against nPEP, but encourages health care providers and patients to weigh the risks and benefits on a case-by-case basis. When the HIV acquisition risk is negligible or when patients seek care > 72 hours after a substantial exposure, nPEP is not recommended. A 3-drug nPEP regimen is recommended for all persons for whom nPEP is indicated. Providing a 28-day nPEP supply or a 3–7 day nPEP starter pack at initiation of nPEP might improve adherence. Providing medications to ameliorate specific side effects for the antiretrovirals prescribed might improve adherence to the nPEP regimen. Figure 2 includes a summary of key nPEP considerations.

Figure 2. nPEP considerations summary

Initial nPEP Evaluation

- Obtain history of potential exposure event
  - HIV and HBV status of exposed person and source person, if available
  - Timing of most recent potential exposure
  - Type of exposure event and risk for HIV acquisition
  - Make determination if nPEP is indicated
- If nPEP is indicated
  - Conduct laboratory testing
    - HIV blood test (rapid combined Ag/Ab test, if available)
    - STIs, HBV, HCV, pregnancy, and chemistries, as indicated
  - Prescribe 28-day nPEP course
    - Educate patient about potential regimen-specific side effects and adverse events
    - Counsel patient about medication adherence
    - Provide patient with nPEP prescription or full 28-day nPEP course or nPEP starter pack and prescription
  - When necessary, assist patients with obtaining nPEP medication through a medication assistance program for the prescribed regimen
- For all persons evaluated
  - Prescribe prophylaxis for STIs and HBV infection, if indicated
  - Provide counseling related to HIV prevention strategies, as appropriate
  - Document sexual assault findings and fulfill local reporting requirements
  - Conduct confidential reporting of newly diagnosed STIs and HIV infection to health department
  - Link HIV-infected persons to relevant medical and psychosocial support services

Follow-up evaluations for persons prescribed nPEP

- Conduct HIV and any other indicated laboratory testing
- Consider changing nPEP regimen if indicated by side effects or results of initial testing
- Provide additional counseling and support for medication adherence and HIV prevention, if indicated

Abbreviations: Ag/Ab, antigen/antibody combination test; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis; STI, sexually transmitted infection.

VIII-A. Plans for Updating These Guidelines

These guidelines are intended to assist U.S. health care providers in reducing the occurrence of new HIV infections through the effective delivery of nPEP to the patients most likely to benefit. As new medications and new information regarding nPEP become available, these guidelines will be revised and published.

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X. APPENDICES

Appendix 1A

Summary of Methods for nPEP Guidelines Development and Roles of Teams and Consultants

Topic	Comment
The guidelines' goal	Provide guidance for medical practitioners regarding nPEP use for persons in the United States.
nPEP Working Group	The nPEP Working Group is composed of 13 members from the Centers for Disease Control and Prevention (CDC) with expertise in nPEP or other subject areas pertinent to the guidelines (e.g., cost-effectiveness, sexual assault, or nPEP adherence), including certain members who were involved in the writing of the previous version(s) of the CDC nPEP guidelines.
nPEP Writing Group	The nPEP Writing Group is composed of 12 members from CDC with expertise in nPEP or other subject areas pertinent to the guidelines (e.g., cost-effectiveness, sexual assault, or nPEP adherence, etc.), including 1 member who was involved in the writing of the previous version of CDC's nPEP guidelines.
nPEP external consultants	External consultants were selected from government, academia, and the health care community by CDC to participate in 2 consultations by telephone conference call regarding nPEP on the basis of the member's area of subject matter expertise. Each consultation was chaired by 1 of the CDC nPEP co-chairs. The list of the external consultants is available in Appendix 2B.
Competing interests and management of conflicts of interest	All internal CDC staff and external consultants involved in developing the guidelines or who served in the external consultations submitted a written financial disclosure statement reporting any potential conflicts of interest related to questions discussed during the consultations or concerns involved in developing of the nPEP guidelines. A list of these disclosures and their last update is available in Appendix 2C. The nPEP co-chairs reviewed each reported association for potential competing interest and determined the appropriate action, as follows: disqualification from the panel, disqualification/recusal from topic review and discussion; or no disqualification needed. A *competing interest* is defined as any direct financial interest related to a product addressed in the section of the guideline to which a panel member contributes content. *Financial interests* include direct receipt by the panel member of payments, gratuities, consultancies, honoraria, employment, grants, support for travel or accommodation, or gifts from an entity having a commercial interest in that product. *Financial interest* also includes direct compensation for membership on an advisory board, data safety monitoring board, or speakers bureau. Compensation and support that filters through a panel member's university or institution (e.g., grants or research funding) is not considered a competing interest.

Topic	Comment
OMB Peer Review and OMB Public Engagement	As recommended by the Office of Management and Budget for scientific documents fitting the classification of Influential Scientific Information, during Oct. 2014–December 2015, the draft nPEP guidelines underwent peer review by independent scientific and technical experts. They were asked to review the scientific and technical evidence that provides the basis for the nPEP guidelines and to provide input on the draft guidelines before they were finalized. Peer reviewers were asked whether any recommendations are based on studies that were inappropriate as supporting evidence or were misinterpreted, whether there are significant oversights, omissions, or inconsistencies that are critical for the intended audience of clinicians, and whether the recommendations for the intended audience of health care providers are justified and appropriate. In addition, the recommendations from the draft nPEP guidelines were presented to the public through 2 public engagement webinars on November 14 and 17, 2014. Based on the responses from both peer review and public engagement, updates were made to the nPEP guidelines prior to their publication. CDC's responses to the comments were also posted on the CDC/ATSDR Peer Review Agenda website at http://www.cdc.gov/od/science/quality/support/peer-review.htm and the CDC Division of HIV/AIDS Prevention Program Planning Scientific Information Quality—Peer Review Agenda website at http://www.cdc.gov/hiv/policies/planning.html.
Guidelines users	Health care providers
Developer	The CDC nPEP Working Group
Funding source	Epidemiology Branch, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, TB Prevention, CDC
Recommendation ratings	Because none of the evidence is based on randomized clinical trials, but rather observational studies or expert opinion, we have elected not to provide graded recommendations for these guidelines.
Abbreviations: AIDS, acquired immunodeficiency virus; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis.	

Appendix 1B

nPEP Guidelines Development Teams and Consultants

CDC nPEP Guidelines Writing Team

Kenneth L. Dominguez, MD, MPH (lead author), Dawn K. Smith, MD, MS, MPH, Vasavi Thomas, RPh, MPH; Nicole Crepaz, PhD; Karen S. Lang, MSW; Walid Heneine, PhD; Janet McNicholl, MD; Laurie Reid, RN, MS; Brandi Freelon, MD; Steven Nesheim, MD; Ya-lin (Aileen) Huang, PhD; and Paul J. Weidle, PharmD, MPH.

CDC nPEP Working Group

Ken Dominguez, MD, MPH (Co-lead); Vasavi Thomas, RPh, MPH (Co-lead), Dawn K. Smith, MD, MS, MPH; Steve Nesheim, MD; Walid Heneine, PhD; Lauri Reed, Brandi Freelon, MD; Nicole Crepaz, PhD; Karen S. Lang, MSW; Ya-lin (Aileen) Huang, PhD; Kathleen Irwin, MD, MPH; Gema Dumitru, MD; David Kuhar, MD; and Lynn Paxton, MD, MPH.

Federal Consultants

CDC: Norma Harris, PhD; John Brooks, MD; Pragna Patel, MD, MPH; and Philip J. Peters, MD.

Other Federal Agencies

Holly Van Lew, PharmD, Indian Health Service; Newton Kendig, MD, Bureau of Prisons; David Burns, MD, National Institutes of Health; Laura Cheever, MD, Health Resources and Services Administration; Maggie Czarnogorski, MD, Department of Veterans Affairs; Heather Huentelman, PharmD, Indian Health Service; Kimberly Struble, PharmD, Food and Drug Administration; Rohan Hazra, MD, National Institutes of Health; Lynne Mofenson, MD, National Institutes of Health; and Steve George Siberry, MD, MPH, National Institutes of Health.

Nonfederal External Consultants

Jeffrey Beal, MD, Florida Department of Health; Ronald H. Goldschmidt, MD, University of California, San Francisco; Donna Greco, MSW, Pennsylvania Coalition Against Rape/National Sexual Violence Resource Center; Angela Kashuba, BScPhm, PharmD, University of Northern Carolina Center for AIDS Research, Chapel Hill; Sally Laskey, MA, National Sexual Violence Resource Center, Enola, Pennsylvania; Kenneth Mayer, MD, Fenway Health Center, Boston, Massachusetts; Thera Meehan, MS, MPH, Massachusetts Department of Public Health, Boston; Jennifer Sayles, MD, Los Angeles County Public Health Department, California; Barbara Sheaffer, MA, Pennsylvania Coalition Against Rape, Enola, Pennsylvania; Lyn Stevens, MS, ACRN, NP, New York State Department of Health, Albany; Elaine Abrams, MD, Columbia University College of Physicians & Surgeons, New York, New York; Michael Brady, MD, Columbus Children's Hospital, Ohio; Ellen Chadwick, MD, Northwestern University's Feinberg School of Medicine, Chicago, Illinois; Rana Chakraborty, MD, Emory University School of Medicine, Atlanta, Georgia; Ellen Cooper, MD, Boston University School of Medicine, Massachusetts; Peter Havens, MD, MPH, Children's Hospital of Wisconsin, Milwaukee; Daniel Johnson, MD, Comer Children's Hospital, University of Chicago, Illinois; Paul Krogstad, MD, University of California at Los Angeles–David Geffen School of Medicine; Natalie Neu, MD, MPH, Columbia University Medical Center, New York, New York; Vicki Peters, MD, New York City Department of Health and Mental Hygiene, New York; Russ van Dyke, MD, Tulane University School of Medicine. New

Orleans, Louisiana; and Geoffrey Weinberg, MD, University of Rochester Medical Center, School of Medicine and Dentistry, New York.

CDC Scientific Support Staff

Beverly Bohannon, RN, MS; and Wayne Hairston II, MPH, MBA, ICF International, Atlanta, Georgia.

CDC editor

C. Kay Smith, Med

Abbreviation: nPEP, nonoccupational postexposure prophylaxis.

Appendix 1C

Financial Disclosures of Potential Competing Interest nPEP Guidelines Consultants and Working Group

Member (affiliation)	Role	Company	Relationship	Determination
Elaine Abrams, MD, Columbia University College of Physicians & Surgeons	Non-federal external consultant	None		
Jeffrey Beal, MD, Florida Department of Health	Non-federal external consultant	CDC Flow Through Money—Perinatal Transmission Project	Principal Investigator	No disqualification needed
Beverly Bohannon, RN, MS, CDC	CDC scientific support staff	None		
Michael Brady, MD, Columbus Children's Hospital	Non-federal external consultant	None		
John Brooks, MD, CDC	Other CDC consultant	None		
David Burns, MD, NIH	Other federal consultant	None		
Ellen Chadwick, MD, Northwestern University's Feinberg School of Medicine	Non-federal external consultant	Abbott Labs	Spouse—Abbott retiree; Spouse—owner of stocks and stock options	Recusal from topic review and discussion of selection of antiretrovirals for nPEP use
Rana Chakraborty, MD, Emory University School of Medicine	Non-federal external consultant	None		
Laura Cheever, MD, HRSA	Other federal consultant	None		
Ellen Cooper, MD, Boston University School of Medicine	Non-federal external consultant	None		
Nicole Crepaz, PhD, CDC	nPEP Writing Team, nPEP Workgroup	None		
Maggie Czarnogorski, MD, Department of Veterans Affairs	Other federal consultant	None		
Kenneth L. Dominguez, MD, MPH, Co-lead, CDC	nPEP Writing Team and nPEP Workgroup (co-lead)	None		
Gema Dumitru, MD, CDC	nPEP Workgroup	None		
Brandi Freelon, MD, CDC	nPEP Writing Team and nPEP Workgroup	None		
Ronald H. Goldschmidt, MD, University of California, San Francisco	Non-federal external consultant	CDC funding PEPline	Director—National HIV/AIDS Clinician's Consultation Center	No disqualification needed
Wayne Hairston II, MPH, MBA, CDC	CDC scientific support staff	None		
Norma Harris, PhD, CDC	Other CDC consultant	None		

Member (affiliation)	Role	Company	Relationship	Determination
Peter Havens, MD, MPH, Children's Hospital of Wisconsin	Non-federal external consultant	None		
Rohan Hazra, MD, NIH	Other federal consultant	None		
Walid Heneine, PhD, CDC	nPEP Writing Team and nPEP Workgroup	None		
Ya-lin (Aileen) Huang, PhD, CDC	nPEP Writing Team and nPEP Workgroup	None		
Heather Huentelman, PharmD, IHS	Other federal consultant	None		
Kathleen Irwin, MD, MPH, CDC	nPEP Workgroup	None		
Daniel Johnson, MD, Comer Children's Hospital; University of Chicago	Non-federal external consultant	None		
Angela Kashuba, BScPhm, PharmD, University of North Carolina Center for AIDS Research	Non-federal external consultant	None		
Newton Kendig, MD, Bureau of Prisons	Other federal consultant			
Paul Krogstad, MD, University of California Los Angeles—David Geffen School of Medicine	Non-federal external consultant	None		
David Kuhar, MD, CDC	nPEP Workgroup	None		
Karen S. Lang, MSW, CDC	nPEP Writing Team and nPEP Workgroup	None		
Sally Laskey, MA, National Sexual Violence Resource Center	Non-federal external consultant	None		
Janet McNicholl, MD, CDC	nPEP Writing Team	None		
Thera Meehan, MS, MPH, Massachusetts Department of Public Health	Non-federal external consultant	None		
Lynne Mofenson, MD, NIH	Other federal consultant	None		
Steven Nesheim, MD, CDC	nPEP Writing Team and nPEP Workgroup	None		
Natalie Neu, MD, MPH, Columbia University Medical Center	Non-federal external consultant	None		
Pragna Patel, MD, CDC	Other CDC consultant	None		
Lynn Paxton, MD, MPH, CDC	nPEP Workgroup	None		
Philip J. Peters, MD, CDC	Other CDC consultant	None		
Vicki Peters, MD, New York City Department of Health and Mental Hygiene	Non-federal external consultant	None		

Member (affiliation)	Role	Company	Relationship	Determination
Laurie Reid, RN, MS, CDC	nPEP Writing Team and nPEP Workgroup	None		
Jennifer Sayles, MD, Los Angeles County Public Health Department	Non-federal external consultant	None		
Barbara Sheaffer, MA, Pennsylvania Coalition Against Rape	Non-federal external consultant	CDC funding—National Sexual Violence Resource Center	Medical Advocacy Coordinator	No disqualification needed
George Steve Siberry, MD, MPH, NIH	Other federal consultant	None		
Dawn Smith, MD, MS, MPH, CDC	nPEP Writing Team and nPEP Workgroup	Salaried by CDC to do nPEP work	Medical Epidemiologist, Biologic Intervention	No disqualification needed
Lyn Stevens, MS, ACRN, NP, New York State Department of Health	Non-federal external consultant	CDC Grant (Adult Viral Hepatitis)	Adult Viral Hepatitis Prevention Coordinator	No disqualification needed
Kimberly Struble, PharmD, FDA	Other federal consultant	None		
Vasavi Thomas, RPh, MPH, CDC	nPEP Writing Team and nPEP Workgroup (co-lead)	None		
Russ van Dyke, MD, Tulane University School of Medicine	Non-federal external consultant	None		
Holly Van Lew, PharmD, Indian Health Service	Other federal consultant	None		
Paul J Weidle, PharmD, MPH, CDC	nPEP Writing Team	None		
Geoffrey Weinberg, MD, University of Rochester Medical Center, School of Medicine and Dentistry	Non-federal external consultant	None		

Abbreviations: CDC, Centers for Disease Control and Prevention; nPEP, nonoccupational postexposure prophylaxis.

Appendix 2

Literature Search Methods for the nPEP Guidelines

Topic	Databases	Research Question	Keywords	Dates of Search	Search Limits
Animal Studies	PubMed	Which studies related to PEP involving animal models were published since 2005?	SIV post exposure prophylaxis, post-exposure prophylaxis, antiretroviral prophylaxis in macaques	January 2005 to July 2015	No limitations
Observational Studies, Case Reports	Web of Knowledge, PubMed, Google Scholar	Which are the results of latest nPEP observational and case studies since 2005 with a focus on populations studied, drug regimens used, completion rates, side effects of medications, number of breakthrough infections?	nPEP, nonoccupational postexposure or post-exposure prophylaxis, and HIV postexposure or post-exposure prophylaxis	January 2005 to July 2015	Excluded opinion pieces; no other limitations
Effects on Risk-Reduction Behaviors	MEDLINE, EMBASE, CINAHI [EBSCOhost]	What are the potential behavioral implications of offering nPEP?	HIV infections, acquired immune deficiency syndrome, seropositivity, serodiagnosis, HIV, AIDS, post exposure or post-exposure prophylaxis, post exposure or post-exposure prevention, non-occupational, non pep, NOPEP, nPEP, PEP	January 1996 to July 2015	No limitations
Cost Effectiveness	PubMed	The cost-effectiveness evaluation of nPEP in the United States and other resource-rich countries.	HIV, post exposure post-exposure prophylaxis, PEP, nPEP, economic evaluation, cost utility, cost-benefit analysis, cost benefit, cost effectiveness	January 2005 to July 2015	English only; excluded occupational exposure; not an economic evaluation; no other limitations
Pregnant Women, Women of Childbearing Potential	PubMed	Which nPEP studies involving pregnant women and women of childbearing potential were conducted since 2005?	pregnant women, women of reproductive age, PEP, nPEP, postexposure or post-exposure HIV prophylaxis	January 2005 to July 2015	No limitations
Children/Adolescents	PubMed	Which nPEP studies involving children or adolescents were conducted since 2005?	Children, pediatrics, adolescents, PEP, nPEP, postexposure or post-exposure HIV prophylaxis	January 2005 to July 2015	No limitations
Sexual Assault Survivors	PubMed	Which nPEP studies involving sexual assault survivors were conducted since 2005?	Sexual assault, sexual abuse, PEP, nPEP, postexposure or post-exposure HIV prophylaxis	January 2005 to July 2015	No limitations
Incarcerated Populations	PubMed	Which nPEP studies involving incarcerated populations were conducted since 2005?	Incarcerated, jail, prison, correctional facility, nPEP, PEP	January 2005 to July 2015	No limitations

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; nPEP, non-PEP, or NOPEP, nonoccupational postexposure prophylaxis; PEP, postexposure prophylaxis.

Appendix 3

Studies Reviewed for the nPEP Guidelines

MSM Studies

Authors, year: Donnell et al, 2010[14]

Type of study: Randomized behavioral intervention trial to assess perceptions and nPEP use over a 4-year period

Location: 6 U.S. cities

Sample size: n=4,295 MSM

Risk: HIV uninfected men who reported unprotected anal sex in the past year

Intervention: Behavioral intervention vs. standard risk-reduction counseling (accompanying nPEP drug regimen not reported)

Drug regimen: Not reported

Time from exposure to nPEP: Not reported

Completion of nPEP: Not reported

HIV seroconversions: 3

Conclusion: Increased odds of nPEP use was observed in participants with multiple partners and participants who had unprotected anal sex with HIV infected and unknown status partners. The availability of nPEP did not lead to an increase in high-risk sex.

Authors, year: Foster et al, 2015[19]

Type of study: Open-label, single-arm nonrandomized trial at 2 public sexual health clinics and 2 hospital EDs during December 23, 2012–June 12, 2014.

Location: Melbourne, and Sydney, Australia

Sample size: n=100 MSM

Risk: Sexual 65% failed to use a condom after anal intercourse; 29% used a condom but it tore or slipped off; 6% source partner removed condom

Intervention: 3-drug single tablet once daily dose regimen

Drug regimen: RPV + FTC + TDF

Time from exposure to nPEP: ≤72 hours; presentation for nPEP initiation at a mean=30 hours; nPEP initiated at a mean of 2 hours after presentation

Completion of nPEP: 92%

HIV seroconversions: 0 seroconversions occurred through week 12 after initiation of nPEP. Adherence was 98.6% by pill count and 98.5% by self–report; 88% tested had plasma TDF levels suggesting full adherence. 88% experienced ≥1 clinical adverse events. Adverse events included mainly fatigue (34%) and nausea (23%); one participant developed acute abdominal pain and vomiting and grade 4 laboratory evidence of acute pancreatitis ≤1 week of completing nPEP.

Conclusion: A triple ARV regimen of RPV, FTC, and TDF administered once daily as a single combination tablet was well tolerated as nPEP with high levels of adherence and regimen completion.

Authors, year: Jain et al, 2015[18]

Type of study: Retrospective medical record review in a large community health center during July1997–August 2013

Location: Boston, Massachusetts

Sample size: n=788 MSM; median age=32.9 years; 21.2% presented for nPEP 2 or more times (range, 1–15 times)

Risk: Consensual unprotected sex most common n=726 (62.2%); n=425 (58.5%) receptive anal; n=277 (38.2%) insertive anal; n=157 (21.6%) receptive oral intercourse; n=351 (31.1%) condom failure or removal; (35.6%) HIV-positive partner

Intervention: nPEP (number of drugs not reported in this study, however, previous studies from this site have reported 2 or 3 drugs)

Drug regimen: Not reported

Time from exposure to nPEP: Not reported but assume 72 hours based on previously published studies from this site

Completion of nPEP: Not reported

HIV seroconversions: 39 seroconversions occurred at >90 days after initially presenting for nPEP; 4 occurred at <180 days: 91, 133, 160, 168 days; 3 of 4 reported completing 28-day regimen; adherence or ongoing sexual risk behavior not reported; 35 (89.7%) seroconversions occurred at ≥180 days after nPEP initiation; seroconversion associated with younger age and/or being African American or Latino; almost 90% of post-nPEP infections were probably due to subsequent risk-taking and not a failure of the initial nPEP regimen

Conclusion: Younger age, being Latino and/or being African American, but not repeated nPEP use, were associated with incident HIV infection. Younger MSM of color who are nPEP users may benefit from early HIV risk reduction and PrEP.

Authors, year: McAllister et al, 2014[17]

Type of study: Nonrandomized, open-label, prospective cohort study at two urban hospital centers

Location: Sydney, Australia

Sample size: n=125 MSM enrolled; n=91 prescribed 3-drug regimen; n=34 prescribed 2-drug regimen; mean age 32–34 years

Risk: Sexual

Intervention: 2-drug or 3-drug regimen

Drug regimen: TDF + FTC or RAL+ TDF + FTC; Mean Adherence to each arm: TDF + FTC (90%); RAL-FTC-TDF (89%); 8 patients reported myalgia on the 3-drug regimen vs. none on the 2-drug regimen; Grade 4 creatinine kinase elevations occurred in 5 subjects on the 3-drug regimen vs. none on the 2-drug regimen. All Grade 4 creatinine kinase elevations resolved to ≤grade 2 after desisting from exercise and increasing oral fluids intake

Time from exposure to nPEP: Not reported

Completion of nPEP: 86/91 (95%) participants prescribed a 3-drug regimen met criteria to stay on nPEP; 79/86 (92%) completed 28-day 3-drug regimen; 31/34 (91%) participants prescribed 2-drug regimen completed 28-day 2-drug regimen; overall 110/120 (91.7%) who met criteria to stay on nPEP completed 28-day regimen; overall 110/125 (88%) who were prescribed nPEP, completed the 28-day regimen

HIV seroconversions: 0

Conclusion: Although the 3-drug and 2-drug arms had similar percentages of patients completing their 28-day regimens, 9% of the 3-drug arm experienced grade 4 creatinine kinase elevations which subsequently resolved with increased fluid intake and desisting exercise. If a RAL-TDF-FTC regimen is used, a preferred nPEP regimen, authors recommend (1) asking patients about concomitant medications associated with rhabdomyolysis (i.e. statins); (2) patient education about possible association between RAL-containing nPEP, exercise, and rhabdomyolysis and the need to report myalgia; (3) laboratory monitoring of serum creatinine

kinase at baseline; if myalgia or weakness develops, conduct additional during treatment and clinical examination for proximal muscle weakness. Completion rates were higher for this study compared to those in other studies, including similar nPEP regimens. This may have been due to a high level of support provided by the study team including an experienced nPEP nurse, 24-hour contact with the nurse consultant, text reminders of appointments, proactive recall after missed appointments and frequent adherence education.

Authors, year: Schechter et al, 2004[16]

Type of study:

Location: Rio de Janeiro, Brazil

Sample size: n=200 participants; median age, 28 years; n=68 received nPEP

Risk: Sexual exposure (gay or bisexual)

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤48 hours

Completion of nPEP: 11 (1 among nPEP users, 10 among patients not using nPEP)

HIV seroconversions:

Conclusion: nPEP was safely tolerated and did not appear to be associated with either increases in reported high-risk behavior or HIV transmission; such findings may limit its impact as a public health intervention

Authors, year: Sonder et al, 2010[15]

Type of study: Observational study comparing 2 nPEP regimens

Location: Amsterdam

Sample size: n=309 MSM

Risk: Sexual exposure

Intervention: One 4-drug regimen and one 3-drug regimen; 2- or 3-pill burden

Drug regimen: Single-dose NVP + ZDV+ 3TC+ NFV or ZDV + 3TC + ATV

Time from exposure to nPEP: Seroconverters presented between 5–36 hours post exposure

Completion of nPEP: 237/261 (91%)

HIV seroconversions: 5 (likely due to ongoing risk behavior)

Conclusion: Common side effects were fatigue, nausea, and diarrhea (worse in regimen 1). There was no significant difference in completion rates of the two regimens. Strategies are needed to prevent subsequent HIV exposures in nPEP-treated individuals

Authors, year: Terzi et al, 2007[13]

Type of study: Case report

Location: Italy

Sample size: n=1 MSM
Risk: Receptive anal intercourse with HIV + male
Intervention: 3-drug regimen; 2-pill burden
Drug regimen: ZDV + 3TC (Combivir) + IDV
Time from exposure to nPEP: 30 hours
Completion of nPEP: Complete adherence
HIV seroconversions:
Conclusion: Sexual exposures to HIV and HCV require prolonged follow-up due to the risk of late seroconversion.

Sexual Assault Studies—Adults, Adolescents, and Children (combined)

Authors, year: Chacko et al, 2012[20]
Type of study: Systematic review of nPEP adherence among victims of sexual assault
Location: U.S. and International
Sample size: n=24 studies of adults, adolescents, and children
Risk: Sexual assault
Intervention: Various 2- and 3-drug regimens
Drug regimen: Most regimens included ZDV
Time from exposure to nPEP: Not reported
Completion of nPEP: 40%
HIV seroconversions: Not reported
Conclusion: Overall adherence was poor but was higher in developing countries compared to developed countries. Common side effects were: nausea and vomiting, diarrhea, and fatigue. More interventions are needed to improve adherence. Standard methods of conducting and reporting nPEP programs are needed.

Authors, year: Draughon and Sheridan, 2011[21]
Type of study: Systematic review spanning 10 years
Location: Sub-Saharan Africa (Kenya, Malawi, and South Africa)
Sample size: n=studies of adults, adolescents, and children
Risk: Sexual assault
Intervention: Not reported
Drug regimen: Not reported
Time from exposure to nPEP: Not reported
Completion of nPEP: 0%–65% (most studies reported > 35%)

HIV seroconversions: Not reported

Conclusion: Overall adherence was low, but was higher in locations where the full 28-day PEP regimen was given up front.

Authors, year: Draughon and Sheridan, 2012[22]

Type of study: Systematic review

Location: Low HIV prevalence countries

Sample size: n=34 studies of adults, adolescents, and children

Risk: Sexual assault

Intervention: nPEP (number of drugs not reported by reviewers)

Drug regimen: Not reported

Time from exposure to nPEP: 24–96 hours

Completion of nPEP: 0%–63%

HIV seroconversions: Not reported

Conclusion: There was wide variation in the provision, acceptance, and adherence to nPEP programs. Anywhere from 5%–100% of eligible patients received nPEP across studies. Further research is needed to understand the experience of sexual assault survivors with the health care system and nPEP following an attack

Authors, year: Loutfy et al, 2008[23]

Type of study: Prospective cohort study

Location: Ontario, Canada

Sample size: n=798 sexual assault survivors presented to sexual assault treatment centers and offered nPEP; females (n=775 [97.1%]), age 4–17 years (n=190 [23.8%]), age 18–80 years (n=608 [77.2%]); 347 accepted nPEP

Risk: Sexual assault

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: Combivir + Kaletra

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 111/347 (31.9%) completed nPEP including (11/46 [23.9%]) of participants at high risk completed therapy and (100/301 [33.2%]) of unknown risk participants completed therapy

HIV seroconversions: Not reported

Conclusion: The PEP program for sexual assault survivors in Ontario proved to be feasible and acceptable among participants. The most common side effects were fatigue, nausea, and diarrhea. Further research is needed to improve loss to follow-up and completion rates of nPEP.

Sexual Assault Studies—Adults and/or Adolescents

Authors, year: Carrieri et al, 2006[33]

Type of study: Retrospective survey of nPEP consultations

Location: Southeastern France

Sample size: n=94 persons, aged 18 years or older, presented to AIDS centers for nonoccupational HIV exposure (female n=88 [93.6%], male n=6 [6.4%]); nPEP prescribed to 86 persons

Risk: Sexual assault

Intervention: 2 and 3 drug regimens

Drug regimen: Not reported

Time from exposure to nPEP: 72% (n=77) ≤48 hours

Completion of nPEP: 25% (n=23) >3 months follow-up

HIV seroconversions: Not reported

Conclusion: Half of all participants were lost to follow-up after the first consultation. During the study period there were 600 additional sexual assaults that were reported to police but did not receive nPEP consultation. Prompt HIV medical assessment is needed for sexual assault survivors as well as strategies to improve nPEP adherence.

Authors, year: Griffith et al, 2010[31]

Type of study: Retrospective chart review in an urban county hospital from June 2007–June 2008

Location: Dallas, TX

Sample size: n=151 adolescent and adult women (151 prescribed nPEP, 62 received follow-up of which 58 self-reported taking nPEP); aged 13–17 years, n=43 (28%); 18–61 years, n=108 (72%)

Risk: Sexual assault

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: Kaletra + Truvada or Combivir

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 62/151 (41%) of women presented for a follow-up visit. 37 of the 62 (60%) took nPEP for ≥21 days or completed prescribed course of therapy

HIV seroconversions: 0 (36 of 58 women who reported taking nPEP at follow-up were HIV screened at week 12 or 24 of follow-up)

Conclusion: Full medication compliance and follow-up counseling remain challenges for sexual assault survivors and providers. A detailed nPEP protocol and continuity of care promotes quality patient management.

Authors, year: Krause et al, 2014[34]

Type of study: Retrospective cohort study of medical records from a level 1 trauma center participating in the Sexual Assault Nurse Examiner (SANE) Program

Location: Northeastern, United States

Sample size: n=179 cases of sexual assault among 171 unique female patients, aged ≥16 years (median: 26 years); nPEP offered to 138 patients for whom PEP was appropriate within the 72-hour window period; an additional 5 patients outside the 72-hour window period were offered PEP; 86% or 124/143 cases who were offered PEP, accepted PEP

Risk: Sexual assault

Intervention: 2-drug or 3-drug regimen

Drug regimen: Either FTC/TDF and LPV/r) (n=85, 59.4%) or FTC/TDF alone (n=32, 22.4%)

Time from exposure to nPEP: ≤72 hours (for most cases; 5 cases were given nPEP outside the 72-hour window)

Completion of nPEP: 34 of 124 (27.4%) cases who followed up with an infectious disease specialist completed nPEP

HIV seroconversions: Not reported

Conclusion: All 138 sexual assault case patients who were eligible for nPEP were offered nPEP. Only a minority of those who were documented to have followed up with an infectious disease specialist completed nPEP. There is a need for a better system for post-assault follow-up.

Authors, year: Linden et al, 2005[30]

Type of study: Retrospective medical record review of female sexual assault survivors presenting to an urban ED during 10/1/99–9/30/2002

Location: Boston, MA

Sample size: n=292 charts reviewed; n=181 in final sample size; mean age 29.1 years (range, 18–82); n=89 patients offered nPEP; n=85 patients accepted

Risk: Sexual assault

Intervention: 2-drug or 3-drug regimen; 1- or 2-pill burden

Drug regimen: Initiated in ED, ZDV + 3TC (Combivir) (n=78); Combivir + NFV (n=4); Initiated in referral clinic: 2-drugs (unspecified) (n=2); 3-drugs (unspecified) (n=1)

Time from exposure to nPEP: Median time from assault to presentation in ED (10.1 hours; range, 0–24 hours)

Completion of nPEP: Overall 18 of 85 (21%), including 15 of 82 (18%) of those initiated on nPEP in ED and 3 of 3 initiated on nPEP after being referred to another clinical care site

HIV seroconversions: No seroconversions during follow-up period in 38 patients with at least 1 follow-up visit

Conclusion: A minority of sexual assault survivors were offered nPEP and few completed full nPEP course.

Authors, year: Olshen et al, 2006[32]

Type of study: Retrospective medical record review of adolescents presenting to urban pediatric EDs ≤72 hours of penetrating sexual assault in 2 academic medical centers during July 1, 2001 to June 30, 2003

Location: Boston, MA

Sample size: n=177 adolescents aged 12–22 years; n=145 adolescents with adequate documentation; n=129 eligible for nPEP; n=110 accepted nPEP; n=85 initiated nPEP

Risk: Sexual assault

Intervention: 2-drug or 3-drug regimen

Drug regimen: 3TC + ZDV (94%); 3TC +ZDV + NFV (3%); 3TC + ZDV + IDV (2%)

Time from exposure to nPEP: ≤ 72 hours

Completion of nPEP: 13/85 (15%) who initiated nPEP completed 28-day course; 37 returned for first follow-up visit

HIV seroconversions: No seroconversions among 23 tested for HIV

Conclusion: Poor rates of nPEP completion among adolescent sexual assault survivors. May be due to uncertainties regarding exposure, high rates of psychiatric comorbidity, and low rates of return for follow-up care.

Sexual Assault Studies Including Children and/or Adolescents

Authors, year: Chesshyre et al, 2009[43]

Type of study: Retrospective review of medical records from January 2005–February 2007

Location: Blantyre, Malawi

Sample size: n=217 children and adolescents presented with history of sexual abuse; ages: n=62 (29%)<5 years; n=113 (52%) 5–10 years; n=42 (19%) 11–16 years; n=92 children were eligible for and received nPEP; n=153 children were not offered nPEP because they presented >72 hours or had chronic history of abuse

Risk: Child sexual abuse

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤ 72 hours

Completion of nPEP: Not reported

HIV seroconversions: No HIV seroconversions in any of the 92 children initiated on nPEP; 7/153 (5%) children who were not offered nPEP tested HIV+

Conclusion: The initiation of an nPEP program for child victims of sexual abuse led to increased numbers of such children presenting for nPEP services and is likely to have resulted in decreased HIV acquisition in this population.

Authors, year: Collings et al, 2008[42]

Type of study: Prospective observational cohort of 200 consecutive cases of child rape referred for assessment to a state hospital, Oct–Dec 2004

Location: KwaZulu-Natal, South Africa

Sample size: n=200 children and adolescents presenting with history of child rape; mean age 10.6 years (range, 1–17 years); 120 children eligible and offered nPEP; n=64 children not eligible due to presentation >72 hours; n=113 followed by hospital; n=7 referred to another nPEP provider

Risk: Child sexual abuse

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤ 72 hours

Completion of nPEP: 40/113 (35.5%) followed by hospital completed 28-day course

HIV seroconversions: No seroconversions among 13/40 children returning for 3-month follow-up and 4/40 children returning at 6-month follow-up.

Conclusion: Poor nPEP adherence and return for follow-up existed; further research is needed to identify reasons for such nonadherence and identify interventions to improve adherence.

Authors, year: Du Mont et al, 2008[44]

Type of study: Retrospective analysis of data on female adolescent sexual assault survivors from the HIV PEP Project, an implementation and evaluation of a program of universal offering of nPEP to sexual assault victims of all ages in 18 hospital-based sexual treatment centers

Location: Ontario, Canada

Sample size: n=386 sexually assaulted female adolescents; mean age 16.7 years (range, 12–19 years); n=325 eligible for nPEP; 307 offered nPEP; n=131 accepted nPEP; the most common reason for declining nPEP was lack of concern about acquiring HIV; students, survivors with marked anxiety, and those encouraged by a health professional were more likely to accept PEP

Risk: Sexual assault

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: Combivir and Kaletra

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 34% (44/131) completed 28-day course nPEP; 47% (61/131) adhered to day 14; the most common side effects were nausea, fatigue, vomiting, and diarrhea; survivors who were white and had known their assailant<24 hours were more likely to complete nPEP; most common reasons for stopping nPEP early: ARV side effects (73%), including most often nausea and fatigue

HIV seroconversions: Permission not obtained to provide results of HIV testing

Conclusion: Stronger health care provider recommendations needed for nPEP; need for training of health care providers to consistently offer and recommend nPEP to all those meeting established risk criteria.

Authors, year: Ellis et al, 2005[37]

Type of study: Prospective study of children presenting to hospital with history of child sexual abuse during January, 1 2004 through December 31, 2004

Location: Blantyre, Malawi

Sample size: n=64 children presented with history of sexual assault; median age 83 months (range, 22–180 months); n=17 children eligible for, offered, and accepted nPEP

Risk: Sexual assault

Intervention: 2-drug regimen

Drug regimen: AZT+3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 11/17 (65%) accepting nPEP completed 28-day course

HIV seroconversions: Among nPEP users, no seroconversions among 11 who returned after 1 month, 7 who returned after 3 months, and 2 who returned at 6 months; 1 of 4 children who did not receive nPEP was screened for HIV and was HIV+

Conclusion: The study found nPEP to be safe, acceptable, and feasible. The authors recommend routine offering of nPEP to all eligible children.

Authors, year: Fajman et al, 2006[41]

Type of study: Retrospective study of medical records of children presenting with child sexual abuse to inner-city pediatric ED in 2002

Location: Atlanta, GA

Sample size: n=227 sexually assaulted children and adolescents with adequate data; age range, 9 months–18 years; n=87 presented ≤72 hours of assault; n=5 sexually assault adolescent survivors were prescribed nPEP; being assaulted by a stranger associated with receiving nPEP (PR=11.9, 95% CI=1.4, 100.2, *P*=0.02).

Risk: Sexual assault

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: Combivir (ZDV + 3TC) + nelfinavir

Time from exposure to nPEP: Within 72 hours

Completion of nPEP: 0 completed 28-day course

HIV seroconversions: No seroconversions reported among the 3 nPEP recipients who were tested, or among the 82 patients who presented within 72 hours but did not receive nPEP

Conclusion: nPEP for pediatric HIV exposures was underutilized in a hospital in a large urban center with high HIV prevalence and underscores the need for physician education about nPEP for children.

Authors, year: Girardet et al, 2009[35]

Type of study: Retrospective medical record review of children and adolescents presenting at a sexual abuse clinic during a 38-month period (January 2001–March 2004)

Location: Houston, Texas

Sample size: Of 4,234 cases of child or adolescent sexual assault, 1,750 (41%) were tested for HIV; n=879 aged<13 years, n=871 adolescents; n=303 were nPEP eligible; 16/303 (5%) were offered nPEP (aged 3–17 years); n=15 accepted nPEP

Risk: Sexual assault

Intervention: 2- or 3-drug regimen

Drug regimen: ZDV + 3TC (14 cases); ZDV + 3TC +LPV/r (1 case of acute genital trauma)

Time from exposure to nPEP: ≤96 hours

Completion of nPEP: Inconsistent reporting; none of the children completed follow-up; no reported significant side effects among the 9 patients reporting for at least 1 follow-up visit

HIV seroconversions: No seroconversions among 9 children who returned for ≥1 follow-up visit

Conclusion: Only 5% of those children or adolescents who were eligible for nPEP were offered nPEP. Adherence was difficult to document based on limited adherence to follow-up visits. Need for research to better define nPEP efficacy in children and adolescents.

Authors, year: Merchant et al, 2004[39]

Type of study: Retrospective medical record review of female adolescents presenting at an urban pediatric ED (January 1999 to December 2000)

Location: New York, New York

Sample size: n=25 adolescent females aged 12–19 years presenting with history of sexual assault; n=15 eligible for and offered nPEP; n=14 accepted nPEP

Risk: Sexual assault

Intervention: 1- or 3-drug regimen

Drug regimen: 1 received ZDV in 1999; 13 received 3-drug regimen, ZDV + 3TC + 3rd drug (n=12); d4T + 3TC + 3rd drug (n=1); (3rd drug was NFV [n=9] or IDV [n=4])

Time from exposure to nPEP: ≤72 hours; nPEP ordered an average of 218 minutes after patient presented to the ED; patient received drugs on average 58 minutes after nPEP was ordered

Completion of nPEP: No patients completed 28-day course

HIV seroconversions: Not reported (efficacy not studied in this study)

Conclusion: There was a significant delay in ordering nPEP and administering nPEP in the emergency room. Highlights importance of expediting nPEP in that setting.

Authors, year: Neu et al, 2007[38]

Type of study: Prospective nonrandomized observational study of children and adolescents presenting to the pediatric ED during March 1999–September 2002

Location: New York City, New York

Sample size: n=70 patients (aged 11–19 years) evaluated for sexual assault; n=33 enrolled in the study (94% female; mean age 15.3 years)

Risk: Sexual assault

Intervention: 2-drug regimen; 1-pill burden

Drug regimen: Combivir

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 8/33 (24%); return rate for follow-up visits: 1st visit, 23/33 (70%); week 2, 20/33 (60%); week 4–6, 11/33 (33%); 12 weeks, 9/33 (27%); 24 weeks, 6/33 (18%)

HIV seroconversions: No seroconversions in those presenting for follow-up at 4–6 weeks (11/33), 12 weeks (9/33), or 24 weeks (6/33)

Conclusion: Inadequate adherence to medications and follow-up were significant problems in this nPEP program for sexually assaulted children and adolescents.

Authors, year: Schremmer et al, 2005[36]

Type of study: Retrospective medical record review of children presenting for evaluation of suspected sexual abuse who were provided nPEP during February 1999–March 2001.

Location: Kansas City, Missouri

Sample size: n=2,865 evaluated for suspected sexual abuse; n=34 children and adolescents received nPEP (aged 12 weeks to 18 years, mean age 13 years); nPEP use associated with stranger assault

Risk: Sexual abuse

Intervention: 1-, 2-, and 3-drug regimens

Drug regimen: ZDV (n=1); ZDV + 3TC (n=32); ZDV+3TC+NFV (n=1)

Time from exposure to nPEP: ≤73 hours (range, 2–73 hours)

Completion of nPEP: 8/34 (24%) patients completed 28-day course

HIV seroconversions: No seroconversions among 33 patients tested at initial evaluation or among the 16 patients who had at least 1 subsequent HIV test after initial evaluation

Conclusion: Inadequate adherence to medication regimen and follow-up in child and adolescent survivors of suspected sexual abuse who received nPEP were noted.

Authors, year: Speight et al, 2006[40]

Type of study: Retrospective medical record review of children presenting with suspected childhood rape to a sexual assault care center during July 2003–March 2004

Location: Thika, Kenya

Sample size: n=48 children aged<18 years (96.8% female) presenting with suspected rape; n=33 eligible for, offered, and accepted nPEP

Risk: Sexual assault

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 15/33 (45%) completed 28-day course

HIV seroconversions: No seroconversions among 3 patients tested for HIV; 3 seroconversions among 15 who were not eligible for nPEP

Conclusion: Majority (86%) of children presented within the 72-hour window period. Providing post-rape care is feasible and acceptable but requires special training for counselors, and providers, including training related to pediatric dosing.

Pediatric and Adolescent Community-acquired Needlestick Injury (CA-NSI) Studies

Authors, year: de Waal et al, 2006[66]

Type of study: Case report of nPEP use among children involved in a mass needlestick injury (1999)

Location: Tygerberg, South Africa

Sample size: n=54 children involved in mass needlestick exposure from discarded needles on a soccer field; n=44 were administered nPEP

Risk: CA-NSI

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: ARV adherence declined from 64% at week 3 to 52% at week 4; 7 patients on nPEP experienced nausea at 3 weeks

HIV seroconversions: No seroconversions to HIV, HBV, or HCV were noted in 44 children tested at 6 months

Conclusion: Follow-up of patients after mass exposure was difficult and adherence to nPEP was poor. Fewer follow-up visits are probably adequate in a non-mobile community (might consider eliminating the 3-month follow-up visit).

Authors, year: Papenburg et al, 2008[65]

Type of study: Combination of prospective and retrospective case series describing community acquired needle stick injuries in children at 2 pediatric tertiary care teaching hospitals (1988–2006 for one hospital and 1995–2000 at another hospital)

Location: Montreal, Canada

Sample size: n=274 pediatric patients with community acquired needlestick injuries; 73% of patients sought care on day of injury; n=210 injuries occurred during an era when nPEP was available; n=87 patients offered nPEP; n=82 patients accepted nPEP

Risk: CA-NSI; blood reported on needle or syringe in 36 injuries; n=71 reported an injury that bled

Intervention: 2-drug or 3-drug regimen

Drug regimen: ZDV + 3TC (n=74); ZDV + 3TC + NFV (n=4); ZDV + 3TC + IDV (n=3); ZDV + 3TC + RTV (n=1)

Time from exposure to nPEP: Not specified

Completion of nPEP: 10/82 (12%) patients discontinued nPEP; unclear from report if remaining 72 completed the full 28-day course

HIV seroconversions: 0 HIV seroconversions occurred at 6 month follow-up visit among 189/274 (nPEP and non-nPEP) patients tested for HIV

Conclusion: There were no seroconversions for HIV, HBV, or HCV among the 274 pediatric, community-acquired needlestick injuries, adding evidence that suggests the risk of transmission of bloodborne viruses in these exposures is low.

Authors, year: Russell et al, 2002[67]

Type of study: Prospective study of children with community-acquired needlestick injuries (published 2002)

Location: Melbourne, Australia

Sample size: n=50 cases of CA-NSI; median age=6.9 years (range, 1.8–14.3 years)

Risk: CA-NSI

Intervention: No nPEP offered

Drug regimen: Not applicable

Time from exposure to nPEP: Not applicable

Completion of nPEP: Not applicable

HIV seroconversions: No seroconversions among 36 children tested for HIV, HBC, HBC

Conclusion: No seroconversions to HIV, HBV, or HCV occurred among 50 cases of CA-NSI; HBV prophylaxis and vaccination was administered and no nPEP for HIV was administered.

Authors, year: Thomas et al, 2006[64]

Type of study: Case report of CA-NSIs sustained by 21 children on primary school playground, including an HIV-infected source patient

Location: London, England

Sample size: n=20 children exposed and started on nPEP; 1 child already known to be HIV infected at baseline, not started on nPEP

Risk: CA-NSI

Intervention: 3-drug regimen

Drug regimen: ZDV + 3TC + NVP

Time from exposure to nPEP: Within 72 hours

Completion of nPEP: 10/20 (50%)

HIV seroconversions: None

Conclusion: Was logistically difficult to provide nPEP under such circumstances, however, it seemed to be effective.

Mixed Populations Studies

Authors, year: Babl et al, 2000[58]

Type of study: Retrospective medical record review of children and adolescents presenting with CA-NSI in to the pediatric emergency room of an urban hospital during June 1997–June 1998

Location: Boston, Massachusetts

Sample size: n=10 pediatric and adolescent patients offered nPEP; n=8 started on nPEP

Risk: Sexual assault (n=6); CA-NSI (n=4)

Intervention: 3-drug regimens

Drug regimen: ZDV + 3TC+ Indinavir (n=7); ZDV + 3TC+ NFV (n=1)

Time from exposure to nPEP:

Completion of nPEP: 2/8 (25%) completed 28-day course; financial concerns, side effects, additional psychiatric and substance abuse issues, degree of parental involvement influenced adherence to nPEP and follow-up

HIV seroconversions: No seroconversions among 5 tested at 4 to 28 weeks.

Conclusion: HIV nPEP presented medical and management challenges and requires coordinated effort. Need for written protocol, coordinated approach, and national guidelines.

Authors, year: Beymer et al, 2014[61]

Type of study: Retrospective medical record review of clients receiving PEP services at LGBT community-based clinic (May 2011–December 2012)

Location: Los Angeles

Sample size: n=649 nPEP clients (n=529 [81.5%] first PEP use, n=120 [18.5%] PEP use 1–5 times previous to current nPEP initiation); whites, Hispanics, and blacks made up 42.5%, 35.4%, and 8.8% of nPEP users, and 30.4%, 42.4%, and 16.7% of HIV-infected persons, respectively

Risk: Gay/homosexual 75.5%, bisexual 11.9%, heterosexual 10.6%, other 1.9%

Intervention: 2-drug regimen

Drug regimen: TDF/FTC

Time from exposure to nPEP: ≤72 hours; mean time from exposure to first PEP medication dose 38.5 hours (SD=19 h)

Completion of nPEP: 93% self-reported taking all 4 pills in the previous 4-day medication recall period at 2 weeks after nPEP initiation

HIV seroconversions: 7 seroconversions occurred during the 6-month study period after nPEP initiation (including the 5 months after completing nPEP; exact timing not described)

Conclusion: 18.5% repeat nPEP users may benefit from PrEP; racial/ethnic inequities found in nPEP use compared with corresponding HIV prevalence deserves attention.

Authors, year: Bogoch et al, 2014[59]

Type of study: Prospective longitudinal study of referrals to nPEP programs in 2 emergency rooms and 2 academic medical centers

Location: Boston, MA

Sample size: n=180 persons referred for nPEP; median age 28 years (interquartile range, 23–35 years); 65.6% women; n=98 (54.4%) attended first nPEP visit

Risk: Sexual (57.2%), 72% nonconsensual, 1% MSM; nonsexual (42.8%), 17.8% injecting-drug use, 40% accidental needlestick injuries, 42.2% accidental mucous membrane or non-needle percutaneous exposures

Intervention: 3-drug regimen

Drug regimen: First line regimen: co-formulated TDF and FTC (Truvada) and LPV/r (Kaletra); RAL was substituted for LPV/r with drug interactions or side effects preventing adherence

Time from exposure to nPEP: Not reported

Completion of nPEP: 43/177 (46%) patients had documented completion of a 28-day course of nPEP; women were less likely to complete a 28-day course of nPEP

HIV seroconversions: Not reported

Conclusion: There were significant attrition rates between the emergency department and nPEP follow-up clinic. Older patients and persons without insurance were significantly less likely to attend initial clinic for nPEP care after presenting to the emergency department. Individuals with exposure to a known HIV-positive source individual were more likely to attend their initial clinic appointment. Women accounted for the majority of nonconsensual sexual exposures and were less likely to have documented completion of their 28-day nPEP regimen.

Authors, year: Chan et al, 2013[52]

Type of study: Retrospective cohort study with medical record review at large urban hospital emergency room, January 1, 2008–December 31, 2010

Location: Toronto, Canada

Sample size: n=241 patients

Risk: All were sexual exposures; MSM 76.8%, heterosexual 23.2%, non-consensual 5.0% of 236 with documentation about whether sex was consensual; HIV-positive source n=102

Intervention: 2-drug regimen (for lower risk exposures), 3-drug regimen (for higher risk exposures)

Drug regimen: Not specified

Time from exposure to nPEP: ≤72 hours; among 205 with known timing of exposure: <24 hr, 70 (34.1%); 24–48 hr, 68 (33.2%); 48–72 hr, 28 (13.7%); >72 hr, 7 (3.4%); not documented, 32 (15.6%)

Completion of nPEP: Of 205 patients given nPEP, n=71 (34.6%) completed a 28-day course; n=20 (9.8%) stopped medications early due to patient preference, cost, low HIV risk, source patient tested HIV negative; n=114 (55.6%) unknown completion status; n=55 with adverse effects, diarrhea (n=20), nonspecific gastrointestinal upset (n=14), nausea (n=13)

HIV seroconversions: Two patients who initially tested HIV negative at baseline subsequently tested HIV-positive at 3-month and 6-month visits; data regarding ongoing sexual exposure was incomplete

Conclusion: While it was encouraging that 92.6% of patients presented within the 72-hour window period, only 34.6% were known to have completed the full 28-day course. It is unclear whether the 2 HIV seroconversions that occurred during the 3-month and 6-month follow-up visits were nPEP failures as sexual histories were incomplete during follow-up.

Authors, year: Diaz-Brito et al, 2012[53]

Type of study: Open label randomized multicenter clinical trial comparing 2 nPEP regimens in patients presenting to emergency rooms in 6 urban hospitals

Location: Barcelona, Spain

Sample size: n=255 patients presenting for nPEP evaluation randomized into ZDV/3TC + LPV/r twice daily arm (n=131) or ZDV/3TC + atazanavir (n=124)

Risk: n=200; nonoccupational n=170 (85%); sexual n=156 (78%); occupational n=30 (1%)

Intervention: 3-drug regimen

Drug regimen: ZDV/3TC + LPV/r or ZDV/3TC + atazanavir

Time from exposure to nPEP: Median interval between exposure and presentation=18h (IQR 5–32); nonoccupational (median=20 hours); occupational (median=5 hours)

Completion of nPEP: 64% completed 28-day course in both arms; 92% of patients reported taking >90% of scheduled doses (without difference between arms); adverse events reported in 46% of patients (49% LPV/r arm and 43% atazanavir arm); gastrointestinal problems more common in LPV/r arm

HIV seroconversions: 0

Conclusion: Rate of completion was similar for both arms; almost 50% of patients of both arms suffered side effects. Strategies to improve adherence are needed.

Authors, year: Fletcher et al, 2013[63]

Type of study: Prospective cohort study

Location: Los Angeles, California

Sample size: n=35 patients; gay n=30; not gay=5; mean age=34.1 years (SD 7.4)

Risk: Not clearly defined; however, participants reported mean of 11.9 (SD 26.5) episodes of unprotected anal intercourse in past 6 months

Intervention: 2-drug regimen

Drug regimen: TDF + FTC (Truvada)

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 25/35 (71.4%) completed the 28-day course; 48.6% took all 28 doses; 14.3% took >90% of doses; at baseline, higher number of lifetime STDs and recent episodes of unprotected anal intercourse were associated with reductions in medication adherence

HIV seroconversions: 1 (participant reported nonadherence to nPEP and multiple subsequent sexual exposures)

Conclusion: There was a significant indirect association between sexual risk taking and nPEP adherence. Interventions to reduce sexual risk taking will reduce risk for HIV acquisition and may play a role in improving nPEP adherence.

Authors, year: Gulholm et al, 2013[54]

Type of study: Retrospective medical record review at urban hospital sexual health clinic (1/2008–12/2011)

Location: Sydney, Australia

Sample size: n=282 patients on 319 occasions presented for nPEP; n=262 (94.3%) male

Risk: n=260 (99.2%) participants had homosexual exposure; of 319 presentations, 203 (63.6%) receptive unprotected anal intercourse, 87 (27.4%) insertive anal intercourse, 12 (3.8%) receptive vaginal intercourse, 5 (1.6%) penile-vaginal sexual assault, 5 (1.6%) receptive fellatio, 5 (1.6%) needlestick injuries, 4 (1.3%) needle-sharing episodes

Intervention: 2-drug or 3-drug regimen

Drug regimen: Mainly TDF/FTC-containing regimens; TDF + FTC (n=136 [42.6%]), TDF + FTC + d4T (n=149 [46.7%])

Time from exposure to nPEP: ≤72 hours; <4 hours (16 [5.1%]), 4–12 hours (59 [19.0%]), 12–24 hours (82 [26.5%]), 24–48 hours (96 [31.0%]), 48–72 hours (57 [18.4%])

Completion of nPEP: 228/319 (71/%) completed nPEP; completion associated with reporting AEs and changing the nPEP regimen; adverse events associated with being prescribed a regimen other than TDF/FTC, younger age, earlier year of nPEP prescription, and changing the nPEP regimen

HIV seroconversions: 2 seroconversions more than 6 months after NPEP due to ongoing high-risk behavior

Conclusion: nPEP was appropriately targeted to highest risk patients. HIV seroconversions due to ongoing high-risk sexual behavior highlight importance of integrating counseling regarding safer sexual behaviors as an integral component of nPEP care.

Authors, year: Jain et al, 2015[60]

Type of study: Retrospective longitudinal study of electronic medical records of nPEP users (1999–2013)

Location: Boston, Massachusetts

Sample size: n=894 patients; n=1,244 nPEP courses; mean age at PEP enrollment=33.9 years

Risk: MSM=788; heterosexual=91; sexual assault=66; transgender=15; injection drug use=14; sexual exposure (non-assault)=1,152

Intervention: n=927 TDF-based treatment regimen; N=592 3-drug regimen

Drug regimen: Either an AZT/3TC or TDF/FTC backbone with or without a third drug.

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 85.7% completion rate overall (463 of 540 with documented completion status); reasons for discontinuing: medication intolerance (48.1%) due to nausea (43.2%), diarrhea (13.5%), rash (13.5%), HIV negative partner (9.1%); increased completion rates associated with having HIV-infected partner or fewer drugs in regimen (2 vs.3)

HIV seroconversions: Not reported

Conclusion: nPEP use increased over time. nPEP users demonstrated recurrent high-risk behavior. A defined group of nPEP users may benefit from earlier, targeted HIV risk-reduction and PrEP counseling.

Authors, year: Mayer et al, 2008[56]

Type of study: Two phase 4 studies of TDF-containing regimens compared to historical controls who took ZDV-containing regimens

Location: Boston, Massachusetts

Sample size: n=353 enrollees; n=44 (TDF/FTC arm); n=68 (TDF/3TC arm); control arms: n=122 ZDV/3TC arm, n=119 ZDV/3TC + 3rd drug arm

Risk: Sexual exposure; TDF/FTC arm, n=41 (93.2%) male (MSM/bisexual), n=41 male (100%); TDF/3TC arm, n=66 (97.1 %) male, n=56 (82.4% MSM/bisexual); ZDV/3TC arm, n=98 (80.3%) male; ZDV/3TC + 3rd drug arm, n=88 (73.9%)

Intervention: 3 separate 2-drug regimens and one 3-drug regimen; 1-, 2-, or 3-pill burden

Drug regimen: TDF + 3TC, TDF + FTC, or ZDV + 3TC (with or w/o a PI)

Time from exposure to nPEP: ≤ 72 hours

Completion of nPEP: 42–87.5% completed nPEP (highest completion in TDF regimens): 72.7% (n=32 TDF/FTV arm), 87.5% (n=63 TDF/3TC arm), 42.1% (n=53 ZDV/3TC arm), 38.8% (n=50 ZDV/3TC + 3rd drug arm [3rd drug was mainly PI])

HIV seroconversions: In TDF arms, n=0 seroconversions; in AZT arms, n=3 (during or shortly after their course of nPEP); Note: Level of adherence in seroconverters not described.

Conclusion: Participants taking TDF-containing regimens for nPEP demonstrated greater adherence and tolerability, with milder side effects than those taking ZDV-containing regimens.

Authors, year: Mayer et al, 2012[57]

Type of study: Evaluation of a novel 3-drug nPEP regimen

Location: Boston, MA

Sample size: TDF-FTC-RAL arm (n=100); control arms: TDF/FTV arm, n=44; AZT/3TC +3rd drug arm, n=119; overall age range, 18–61 years; males (73.9%–100%—all arms); MSM/bisexual (70.5%–71.5% in TDF arms)

Risk: Sexual exposure to HIV-infected partner or partner of unknown HIV status

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: RAL + fixed dose combination TDF and FTC (Truvada)

Time from exposure to nPEP: ≤ 72 hours

Completion of nPEP: 57% (n=57) completed TDF-FTC-RAL arm (an additional 27% completed a modified regimen.); 72.7% (n=32) completed TDF/FTV arm; 38.8% (n=46) completed AZT/3TC arm

HIV seroconversions: 0

Conclusion: Tolerability to the 3-drug regimen, with integrase inhibitor, RAL, was high. The most common side effects were nausea and vomiting, diarrhea, abdominal discomfort, headache, and fatigue.

Authors, year: McDougal et al, 2014[62]

Type of study: Retrospective medical record abstraction of patients attending a publicly funded HIV clinic between 2000 and 2010

Location: Seattle, Washington

Sample size: 360 evaluated for nPEP; 324 prescribed nPEP; median age 30 years (range, 14 years–68 years)

Risk: Among patients evaluated for nPEP: sexual exposures (928%), MSM (59%), sexual assault (22%)

Intervention: 66% (n=214) 3-drug regimen

Drug regimen:

Time from exposure to nPEP: 334/260 (93%) initiated ≤72 hours, 177/360 (49%) within 24 hours

Completion of nPEP: 287/324 (89%) completed nPEP

HIV seroconversions: n=4; 2 tested positive at 2 and 5 months; 1 tested negative at baseline and 11 days and positive at 5 months; 1 tested positive at 12 months after nPEP initiation; adherence to nPEP and history of ongoing sexual exposures not described

Conclusion: Must increase education and promotion of HIV prevention, including nPEP for populations who would benefit most. Established nPEP service sites may have added benefit of also serving as locations for HIV case-finding and PrEP referrals.

Authors, year: Olowookere et al, 2010[51]

Type of study: Retrospective medical record abstraction of clients presenting for HIV nPEP at an antiretroviral therapy clinic during January 2005–December 2006

Location: Ibadan, Nigeria

Sample size: n=48 clients received nPEP; mean age 27.9 years ± 12.3 years (n=6, <15 years); about 1/3 were children and adolescents

Risk: Nonoccupational exposures: sexual assault (50%); occupational exposures: needlesticks (25%), blood splash into mucous membranes (25%)

Intervention: 3-drug regimen

Drug regimen: Either ZDV + 3TC + 3rd drug or D4T + 3TC + 3rd drug; 3rd drug=EFV, IDV or LPV/r

Time from exposure to nPEP: Not reported

Completion of nPEP: 38/48 (79%) completed therapy

HIV seroconversions: No seroconversions among 40 clients at 6 months of follow-up

Conclusion: 24% of clients receiving nPEP could not complete therapy due to side effects.

Authors, year: Pierce et al, 2011[45]

Type of study: Data linkage study using an nPEP service database and an HIV surveillance registry

Location: Australia

Sample size: n=1,420 male nPEP recipients; age range, 14–78 years; median=34.5 years

Risk: Indirect data suggest most participants presenting for NPEP are MSM, but risk behaviors were not collected for these participants

Intervention: Number of drugs in nPEP regimen not reported.

Drug regimen: Not reported

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: Not reported

HIV seroconversions: n=3 nPEP related failures; n=34 additional seroconversions >6 months after nPEP initiation and deemed related to ongoing risk behavior

Conclusion: Frequency of nPEP use was not associated with risk of HIV seroconversion. Note: Data on nPEP adherence and completion were not available, but may have provided an explanation for drug failure.

Authors, year: Rey et al, 2008[46]

Type of study: Retrospective medical record abstraction of all consultations for nPEP in three consultation centers January 2001–December 2002

Location: Southeastern France

Sample size: n=910 exposures; age range, 15–18 yr (5.9%), 19–35 yr (68.6%), 36–50 yr (21.4%), >50 yr (4.1%); men=60.4%; female=39.2%; transsexual=0.3%; n=800 given initial nPEP prescription; n=776 accepted nPEP; n=527 received remaining nPEP prescription to complete 28-day course

Risk: n=910 sexual exposures, including 108 sexual assaults, 220 homosexual contacts among men

Intervention: 2- or 3-drug regimen

Drug regimen: Not reported

Time from exposure to nPEP: nPEP given before and after the 72 hour window period

Completion of nPEP: 355/776 (44%) who accepted nPEP completed 28-day course

HIV seroconversions: 1 seroconversion occurred in a patient after completing nPEP but who presented >72 hours after a high-risk exposure (not considered an nPEP failure)

Conclusion: Follow-up rates were poor; strategies need to improve follow-up, including a tracking process and psychosocial support for youngest patients and survivors of sexual assault.

Authors, year: Shoptaw et al, 2008[55]

Type of study: Biobehavioral HIV prevention intervention

Location: Los Angeles

Sample size: n=100 enrollees

Risk: High-risk sexual or drug-related exposure; n=45 drug use, n=1 injection drug use, n=63 MSM, n=9 bisexual, n=9 heterosexual; mean age 31.8 years

Intervention: 2-drug regimen; 1-pill burden

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: n=84 individuals received the full 28-day supply of study drug; 63/84 (75%) completed nPEP

HIV seroconversions: 0

Conclusion: nPEP provision for persons at high risk for HIV is feasible and safe at the community level. The most common adverse events were fatigue, nausea, headache, and gastrointestinal complaints.

Authors, year: Siika et al, 2009[47]

Type of study: Retrospective cohort study of electronic medical records of patients enrolled for HIV nonoccupational and occupational PEP during November 2001–December 2006 (Note: Only results for nPEP patients summarized in this table)

Location: Eldoret, Kenya

Sample size: n=355 nPEP exposures among children, adolescents, and adults; 100% accepted nPEP; n=296 advised to continue nPEP after testing HIV negative at baseline

Risk: Sexual assault (n=292 [82%]; female adult [n=189], female child [n=91], male child [n=15]); unprotected consensual sex, condom malfunction, human bites, exposure to body fluids of individuals suspected to be HIV infected, and barber cuts (n=63 [18%])

Intervention: 3-drug regimen; 2- or 3-pill burden

Drug regimen: D4T + 3TC + NVP; ZDV + 3TC + LPV/r (Note: Authors do not distinguish between ARVs used for nPEP or oPEP)

Time from exposure to nPEP: Median time=19 hours (range, 1–672 hours; 86% <72 hours)

Completion of nPEP: 104/296 (35%) completed nPEP. No statistically significant difference in reported side effects between NVP arm (21%) and LPR/r arm (14%) (P=0.44). No difference in completion rates for two arms (P=0.91). 1 death related to ARV-associated acute hepatitis associated with NVP arm.

HIV seroconversions: 1 HIV seroconversion at 6 weeks after nPEP initiation using RNA PCR test among 129 patients; seroconversion occurred in sexually assaulted child who presented ≤4 hours of assault and completed nPEP. HIV ELISA tests were negative in 87 patients; however, child who seroconverted did not undergo ELISA testing as well.

Conclusion: It is feasible to provide nPEP and oPEP in resource-constrained settings. Lack of HIV testing, delayed presentation, ARV discontinuation, and loss to follow-up are challenges in Western Kenya. Centralization of PEP services may improve coordination and supervision.

Authors, year: Tissot et al, 2010[48]

Type of study: Retrospective medical record abstraction of nPEP administrations during 1998–2007

Location: Lausanne, Switzerland

Sample size: n=1,233 consultations for potential HIV exposure; n=910 exposures among 867 persons included in final analysis; n=830 individuals requested nPEP at least once; n=710 initiated nPEP; 64% male, median age 30 years (range, 14–87 years)

Risk: 58%=heterosexual; 15%=homosexual; 6%=sexual assault; 20%=nonsexual (mainly CA-NSI or sharing of injection drug equipment)

Intervention: 3-drug regimen

Drug regimen: Mainly ZDV + 3TC + NFV (n=548, 77%) or ZDV + 3TC + LPV/r (n=108, 15%)

Time from exposure to nPEP: 60% sought care ≤24 hours after exposure and 82% sought care ≤48 hours

Completion of nPEP: 423/710 (60%) completed 28-day course; 396/620 (64%) for which data were available, reported side effects (mainly gastrointestinal disturbance and fatigue)

HIV seroconversions: 2 seroconversions occurred during follow-up, not attributable to nPEP failures

Conclusion: HIV testing in source persons avoided nPEP in 31% of exposures.

Authors, year: Tosini et al, 2010[49]

Type of study: Multi-site prospective study to evaluate the tolerability of nPEP with TDF/FTC +LPV/r

Location: France

Sample size: n=249 men and women; mean age 31.5 years; n=166 completed 28 days of PEP (tolerability good in 58%)

Risk: Nonoccupational exposures: sexual intercourse n=204 (82%), other n=5 (2%); occupational exposures (n=40)

Intervention: One 3-drug regimen; 2-pill burden

Drug regimen: TDF + FTC + LPV/r vs. historical controls taking ZDV containing regimens or TDF + ATV

Time from exposure to nPEP: ≤48 hours

Completion of nPEP: 166/188 (88%)

HIV seroconversions: No HIV seroconversions were recorded during the study

Conclusion: The TDF/FTC + LPV/r regimen proved easy to use, well-tolerated, and had less participants to discontinue medications secondary to adverse effects when compared with historical controls. The authors recommend this regimen as standard of care for HIV nPEP. Among those with ≥1 side effect, 78% diarrhea, 78% asthenia, 59% nausea and/or vomiting.

Authors, year: Wong et al, 2010[50]

Type of study: Observational study of nPEP use following nPEP protocol and guidelines development in one Canada province

Location: Alberta, Canada

Sample size: n=174 persons received nPEP (135 females, 39 males); median age 24 years (range 4–69 years)

Risk: Sexual assault (68%, n=118), percutaneous (21%, n=36), consensual sex (7%, n=12), mucosal (3%, n=5), other (0.6%, n=1), not documented (1%, n=2)

Intervention: Primarily 2 and 3-drug regimens, one 4-drug regimen

Drug regimen: Not explicitly reported; most regimens included ZDV

Time from exposure to nPEP: 86% of cases ≤48 hours

Completion of nPEP: 86/174 (49%)

HIV seroconversions: 0 of 143

Conclusion: The majority of nPEP cases were sexual assaults in young women. No seroconversions were observed, however, lack of follow-up and early discontinuation of medication were problematic. NPEP programs need to better address adherence and follow-up.

Blood Transfusion Study

Authors, year: Al-Hajjar et al, 2014[71]

Type of study: Case report of nPEP use following inadvertent HIV-infected blood transfusion

Location: Riyadh, Saudi Arabia

Sample size: One 12 year old girl with sickle cell disease

Risk: Child was inadvertently transfused with large volume of HIV-infected packed red blood cells

Intervention: 4-drug regimen

Drug regimen: TDF, FTC, DRV/r and RAL (DRV/r subsequently changed to LPV)

Time from exposure to nPEP: At 24 hours after transfusion

Completion of nPEP: Completed 13 weeks of ARV PEP

HIV seroconversions: Patient did not seroconvert (negative for HIV-1 DNA and plasma HIV-1 RNA by PCR through 8 months following exposure)

Conclusion: Authors report successful use of combination ART nPEP after a large volume transfusion of HIV-contaminated blood despite detection initially of HIV antibodies immediately after the transfusion. The fact that antibodies disappeared after nPEP initiation cautions against not starting or stopping nPEP in patients with detectable antibodies immediately after a contaminated blood transfusion.

Abbreviations

3TC, lamivudine; ATV, atazanavir; AZT, zidovudine; CA-NSI, community-acquired needlestick injury; d4T, stavudine; DRV/r, darunavir + ritonavir; ED, emergency department; ELISA, enzyme-linked immunosorbent assay; EFV, efavirenz; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDV, indinavir; LPV, lopinavir; LPV/r, lopinavir/ritonavir; MSM, men who have sex with men; NFV, nelfinavir; nPEP, nonoccupational postexposure prophylaxis; NVP, nevirapine; oPEP, occupational postexposure prophylaxis; PEP, postexposure prophylaxis; PI, protease inhibitor; PrEP, preexposure prophylaxis; RAL, raltegravir; RNA PCR, ribonucleic acid polymerase chain reaction; RPV, rilpivirine; SD, standard deviation; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

Trade-named Drug Compositions

Combivir, ZDV+3TC; Kaletra, LPV/r (lopinavir + ritonavir); Truvada, TDF + FTC.

Appendix 4

Consideration of Other Alternative HIV nPEP Antiretroviral Regimens[a]

Create a combination regimen alternative to those in Table 5: May combine 1 drug or drug pair from Column A with 1 pair of nucleoside/nucleotide reverse transcriptase inhibitors from Column B.

Or

Use an existing fixed-dose combination alternative to those in Table 5.

Prescribers unfamiliar with these medications should consult physicians familiar with the agents and their toxicities.

Column A	Column B
Raltegravir	Tenofovir DF+ emtricitabine
Darunavir + ritonavir	Tenofovir DF + lamivudine
Etravirine	Zidovudine + lamivudine
Rilpivirine	Zidovudine + emtricitabine
Atazanavir + ritonavir	
Lopinavir/ritonavir	
Dolutegravir	

Fixed-dose combinations

The fixed-dose combinations Stribild (elvitegravir, cobicistat, tenofovir DF, emtricitabine) and Complera (rilpivirine, tenofovir DF, and emtricitabine) are complete regimens and no additional antiretrovirals are needed.

ALTERNATIVE ANTIRETROVIRAL MEDICATIONS FOR USE AS nPEP ONLY WITH EXPERT CONSULTATION

Efavirenz
Enfuvirtide
Fosamprenavir
Maraviroc
Saquinavir
Stavudine

ANTIRETROVIRAL MEDICATIONS GENERALLY NOT RECOMMENDED FOR USE AS nPEP

Didanosine
Nelfinavir
Tipranavir
Abacavir

ANTIRETROVIRAL MEDICATIONS CONTRAINDICATED AS nPEP

Nevirapine
Efavirenz (not for pregnant women)
Tenofovir (not for persons with eCrCl < 60 ml/min)

Abbreviations: DF, disoproxil fumarate; eCrCl, estimated creatinine clearance; nPEP, nonoccupational postexposure prophylaxis; TM, trademark.

[a] These antiretrovirals can be considered for use in regimens alternative to those in Table 5. For detailed information on each drug, please refer to individual drug package inserts available at: AIDSInfo Drugs Database at: http://aidsinfo.nih.gov/drugs. For consultation or assistance with HIV nPEP, contact PEPline (telephone 888-448-4911; internet site: http://www.nccc.ucsf.edu/about_nccc/pepline/).

EXHIBIT 13

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports January 21, 2005 / Vol. 54 / No. RR-2

Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

Recommendations from the U.S. Department of Health and Human Services

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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CONTENTS

Disclosure of Relationship

CDC, our planners, and our content specialists wish to disclose they have no financial interests or other relationships with the manufactures of commercial products, suppliers of commercial services, or commercial supporters. This report does not include any discussion of a product under investigational use. However, this report does contain discussion of certain drugs indicated for use in a nonlabeled manner and that are not Food and Drug Administration (FDA) approved for such use. Information included in these guidelines might not represent FDA approval or approved labeling for the particular products or indications being discussed. Specifically, the terms *safe* and *effective* might not be synonymous with the FDA-defined legal standards for product approval.

Vol. 54 / RR-2 Recommendations and Reports 1

Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

Recommendations from the U.S. Department of Health and Human Services

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Summary

The most effective means of preventing human immunodeficiency virus (HIV) infection is preventing exposure. The provision of antiretroviral drugs to prevent HIV infection after unanticipated sexual or injection-drug–use exposure might be beneficial. The U.S. Department of Health and Human Services (DHHS) Working Group on Nonoccupational Postexposure Prophylaxis (nPEP) made the following recommendations for the United States. For persons seeking care ≤72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV infected, when that exposure represents a substantial risk for transmission, a 28-day course of highly active antiretroviral therapy (HAART) is recommended. Antiretroviral medications should be initiated as soon as possible after exposure. For persons seeking care ≤72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person of unknown HIV status, when such exposure would represent a substantial risk for transmission if the source were HIV infected, no recommendations are made for the use of nPEP. Clinicians should evaluate risks and benefits of nPEP on a case-by-case basis. For persons with exposure histories that represent no substantial risk for HIV transmission or who seek care >72 hours after exposure, DHHS does not recommend the use of nPEP. Clinicians might consider prescribing nPEP for exposures conferring a serious risk for transmission, even if the person seeks care >72 hours after exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the risks for transmission and adverse events. For all exposures, other health risks resulting from the exposure should be considered and prophylaxis administered when indicated. Risk-reduction counseling and indicated intervention services should be provided to reduce the risk for recurrent exposures.

Introduction

The most effective methods for preventing human immunodeficiency virus (HIV) infection are those that protect against exposure to HIV. Antiretroviral therapy cannot replace behaviors that help avoid HIV exposure (e.g., sexual abstinence, sex only in a mutually monogamous relationship with a noninfected partner, consistent and correct condom use, abstinence from injection-drug use, and consistent use of sterile equipment by those unable to cease injection-drug use). Medi-

The material presented in this report originated in the Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, Janet L. Collins, MD, Acting Director.

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cal treatment after sexual, injection-drug–use, or other nonoccupational HIV exposure* is less effective than preventing HIV infection by avoiding exposure.

In July 1997, CDC sponsored the External Consultants Meeting on Antiretroviral Therapy for Potential Nonoccupational Exposures to HIV. This panel of scientists, public health specialists, clinicians, ethicists, members of affected communities, and representatives from professional associations and industry evaluated the available evidence related to use of antiretroviral medications after nonoccupational HIV exposure. In 1998, DHHS issued a statement that outlined the available information and concluded that evidence was insufficient about the efficacy of nonoccupational postexposure prophylaxis (nPEP) to recommend either for or against its use (*1*).

Since 1998, additional data about the potential efficacy of nPEP have accumulated from human, animal, and laboratory studies. Clinicians and organizations have begun providing nPEP to patients they believe might benefit. In certain instances, health departments have issued advisories or recommendations or otherwise supported the establishment of nPEP treatment programs in their jurisdictions (*2*–*6*). In May 2001, CDC convened the second external consultants meeting on nonoccupational post-exposure prophylaxis to review and discuss the available data. This report summarizes knowledge about the use and potential efficacy of nPEP and details guidelines for its use in the United States.† The recommendations are intended for nonoccupational exposures and are not applicable for occupational exposures.

Evidence of Possible Benefits from nPEP

For ethical and logistical reasons, a randomized, placebo-controlled clinical trial of nPEP probably will not be performed. However, data are available from animal transmission models, perinatal clinical trials, studies of health-care workers receiving prophylaxis after occupational exposures, and from observational studies. These data indicate that nPEP might sometimes reduce the risk for HIV infection after nonoccupational exposures.

* In this report, a nonoccupational exposure is any direct mucosal, percutaneous, or intravenous contact with potentially infectious body fluids that occurs outside perinatal or occupational situations (e.g., health-care, sanitation, public safety, or laboratory employment). Potentially infectious body fluids are blood, semen, vaginal secretions, rectal secretions, breast milk or other body fluid that is contaminated with visible blood.

† Information included in these recommendations might not represent Food and Drug Administration (FDA) approval or approved labeling for the particular products or indications in question. Specifically, the terms safe and effective might not be synonymous with the FDA-defined legal standards for product approval.

Animal Studies

Animal studies have demonstrated mixed results (*1,7*). In macaques, PMPA (tenofovir) blocked simian immunodeficiency virus (SIV) infection after intravenous challenge if administered within 24 hours of exposure and continued for 28 days. PMPA was not as effective if initiated 48 or 72 hours postexposure or if continued for only 3 or 10 days (*8*). Two macaque studies of combination antiretroviral therapy (zidovudine, lamivudine, and indinavir) initiated 4 hours after simian/human immunodeficiency virus (SHIV) challenge and continued for 28 days did not protect against infection but did result in reduced viral load among the animals infected (*9*). In a macaque study designed to model nPEP for mucosal HIV exposure, all animals administered PMPA for 28 days, beginning 12 hours (four animals) or 36 hours (four animals) after vaginal HIV-2 exposure, were protected. Three of four animals treated 72 hours after exposure were also protected; the fourth animal had delayed seroconversion and maintained a low viral load after treatment (*10*).

These findings are consistent with those of macaque studies of the biology of vaginal SIV transmission. After atraumatic vaginal inoculation, lamina propria cells of the cervicovaginal subepithelium were infected first, virus was present in draining lymph nodes within 2 days, and virus was disseminated to the blood stream by 5 days (*11*). Similarly, in another study, SIV-RNA was detected in dendritic cells from the vaginal epithelium within 1 hour of intravaginal viral exposure, and SIV-infected cells were detected in the lymph nodes within 18 hours (*12*). These data indicate a small window of opportunity during which it might be possible to interrupt either the initial infection of cells in the cervicovaginal mucosa or the dissemination of local infection by the prompt administration of antiretroviral medications.

Postnatal Prophylaxis

Abbreviated regimens for reducing mother-to-child HIV transmission have been studied extensively. Certain regimens have included a postexposure component (antiretroviral medications given to the neonate). Although reduction in maternal viral load during late pregnancy, labor, and delivery seems to be a major factor in the effectiveness of these regimens, an additional effect is believed to occur because the neonate receives prophylaxis, which protects against infection from exposure to maternal HIV during labor and delivery (*13,14*). In a Ugandan perinatal trial, the rate of transmission at 14–16 weeks postpartum was substantially lower for women who received a single dose of nevirapine at the beginning of labor followed by a single dose of nevirapine to the neonate within

72 hours of birth (transmission rate: 13.1%) than for the women who received intrapartum zidovudine followed by 1 week of zidovudine to the neonate (transmission rate: 25.1%) (*15*). Similarly low transmission rates were noted in a study in South Africa in which intrapartum and postpartum antiretroviral medications were used. At 8 weeks postpartum, the transmission rate was 9.3% after intrapartum zidovudine and lamivudine followed by 1 week of zidovudine and lamivudine to mother and neonate, and the transmission rate was 12.3% after a single dose of nevirapine administered to the mother during labor and then to the neonate within 72 hours of birth (*16*). Although these studies lacked control groups, these dosing schedules could not have substantially reduced HIV exposure of the neonate through reducing maternal viral load, demonstrating that a combination of preexposure and postexposure prophylaxis for the neonate reduces HIV transmission. A study in Malawi among women who did not receive intrapartum antiretrovirals compared postnatal prophylaxis with single-dose nevirapine with and without zidovudine for 1 week. The transmission rate at 6–8 weeks was 7.7% among infants who received zidovudine plus nevirapine compared with 12.1% among those who received nevirapine alone (*17*). Although this study did not have a placebo or no-prophylaxis arm, the transmission rate for the zidovudine-nevirapine arm compares favorably with the rate of 21% at 4 weeks, noted in the placebo arm of a study of zidovudine prophylaxis conducted in Cote d'Ivoire (*18*).

Two observational studies with relatively limited numbers documented a potential effect of postnatal zidovudine prophylaxis alone (without intrapartum medication). A review of medical records in New York indicated that zidovudine monotherapy administered to the mother intrapartum or to the infant within 72 hours of birth reduced perinatal transmission >50%; initiating monotherapy for the infant >72 hours after birth was less effective (*19*). Similarly, an analysis of births in the PACTS study demonstrated that zidovudine administered to infants within 24 hours of birth, when mothers had not been treated either antepartum or intrapartum, compared with no treatment for mothers or infants, reduced perinatal transmission by 48% (*20*).

Observational Studies of nPEP

The most direct evidence supporting the efficacy of postexposure prophylaxis is a case-control study of needlestick injuries to health-care workers. In this study, the prompt initiation of zidovudine was associated with an 81% decrease in the risk for acquiring HIV (*21*). Although analogous clinical studies of nPEP have not been conducted, data are available from observational studies and registries.

In a high-risk HIV incidence cohort in Brazil, nPEP instruction and 4-day starter packs of zidovudine and lamivudine were administered to 200 homosexual and bisexual men. Men who began taking nPEP after a self-identified high-risk exposure were evaluated within 96 hours; 92% met the event eligibility criteria (clinician-defined high-risk exposure). Seroincidence was 0.7 per 100 person-years (one seroconversion) among men who took nPEP and 4.1 per 100 person-years among men who did not take nPEP (11 seroconversions) (*22,23*). Subsequent analysis of data from patients who took nPEP and had been followed for a median of 24.2 months indicated 11 seroconversions and a seroincidence of 2.9 per 100 person-years, compared with an expected seroincidence of 3.1 per 100 person years, p>0.97) (*24*). In a study of sexual assault survivors in Sao Paolo, Brazil, women who sought care within 72 hours after exposure were treated for 28 days with either zidovudine and lamivudine (for those without mucosal trauma) or zidovudine, lamivudine, and indinavir (for those with mucosal trauma or those subjected to unprotected anal sex) for 28 days. Women were not treated if they sought care >72 hours after assault, if the assailant was HIV-negative, or if a condom was used and no mucosal trauma was seen. Of 180 women treated, none seroconverted. Of 145 women not treated, four (2.7%) seroconverted (*25*). Although these studies demonstrate that nPEP might reduce the risk for infection after sexual HIV exposures, participants were not randomly assigned, and sample sizes were too small for statistically significant conclusions.

In a study of rape survivors in South Africa, of 480 initially seronegative survivors begun on zidovudine and lamivudine and followed up for at least 6 weeks, one woman seroconverted. She had started taking medications 96 hours after the assault. An additional woman, who sought treatment 12 days after assault, was seronegative at that time but not offered nPEP. At retesting 6 weeks after the assault, she had seroconverted and had a positive polymerase chain reaction result (Personal communication, A. Wulfsohn, MD, Sunninghill Hospital, Gauteng, South Africa).

In a feasibility trial of nPEP conducted in San Francisco, 401 persons with eligible sexual and injection-drug–use exposures were enrolled. No seroconversions were observed among those who completed treatment, those who interrupted treatment, or those who did not receive nPEP (*26*). In a study in British Columbia of 590 persons who completed a course of nPEP, no seroconversions were observed (*27*). In registries from four countries (Australia, France, Switzerland, and the United States), including approximately 2,000 nonoccupational exposure case reports, no confirmed seroconversions

have been attributed to a failure of nPEP in approximately 350 nPEP-treated persons reported to have been exposed to HIV-infected sources. However, the absence of seroconversions might not be attributed to receipt of nPEP but rather to the low per-act risk for infection and incomplete follow-up in the registries.

Case Reports

In addition to these studies, two case reports are of note. In one, a patient who received a transfusion of red blood cells from a person subsequently determined to have early HIV infection began taking combination PEP 1 week after transfusion and continued for 9 months. The patient did not become infected despite the high risk associated with the transfusion of HIV-infected blood (*28*). In the other case, nPEP was initiated 10 days after self-insemination with semen from a homosexual man later determined to have early HIV infection. The woman did not become infected but did become pregnant and gave birth to a healthy infant (*29*).

Although data from the studies and case reports do not provide definitive evidence of the efficacy of nPEP after sexual, injection-drug–use, and other nonoccupational exposures to HIV, the cumulative data demonstrate that antiretroviral therapy initiated soon after exposure and continued for 28 days might reduce the risk for acquiring HIV.

Evidence of Possible Risks from nPEP

Concerns about the potential risks from nPEP as a public health intervention include possible decrease in risk-reduction behaviors resulting from a perception that postexposure treatment is available, the occurrence of serious adverse effects from antiretroviral treatment in otherwise healthy persons, and potential selection for resistant virus (particularly if adherence is poor during the nPEP course). Evidence indicates that these theoretical risks might not be major problems.

Effects on Risk-Reduction Behaviors

The availability or use of nPEP might not lead to increases in risk behavior. Of participants in the nPEP feasibility study in San Francisco, 72% reported a decrease in risk behavior over the next 12 months relative to baseline reported risk behavior, 14% reported no change, and 14% reported an increase (*30*). However, 17% of participants requested a second course of nPEP during the year after the first course, indicating that although participants did not increase risk behaviors, a substantial proportion of the participants did not eliminate risk behaviors. A similar proportion of participants (14%) requested a second course of nPEP at the Fenway Clinic in Boston (*31*). In the Brazil nPEP study of homosexual and bisexual men followed up for a median of 24 months, all groups, including those who elected to take nPEP, reported decreases in risk behavior (*24,32*). Among highly educated (75% with ≥4 years of college), predominantly white (74%) homosexual men who completed a street-outreach interviewer-administered survey in San Francisco, those who reported that they were aware of the availability of nPEP did not report more risk behavior than those who were not aware (*33*). In a study of discordant heterosexual couples, none reported decreased condom use because of the availability of nPEP (*34*).

Antiretroviral Side Effects and Toxicity

Initial concerns about severe side effects and toxicities have been ameliorated by experience with health-care workers who have taken PEP after occupational exposures. Of 492 health-care workers reported to the occupational PEP registry, 63% took at least three medications. Overall, 76% of workers who received PEP and had 6 weeks of follow-up reported certain symptoms (i.e., nausea [57%] and fatigue or malaise [38%]). Only 8% of these workers had laboratory abnormalities, few of which were serious and all of which resolved promptly at the end of antiretroviral treatment (*35*). Six (1.3%) reported severe adverse events, and four stopped taking PEP because of them. Of 68 workers who stopped taking PEP despite exposure to a source person known to be HIV-positive, 29 (43%) stopped because of side effects. According to the U.S. nPEP surveillance registry, among 107 exposures for which nPEP was taken, the regimen initially prescribed was stopped or modified in 22%; modifications or stops were reported because of side effects in half of these instances (*36*). In addition to reports in these registries, serious side effects have been reported (e.g., nephrolithiasis and hepatitis) in the literature.

During 1997–2000, a total of 22 severe adverse events in persons who had taken nevirapine-containing regimens for occupational or nonoccupational postexposure prophylaxis were reported to FDA (*37–38*). Severe hepatotoxicity occurred in 12 (one requiring liver transplantation), severe skin reactions in 14, and both hepatic and cutaneous manifestations occurred in four. Because the majority of occupational exposures do not lead to HIV infection, the risk for using a nevirapine-containing regimen for occupational PEP outweighs the potential benefits. The same rationale indicates that nevirapine should not be used for nPEP.

Selection of Resistant Virus

Antiretroviral PEP does not prevent all infections in occupational and perinatal settings. Similarly, PEP is not expected to have complete efficacy after nonoccupational exposures. In instances where nPEP fails to prevent infection, selection of resistant virus by the antiretroviral drugs is theoretically possible. However, because of the relative paucity of documented nPEP failures for which resistance testing was performed, the likelihood of this occurring is unknown.

PEP failures have been documented after at least one sexual (*39*) and 21 occupational (*38,40*) exposures. Three fourths of these patients were treated with zidovudine monotherapy. Only three received three or more antiretroviral medications for PEP. Among the patients tested, several were infected with strains that were resistant to antiretroviral medications. In a study in Brazil (*24*), virus obtained on day 28 of therapy from the only treated person who seroconverted (whose regimen included 3TC) had a 3TC-resistance mutation. However, the source-person could not be tested. Therefore, whether the mutation was present when the virus was transmitted or whether it developed during nPEP could not be determined.

Selection of resistant virus might occasionally result from the use of nPEP. However, because the majority of nonoccupational exposures do not lead to HIV infection and because the use of combination antiretroviral therapy might reduce further the transmission rate, such occurrences are probably rare. For patients who seroconvert despite nPEP, resistance testing should be considered to guide early and subsequent treatment decisions.

Cost-Effectiveness of nPEP

Although the potential benefits of nPEP to persons are measured by balancing its anticipated efficacy after a given exposure against individual health risks, the value of nPEP as a public health intervention is best addressed at the population level by using techniques such as cost-benefit analysis. Such analyses have been published. One cost-effectiveness evaluation of nPEP in different potential exposure scenarios in the United States reported it to be cost-effective only in situations in which the sex partner source was known to be HIV-infected or after unprotected receptive anal intercourse with a homosexual or bisexual man of unknown serostatus (*41,42*). A similar analysis in France reported that nPEP was cost-saving for unprotected receptive anal intercourse with a partner known to be HIV-infected and cost-effective for receptive anal intercourse with a homosexual or bisexual partner of unknown serostatus. It was not cost-effective for penile-vaginal sex, insertive anal intercourse, or other exposures considered (*43*).

Another study and anecdotal reports indicate difficulty limiting nPEP to the exposures most likely to benefit from it. In British Columbia, where guidelines for nPEP use have been implemented (*5*), an analysis indicated that >50% of those receiving nPEP should not, according to the guidelines, have been treated (e.g., for exposure to intact skin). The use of nPEP in these circumstances doubled the estimated cost per HIV infection prevented ($530,000 versus $230,000) (*44*).

Even if nPEP is cost-effective for the highest risk exposures, behavioral interventions are more cost-effective (*41,45*). This emphasizes the importance, when considering nPEP, of providing risk-avoidance and risk-reduction counseling to reduce the occurrence of future HIV exposures.

Evidence of Current Practice

Although 40,000 new HIV infections occur in the United States each year, relatively few exposed persons seek care after nonoccupational exposure. Certain exposures are unrecognized. Certain patients have frequently recurring exposures and would not benefit from nPEP because 4 weeks of potential protection cannot substantially reduce their overall risk for acquiring HIV infection. In addition, certain clinicians and exposed patients are unaware of the availability of nPEP or unconvinced of its efficacy and safety. Finally, access to knowledgeable clinicians or a means of paying for nPEP might constrain its use.

Certain populations in the United States remain at high risk for exposure. In a cohort study of homosexual and bisexual men, 17% reported at least one condom failure during the 6 months preceding study enrollment (*46*). Other studies indicate that increasing use of highly active antiretroviral therapy (HAART) by HIV-infected persons might be leading some persons to have unprotected sex more frequently, in part because of the belief that lowered viral load substantially reduces infectivity (*47–50*). This finding is supported by increased rates of sexually transmitted infections among HIV-infected patients (*51*). In a California study, 69% of discordant heterosexual couples reported having had unprotected sex during the preceding 6 months (*34*).

Since 1998, certain clinicians have recommended wider availability and use of nPEP (*52–58*), and others have been more cautious about implementing it in the absence of definitive evidence of efficacy (*59,60*). Multiple public health jurisdictions, including the New York State AIDS Institute, the San Francisco County Health Department, the Massachusetts Department of Public Health, the Rhode Island

Department of Health, and the California State Office of AIDS, have issued policies or advisories for nPEP use. Some of these recommendations have focused on sexual assault survivors, who constitute few of the estimated 40,000 new HIV infections annually in the United States.

Surveys of clinicians and facilities indicate a need for more widespread implementation of guidelines and protocols for nPEP use (*61*). In a survey of Massachusetts emergency department directors, 52% of facilities had received nPEP requests during the preceding year, but only 15% had written nPEP protocols (*62*). Similarly, in a survey of Massachusetts clinicians, approximately 20% had a written nPEP protocol (*63*). Among pediatric emergency medicine specialists surveyed throughout the United States and Canada, approximately 20% had a written policy about nPEP use, but 33% had prescribed it for children and adolescents; different prescribing practices were reported (*64*). In a survey of 27 European Union countries, 23 had guidelines for occupational PEP use, but only six had guidelines for nPEP use (*65*).

Evidence indicates considerable awareness of nPEP and interest in its use among potential patients. In a cohort study of homosexual and bisexual men, 60% were willing to participate in a study of nPEP if it involved a single daily dose of medication; 30% were willing to take 3 doses daily (*66*). Among men surveyed at a "gay pride" festival in Atlanta, although only 3% had used nPEP, 26% planned to if exposed in the future (*67*). When nPEP studies were established in San Francisco, approximately 400 persons sought treatment in 2½ years (*24*). At a clinic primarily serving homosexual and bisexual men in Boston, 71 requests for nPEP were evaluated in 1½ years (*30*). In a California study of heterosexual discordant couples, 28% had heard of nPEP, 55% of seronegative partners believed that it was effective, and 78% reported they would take it if exposed (*34*).

No nationally representative data exists on nPEP use in the United States. In 1998, CDC established a national nPEP surveillance registry that accepts voluntary reports by clinicians. Although approximately 800 reports have been received, the majority of clinicians prescribing nPEP do not report to the registry. Similarly, low reporting rates were obtained in attempts to establish voluntary registries to monitor occupational PEP and antiretroviral use during pregnancy. No national surveys of clinicians have been reported. However, one multisite HIV vaccine trial largely conducted in the United States has assessed nPEP use by 5,418 participants, who included men who have sex with men (94%) and heterosexual women at high risk (6%). Two percent of trial participants from 27 study sites reported having taken nPEP during the trial. Supplementary data from six U.S. sites indicated that 46% of participants had heard of nPEP. Enrollment at one of seven California sites (odds ratio [OR] = 3.2), having a known positive partner (OR = 2.0), higher educational level (OR = 1.4), and greater recreational drug use (OR = 1.2) were significant predictors of having used nPEP ($p<0.05$) (*68*).

Evaluation of Persons Seeking Care After Potential Nonoccupational Exposure to HIV

The effective delivery of nPEP after exposures that have a substantial risk for HIV infection requires prompt evaluation of patients and consideration of biomedical and behavioral interventions to address current and ongoing health risks. This evaluation should include determination of the HIV status of the potentially exposed person, the timing and characteristics of the most recent exposure, the frequency of exposures to HIV, the HIV status of the source, and the likelihood of concomitant infection with other pathogens or negative health consequences of the exposure event.

HIV Status of the Potentially Exposed Person

Because persons who are infected with HIV might not be aware they are infected, baseline HIV testing should be performed on all persons seeking evaluation for potential nonoccupational HIV exposure. If possible, this should be done with an FDA-approved rapid test kit (with results available within an hour). If rapid tests are not available, an initial treatment decision should be made based on the assumption that the potentially exposed patient is not infected, pending HIV test results.

Timing and Frequency of Exposure

Available data indicate that nPEP is less likely to be effective if initiated >72 hours after HIV exposure. If initiation of nPEP is delayed, the likelihood of benefit might not outweigh the risks inherent in taking antiretroviral medications.

Because nPEP is not 100% effective in preventing transmission and because antiretroviral medications carry a certain risk for adverse effects and serious toxicities, nPEP should be used only for infrequent exposures. Persons who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of antiretroviral medications (e.g., discordant sex partners who rarely use condoms or injection-drug users who often share injection equipment) should not take nPEP. In these instances, exposed persons should instead be provided with intensive risk-reduction interventions.

HIV Status of Source

Patients who have had sexual, injection-drug–use, or other nonoccupational exposures to potentially infectious fluids of persons known to be HIV infected are at risk for acquiring HIV infection and should be considered for nPEP if they seek treatment within 72 hours of exposure. If possible, source persons should be interviewed to determine his or her history of antiretroviral use and most recent viral load because this information might provide information for the choice of nPEP medications.

Persons with exposures to potentially infectious fluids of persons of unknown HIV status might or might not be at risk for acquiring HIV infection. When the source is known to be from a group with a high prevalence of HIV infection (e.g., a homosexual or bisexual man, an injection–drug user, or a commercial sex worker), the risk for transmission might be increased. The risk for transmission might be especially great if the source person has been infected recently, when viral burden in blood and semen might be particularly high (*69,70*). However, ascertaining this in the short time available for nPEP evaluation is rarely possible. When the HIV status of the source is unknown, it should be determined whether the source is available for HIV testing. If the risk associated with the exposure is considered substantial, nPEP can be started pending determination of the HIV status of the source and then stopped if the source is determined to be noninfected.

Transmission Risk from the Exposure

Although the estimated per-act transmission risk from unprotected exposure to a partner known to be HIV infected is relatively low for different types of exposure (Table 1), different nonoccupational exposures are associated with different levels of risk (*71–79*). The highest levels of estimated per-act risk for HIV transmission are associated with blood transfusion, needle sharing by injection-drug users, receptive anal intercourse, and percutaneous needlestick injuries. Insertive anal intercourse, penile-vaginal exposures, and oral sex represent substantially less per-act risk.

TABLE 1. Estimated per-act risk for acquisition of HIV, by exposure route*

Exposure route	Risk per 10,000 exposures to an infected source	Reference
Blood transfusion	9,000	74
Needle-sharing injection-drug use	67	75
Receptive anal intercourse	50	76, 77
Percutaneous needle stick	30	78
Receptive penile-vaginal intercourse	10	76, 77, 79
Insertive anal intercourse	6.5	76, 77
Insertive penile-vaginal intercourse	5	76, 77
Receptive oral intercourse	1	77†
Insertive oral intercourse	0.5	77†

* Estimates of risk for transmission from sexual exposures assume no condom use.
† Source refers to oral intercourse performed on a man.

A history should be taken of the specific sexual, injection-drug–use, or other behaviors that might have led to, or modified, a risk for acquiring HIV infection. Eliciting a complete description of the exposure and information about the HIV status of the partner(s) can substantially lower (e.g., if the patient was the insertive partner or a condom was used) or increase (e.g., if the partner is known to be HIV-positive) the estimate of risk for HIV transmission resulting from a specific exposure.

In addition to sexual and injection-drug–use exposures, percutaneous injuries from needles discarded in public settings (e.g., parks and buses) result in requests for nPEP with a certain frequency. Although no HIV infections from such injuries have been documented, concern exists that syringes discarded by injection-drug users (e.g., for whom the HIV infection rate is higher than that for diabetics) might pose a substantial risk. However, these injuries typically involve small-bore needles that contain only limited amounts of blood, and the viability of any virus present is limited. In a study of syringes used to administer medications to HIV-infected persons, only 3.8% had detectable HIV RNA (*72*). In a study of the viability of virus in needles, viable virus was recovered from 8% at 21 days when the needles had been stored at room temperature; <1% had viable virus after 1 week of storage at higher temperatures (*73*).

Bite injuries represent another potential means of transmitting HIV. However, HIV transmission by this route has been reported rarely (*80-82*). Transmission might theoretically occur either though biting or receiving a bite from an HIV-infected person. Biting an HIV-infected person, resulting in a break in the skin, exposes the oral mucous membranes to infected blood; being bitten by an HIV-infected person exposes nonintact skin to saliva. Saliva that is contaminated with infected blood poses a substantial exposure risk. Saliva that is not contaminated with blood contains HIV in much lower titers and constitutes a negligible exposure risk (*83*).

Evaluation for Sexually Transmitted Infections, Hepatitis, and Emergency Contraception

Evaluation for sexually transmitted infections is important because these infections might increase the risk for acquiring HIV infection from a sexual exposure. In 1996, an estimated 5,042 new HIV infections were attributable to sexually transmitted infection at the time of HIV exposure (*84*). In addi-

tion, any sexual exposure that presents a risk for HIV infection might also place a patient at risk for acquiring other sexually transmitted infections, including hepatitis B. Prophylaxis for sexually transmitted disease, testing for hepatitis, and vaccination for hepatitis B (for those not immune) should be considered (*85*).

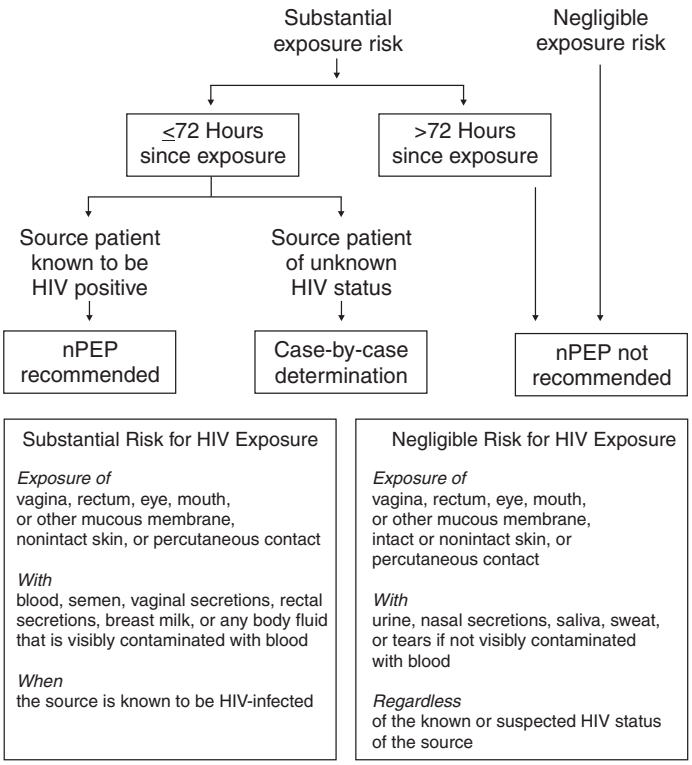
For women of reproductive capacity who have had genital exposure to semen, the risk for pregnancy also exists. In these instances, emergency contraception should be discussed with the potentially exposed patient.

Recommendations for Use of Antiretroviral nPEP

A 28-day course of HAART is recommended for persons who have had nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of a persons known to be HIV infected when that exposure represents a substantial risk for HIV transmission (Figure 1) and when the person seeks care within 72 hours of exposure. When indicated, antiretroviral nPEP should be initiated promptly for the best chance of success.

Evidence from animal studies and human observational studies demonstrate that nPEP administered within 48–72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational exposures. The sooner nPEP is administered after exposure, the more likely it is to interrupt transmission. Because HIV is an incurable transmissible infection that affects the quality and duration of life, HAART should be used to maximally suppress local viral replication that otherwise might occur in the days after exposure and potentially lead to a disseminated, established infection (*11,86*). One of the HAART combinations recommended for the treatment of persons with established HIV infection should be selected on the basis of adherence, toxicity, and cost considerations (Tables 2 and 3) (*87,88*).

FIGURE 1. Algorithm for evaluation and treatment of possible nonoccupational HIV exposures



No evidence indicates that any specific antiretroviral medication or combination of medications is optimal for use as nPEP. However, on the basis of the degree of experience with individual agents in the treatment of HIV-infected persons, certain agents and combinations are preferred. Preferred regimens include efavirenz and lamivudine or emtricitabine with zidovudine or tenofovir (as a nonnucleoside-based regimen) and lopinavir/ritonavir (coformulated in one tablet as Kaletra®) and zidovudine with either lamivudine or emtricitabine. Different alternative regimens are possible (Table 2).

No evidence indicates that a three-drug HAART regimen is more likely to be effective than a two-drug regimen. The recommendation for a three-drug HAART regimen is based on the assumption that the maximal suppression of viral replication afforded by HAART (the goal in treating HIV-infected persons) will provide the best chance of preventing infection in a person who has been exposed. Clinicians and patients who are concerned about potential adherence and toxicity issues associated with a three-drug HAART regimen might consider the use of a two-drug regimen (i.e., a combination of two reverse transcriptase inhibitors). Regardless of the regimen chosen, the exposed person should be counseled about the potential associated side effects and adverse events that require immediate medical attention. The use of medications to treat symptoms (e.g., antiemetics or antimotility agents) might improve adherence in certain instances.

Although certain preliminary studies have evaluated the penetration of antiretroviral medications into genital tract secretions and tissues (*89,90*), evidence is insufficient to recommend a specific antiretroviral medication as most effective for nPEP. In addition, new antiretroviral medications might become available. As new medications and new information become available, these recommendations will be amended and updated.

When the source-person is available for interview, his or her history of antiretroviral medication use and most recent

TABLE 2. Antiretroviral regimens for nonoccupational postexposure prophylaxis of HIV infection

Preferred regimens	
NNRTI*-based	Efavirenz† plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)
Protease inhibitor (PI)-based	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus zidovudine
Alternative regimens	
NNRTI-based	Efavirenz plus (lamivudine or emtricitabine) plus abacavrir or didanosine or stavudine§
PI-based	Atazanavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or didanosine) or (tenofovir plus ritonavir [100 mg/day])
	Fosamprenavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine) or (abacavir or tenofovir or didanosine)
	Fosamprenavir/ritonavir¶ plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Indinavir/ritonavir¶** plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus (stavudine or abacavir or tenofovir or idanosine)
	Nelfinavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Saquinavir (hgc* or sgc*)/ritonavir† plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
Triple NRTI*	Abacavir plus lamivudine plus zidovudine (only when an NONRTI- or PI-based regimen cannot or should not be used)

* NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; sgc = soft-gel saquinavir capsule (Fortovase); hgc = hard-gel saquinavir capsule (Invirase).
† Efavirenz should be avoided in pregnant women and women of childbearing potential.
§ Higher incidence of lipoatrophy, hyoerlipidemia, and mitochondrial toxicities associated with stavudine than with other NRTIs.
¶ Low-dose (100–400 mg) ritonavir. See Table 4 for doses used with specific PIs.
** Use of ritonavir with indinavir might increase risk for renal adverse events.
Source: U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, October 29,2004 revision. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50. This document is updated periodically; refer to website for updated versions.

viral load measurement should be considered when selecting antiretroviral medications for nPEP. This information might help avoid prescribing antiretroviral medications to which the source-virus is likely to be resistant. If the source-person is willing, the clinician might consider drawing blood for viral load and resistance testing, the results of which might be useful in modifying the initial nPEP medications if the results can be obtained promptly (*91*).

For persons who have had nonoccupational exposure to potentially infected body fluids of a person of unknown HIV infection status, when that exposure represents a substantial risk for HIV transmission (Figure 1) and when care is sought within 72 hours of exposure, no recommendations are made either for or against the use of antiretroviral nPEP. Clinicians should evaluate the risk for and benefits of this intervention on a case-by-case basis.

When a source-person is not known to be infected with HIV, the risk for exposure (and therefore the potential benefit of nPEP) is unknown. Prescribing antiretroviral medication in these cases might subject patients to risks that are not balanced with the potential benefit of preventing the acquisition of HIV infection. Judging whether the balance is appropriate depends entirely on the circumstances of the possible exposure (i.e., the risk that the source is HIV infected and the risk for transmission if the source is HIV infected) and is best determined through discussion between the clinician and the patient.

If the source-person is available for interview, additional information about risk history can be obtained and permission for an HIV test requested to assist in determining the likelihood of HIV exposure. When available, FDA-approved rapid HIV tests are preferable for obtaining this information as quickly as possible. These additional factors might assist in the decision whether to start or complete a course of nPEP. If data to clearly determine risk are not immediately available, clinicians might consider initiating nPEP while further assessments are being made and then stopping it when other information is available (e.g., the source-person is determined to be noninfected).

For persons whose exposure histories represent no substantial risk for HIV transmission (Figure 1) or who seek care >72 hours after potential nonoccupational HIV exposure, the use of antiretroviral nPEP is not recommended. When the risk for HIV transmission is negligible, limited benefit is anticipated from the use of nPEP. In addition, animal and human study data demonstrate that nPEP is less likely to prevent HIV transmission when initiated >72 hours after exposure. Because the risks associated with antiretroviral medications are likely to outweigh the potential benefit of nPEP in these circumstances, nPEP is not recommended for such exposures, regardless of the HIV status of the source. However, it cannot be concluded on the basis of the available data that nPEP will be completely ineffective when initiated >72 hours after exposure. Moreover, data do not indicate an absolute time after exposure beyond which nPEP will not be effective. When

TABLE 3. Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks†	Side effects and toxicities
Combination tablets			
Lopinavir/ritonavir (Kaletra®) §	3 tablets twice daily 400 mg lopinavir/100 mg ritonavir	650	Diarrhea, nausea, vomiting; asthenia; elevated transaminases; hyperglycemia; fat redistribution; lipid abnormalities; possible increased bleeding in persons with hemophilia; and pancreatitis
Zidovudine/lamivudine (Combivir®)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine	640	See following individual medications
Zidovudine/lamivudine/abacavir (Trizivir®)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine/ 300 mg abacavir	1,020	See following individual medications
Lamivudine/abacavir (Epzicom®)	1 tablet once daily 300 mg lamivudine/600 mg abacavir	760	See following individual medications
Emtricitabine/tenofovir (Truvada®)	1 tablet once daily 200 mg emtricitabine/300 mg tenofovir	800	See following individual medications
Single agents			
Nucleoside and nucleotide reverse transcriptase inhibitors (Side effects as a class: lactic acidosis, severe hepatomegaly with steatosis, including some fatal cases)			
Abacavir (Ziagen®, ABC)§	300 mg twice daily or 600 mg once daily	400	Severe hypersensitivity reaction (can be fatal); nausea; and vomiting
Didanosine (Videx®, ddI)§	>60 kg (132 lb) body weight: 200 mg twice daily or 400 mg daily; if with tenofovir, 250 mg/daily	260	Pancreatitis; nausea, diarrhea; and peripheral neuropathy
	<60 kg (132 lb): 125 mg twice daily or 250 mg daily; if with tenofovir, dose not established		
	Do not use with stavudine (d4T, Zerit) during pregnancy; avoid ddI/d4T combination in general because of increased risk for adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)		
Emtricitabine (Emtriva®, FTC)	200 mg once daily	280	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Lamivudine (Epivir®, 3TC)§	150 mg twice daily or 300 mg once daily	300	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Stavudine (Zerit®, d4T)§	>60 kg (132 lb) body weight: 40 mg twice daily	320	Pancreatitis; peripheral neuropathy; rapidly progressive ascending neuromuscular weakness (rare)
	<60 kg (132 lb) body weight: 30 mg twice daily		
	Do not use with didanosine (ddI, Videx) during pregnancy; avoid ddI/d4T combination in general because of increased risk for adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)		
Tenofovir (Viread®)	300 mg daily	400	Nausea, vomiting, diarrhea; headache; asthenia; flatulence; and renal impairment
Zidovudine (Retrovir®, AZT)§	200 mg three times daily or 300 mg twice daily	350	Bone marrow suppression (anemia, neutropenia); gastrointestinal intolerance; headache; insomnia; asthenia; and myopathy

TABLE 3. (*Continued*) Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks†	Side effects and toxicities
Single agents			
Non-nucleoside reverse transcriptase inhibitors (Side effects as a class: Stevens-Johnson syndrome)			
Efavirenz (Sustiva®)	600 mg daily at bedtime Do not use during known or possible pregnancy	420	Rash; central nervous system symptoms (e.g., dizziness, impaired concentration, insomnia, and abnormal dreams); transaminase elevation; and false-positive cannabinoid test
Protease inhibitors (Side effects as a class: gastrointestinal intolerance, hyperlipidemia, hyperglycemia, diabetes, fat redistribution, and possible increased bleeding in hemophiliacs)			
Atazanavir (Reyataz®)	400 mg once daily; if administered with tenofovir plus ritonavir, 300 mg once daily	760	Indirect hyperbilirubinemia; prolonged PR interval (use caution in patients with underlying cardiac conduction defects or on concomitant medications that can cause PR prolongation)
Fosamprenavir (Lexiva®)§	1,400 mg twice daily	1,260	Gastrointestinal intolerance, nausea, vomiting, diarrhea; rash; elevated transaminases; and headache
Indinavir (Crixivan®)	800 mg every 8 hours With ritonavir (might increase risk for renal adverse events): 800 mg indinavir and 100 mg ritonavir every 12 hours or 800 mg indinavir and 200 mg ritonavir every 12 hours	500	Gastrointestinal intolerance, nausea; nephrolithiasis; headache; asthenia; blurred vision; metallic taste; thrombocytopenia; hemolytic anemia; and indirect hyperbilirubinemia (inconsequential)
Nelfinavir (Viracept®)§	750 mg three times daily or 1,250 mg twice daily	600	Diarrhea; and elevated transaminases
Ritonavir (Norvir®)§	See doses used in combination with other specific protease inhibitors	700–2,800	Gastrointestinal intolerance; nausea, vomiting, diarrhea; paresthesias; hepatitis; panreatitis; asthenia; and taste perversion; many drug interactions
Saquinavir (hard-gel capsule) (Invirase®)	With ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1,000 mg saquinavir and 100 mg ritonavir twice daily	270	Gastrointestinal intolerance; nausea, diarrhea; headache; and elevated transaminases
Saquinavir (soft-gel capsule) (Fortavase®)	With Ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1,000 mg saquinavir and 100 mg ritonavir twice daily	460	Gastrointestinal intolerance; nausea, diarrhea; abdominal pain; dyspepsia; headache; and elevated transaminases

* For pediatric dosing information, see *Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection* (available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=51)

† Available at http://www.cvs.com/CVSApp/cvs/gateway/rxpriceqrequest

§ Pediatric formulation available.

Sources: U.S. Department of Health and Human Services and the Henry J.Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50 (refer to website for updated versions). Bartlett JG, Finkbeiner AK. HIV drugs: the guide to living with HIV infection. 2001. 11-13-2001. Available at http://www.thebody.com/jh/bartlett/drugs.html.

safer and more tolerable drugs are used, the risk-benefit ratio of providing nPEP >72 hours postexposure is more favorable. Therefore, clinicians might consider prescribing nPEP after exposures that confer a serious risk for transmission, even if the exposed person seeks care >72 hours postexposure if, in the clinician's judgment, the diminished potential benefit of nPEP outweighs the potential risk for adverse events from antiretroviral drugs.

Considerations for All Patients Treated with Antiretroviral nPEP

Use of Starter Packs

Patients might be under considerable emotional stress when seeking care after a potential HIV exposure and might not attend to, or retain, all the information relevant to making a decision about nPEP. Clinicians should give an initial prescription for 3–5 days of medication and schedule a follow-up visit to review the results of baseline HIV testing (if rapid tests are not used), provide additional counseling and support, assess medication side effects and adherence, and provide additional medication if appropriate (with an altered regimen if indicated by side effects or laboratory test results).

Scientific Consultation

When clinicians are not experienced with using HAART or when information from source-persons indicates the possibility of antiretroviral resistance, consultation with infectious disease or other HIV-care specialists, if it is available immediately, might be warranted before prescribing nPEP. Similarly, when considering prescribing nPEP to pregnant women or children, consultation with obstetricians or pediatricians might be advisable. However, if such consultation is not immediately available, initiation of nPEP should not be delayed. An initial nPEP regimen should be started and, if necessary, revised after consultation is obtained. Patients who seek nPEP might benefit from referral for psychological counseling that helps ease the anxiety about possible HIV exposure, strengthens risk-reduction behaviors, and promotes adherence to nPEP regimens if prescribed.

Facilitating Adherence

Adherence to antiretroviral medications can be challenging, even for 28 days. In addition to common side effects such as nausea and fatigue, each dose reminds the patient of his or her risk for acquiring HIV infection. Adherence has been reported to be especially poor among sexual assault survivors (*92–96*). Steps to maximize medication adherence include prescribing medications with fewer doses and fewer pills per dose, educating patients about the importance of adherence and about potential side effects, offering ancillary medications for side effects (e.g., anti-emetics) if they occur, and providing access to ongoing encouragement and consultation by phone or office visit.

Follow-up Testing and Care

All patients seeking care after HIV exposure should be tested for the presence of HIV antibodies at baseline and at 4–6 weeks, 3 months, and 6 months after exposure to determine whether HIV infection has occurred. In addition, testing for sexually transmitted diseases, hepatitis B and C, and pregnancy should be offered (Table 4).

Patients should be instructed about the signs and symptoms associated with acute retroviral infection (Table 5), especially fever and rash (*97*), and asked to return for evaluation if these occur during or after nPEP. Acute HIV infection is associated with high viral loads. However, clinicians should be aware that available assays might yield low viral-load results (e.g., <3,000) in noninfected persons. Such false-positive results can lead to misdiagnosis of HIV infection (*98*).

Transient, low-grade viremia has been observed both in macaques exposed to SIV (*99*) and humans exposed to HIV who were administered antiretroviral PEP (*100*) and did not become infected. In certain cases, this outcome might represent aborted infection rather than false-positive test results, but this can be determined only through further study. For patients with clinical or laboratory evidence of acute HIV infection, continuing antiretroviral therapy for >28 days might be prudent because such early treatment (no longer prophylaxis) might slow the progression of HIV disease (*101*). Patients with acute HIV infection should be transferred to the care of HIV treatment specialists.

In addition, clinicians who provide nPEP should monitor liver function, renal function, and hematologic parameters as indicated by the prescribing information found in antiretroviral treatment guidelines (*87,102,103*), package inserts, and the *Physician's Desk Reference* (Table 3). Unusual or severe toxicities from antiretroviral drugs should be reported to the manufacturer or FDA.

HIV Prevention Counseling

The majority of persons who seek care after a possible HIV exposure do so because of failure to initiate or maintain effective risk-reduction behaviors. Notable exceptions are sexual assault survivors and children with community-acquired needlestick injuries.

TABLE 4. Recommended laboratory evaluation for nonoccupational postexposure prophylaxis (nPEP) of HIV infection

Test	Baseline	During nPEP*	4–6 Weeks after exposure	3 Months after exposure	6 Months after exposure
HIV antibody testing	E†, S§		E	E	E
Complete blood count with differential	E	E			
Serum liver enzymes	E	E			
Blood urea nitrogen/creatinine	E	E			
Sexually transmitted diseases screen (gonorrhea, chlamydia, syphilis)	E, S	E¶	E¶		
Hepatitis B serology	E, S		E¶	E¶	
Hepatitis C serology	E, S			E	E
Pregnancy test (for women of reproductive age)	E	E¶	E¶		
HIV viral load	S		E**	E**	E**
HIV resistance testing	S		E**	E**	E**
$CD4^+$T lymphocyte count	S		E**	E**	E**

* Other specific tests might be indicated dependent on the antiretrovirals prescribed. Literature pertaining to individual agents should be consulted.
† E = exposed patient, S = source.
§ HIV antibody testing of the source patient is indicated for sources of unknown serostatus.
¶ Additional testing for pregnancy, sexually transmitted diseases, and hepatitis B should be performed as clinically indicated.
** If determined to be HIV infected on follow-up testing; perform as clinically indicated once diagnosed.

TABLE 5. Expected frequency of associated signs and symptoms among persons with signs and symptoms of acute retroviral syndrome

Symptom/sign	%
Fever	96
Lymphadenopathy	74
Pharyngitis	70
Rash Erythematous maculopapular with lesions on face, trunk and sometimes extremities, including palms and soles; mucocutaneous ulceration involving mouth, esophagus or genitals	70
Myalgia or arthralgia	54
Diarrhea	32
Headache	32
Nausea and vomiting	27
Hepatosplenomegaly	14
Weight loss	13
Thrush	12
Neurologic symptoms Meningoencephalitis or aseptic meningitis; peripheral neuropathy or radiculopathy; facial palsy; Guillain-Barré syndrome; brachial neuritis; or cognitive impairment or psychosis	12

Although nPEP might reduce the risk for HIV infection, it is not believed to be 100% effective. Therefore, patients should practice protective behaviors with sex partners (e.g., abstinence or consistent use of male condoms) or drug-use partners (e.g., avoidance of shared injection equipment) throughout the course of nPEP to avoid transmission to others if they become infected, and after nPEP to avoid future HIV exposures.

At follow-up visits, clinicians should assess their patients' needs for behavioral intervention, education, and services. This assessment should include frank, nonjudgmental questions about sexual behaviors, alcohol use, and illicit drug use. Clinicians should help patients identify ongoing risk issues and develop plans for improving their use of protective behaviors (*104*).

To help patients obtain indicated interventions and services, clinicians should be aware of local resources for high-quality HIV education and ongoing behavioral risk reduction, counseling and support, inpatient and outpatient alcohol and drug-treatment services, substance/drug abuse treatment programs, family and mental health counseling services, and support programs for HIV-infected persons. Information about publicly funded HIV prevention programs can be obtained from state or local health departments.

Management of Source Persons

When source-persons are seen during the course of evaluating a patient for potential HIV exposure, clinicians should also assess the source-person's access to relevant medical care, behavioral intervention, and social support services. If needed care cannot be provided directly, clinicians should help source-persons obtain care in the community.

If a new diagnosis of HIV infection is made or evidence of other sexually transmitted infection is identified, the patient

should be assisted in notifying their sexual and drug-use contacts. Assistance with confidential partner notification (without revealing the patient's identity) is available through local health departments.

Reporting and Confidentiality

Because of the emotional, social, and potential financial consequences of possible HIV infection, clinicians should handle nPEP evaluations with the highest level of confidentiality. Confidential reporting of sexually transmitted infections and newly diagnosed HIV infections to health departments should take place as dictated by local law and regulations.

For cases of sexual assault, clinicians should document their findings and assist patients with notifying local authorities. HIV test results should be recorded separately from the findings of the sexual assault examination to protect patients' confidentiality in the event that medical records are later released for legal proceedings. Certain states and localities have special programs to provide reimbursement for medical therapy, including antiretroviral medication after sexual assault, and these areas might have specific reporting requirements. When the sexual abuse of a child is suspected or documented, the clinician should report it in compliance with state and local law and regulations.

Considerations for Vulnerable Populations

Pregnant Women and Women of Childbearing Potential

Considerable experience has been gained in recent years in the safe and appropriate use of antiretroviral medications during pregnancy, either for the benefit of the HIV-infected woman's health or to prevent transmission to newborns. To facilitate the selection of antiretroviral medications likely to be both effective and safe for the developing fetus, clinicians should consult DHHS guidelines (*102*) before prescribing nPEP for a woman who is or might be pregnant.

Because of potential teratogenicity, efavirenz should not be used in any nPEP regimen during pregnancy or among women of childbearing age at risk for becoming pregnant during the course of antiretroviral prophylaxis (Table 3). A protease inhibitor- or nucleoside reverse transcriptase inhibitor-based regimen should be considered in these circumstances. When efavirenz is prescribed to women of childbearing potential, they should be instructed about the need to avoid pregnancy. Because the effect of efavirenz on hormonal contraception is unknown, women using such contraception should be informed of the need to use an additional method (e.g., barrier contraception). In addition, because of reports of maternal and fetal mortality attributed to lactic acidosis associated with prolonged use of d4T in combination with ddI in HIV-infected pregnant women, this combination is not recommended for use in an nPEP regimen (*105*).

Children

Potential HIV exposures in children occur most often by accident (e.g., needlesticks in the community, fights, or playground incidents resulting in bleeding by an HIV-infected child) or by sexual abuse or assaults (*106*). In a review of charts from 1 year in the pediatric emergency department of one hospital, 10 children considered for nPEP were identified (six because of sexual assault and four because of needlestick injury). Eight began taking nPEP, but only two completed the 4-week course (*63,107*). An analysis of 9,136 reported acquired immunodeficiency syndrome cases in children identified 26 who were sexually abused with confirmed or suspected exposure to HIV infection (*108*).

The American Academy of Pediatrics has issued nPEP guidelines for pediatric patients (*109*). In addition, DHHS pediatric antiretroviral treatment guidelines (*103*) provide information about the use of antiretroviral agents in children. For young children who cannot swallow capsules or tablets and to ensure appropriate dosing for drugs that do not have capsule/tablet formulations that allow pediatric dosing, drugs for which pediatric formulations are available might need to be prescribed (Table 3). Adherence to the prescribed medications will depend on the involvement of, and support provided to, parents or guardians.

Sexual Assault Survivors

Use of nPEP for sexual assault survivors has been widely encouraged both in the United States and elsewhere (*56, 94,110,111*). Sexual assault is relatively common among women: 13% of a national sample of adult women reported having ever been raped (60% before age 18), and 5% reported having been raped more than once (*112*). Sexual assault is not uncommon among men. In one series from an emergency department, 5% of reported rapes involved men sexually assaulted by men (*113*). Males accounted for 11.6 % of rapes reported among persons aged ≥12 years who responded to the National Crime Victimization Survey in 1999 (*114*). However, only three documented cases of HIV infection resulting from sexual assault have been published (*94,115,116*). In observational studies, HIV infections have been temporally associated with sexual assault (Personal communication,

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Studies have examined HIV infection rates for sexual assailants (*117,118*). The largest of these, an evaluation of men incarcerated in Rhode Island, determined that 1% of those convicted of sexual assault were HIV infected when they entered prison, compared with 3% of all prisoners and 0.3% of the general male population (*119*).

Sexual assault typically has multiple characteristics that increase the risk for HIV transmission if the assailant is infected. In one prospective study of 1,076 sexual assault cases, 20% were attacked by multiple assailants, 39% were assaulted by strangers, 83% of females were vaginally penetrated, and 17% overall were sodomized. Genital trauma was documented in 53% of those assaulted, and sperm or semen was detected in 48% (*120*). In another study, in which toluidine blue dye was used as an adjunct to naked-eye examination, 40% of assaulted women (70% of nulliparas) had detectable vaginal lacerations, compared with 5% of women examined after consensual sex (*121*).

Despite these risks and the establishment of multidisciplinary support services, sexual assault survivors often decline nPEP, and many who do take it do not complete the 28-day course. This pattern has been reported in several countries and several programs in North America. In Vancouver, 71 of 258 assault survivors accepted the 5-day starter pack of nPEP, 29 returned for additional doses, and eight completed 4 weeks of therapy (*96*). Those with the highest risk for HIV exposure (i.e., source known to be HIV infected, a homosexual or bisexual man, or an injection-drug user) were more likely to begin and complete nPEP.

Patients who have been sexually assaulted will benefit from supportive services to improve adherence to nPEP if it is prescribed, and from psychological and other support provided by sexual assault crisis centers. All sexually assaulted patients should be tested and administered prophylaxis for sexually transmitted infections (*85*), and women who might become pregnant should be offered emergency contraception (*122*).

Inmates

Certain illegal behaviors that result in imprisonment (e.g., prostitution and injection-drug use) also might be associated with a higher prevalence of HIV infection among prison inmates than among the general population (*119*). However, studies indicate that the risk for becoming infected in prison is probably less than the risk outside prison (*122–125*). However, when exposure does occur, because sexual contact and injection-drug use are prohibited in jails and prisons, prisoners who have experienced such exposures might be unable or unwilling to report the behaviors to health-care providers.

Administrators and health-care providers working in correctional settings should develop and implement systems to make HIV education and risk-reduction counseling, nPEP, voluntary HIV testing, and HIV care confidentially available to inmates. Such programs will allow inmates to benefit from nPEP when indicated, facilitate treatment services for those with drug addiction, and assist in the identification and treatment of sexual assault survivors.

Injection-Drug Users

A history of injection-drug use should not deter clinicians from prescribing nPEP if the exposure provides an opportunity to reduce the risk for consequent HIV infection. A survey of clinicians serving injection-drug users determined a high degree of willingness to provide nPEP after different types of potential HIV exposure (*126*).

In judging whether exposures are isolated, episodic, or ongoing, clinicians should consider that persons who continue to engage in risk behaviors (e.g., commercial sex workers or users of illicit drugs) might be practicing risk reduction (e.g., using condoms with every client, not sharing syringes, and using a new sterile syringe for each injection). Therefore, a high-risk exposure might represent an exceptional occurrence for such persons despite their ongoing risk behavior.

Injection-drug users should be assessed for their interest in substance abuse treatment and their knowledge and use of safe injection and sex practices. Patients desiring substance abuse treatment should be referred for such treatment. Persons who continue to inject or who are at risk for relapse to injection-drug use should be instructed in the use of a new sterile syringe for each injection and the importance of avoiding the sharing of injection equipment. In areas where programs are available, health-care providers should refer such patients to appropriate sources of sterile injection equipment.

Conclusion

Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon as possible within 48–72 hours of sexual, injection-drug–use, and other substantial nonoccupational HIV exposure and continued for 28 days might reduce the likelihood of transmission. Because of these findings, DHHS recommends the prompt initiation of nPEP with HAART when persons seek care within 72 hours after exposure, the source is known to be HIV infected, and the exposure event presents a substantial risk for transmission. When the HIV

status of the source is not known and the patient seeks care within 72 hours after exposure, DHHS does not recommend for or against nPEP but encourages clinicians and patients to weigh the risks and benefits on a case-by-case basis. When the transmission risk is negligible or when patients seek care >72 hours after a substantial exposure, nPEP is not recommended; however, clinicians might consider prescribing nPEP for patients who seek care >72 hours after a substantial exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the potential risk for adverse events from antiretroviral medications. These recommendations are intended for the United States and might not apply in other countries.

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MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports January 21, 2005 / Vol. 54 / No. RR-2

Continuing Education Activity Sponsored by CDC

Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

Recommendations from the U.S. Department of Health and Human Services

EXPIRATION — January 21, 2008

You must complete and return the response form electronically or by mail by **January 21, 2008**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.0 hours Continuing Medical Education (CME) credit; 0.15 Continuing Education Units (CEUs); or 2.2 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 54, RR-2), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at http://www.cdc.gov/mmwr/cme/conted.html.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
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5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **January 21, 2008**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 54, RR-2), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, or CNE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **January 21, 2008**, to
   Fax: 404-498-6035 Mail: MMWR CE Credit
   Division of Scientific Communications
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   Centers for Disease Control and Prevention
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ACCREDITATION

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 2.0 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This *MMWR* describes the potential risks and benefits of antiretroviral postexposure prophylaxis after nonoccupational exposures to human immunodeficiency virus (HIV). These recommendations were developed by CDC staff in collaboration with scientists, public health officials, clinicians, ethicists, members of affected communities, and representatives from professional associations and industry. The goal of this report is to provide information on which to base decisions regarding postexposure prophylaxis after a nonoccupational exposure to HIV. After completing this educational activity, the reader should be able to 1) describe the characteristics of a potential HIV exposure; 2) describe situations in which postexposure prophylaxis is most likely to be beneficial; 3) describe sources for obtaining information on antiretroviral regimens; and 4) describe appropriate follow-up schedules for persons who are prescribed antiretroviral postexposure prophylaxis.

To receive continuing education credit, please answer all of the following questions.

1. Evidence from controlled studies among humans indicates that the administration of antiretroviral postexposure prophylaxis after nonoccupational exposures to HIV is an effective means of preventing HIV infection.

A. True.
B. False.

2. On the basis of available evidence from animal studies, antiretroviral postexposure prophylaxis is most likely to be beneficial when initiated as soon as possible after exposure, and in the majority of cases, should not be initiated if >____ hours have elapsed since exposure.

A. 72.
B. 24.
C. 36.
D. None of the above.

3. Contact of which of the following body sites with HIV-infected bodily fluids constitutes a substantial HIV exposure?

A. Vagina.
B. Eye.
C. Intact skin.
D. Rectum.
E. A and D are correct.
F. A, B, and D are correct.

4. In a person with HIV infection, potentially infectious fluids include all of the following, except . . .

A. blood.
B. saliva visibly contaminated with blood.
C. urine not visibly contaminated with blood.
D. genital secretions.
E. none of the above; all are potentially infectious.

5. Which of the following lists of exposure types are correctly ordered from greatest risk of infection to least risk of infection?

A. Insertive anal is greater than insertive oral, which is greater than insertive vaginal.
B. Receptive anal is greater than receptive vaginal, which is greater than receptive oral.
C. Insertive anal is greater than receptive anal, which is greater than receptive oral.
D. None of the above.

6. The recommended duration of antiretroviral postexposure prophylaxis is . . .

A. 10 days.
B. 14 days.
C. 28 days.
D. none of the above.

7. Antiretroviral medications that should be avoided for pregnant women and women of childbearing potential include . . .

A. efavirenz.
B. nevirapine.
C. azidothymidine (AZT).
D. stavudine (D4T) in combination with didanosine (ddI).
E. A, B, and D.

8. Patients who are prescribed antiretroviral postexposure prophylaxis should be instructed about the symptoms of acute retroviral infection, which can include . . .

A. thrush.
B. fever.
C. rash.
D. all of the above.
E. B and C only.

9. Follow-up visits and testing of persons who are prescribed antiretroviral postexposure prophylaxis should be performed at approximately . . .

A. 4–6 weeks.
B. 3 months.
C. 6 months.
D. all of the above.

10. In addition to HIV antibody testing, follow-up laboratory testing of persons who are prescribed antiretroviral postexposure prophylaxis should include . . .

A. hepatitis A serology.
B. hepatitis B serology.
C. hepatitis C serology.
D. complete blood count, blood urea nitrogen/creatinine, and hepatic enzymes.
E. all of the above.
F. B, C, and D.

11. Which best describes your professional activities?

A. Physician.
B. Nurse.
C. Health educator.
D. Office staff.
E. Other.

12. I plan to use these recommendations as the basis for . . . (*Indicate all that apply.*)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

13. Each month, approximately how many patients with a potential HIV exposure do you treat?

A. None.
B. 1–5.
C. 6–20.
D. 21–50.
E. 51–100.
F. >100.

14. How much time did you spend reading this report and completing the exam?

A. <2.0 hours.
B. >2.0 hours but <3.0 hours.
C. >3.0 hours but <4.0.
D. >4.0 hours.

15. After reading this report, I am confident I can describe the characteristics of a potential HIV exposure.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe situations in which postexposure prophylaxis is most likely to be beneficial.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe sources for obtaining information on antiretroviral regimens.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe appropriate follow-up schedules for persons who are prescribed antiretroviral postexposure prophylaxis.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

MMWR Response Form for Continuing Education Credit
January 21, 2005/Vol. 54/No. RR-2
Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States
Recommendations from the U.S. Department of Health and Human Services

To receive continuing education credit, you must
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Check One
☐ *CME Credit*
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Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [ ]A [ ]B
2. [ ]A [ ]B [ ]C [ ]D
3. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F
4. [ ]A [ ]B [ ]C [ ]D [ ]E
5. [ ]A [ ]B [ ]C [ ]D
6. [ ]A [ ]B [ ]C [ ]D
7. [ ]A [ ]B [ ]C [ ]D [ ]E
8. [ ]A [ ]B [ ]C [ ]D [ ]E
9. [ ]A [ ]B [ ]C [ ]D
10. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F
11. [ ]A [ ]B [ ]C [ ]D [ ]E
12. [ ]A [ ]B [ ]C [ ]D [ ]E
13. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F
14. [ ]A [ ]B [ ]C [ ]D
15. [ ]A [ ]B [ ]C [ ]D [ ]E
16. [ ]A [ ]B [ ]C [ ]D [ ]E
17. [ ]A [ ]B [ ]C [ ]D [ ]E
18. [ ]A [ ]B [ ]C [ ]D [ ]E
19. [ ]A [ ]B [ ]C [ ]D [ ]E
20. [ ]A [ ]B [ ]C [ ]D [ ]E
21. [ ]A [ ]B [ ]C [ ]D [ ]E
22 [ ]A [ ]B [ ]C [ ]D [ ]E
23. [ ]A [ ]B [ ]C [ ]D [ ]E
24. [ ]A [ ]B [ ]C [ ]D [ ]E
25. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F

Signature ***Date I Completed Exam***

19. The objectives are relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

20. The teaching strategies used in this report (text, figure, and tables) were useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

21. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. These recommendations will affect my practice.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. The content of this activity was appropriate for my educational needs.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

24. The availability of continuing education credit influenced my decision to read this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

25. How did you learn about this continuing education activity?

A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10.
1. B, 2. A, 3. F, 4. C, 5. B, 6. C, 7. E, 8. D, 9. D, 10. F.

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EXHIBIT 14

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A CASE–CONTROL STUDY OF HIV SEROCONVERSION IN HEALTH CARE WORKERS AFTER PERCUTANEOUS EXPOSURE

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ABSTRACT

Background The average risk of human immunodeficiency virus (HIV) infection after percutaneous exposure to HIV-infected blood is 0.3 percent, but the factors that influence this risk are not well understood.

Methods We conducted a case–control study of health care workers with occupational, percutaneous exposure to HIV-infected blood. The case patients were those who became seropositive after exposure to HIV, as reported by national surveillance systems in France, Italy, the United Kingdom, and the United States. The controls were health care workers in a prospective surveillance project who were exposed to HIV but did not seroconvert.

Results Logistic-regression analysis based on 33 case patients and 665 controls showed that significant risk factors for seroconversion were deep injury (odds ratio = 15; 95 percent confidence interval, 6.0 to 41), injury with a device that was visibly contaminated with the source patient's blood (odds ratio = 6.2; 95 percent confidence interval, 2.2 to 21), a procedure involving a needle placed in the source patient's artery or vein (odds ratio = 4.3; 95 percent confidence interval, 1.7 to 12), and exposure to a source patient who died of the acquired immunodeficiency syndrome within two months afterward (odds ratio = 5.6; 95 percent confidence interval, 2.0 to 16). The case patients were significantly less likely than the controls to have taken zidovudine after the exposure (odds ratio = 0.19; 95 percent confidence interval, 0.06 to 0.52).

Conclusions The risk of HIV infection after percutaneous exposure increases with a larger volume of blood and, probably, a higher titer of HIV in the source patient's blood. Postexposure prophylaxis with zidovudine appears to be protective. (N Engl J Med 1997;337:1485-90.)

THE average risk of transmission of human immunodeficiency virus (HIV) to a health care worker after percutaneous exposure to HIV-infected blood has been estimated as 0.3 percent.[1-4] However, the factors that influence this risk have not been determined, and the efficacy of postexposure prophylaxis with antiretroviral drugs has not been clinically evaluated. If postexposure prophylaxis is effective, it would offer an entirely new strategy for preventing HIV transmission in nonoccupational settings as a supplement to the preferred strategy of preventing exposure. Study of occupational exposure to HIV presents an important opportunity to evaluate postexposure prophylaxis, because the source, time, and many details of the exposure are known. A nationwide, prospective, placebo-controlled trial of prophylaxis with zidovudine after percutaneous exposure to HIV among health care workers was discontinued when only 84 health care workers enrolled after one year, since many thousands would be needed to assess reduction of a 0.3 percent risk of transmission.[1,5] Nevertheless, occupational exposure to HIV and infection continue to occur, and there is a compelling public health need for data on the efficacy of postexposure prophylaxis.

We conducted a case–control study to identify

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risk factors for the transmission of HIV to a health care worker after percutaneous exposure to HIV-infected blood.

METHODS

Definitions

Case patients were health care workers who had a documented occupational, percutaneous exposure to HIV-infected blood by a needle stick or a cut with a sharp object, HIV seroconversion that was temporally associated with the exposure, and no other reported concurrent exposure to HIV. Control subjects were health care workers with a documented occupational, percutaneous exposure to HIV-infected blood who were HIV seronegative at the time of exposure and at least six months later.

Identification of Case Patients and Controls

Case patients were identified through reports to national surveillance systems for occupationally acquired HIV infection that were operated by the Centers for Disease Control and Prevention (CDC), in cooperation with state and local health departments in the United States; the Réseau National de Santé Publique in France; the Centro di Riferimento AIDS in Italy; and the Public Health Laboratory Service Communicable Disease Surveillance Centre in the United Kingdom. Controls were identified through reports to a voluntary CDC surveillance project, Prospective Evaluation of Health Care Workers Exposed to Blood of Patients Infected with HIV, also called the CDC Needlestick Study. This project has enrolled health care workers from approximately 300 health care institutions in the United States since 1983.[1]

All case patients reported in the United States by August 1994 who were exposed after 1987 and all controls exposed after 1987 whose six-month follow-up evaluation was completed as of August 1994 were studied. Case patients and controls reported in the United States before 1988 were excluded from the analysis because information on many variables of interest was not routinely collected before 1988 and because postexposure prophylaxis was rare.[1] For the same reason, the analysis was limited to all case patients reported in France and Italy after 1989 and in the United Kingdom after 1987. Information on two case patients from Italy had been collected but was not available for analysis in an earlier brief report.[6]

Case patients were normally reported to public health authorities after seroconversion. Most variables of interest were obtained by reviewing incident reports that had been completed at the time of exposure and other records in which documentation was considered to be objective (e.g., medical records). Controls were reported to the CDC at the time of exposure; information was collected with a standardized protocol.[1] Information regarding the date of death of source patients was retrospectively collected for case patients and controls.

Data Collection

For each case patient and control, personal information was collected as well as information on the source patient and the injury. Information about the health care worker included age, sex, occupation, work location, whether antiretroviral agents were offered after exposure, and if taken, the interval between exposure and the first dose and the regimen followed. Information about the source patient included the stage of HIV disease (the acquired immunodeficiency syndrome [AIDS], symptomatic, or asymptomatic) at the time of the health care worker's exposure, use of antiretroviral drugs at that time, and whether the source patient died of AIDS within two months after the health care worker's exposure (referred to as terminal illness). Information about the injury included the type of device involved, the gauge of hollow-bore needle, the type of procedure performed, the urgency of the procedure, the use of gloves, the interval between the use of the device and injury, the presence or absence of visible blood from the source patient on the device, and the severity of injury. Procedures involving a needle placed in the source patient's artery or vein (e.g., phlebotomy, insertion of an intravenous catheter, and arterial-blood gas collection) were distinguished from other procedures (e.g., intramuscular injection and injection into an intravenous catheter). The severity of injury was defined as superficial (surface scratch and the absence of bleeding), moderate (penetration of the skin and bleeding), or deep (deep puncture or wound with or without bleeding).

Statistical Analysis

Univariate and stratified multivariate analyses were performed with Fisher's exact test and Cochran–Mantel–Haenszel techniques. All variables that were either statistically significant in univariate analyses or potentially important with respect to prevention (e.g., the use of gloves, whether zidovudine was offered after exposure, and whether zidovudine was taken) were included in logistic-regression analyses.

When a dichotomous variable had data missing among both case patients and controls, health care workers with missing data were not excluded from the logistic-regression analyses; instead, "missing" was considered a third response category for that variable. A missing-value indicator variable (assigned a value of 1 if missing and a value of zero otherwise) was created and forced into the model, and the missing value was recorded as zero. Thus, we maximized the number of health care workers in the analysis and assessed the potential confounding influence of missing values on the estimated effects of the other risk factors.

Data were analyzed with the Statistical Analysis System (SAS Institute, Cary, N.C.). All P values are two-tailed.

RESULTS

The study population included 33 case patients (23 from the United States, 5 from France, 3 from the United Kingdom, and 2 from Italy) and 679 controls (from 190 of the U.S. health care facilities involved in the CDC Needlestick Study). There was no significant difference between case patients and controls with respect to the year of exposure ($P = 0.84$). Of the injuries sustained by the case patients, 30 (91 percent) were needle sticks (all with hollow-bore needles) and 3 (9 percent) involved other sharp objects. Of the injuries sustained by controls, 620 (91 percent) were needle sticks (594 with hollow-bore needles and 26 with suture needles) and 59 (9 percent) involved other sharp objects.

Univariate analysis revealed that HIV transmission was significantly associated with injuries with a large-diameter needle (a gauge of less than 18), deep injury, visible blood on the device, procedures involving a needle placed in the source patient's vein or artery, emergency procedures, and terminal illness in the source patient (Table 1). No significant difference in risk was found between exposure involving a hollow-bore needle and that involving a suture needle. By univariate analysis, there was no significant difference between case patients and controls in the use of zidovudine after exposure (9 of 33 case patients, or 27 percent, vs. 247 of 679 controls, or 36 percent; odds ratio = 0.7; $P = 0.35$). There was no evidence that case patients were more or less likely than controls to be offered zidovudine. Twenty-five case patients (76 percent) and 500 controls (74 per-

TABLE 1. CHARACTERISTICS OF INJURIES SUSTAINED BY CASE PATIENTS AND CONTROLS.

RISK FACTOR	CASE PATIENTS		CONTROLS		CRUDE ODDS RATIO (95% CI)*	P VALUE†
	NO. OF PATIENTS‡	% WITH RISK FACTOR	NO. OF PATIENTS‡	% WITH RISK FACTOR		
Large-gauge (<18) hollow-bore needle	27	15	488	1.2	14 (4.9–39)	0.001
Deep injury	33	52	675	6.8	15 (8.0–26)	<0.001
Visible blood on device	32	84	632	35	10 (4.6–23)	<0.001
Procedure involving needle in artery or vein	33	73	669	31	5.9 (2.9–12)	<0.001
Emergency procedure	33	12	661	2.4	5.6 (2.0–16)	0.012
Use of gloves	32	78	679	78	1.0 (0.4–2.4)	1.0
AIDS in source patient	33	82	676	70	1.9 (0.8–4.6)	0.18
Terminal illness in source patient§	27	48	349	16	4.8 (2.3–10)	<0.001
Postexposure use of zidovudine	33	27	679	36	0.7 (0.3–1.4)	0.35

*CI denotes confidence interval. Odds ratios are for the odds of seroconversion after exposure in workers with the risk factor as compared with those without it.

†P values were determined by the two-tailed Fisher's exact test.

‡The numbers are the numbers of subjects for whom data were available.

§Terminal illness was defined as disease leading to the death of the source patient from AIDS within two months after the health care worker's exposure.

cent) were exposed during 1990 to 1994, when postexposure use of zidovudine had become more common.[1] Among the 23 of these 25 case patients for whom information was available, 19 (83 percent) had been offered the drug (11 of 13 U.S. case patients and 8 of 10 European case patients). From September 1990 through August 1994, 268 of 338 controls (79 percent) had been offered zidovudine ($P = 1.0$). Among health care workers who were known to have been offered zidovudine, 9 case patients (47 percent) and 172 controls (64 percent) took the drug ($P = 0.15$).

Logistic-Regression Model

The final logistic-regression model, which included 33 case patients and 665 controls (14 controls were eliminated because of missing values), identified several risk factors that were associated with HIV transmission: deep injury, injury with a device that was visibly contaminated with the source patient's blood, procedures involving a needle placed in the source patient's vein or artery, and terminal illness in the source patient (Table 2). After control for these factors, no differences were detected in the rates at which case patients and controls were offered postexposure prophylaxis with zidovudine (odds ratio = 0.92, $P = 0.90$). However, case patients were significantly less likely to have taken zidovudine than controls (odds ratio = 0.19, $P = 0.003$). This is a classic example of confounding, since the adjusted odds ratio differed from the crude odds ratio (0.7) because zidovudine use was more likely among both case patients and controls after exposure characterized by one or more of the four risk factors in the model. These risk factors were more prevalent among case patients than among controls, indicating that the case patients had more serious exposure than the

TABLE 2. LOGISTIC-REGRESSION ANALYSIS OF RISK FACTORS FOR HIV TRANSMISSION AFTER PERCUTANEOUS EXPOSURE TO HIV-INFECTED BLOOD.

RISK FACTOR	U.S. CASES*	ALL CASES†
	adjusted odds ratio (95% CI)‡	
Deep injury	13 (4.4–42)	15 (6.0–41)
Visible blood on device	4.5 (1.4–16)	6.2 (2.2–21)
Procedure involving needle in artery or vein	3.6 (1.3–11)	4.3 (1.7–12)
Terminal illness in source patient§	8.5 (2.8–28)	5.6 (2.0–16)
Postexposure use of zidovudine	0.14 (0.03–0.47)	0.19 (0.06–0.52)

*All risk factors were significant ($P<0.02$).

†All risk factors were significant ($P<0.01$).

‡CI denotes confidence interval. Odds ratios are for the odds of seroconversion after exposure in workers with the risk factor as compared with those without it.

§Terminal illness was defined as disease leading to the death of the source patient from AIDS within two months after the health care worker's exposure.

TABLE 3. POSTEXPOSURE USE OF ZIDOVUDINE AMONG CASE PATIENTS AND CONTROLS, ACCORDING TO THE NUMBER OF RISK FACTORS PRESENT.*

NO. OF RISK FACTORS	CASE PATIENTS		CONTROLS		UNADJUSTED ODDS RATIO
	TOTAL	POSTEXPOSURE ZIDOVUDINE USE	TOTAL	POSTEXPOSURE ZIDOVUDINE USE	
	number (percent)				
0	0	—	128 (40)	40 (31)	—
1	3 (11)	0	124 (39)	51 (41)	0.20
2	11 (41)	2 (18)	55 (17)	33 (60)	0.15
3	8 (30)	1 (12)	12 (4)	7 (58)	0.10
4	5 (19)	5 (100)	1 (0.3)	0	33
Total	27 (100)	8 (30)	320 (100)	131 (41)	0.61

*Case patients and controls with missing values for one or more risk factors in Table 2 were excluded from the analysis. The Cochran–Mantel–Haenszel estimate of the odds ratio for postexposure use of zidovudine among these case patients and controls, with adjustment for the number of risk factors present, is 0.21 ($P=0.002$), whereas the estimate of the crude (unadjusted) odds ratio is 0.61 ($P=0.31$).

controls; hence, the crude odds ratio for zidovudine use was severely confounded.

In a separate analysis performed after we excluded case patients and controls with missing values for one or more of the risk factors and stratified subjects according to the number of risk factors present, the adjusted odds ratio for zidovudine use (0.21) obtained by Cochran–Mantel–Haenszel techniques was similar to the adjusted odds ratio calculated with the logistic-regression model (0.19) (Table 3). A significant ($P<0.05$) protective effect of zidovudine use was also observed after control for the influence of any two of the four risk factors.

No significant interactions were found among the risk factors in the model or between the risk factors and the missing-value indicators forced into the model (for visible blood on the device and terminal illness in the source patient). When all health care workers with missing values were excluded, all factors remained significant, with similar adjusted odds ratios but slightly larger confidence intervals. All factors in the model also remained significant when the analysis was restricted to case patients from the United States (Table 2).

Postexposure Zidovudine Regimens

Among the health care workers who took zidovudine, 67 percent of controls and 89 percent of case patients had their first dose within four hours after exposure ($P=0.28$). Sixty-six percent of controls and 44 percent of case patients continued postexposure prophylaxis for at least four weeks ($P=0.28$); 78 percent of controls and 75 percent of case patients took at least 1000 mg of zidovudine per day ($P=1.0$).

The degree of susceptibility of HIV strains from most source patients to zidovudine is unknown. Information about antiretroviral drugs taken by source patients at the time of exposure was available for 7 case patients and 124 controls who took zidovudine. In the case of 5 (71 percent) of the case patients and 87 (70 percent) of the controls, the source patients were receiving zidovudine at the time of the health care workers' exposure.

DISCUSSION

In this study, the risk of HIV transmission to a health care worker after percutaneous exposure to HIV-infected blood appeared to be influenced by several factors. Increased risk was associated with three factors that were probably indirect measures of the quantity of blood transferred in the exposure: deep injury, injury with a device that was visibly contaminated with the source patient's blood, and a procedure that involved a needle placed in the source patient's vein or artery, which means that the needle probably contained undiluted blood. When the logistic-regression analysis was restricted to needle sticks with hollow-bore needles, large-diameter needles were weakly associated with an increased risk of seroconversion ($P=0.08$), supporting the premise that the volume of blood involved is important. The risk of HIV transmission was also increased if a health care worker was exposed to blood from a source patient in the terminal stage of AIDS. This association is probably due to the higher titer of HIV in the blood of patients late in the course of AIDS, but it could possibly be due to other factors, such as syncytium-inducing HIV strains in these patients.[7,8]

After controlling for other factors associated with the risk of HIV transmission, our model indicated that the odds of HIV infection among health care workers who took zidovudine prophylactically after exposure were reduced by approximately 81 percent (95 percent confidence interval, 48 to 94 percent). Because it is difficult to control for known and unknown factors that contribute to HIV transmission, a retrospective case–control study is not the optimal design for assessing the efficacy of zidovudine; however, a prospective, placebo-controlled trial has not been possible.[1,5]

The apparent efficacy of postexposure prophylaxis with zidovudine in this study is consistent with data from other sources. In a prospective trial, administration of zidovudine to HIV-infected pregnant women and their infants reduced perinatal transmission by 67 percent[9]; a direct prophylactic effect on the fetus or infant was suggested, since only a small portion of the protective effect of zidovudine was due to a reduction of the HIV titer in maternal blood.[10]

Studies of antiretroviral chemoprophylaxis in animals have yielded mixed results, and their applicability to humans has been difficult to assess, but prophylaxis has prevented or ameliorated infection in several studies.[11,12]

Zidovudine is beneficial in the treatment of acute HIV infection in humans,[13] and its efficacy for postexposure prophylaxis would be consistent with a new understanding of HIV pathogenesis in which the virus is cleared by the human immune system while the immune system is still intact.[14] At least 13 instances of failure of postexposure prophylaxis with zidovudine in health care workers have been documented worldwide, indicating that any protection provided is not absolute.[15-17]

This study has several potential limitations, primarily because it was a retrospective review of surveillance data obtained from different sources and the number of case patients is relatively small. Reporting bias may have resulted if health care workers preferentially reported exposure that they believed was more likely to result in HIV transmission or for which they wanted zidovudine treatment (or both). This tendency would presumably be similar, however, among case patients and controls. Ascertainment bias may have affected some data, particularly subjective variables such as the severity of injury, because information for controls was obtained prospectively soon after exposure, whereas for some case patients, information was obtained after HIV seroconversion. However, for most variables there was objective documentation from incident reports and medical records.

We could not rule out, but did not identify, biases related to the use of zidovudine. If controls were more likely to have been offered zidovudine or more strongly encouraged to take it, the use of the drug might have been statistically associated with the absence of HIV seroconversion, even if the drug was not truly protective. Controls did not appear more likely than case patients to have been offered zidovudine, but it was impossible to assess whether controls may have been more strongly encouraged to take the drug. There was no difference in the rate of zidovudine use between the controls and health care workers who reported exposure to HIV in the hospitals participating in the CDC Needlestick Study but who did not complete the six-month follow-up.

The absence of statistically significant interaction terms in the logistic-regression model implies that the effect of zidovudine use was the same for all types of exposure and that the odds of HIV transmission after exposure was the product of the odds associated with each of the risk factors present. However, the small number of case patients made it very unlikely that we would find significant interactions in the analysis. There were no significant differences between zidovudine regimens (i.e., daily dose, duration of treatment, and interval between exposure and the initial dose) used by controls and case patients; however, the small number of case patients who took zidovudine limited our ability to detect such differences. Finally, in the case of approximately 70 percent of the case patients and controls who took zidovudine, the source patients were taking zidovudine at the time of the health care workers' exposure. If exposure to zidovudine-resistant virus was more common among case patients than controls, the efficacy of the drug after exposure to a sensitive virus may be even higher than we estimated.

The results of this study have important implications for the counseling and treatment of a health care worker after exposure to HIV and for public health. We estimate that the risk of transmission for exposure involving relatively large quantities of blood, particularly when the source patient's viral load is probably high, is higher than the average risk of 0.3 percent. This type of exposure should be a particular focus of preventive measures[18] and postexposure prophylaxis. Interviews of exposed health care workers should elicit information about factors associated with an increased risk of HIV transmission. Risk assessment should take into account the specific risk factors identified in this study, but it should be recognized that these factors are probably surrogates for an increased volume of blood and an increased viral load. Other factors, such as injection of blood or exposure involving a hollow-bore rather than a solid needle, may also be important but either were not assessed in this study or may not have been statistically significant because of the small number of cases involved.

In part on the basis of the results of this study, the Public Health Service and the International AIDS Society have recommended chemoprophylaxis after certain types of occupational exposure to HIV.[19-21] The decision to recommend prophylaxis and the drug used depend on the type of exposure; the likelihood of drug resistance in the source patient's HIV strain or strains is also a factor in drug selection. Since chemoprophylaxis should be initiated promptly after exposure, implementation of these recommendations requires rapid, confidential mechanisms for evaluating exposed health care workers, ascertaining the HIV status of source patients, and starting prophylaxis, if appropriate.[22,23] Although the current recommendations of the Public Health Service are limited to occupational exposure, others have extended these recommendations to include exposure related to sexual contact.[24] It is unclear, however, whether the extent of the protective effect of postexposure prophylaxis after percutaneous exposure to HIV-infected blood would be similar for other types of exposure.

Finally, the results of this study may interest expert review panels that determine which jobs are

appropriate for HIV-infected health care workers.[25] Although our study does not address this topic directly, it provides more precise documentation than was previously available regarding the influence of the volume of blood and stage of HIV infection on the risk of transmission after exposure to HIV-infected blood. The finding that the stage of AIDS of the source patient was an important predictor of the risk of HIV transmission suggests that previous estimates, which did not take into account the stage of HIV disease in infected health care workers, may have overestimated the risk to patients who were exposed to blood from health care workers in earlier stages of HIV infection.[26]

A major problem in developing recommendations for postexposure prophylaxis is the relatively limited amount of data on the safety and tolerability of new antiretroviral drugs in exposed, uninfected persons, most of whom would not become infected even without prophylaxis. To increase the amount of information available, health care providers in the United States are encouraged to enroll all workers who receive chemoprophylaxis in a national registry (without personal identifiers) at the following telephone number: 888-737-4448 (888-PEP-4HIV).

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EXHIBIT 15

MMWR™

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Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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CONTENTS

Disclosure of Relationship

CDC, our planners, and our content experts wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.

The antiretroviral agents mentioned in the article do not have an approved indication by the FDA for postexposure prophylaxis. The material presented is based on expert review and does not reflect the views of the FDA.

Vol. 54 / RR-9 Recommendations and Reports 1

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

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Summary

This report updates U.S. Public Health Service recommendations for the management of health-care personnel (HCP) who have occupational exposure to blood and other body fluids that might contain human immunodeficiency virus (HIV). Although the principles of exposure management remain unchanged, recommended HIV postexposure prophylaxis (PEP) regimens have been changed. This report emphasizes adherence to HIV PEP when it is indicated for an exposure, expert consultation in management of exposures, follow-up of exposed workers to improve adherence to PEP, and monitoring for adverse events, including seroconversion. To ensure timely postexposure management and administration of HIV PEP, clinicians should consider occupational exposures as urgent medical concerns.

Introduction

Although preventing exposures to blood and body fluids is the primary means of preventing occupationally acquired human immunodeficiency virus (HIV) infection, appropriate postexposure management is an important element of workplace safety. In 1996, the first U.S. Public Health Service (PHS) recommendations for the use of postexposure prophylaxis (PEP) after occupational exposure to HIV were published; these recommendations have been updated twice (*1*–*3*). Since publication of the most recent guidelines in 2001, new antiretroviral agents have been approved by the Food and Drug Administration (FDA), and additional information has become available regarding the use and safety of HIV PEP. In August 2003, CDC convened a meeting of a PHS interagency working group* and consultants to assess use of HIV PEP. On the basis of this discussion, the PHS working group decided that updated recommendations for the management of occupational exposure to HIV were warranted.

This report modifies and expands the list of antiretroviral medications that can be considered for use as PEP. This report also emphasizes prompt management of occupational exposures, selection of tolerable regimens, attention to potential drug interactions involving drugs that could be included in HIV PEP regimens and other medications, consultation with experts for postexposure management strategies (especially determining whether an exposure has actually occurred) and selection of HIV PEP regimens, use of HIV rapid testing, and counseling and follow-up of exposed personnel.

Recommendations on the management of occupational exposures to hepatitis B virus or hepatitis C virus have been published previously (*3*) and are not included in this report. Recommendations for nonoccupational (e.g., sexual, pediatric, and perinatal) HIV exposures also have been published previously (*4*–*6*).

* This interagency working group included representatives from CDC, FDA, the Health Resources and Services Administration, and the National Institutes of Health. Information included in these recommendations might not represent FDA approval or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" might not be synonymous with the FDA-defined legal standard for product approval.

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Definition of Health-Care Personnel and Exposure

The definitions of health-care personnel (HCP) and occupational exposures are unchanged from those used in 2001 (*3*). The term HCP refers to all paid and unpaid persons working in health-care settings who have the potential for exposure to infectious materials (e.g., blood, tissue, and specific body fluids and medical supplies, equipment, or environmental

surfaces contaminated with these substances). HCP might include, but are not limited to, emergency medical service personnel, dental personnel, laboratory personnel, autopsy personnel, nurses, nursing assistants, physicians, technicians, therapists, pharmacists, students and trainees, contractual staff not employed by the health-care facility, and persons not directly involved in patient care but potentially exposed to blood and body fluids (e.g., clerical, dietary, housekeeping, maintenance, and volunteer personnel). The same principles of exposure management could be applied to other workers who have potential for occupational exposure to blood and body fluids in other settings.

An exposure that might place HCP at risk for HIV infection is defined as a percutaneous injury (e.g., a needlestick or cut with a sharp object) or contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other body fluids that are potentially infectious. In addition to blood and visibly bloody body fluids, semen and vaginal secretions also are considered potentially infectious. Although semen and vaginal secretions have been implicated in the sexual transmission of HIV, they have not been implicated in occupational transmission from patients to HCP. The following fluids also are considered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. The risk for transmission of HIV infection from these fluids is unknown; the potential risk to HCP from occupational exposures has not been assessed by epidemiologic studies in health-care settings. Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious unless they are visibly bloody; the risk for transmission of HIV infection from these fluids and materials is low (*7*).

Any direct contact (i.e., contact without barrier protection) to concentrated virus in a research laboratory or production facility requires clinical evaluation. For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to bloodborne pathogens. Transmission of HIV infection by this route has been reported rarely, but not after an occupational exposure (*8–12*).

Risk for Occupational Transmission of HIV

The risks for occupational transmission of HIV have been described; risks vary with the type and severity of exposure (*2,3,7*). In prospective studies of HCP, the average risk for HIV transmission after a percutaneous exposure to HIV-infected blood has been estimated to be approximately 0.3% (95% confidence interval [CI] = 0.2%–0.5%) (*7*) and after a mucous membrane exposure, approximately 0.09% (CI = 0.006%–0.5%) (*3*). Although episodes of HIV transmission after nonintact skin exposure have been documented, the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood also has not been quantified but is probably considerably lower than for blood exposures.

Epidemiologic and laboratory studies suggest that multiple factors might affect the risk for HIV transmission after an occupational exposure (*3*). In a retrospective case-control study of HCP who had percutaneous exposure to HIV, increased risk for HIV infection was associated with exposure to a larger quantity of blood from the source person as indicated by 1) a device (e.g., a needle) visibly contaminated with the patient's blood, 2) a procedure that involved a needle being placed directly in a vein or artery, or 3) a deep injury. The risk also was increased for exposure to blood from source persons with terminal illness, possibly reflecting either the higher titer of HIV in blood late in the course of acquired immunodeficiency syndrome (AIDS) or other factors (e.g., the presence of syncytia-inducing strains of HIV). A laboratory study that demonstrated that more blood is transferred by deeper injuries and hollow-bore needles lends further support for the observed variation in risk related to blood quantity (*3*).

The use of source-person viral load as a surrogate measure of viral titer for assessing transmission risk has not yet been established. Plasma viral load (e.g., HIV RNA) reflects only the level of cell-free virus in the peripheral blood; latently infected cells might transmit infection in the absence of viremia. Although a lower viral load (e.g., <1,500 RNA copies/mL) or one that is below the limits of detection probably indicates a lower titer exposure, it does not rule out the possibility of transmission.

Antiretroviral Agents for PEP

Antiretroviral agents from five classes of drugs are currently available to treat HIV infection (*13,14*). These include the nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and a single fusion inhibitor. Only antiretroviral agents approved by FDA for treatment of HIV infection are included in these guidelines. The recommendations in this report provide guidance for two- or-more drug PEP regimens on the basis of the level of risk for HIV transmission represented by the exposure (Tables 1 and 2; Appendix).

TABLE 1. Recommended HIV postexposure prophylaxis (PEP) for percutaneous injuries

	Infection status of source				
Exposure type	HIV-positive, class 1*	HIV-positive, class 2*	Source of unknown HIV status†	Unknown source§	HIV-negative
Less severe¶	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings in which exposure to HIV-infected persons is likely	No PEP warranted
More severe§§	Recommend expanded 3-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings in which exposure to HIV-infected persons is likely	No PEP warranted

* HIV-positive, class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 ribonucleic acid copies/mL). HIV-positive, class 2 — symptomatic HIV infection, acquired immunodeficiency syndrome, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

† For example, deceased source person with no samples available for HIV testing.

§ For example, a needle from a sharps disposal container.

¶ For example, solid needle or superficial injury.

** The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

†† If PEP is offered and administered and the source is later determined to be HIV-negative, PEP should be discontinued.

§§ For example, large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein.

TABLE 2. Recommended HIV postexposure prophylaxis (PEP) for mucous membrane exposures and nonintact skin* exposures

	Infection status of source				
Exposure type	HIV-positive, class 1†	HIV-positive, class 2†	Source of unknown HIV status§	Unknown source¶	HIV-negative
Small volume**	Consider basic 2-drug PEP††	Recommend basic 2-drug PEP	Generally, no PEP warranted§§	Generally, no PEP warranted	No PEP warranted
Large volume¶¶	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP†† for source with HIV risk factors§§	Generally, no PEP warranted; however, consider basic 2-drug PEP†† in settings in which exposure to HIV-infected persons is likely	No PEP warranted

* For skin exposures, follow-up is indicated only if evidence exists of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).

† HIV-positive, class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 ribonucleic acid copies/mL). HIV-positive, class 2 — symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

§ For example, deceased source person with no samples available for HIV testing.

¶ For example, splash from inappropriately disposed blood.

** For example, a few drops.

†† The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

§§ If PEP is offered and administered and the source is later determined to be HIV-negative, PEP should be discontinued.

¶¶ For example, a major blood splash.

Toxicity and Drug Interactions of Antiretroviral Agents

Persons receiving PEP should complete a full 4-week regimen (*3*). However, as a result of toxicity and side effects among HCP, a substantial proportion of HCP have been unable to complete a full 4-week course of HIV PEP (*15–20*). Because all antiretroviral agents have been associated with side effects (Table 3), the toxicity profile of these agents, including the frequency, severity, duration, and reversibility of side effects, is an important consideration in selection of an HIV PEP regimen. The majority of data concerning adverse events have been reported primarily for persons with established HIV infection receiving prolonged antiretroviral therapy and therefore might not reflect the experience of uninfected persons who take PEP. Anecdotal evidence from clinicians knowledgeable about HIV treatment indicates that antiretroviral agents are tolerated more poorly among HCP taking HIV PEP than among HIV-infected patients on antiretroviral medications.

TABLE 3. Primary side effects and toxicities associated with antiretroviral agents used for HIV postexposure prophylaxis, by class and agent

Class and agent	Side effect and toxicity
Nucleoside reverse transcriptase inhibitors (NRTI)	**Class warning: all NRTIs have the potential to cause lactic acidosis with hepatic steatosis**
Zidovudine (Retrovir®; ZDV, AZT)	Anemia, neutropenia, nausea, headache, insomnia, muscle pain, and weakness
Lamivudine (Epivir®, 3TC)	Abdominal pain, nausea, diarrhea, rash, and pancreatitis
Stavudine (Zerit™; d4T)	Peripheral neuropathy, headache, diarrhea, nausea, insomnia, anorexia, pancreatitis, elevated liver function tests (LFTs), anemia, and neutropenia
Didanosine (Videx®; ddI)	Pancreatitis, lactic acidosis, neuropathy, diarrhea, abdominal pain, and nausea
Emtricitabine (Emtriva, FTC)	Headache, nausea, vomiting, diarrhea, and rash. Skin discoloration (mild hyperpigmentation on palms and soles), primarily among nonwhites
Nucleotide analogue reverse transcriptase inhibitor (NtRTI)	**Class warning: All NtRTIs have the potential to cause lactic acidosis with hepatic steatosis**
Tenofovir (Viread®; TDF)	Nausea, diarrhea, vomiting, flatulence, and headache
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	
Efavirenz (Sustiva®; EFV)	Rash (including cases of Stevens-Johnson syndrome), insomnia, somnolence, dizziness, trouble concentrating, abnormal dreaming, and teratogenicity
Protease inhibitor	
Indinavir (Crixivan®; IDV)	Nausea, abdominal pain, nephrolithiasis, and indirect hyperbilirubinemia
Nelfinavir (Viracept®; NFV)	Diarrhea, nausea, abdominal pain, weakness, and rash
Ritonavir (Norvir®; RTV)	Weakness, diarrhea, nausea, circumoral paresthesia, taste alteration, and elevated cholesterol and triglycerides
Saquinavir (Invirase®; SQV)	Diarrhea, abdominal pain, nausea, hyperglycemia, and elevated LFTs
Fosamprenavir (Lexiva®, FOSAPV)	Nausea, diarrhea, rash, circumoral paresthesia, taste alteration, and depression
Atazanavir (Reyataz®; ATV)	Nausea, headache, rash, abdominal pain, diarrhea, vomiting, and indirect hyperbilirubinemia
Lopinavir/ritonavir (Kaletra®; LPV/RTV)	Diarrhea, fatigue, headache, nausea, and increased cholesterol and triglycerides
Fusion inhibitor	
Enfuvirtide (Fuzeon®; T-20)	Local injection site reactions, bacterial pneumonia, insomnia, depression, peripheral neuropathy, and cough

Sources: Package inserts; Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents—April 7, 2005. Washington, DC: National Institutes of Health; 2005. Available at http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=50.

Side effects have been reported frequently by persons taking antiretroviral agents as PEP (*15–23*). In multiple instances, a substantial (range: 17%–47%) proportion of HCP taking PEP after occupational exposures to HIV-positive sources did not complete a full 4-week course of therapy because of inability to tolerate the drugs (*15–17,19,20*). Data from the National Surveillance System for Health Care Workers (NaSH), CDC's occupational surveillance system for occupational exposures and infections in hospitals, for June 1995–December 2004 indicate that 401 (46.9%) of 921 HCP with at least one follow-up visit after starting PEP experienced one or more symptoms. The symptom reported most frequently was nausea (26.5%), followed by malaise and fatigue (22.8%) (CDC, unpublished data, 2005). Of 503 HCP who stopped HIV PEP prematurely (<28 days), 361 (24.0%) did so because of adverse effects of the drugs. Similar data have been reported from the Italian Registry of Antiretroviral Postexposure Prophylaxis, which includes data primarily on HCP taking PEP but also collects data on those taking PEP after nonoccupational exposures (*18*). In multivariate analysis, those taking regimens that include PI were more likely to experience PEP-associated side effects and to discontinue PEP prematurely (<28 days). Because side effects are frequent and

particularly because they are cited as a major reason for not completing PEP regimens as prescribed, the selection of regimens should be heavily influenced toward those that are tolerable for short-term use.

In addition, all approved antiretroviral agents might have potentially serious drug interactions when used with certain other drugs, requiring careful evaluation of concomitant medications, including over-the-counter medications and supplements (e.g., herbals), used by an exposed person before prescribing PEP and close monitoring for toxicity of anyone receiving these drugs (*24–33*) (Tables 3–5). PIs and NNRTIs have the greatest potential for interactions with other drugs. Information regarding potential drug interactions has been published (*13,24–33*). Additional information is included in the manufacturers' package inserts. Because of interactions, certain drugs should not be administered concomitantly with PIs or with efavirenz (EFV) (Tables 4 and 5). Consultation with a pharmacist might be considered.

Selection of HIV PEP Regimens

Determining which agents and how many to use or when to alter a PEP regimen is primarily empiric (*34*). Guidelines for treating HIV infection, a condition typically involving a high total body burden of HIV, recommend use of three or more drugs (*13,14*); however, the applicability of these recommendations to PEP is unknown. Among HIV-infected patients, combination regimens with three or more antiretroviral agents have proved superior to monotherapy and dual-therapy regimens in reducing HIV viral load, reducing incidence of opportunistic infections and death, and delaying onset of drug resistance (*13,14*). In theory, a combination of drugs with activity at different stages in the viral replication cycle (e.g., nucleoside analogues with a PI) might offer an additive preventive effect in PEP, particularly for occupational exposures that pose an increased risk for transmission or for transmission of a resistant virus. Although use of a three- (or more) drug regimen might be justified for exposures that pose an increased risk for transmission, whether the potential added toxicity of a third or fourth drug is justified for lower-risk exposures is uncertain, especially in the absence of data supporting increased efficacy of more drugs in the context of occupational PEP. Offering a two-drug regimen is a viable option, primarily because the benefit of completing a full course of this regimen exceeds the benefit of adding the third agent and risking noncompletion (*35*). In addition, the total body burden of HIV is substantially lower among exposed HCP than among persons with established HIV infection. For these reasons, the recommendations in this report provide guidance for two- and three- (or more) drug PEP regimens on the basis of the level of risk for HIV transmission represented by the exposure (Tables 1 and 2; Appendix).

Resistance to Antiretroviral Agents

Known or suspected resistance of the source virus to antiretroviral agents, particularly those that might be included in a PEP regimen, is a concern for persons making decisions about PEP (*36*). Drug resistance to all available antiretroviral agents has been reported, and cross-resistance within drug classes is frequent (*37*). Although occupational transmission of drug-resistant HIV strains has been reported despite PEP

TABLE 4. Prescription and over-the-counter drugs that should not be administered with protease inhibitors (PIs) because of drug interactions*

Drug	Comment
Antimycobacterials: rifampin	Decreases plasma concentrations and area under plasma concentration curve of the majority of PIs by approximately 90%, which might result in loss of therapeutic effect and development of resistance
Benzodiazepines: midazolam, triazolam	Contraindicated because of potential for serious or life-threatening events (e.g., prolonged or increased sedation or respiratory depression)
Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine	Contraindicated because of potential for serious or life-threatening events (e.g., acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues)
Gastrointestinal motility agent: cisapride	Contraindicated because of potential for serious or life-threatening events (e.g., cardiac arrhythmias)
HMG-CoA reductase inhibitors ("statins"): lovastatin, simvastatin	Potential for serious reactions (e.g., myopathy, including rhabdomyolysis); atorvastatin may be used cautiously, beginning with lowest possible starting dose, and monitoring for adverse events
Neuroleptic: pimozide	Contraindicated because of potential for serious or life-threatening events (e.g., cardiac arrhythmias)
Inhaled steroids: fluticasone	Coadministration of fluticasone and ritonavir-boosted protease inhibitors are not recommended unless the potential benefit to the patient outweighs the risk for systemic corticosteroid side effect
Herbal products:	Coadministration might reduce plasma concentrations of protease inhibitors, which might result in loss of therapeutic effect and development of resistance
St. John's wort (hypericum perforatum), garlic	Garlic might lower saquinavir level

* This table does not list all products that should not be administered with PIs (atazanavir, lopinavir/ritonavir, fosamprenavir, indinavir, nelfinavir, saquinavir). Product labels should be consulted for additional information regarding drug interactions.

Sources: US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: US Department of Health and Human Services; 2005. Available at http://www.aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf; University of California at San Francisco Center for HIV Information. Database of antiretroviral drug interactions. Available at http://hivinsite.ucsf.edu/InSite?page=ar-00-02.

TABLE 5. Prescription and over-the-counter drugs that should not be administered with efavirenz because of drug interactions*

Drug	Comment
Antifungal: voriconazole	Contraindicated because efavirenz substantially decreases voriconazole plasma concentrations
Benzodiazepines: midazolam, triazolam	Contraindicated because of potential for serious or life-threatening events (e.g., prolonged or increased sedation or respiratory depression)
Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine	Contraindicated because of potential for serious or life-threatening events (e.g., acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues)
Gastrointestinal motility agent: cisapride	Contraindicated because of potential for serious or life-threatening events (e.g., cardiac arrhythmias)
Herbal products:	Coadministration might reduce plasma concentrations of protease inhibitors, which might result in loss of therapeutic effect and development of resistance
St. John's wort (hypericum perforatum), garlic	Garlic might lower saquinavir levels

* This table does not list all products that should not be coadministered with efavirenz. Efavirenz product labeling should be consulted for additional information regarding drug interactions.

Sources: US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: US Department of Health and Human Services; 2005. Available at http://www.aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf; University of California at San Francisco Center for HIV Information. Database of antiretroviral drug interactions. Available at http://hivinsite.ucsf.edu/InSite?page=ar-00-02.

with combination drug regimens (*36,38–40*), the effect of exposure to a resistant virus on transmission and transmissibility is not well understood.

Since publication of the previous guidelines, an additional report of an occupational HIV seroconversion despite combination HIV PEP has been published (Table 6) (*38*), bringing the total number of reports worldwide to six. The exposure was a percutaneous injury sustained by a nurse performing a phlebotomy on a heavily treatment-experienced patient. At the time of the exposure, the source patient was failing treatment with stavudine (d4T), lamivudine (3TC), ritonavir (RTV), and saquinavir (SQV) and had a history of previous treatment with zidovudine (ZDV) and zalcitabine (ddC). Genotypic resistance testing performed within 1 month of the exposure suggested resistance to ZDV and 3TC. Phenotypic testing confirmed resistance to 3TC but demonstrated relative susceptibility to ZDV and d4T. The source virus demonstrated no evidence of resistance to nevirapine (NVP) or other NNRTIs. The initial HIV PEP regimen started within 95 minutes of the exposure was ZDV, 3TC, and indinavir.

TABLE 6. Reported instances of failure of combination drug postexposure prophylaxis (PEP) to prevent HIV-infection among health-care personnel exposed to HIV-infected blood through percutaneous injury

Year of incident	Device	PEP regimen*	Time to first dose (hrs)	No. of days to onset of retroviral illness	No. of days to document seroconversion†	Source-patient		
						HIV-infection status	On anti retrovirals	Virus resistant to antiretrovirals§
1992¶	Biopsy needle	ZDV, ddI	0.5	23	23	AIDS, terminally ill	Yes	Unknown
1996**	Hollow-bore needle	ZDV, ddI††	1.5	45	97	Asymptomatic HIV infection	No	Not tested
1997**	Large or hollow-bore needle	ZDV, 3TC, IDV§§	1.5	40	55	AIDS	Yes	No
1998¶¶	Hollow-bore needle	ZDV, 3TC, ddI, IDV	0.7	70	83	AIDS	Yes	Yes
1999***	Unknown sharp	ddI, d4T, NVP†††	2.0	42	100	AIDS	Yes	Yes
2001§§§	Phlebotomy needle	ZDV, 3TC, IDV¶¶¶	1.6	24	~90	AIDS	Yes	Yes

* ZDV = zidovudine; ddI = didanosine; 3TC = lamivudine; IDV = indinavir; d4T = stavudine; and NVP = nevirapine.

† By enzyme immunoassay for HIV-1 antibody and Western blot.

§ By genotypic or phenotypic resistance testing.

¶ **Source:** Jochimsen EM. Failures of zidovudine postexposure prophylaxis. Am J Med 1997;102(Suppl 5B):52–5.

** **Source:** Lot F, Abiteboul D. Occupational infections with HIV in France among health-care personnel [French]. Bull Epi Hebdom 1999;18:69–70.

†† ZDV and ddI taken for 48 hours and then changed to ZDV alone.

§§ ZDV, 3TC, and IDV taken for 48 hours and then changed to d4T, 3TC, and IDV.

¶¶ **Source:** Perdue B, Wolde Rufael D, Mellors J, Quinn T, Margolick J. HIV-1 transmission by a needlestick injury despite rapid initiation of four-drug postexposure prophylaxis [Abstract no 210]. In: Program and abstracts of the 6th Conference on Retroviruses and Opportunistic Infections. Chicago, IL: Foundation for Retrovirology and Human Health; 1999.

*** **Source:** Beltrami EM, Luo C-C, de la Torre N, Cardo DM. Transmission of drug-resistant HIV after an occupational exposure despite postexposure prophylaxis with a combination drug regimen. Infect Control Hosp Epidemiol 2002;23:345–8; CDC, unpublished data, 1999.

††† ZDV and 3TC taken for 1 dose and then changed to ddI, d4T, and NVP; ddI was discontinued after 3 days as a result of severe vomiting.

§§§ **Source:** Hawkins DA, Asboe D, Barlow K, Evans B. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. J Infect 2001;43:12–5.

¶¶¶ ZDV, 3TC, and IDV initially and then changed after first dose to d4T, ddI, and NVP; then ddI discontinued after 8 days; and d4T and NVP taken for 4 weeks.

The worker was referred to a hospital where the regimen was changed within 6 hours of the exposure to didanosine (ddI), d4T, and NVP because of concerns regarding possible drug resistance to certain or all of the components of the initial PEP regimen. The exposed worker stopped ddI after 8 days because of symptoms but continued to take d4T and NVP, stopping at day 24 because of a generalized macular pruritic rash and mild thrombocytopenia. Seroconversion was documented at 3 months. Sequencing of viruses from the source and exposed worker demonstrated their close relatedness. Virus from the worker demonstrated the same resistance patterns as those in the source patient. In addition, the worker's virus had a mutation suggesting resistance to the NNRTI class (*38*).

Empiric decisions regarding the presence of antiretroviral drug resistance are often difficult because patients frequently take more than one antiretroviral agent. Resistance should be suspected in a source patient when clinical progression of disease or a persistently increasing viral load or decline in CD4+ T-cell count occurs despite therapy, or when no virologic response to therapy occurs. However, resistance testing of the source virus at the time of an exposure is impractical because the results will not be available in time to influence the choice of the initial PEP regimen. No data suggest that modification of a PEP regimen after resistance testing results become available (usually 1–2 weeks) improves efficacy of PEP (*41*).

Antiretroviral Drugs During Pregnancy

Data regarding the potential effects of antiretroviral drugs on the developing fetus or neonate are limited (*3*). Carcinogenicity and mutagenicity are evident in certain in vitro screening tests for ZDV and all other FDA-licensed NRTIs. The relevance of animal data to humans is unknown; however, because teratogenic effects were reported among primates at drug exposures similar to those representing human therapeutic exposure, pregnant women should not use efavirenz (EFV). Indinavir (IDV) is associated with infrequent side effects in adults (i.e., hyperbilirubinemia and renal stones) that could be problematic for a newborn. Because the half-life of IDV in adults is short, these concerns might be relevant only if the drug is administered shortly before delivery. Other concerns regarding use of PEP during pregnancy have been raised by reports of mitochondrial dysfunction leading to neurologic disease and death among uninfected children whose mothers had taken antiretroviral drugs to prevent perinatal HIV transmission and of fatal and nonfatal lactic acidosis in pregnant women treated throughout gestation with a combination of d4T and ddI (*3*).

Management of Occupational Exposure by Emergency Physicians

Although PHS guidelines for the management of occupational exposures to HIV were first published in 1985 (*42*), HCP often are not familiar with these guidelines. Focus groups conducted among emergency department (ED) physicians in 2002 indicated that of 71 participants, >95% had not read the 2001 guidelines before being invited to participate (*43*). All physicians participating in these focus groups had managed occupational exposures to blood or body fluids. They cited three challenges in exposure management most frequently: evaluation of an unknown source patient or a source patient who refused testing, inexperience in managing occupational HIV exposures, and counseling of exposed workers in busy EDs.

Occupational HIV Exposure Management and PEP Use in U.S. Hospitals

Analysis of NaSH data for June 1995–December 2004 provides information regarding the management of occupational exposure to HIV in a convenience sample of 95 U.S. hospitals. These data indicate improved adherence to PHS recommendations concerning use of HIV PEP after occupational exposures. A total of 28,010 exposures to blood and body fluids were reported by these hospitals (CDC, unpublished data, 2005). For all 25,510 exposures with known sources, 1,350 (5.3%) were to HIV-positive sources, 15,301 (60.0%) to HIV-negative sources, and 8,859 (34.7%) to sources of unknown HIV status. Of 1,350 HCP exposed to a known HIV-positive source, 788 (58.4%) started PEP, and 317 (49%) of 647 for whom follow-up information was available took PEP for ≥21 days. The overall median duration of HIV PEP after exposure to an HIV-positive source was 27 days, increasing from 10 days in 1995 to 26.5 days in 2004; the overall median duration of HIV PEP after exposure to an HIV-negative source was 2 days, decreasing from 7.5 days in 1995 to 1 day in 2004. The use of rapid HIV tests for evaluation of source patients has increased; during 1995–1997, none of 25 NaSH facilities used rapid HIV tests, whereas in 2004, a total of 21 (84%) did (CDC, unpublished data, 2005). Rapid HIV tests could result in decreased use of PEP and spare personnel both undue anxiety and adverse effects of antiretroviral PEP (*44–47*). The annual median time to initiation of PEP was consistent (2 hours). Of 1,350 HCP with exposures to HIV-positive sources, 909 (67.1%) had at least one follow-up serologic test recorded, but only 289 (31.8%) had tests recorded at 4–6 months (CDC, unpublished data, 2005).

In 1996, of 24 HCP taking PEP after exposure to HIV-positive sources, 10 (42%) took a three-drug PEP regimen compared with 30 (76.9%) of 39 in 2004 (CDC, unpublished data, 2005). After 227 HIV exposures for which only a two-drug PEP regimen was recommended (i.e., the exposure was to mucous membranes or skin or was a superficial percutaneous injury and the source person did not have end-stage AIDS or acute HIV illness), 104 (45.8%) HCP initiated a three-drug HIV PEP regimen. The National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline)† reports similar findings. PEPline staff recommended changing or discontinuing PEP regimens for 45 (38%) of 118 exposures involving source patients with known viral load or CD4 cell count concerning which they were consulted during April 2002–March 2003 (*48*; R. Goldschmidt, PEPline, personal communication, 2004). For 14 (11.9%) HCP, the recommendation was to decrease the number of drugs in the PEP regimens; for 22 (18.7%) HCP, the recommendation was to increase the number of drugs; and for nine (7.6%), the recommendation was to change the PEP regimen, keeping the same number of drugs.

Recommendations for the Management of HCP Potentially Exposed to HIV

Exposure prevention remains the primary strategy for reducing occupational bloodborne pathogen infections. However, occupational exposures will continue to occur, and PEP will remain an important element of exposure management.

HIV PEP

The recommendations provided in this report (Tables 1 and 2; Appendix) apply to situations in which HCP have been exposed to a source person who either has or is considered likely to have HIV infection. These recommendations are based on the risk for HIV infection after different types of exposure and on limited data regarding efficacy and toxicity of PEP. If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued. Although concerns have been expressed regarding HIV-negative sources being in the window period for seroconversion, no case of transmission involving an exposure source during the window period has been reported in the United States (*39*). Rapid HIV testing of source patients can facilitate making timely decisions regarding use of HIV PEP after occupational exposures to sources of unknown HIV status. Because the majority of occupational HIV exposures do not result in transmission of HIV, potential toxicity must be considered when prescribing PEP. Because of the complexity of selecting HIV PEP regimens, when possible, these recommendations should be implemented in consultation with persons having expertise in antiretroviral therapy and HIV transmission. Reevaluation of exposed HCP should be strongly encouraged within 72 hours postexposure, especially as additional information about the exposure or source person becomes available.

Timing and Duration of PEP

PEP should be initiated as soon as possible, preferably within hours rather than days of exposure. If a question exists concerning which antiretroviral drugs to use, or whether to use a basic or expanded regimen, the basic regimen should be started immediately rather than delay PEP administration. The optimal duration of PEP is unknown. Because 4 weeks of ZDV appeared protective in occupational and animal studies, PEP should be administered for 4 weeks, if tolerated (*49–52*).

Recommendations for the Selection of Drugs for HIV PEP

The selection of a drug regimen for HIV PEP must balance the risk for infection against the potential toxicities of the agent(s) used. Because PEP is potentially toxic, its use is not justified for exposures that pose a negligible risk for transmission (Tables 1 and 2). The initial HIV PEP regimens recommended in these guidelines should be viewed as suggestions that can be changed if additional information is obtained concerning the source of the occupational exposure (e.g., possible treatment history or antiretroviral drug resistance) or if expert consultation is provided. Given the complexity of choosing and administering HIV PEP, whenever possible, consultation with an infectious diseases consultant or another physician who has experience with antiretroviral agents is recommended, but it should not delay timely initiation of PEP.

Consideration should be given to the comparative risk represented by the exposure and information regarding the exposure source, including history of and response to antiretroviral therapy based on clinical response, CD4+ T-cell counts, viral load measurements, and current disease stage. When the source person's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen, the selection of drugs to which the source person's virus is unlikely to be resistant is recommended; expert consultation is advised. If this information is not immediately available, initiation of PEP, if indicated, should not be delayed; changes

† Administered by staff members from the University of California at San Francisco and San Francisco General Hospital; supported by the Health Resources and Services Administration Ryan White CARE Act and AIDS Education and Training Centers, and by CDC.

in the regimen can be made after PEP has started, as appropriate. For HCP who initiate PEP, re-evaluation of the exposed person should occur within 72 hours postexposure, especially if additional information about the exposure or source person becomes available.

PHS continues to recommend stratification of HIV PEP regimens based on the severity of exposure and other considerations (e.g., concern for antiretroviral drug resistance in the exposure source). The majority of HIV exposures will warrant a two-drug regimen, using two NRTIs or one NRTI and one NtRTI (Tables 1 and 2; Appendix). Combinations that can be considered for PEP include ZDV and 3TC or emtricitabine (FTC); d4T and 3TC or FTC; and tenofovir (TDF) and 3TC or FTC. In the previous PHS guidelines, a combination of d4T and ddI was considered one of the first-choice PEP regimens; however, this regimen is no longer recommended because of concerns about toxicity (especially neuropathy and pancreatitis) and the availability of more tolerable alternative regimens (*3*).

The addition of a third (or even a fourth) drug should be considered for exposures that pose an increased risk for transmission or that involve a source in whom antiretroviral drug resistance is likely. The addition of a third drug for PEP after a high-risk exposure is based on demonstrated effectiveness in reducing viral burden in HIV-infected persons. However, no definitive data exist that demonstrate increased efficacy of three- compared with two-drug HIV PEP regimens. Previously, IDV, nelfinavir (NFV), EFV, or abacavir (ABC) were recommended as first-choice agents for inclusion in an expanded PEP regimen (*3*).

PHS now recommends that expanded PEP regimens be PI-based. The PI preferred for use in expanded PEP regimens is lopinavir/ritonavir (LPV/RTV). Other PIs acceptable for use in expanded PEP regimens include atazanavir, fosamprenavir, RTV-boosted IDV, RTV-boosted SQV, or NFV (Appendix). Although side effects are common with NNRTIs, EFV may be considered for expanded PEP regimens, especially when resistance to PIs in the source person's virus is known or suspected. Caution is advised when EFV is used in women of childbearing age because of the risk of teratogenicity.

Drugs that may be considered as alternatives to the expanded regimens, with warnings about side effects and other adverse events, are EFV or PIs as noted in the Appendix in combination with ddI and either 3TC or FTC. The fusion inhibitor enfuvirtide (T20) has theoretic benefits for use in PEP because its activity occurs before viral-host cell integration; however, it is not recommended for routine HIV PEP because of the mode of administration (subcutaneous injection twice daily). Furthermore, use of T20 has the potential for production of anti-T20 antibodies that cross react with HIV gp41. This could result in a false-positive, enzyme immunoassay (EIA) HIV antibody test among HIV-uninfected patients. A confirmatory Western blot test would be expected to be negative in such cases. T20 should only be used with expert consultation.

Antiviral drugs not recommended for use as PEP, primarily because of the higher risk for potentially serious or life-threatening adverse events, include ABC, delavirdine, ddC, and, as noted previously, the combination of ddI and d4T. NVP should not be included in PEP regimens except with expert consultation because of serious reported side effects, including hepatotoxicty (with one instance of fulminant liver failure requiring liver transplantation), rhabdomyolysis, and hypersensitivity syndrome (*53–55*).

Because of the complexity of selection of HIV PEP regimens, consultation with persons having expertise in antiretroviral therapy and HIV transmission is strongly recommended. Certain institutions have required consultation with a hospital epidemiologist or infectious diseases consultant when HIV PEP use is under consideration. This can be especially important in management of a pregnant or breastfeeding worker or a worker who has been exposed to a heavily treatment-experienced source (Box 1).

Resources for consultation are available from the following sources:

- PEPline at http://www.ucsf.edu/hivcntr/Hotlines/PEPline; telephone 888-448-4911;
- HIV Antiretroviral Pregnancy Registry at http://www.apregistry.com/index.htm; Address: Research Park, 1011 Ashes Drive, Wilmington, NC 28405. Telephone: 800-258-4263; Fax: 800-800-1052; E-mail: registry@nc.crl.com;
- FDA (for reporting unusual or severe toxicity to antiretroviral agents) at http://www.fda.gov/medwatch; telephone: 800-332-1088; address: MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857;
- CDC (for reporting HIV infections in HCP and failures of PEP) at telephone 800-893-0485; and
- HIV/AIDS Treatment Information Service at http://aidsinfo.nih.gov.

Follow-Up of Exposed HCP

Postexposure Testing

HCP with occupational exposure to HIV should receive follow-up counseling, postexposure testing, and medical evaluation regardless of whether they receive PEP. HIV-antibody

BOX 1. Situations for which expert consultation* for HIV postexposure prophylaxis (PEP) is advised

- Delayed (i.e., later than 24–36 hours) exposure report
  - — Interval after which lack of benefit from PEP undefined
- Unknown source (e.g., needle in sharps disposal container or laundry)
  - — Use of PEP to be decided on a case-by-case basis
  - — Consider severity of exposure and epidemiologic likelihood of HIV exposure
  - — Do not test needles or other sharp instruments for HIV
- Known or suspected pregnancy in the exposed person
  - — Use of optimal PEP regimens not precluded
  - — PEP not denied solely on basis of pregnancy
- Breastfeeding in the exposed person
  - — Use of optimal PEP regimens not precluded
  - — PEP not denied solely on basis of breastfeeding
- Resistance of the source virus to antiretroviral agents
  - — Influence of drug resistance on transmission risk unknown
  - — If source person's virus is known or suspected to be resistant to one or more of the drugs considered for PEP, selection of drugs to which the source person's virus is unlikely to be resistant recommended
  - — Resistance testing of the source person's virus at the time of the exposure not recommended
  - — Initiation of PEP not to be delayed while awaiting any results of resistance testing
- Toxicity of the initial PEP regimen
  - — Adverse symptoms (e.g., nausea and diarrhea) common with PEP
  - — Symptoms often manageable without changing PEP regimen by prescribing antimotility or antiemetic agents
  - — In other situations, modifying the dose interval (i.e., taking drugs after meals or administering a lower dose of drug more frequently throughout the day, as recommended by the manufacturer) might help alleviate symptoms when they occur

* Either with local experts or by contacting the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline), telephone 888-448-4911.

testing by enzyme immunoassay should be used to monitor HCP for seroconversion for >6 months after occupational HIV exposure. After baseline testing at the time of exposure, follow-up testing could be performed at 6 weeks, 12 weeks, and 6 months after exposure. Extended HIV follow-up (e.g., for 12 months) is recommended for HCP who become infected with HCV after exposure to a source coinfected with HIV and HCV. Whether extended follow-up is indicated in other circumstances (e.g., exposure to a source co-infected with HIV and HCV in the absence of HCV seroconversion or for exposed persons with a medical history suggesting an impaired ability to mount an antibody response to acute infection) is unclear. Although rare instances of delayed HIV seroconversion have been reported (*56,57*), the infrequency of this occurrence does not warrant adding to exposed persons' anxiety by routinely extending the duration of postexposure follow-up. However, this should not preclude a decision to extend follow-up in a particular situation based on the clinical judgment of the exposed person's health-care provider. The routine use of direct virus assays (e.g., HIV p24 antigen EIA or tests for HIV ribonucleic acid) to detect infection among exposed HCP usually is not recommended (*58*). Despite the ability of direct virus assays to detect HIV infection a few days earlier than EIA, the infrequency of occupational seroconversion and increased costs of these tests do not warrant their routine use in this setting. In addition, the relatively high rate of false-positive results of these tests in this setting could lead to unnecessary anxiety or treatment (*59,60*). Nevertheless, HIV testing should be performed on any exposed person who has an illness compatible with an acute retroviral syndrome, regardless of the interval since exposure. A person in whom HIV infection is identified should be referred for medical management to a specialist with expertise in HIV treatment and counseling. Health-care providers caring for persons with occupationally acquired HIV infection can report these cases to CDC at telephone 800-893-0485 or to their state health departments.

Monitoring and Management of PEP Toxicity

If PEP is used, HCP should be monitored for drug toxicity by testing at baseline and again 2 weeks after starting PEP. The scope of testing should be based on medical conditions in the exposed person and the toxicity of drugs included in the PEP regimen. Minimally, laboratory monitoring for toxicity should include a complete blood count and renal and hepatic function tests. Monitoring for evidence of hyperglycemia should be included for HCP whose regimens include any PI; if the exposed person is receiving IDV, monitoring for crystalluria, hematuria, hemolytic anemia, and hepatitis also should be included. If toxicity is noted, modification of the regimen should be considered after expert consultation; further diagnostic studies might be indicated.

Exposed HCP who choose to take PEP should be advised of the importance of completing the prescribed regimen. Information should be provided about potential drug interactions and drugs that should not be taken with PEP, side effects of prescribed drugs, measures to minimize side effects, and methods of clinical monitoring for toxicity

during the follow-up period. HCP should be advised that evaluation of certain symptoms (e.g., rash, fever, back or abdominal pain, pain on urination or blood in the urine, or symptoms of hyperglycemia (e.g., increased thirst or frequent urination) should not be delayed.

HCP often fail to complete the recommended regimen often because they experience side effects (e.g., nausea or diarrhea). These symptoms often can be managed with antimotility and antiemetic agents or other medications that target specific symptoms without changing the regimen. In other situations, modifying the dose interval (i.e., administering a lower dose of drug more frequently throughout the day, as recommended by the manufacturer) might facilitate adherence to the regimen. Serious adverse events[§] should be reported to FDA's MedWatch program.

Although recommendations for follow-up testing, monitoring, and counseling of exposed HCP are unchanged from those published previously (*3*), greater emphasis is needed on improving follow-up care provided to exposed HCP (Box 2). This might result in increased adherence to HIV PEP regimens, better management of associated symptoms with ancillary medications or regimen changes, improved detection of serious adverse effects, and serologic testing among a larger proportion of exposed personnel to determine if infection is transmitted after occupational exposures. Closer follow-up should in turn reassure HCP who become anxious after these events (*61,62*). The psychologic impact on HCP of needlesticks or exposure to blood or body fluid should not be underestimated. Providing HCP with psychologic counseling should be an essential component of the management and care of exposed HCP.

Reevaluation and Updating of HIV PEP Guidelines

As new antiretroviral agents for treatment of HIV infection and additional information concerning early HIV infection and prevention of HIV transmission become available, the PHS Interagency Working Group will assess the need to update these guidelines. Updates will be published periodically as appropriate.

[§] Defined by FDA as follows: "Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition" (*63*).

BOX 2. Follow-up of health-care personnel (HCP) exposed to known or suspected HIV-positive sources

- Exposed HCP should be advised to use precautions (e.g., avoid blood or tissue donations, breastfeeding, or pregnancy) to prevent secondary transmission, especially during the first 6–12 weeks postexposure.
- For exposures for which PEP is prescribed, HCP should be informed regarding
  - — possible drug toxicities and the need for monitoring,
  - — possible drug interactions, and
  - — the need for adherence to PEP regimens.
- Consider reevalution of exposed HCP 72 hours postexposure, especially after additional information about the exposure or source person becomes available.

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APPENDIX

Basic and Expanded HIV Postexposure Prophylaxis Regimens

BASIC REGIMEN

- **Zidovudine (Retrovir™; ZDV; AZT) + lamivudine (Epivir®; 3TC); available as Combivir™**

Preferred dosing

- ZDV: 300 mg twice daily or 200 mg three times daily, with food; total: 600 mg daily
- 3TC: 300 mg once daily or 150 mg twice daily
- Combivir: one tablet twice daily

Dosage forms

- ZDV: 100 mg capsule, 300 mg tablet
- 3TC: 150 or 300 mg tablet
- Combivir: tablet, 300 mg ZDV + 150 mg 3TC

Advantages

- ZDV associated with decreased risk for HIV transmission
- ZDV used more often than other drugs for PEP for health-care personnel (HCP)
- Serious toxicity rare when used for PEP
- Side effects predictable and manageable with antimotility and antiemetic agents
- Can be used by pregnant HCP
- Can be given as a single tablet (COMBIVIR™) twice daily

Disadvantages

- Side effects (especially nausea and fatigue) common and might result in low adherence
- Source-patient virus resistance to this regimen possible
- Potential for delayed toxicity (oncogenic/teratogenic) unknown

- **Zidovudine (Retrovir®; ZDV; AZT) + emtrictabine (Emtriva™; FTC)**

Preferred dosing

- ZDV: 300 mg twice daily or 200 mg three times daily, with food; total: 600 mg/day, in 2–3 divided doses
- FTC: 200 mg (one capsule) once daily

Dosage forms
- ZDV: see above
- FTC: 200 mg capsule

FTC general comments
- Nucleoside analogue; same structure as 3TC, except fluoride residue at position 5 on pyrimidine ring
- Same resistance and safety profile as 3TC
- No apparent advantage over 3TC; tolerability and virologic response rates appear better than regimens containing ddI + d4T

Advantages
- ZDV: see above.
- FTC
  - Convenient (once daily)
  - Well tolerated
  - Long intracellular half-life (~40 hours)

Disadvantages
- ZDV: see above.
- FTC
  - Rash perhaps more frequent than with 3TC
  - No long-term experience with this drug
  - Cross resistance to 3TC
  - Hyperpigimentation among non-Caucasians with long-term use: 3%

- **Tenofovir DF (Viread®; TDF) + lamivudine (Epivir®; 3TC)**

Preferred dosing
- TDF: 300 mg once daily
- 3TC: 300 mg once daily or 150 mg twice daily

Dosage forms
- TDF: 300 mg tablet
- 3TC: see above

Advantages
- 3TC: see above
- TDF
  - Convenient dosing (single pill once daily)
  - Resistance profile activity against certain thymidine analogue mutations
  - Well tolerated

Disadvantages
- TDF
  - Same class warnings as nucleoside reverse transcriptase inhibitors (NRTIs)
  - Drug interactions
  - Increased TDF concentrations among persons taking atazanavir and lopinavir/ritonavir; need to monitor patients for TDF-associated toxicities
- Preferred dosage of atazanavir if used with TDF: 300 mg + ritonavir 100 mg once daily + TDF 300 mg once daily

- **Tenofovir DF (Viread®; TDF) + emtricitabine (Emtriva™; FTC); available as Truvada™**

Preferred dosing
- TDF: 300 mg once daily
- FTC: 200 mg once daily
- As Truvada™: one tablet daily

Dosage forms
- TDF: 300 mg tablet
- FTC: see FTC
- Truvada™ (TDF 300 mg plus FTC 200 mg)

Advantages
- FTC: see above
- TDF
  - Convenient dosing (single pill once daily)
  - Resistance profile activity against certain thymidine analogue mutations
  - Well tolerated

Disadvantages
- TDF
  - Same class warnings as NRTIs
  - Drug interactions
  - Increased TDF concentrations among persons taking atazanavir and lopinavir/ritonavir; need to monitor patients for TDF-associated toxicities
  - Preferred dosing of atazanavir if used with TDF: 300 mg + ritonavir 100 mg once daily + TDF 300 mg once daily

ALTERNATE BASIC REGIMENS

- **Lamivudine (Epivir®; 3TC) + stavudine (Zerit®; d4T)**

Preferred dosing
- 3TC: 300 mg once daily or 150 mg twice daily
- d4T: 40 mg twice daily (can use lower doses of 20–30 mg twice daily if toxicity occurs; equally effective but less toxic among HIV-infected patients with peripheral neuropathy); 30 mg twice daily if body weight is <60 kg

Dosage forms
- 3TC: see above
- d4T: 15, 20, 30, and 40 mg tablet

Advantages
- 3TC: see above
- d4T: gastrointestinal (GI) side effects rare

Disadvantages
- Possibility that source-patient virus is resistant to this regimen
- Potential for delayed toxicity (oncogenic/teratogenic) unknown

- **Emtricitabine (Emtriva™; FTC) + stavudine (Zerit®; d4T)**

Preferrred dosing
- FTC: 200 mg daily
- d4T: 40 mg twice daily (can use lower doses of 20–30 mg twice daily if toxicity occurs; equally effective but less toxic among HIV-infected patients who developed peripheral neuropathy); if body weight is <60 kg, 30 mg twice daily

Dosage forms
- FTC: see above
- d4T: see above

Advantages
- 3TC and FTC: see above; d4T's GI side effects rare

Disadvantages
- Potential that source-patient virus is resistant to this regimen
- Unknown potential for delayed toxicity (oncogenic/teratogenic) unknown

- **Lamivudine (Epivir®; 3TC) + didanosine (Videx®; ddI)**

Preferred dosing
- 3TC: 300 mg once daily or 150 mg twice daily
- ddI: Videx® chewable/dispersible buffered tablets can be administered on an empty stomach as either 200 mg twice daily or 400 mg once daily. Patients must take at least two of the appropriate strength tablets at each dose to provide adequate buffering and prevent gastric acid degradation of ddI. Because of the need for adequate buffering, the 200-mg strength tablet should be used only as a component of a once-daily regimen. The dose is either 200 mg twice daily or 400 mg once daily for patients weighing >60 kg and 125 mg twice daily or 250 mg once daily for patients weighing >60 kg.

Dosage forms
- 3TC: 150 or 300 mg tablets
- ddI: 25, 50, 100, 150, or 200 mg buffered white tablets

Advantages
- ddI: once daily dosing option
- 3TC: see above

Disadvantages
- Tolerability: diarrhea more common with buffered preparation than with enteric-coated preparation
- Associated with toxicity: peripheral neuropathy, pancreatitis, and lactic acidosis
- Must be taken on empty stomach except with TDF
- Drug interactions
- 3TC: see above

- **Emtricitabine (Emtriva™; FTC) + didanosine (Videx®; ddI)**

Preferred dosing
- FTC: 200 mg once daily
- ddI: see above

Dosage forms
- ddI: see above
- FTC: see above

Advantages
- ddI: see above
- FTC: see above

Disadvantages
- Tolerability: diarrhea more common with buffered than with enteric-coated preparation
- Associated with toxicity: peripheral neuropathy, pancreatitis, and lactic acidosis
- Must be taken on empty stomach except with TDF
- Drug interactions
- FTC: see above

PREFERRED EXPANDED REGIMEN

Basic regimen plus:

- **Lopinavir/ritonavir (Kaletra®; LPV/RTV)**

Preferred dosing
- LPV/RTV: 400/100 mg = 3 capsules twice daily with food

Dosage form
- LPV/RTV: 133/33 mg capsules

Advantages
- Potent HIV protease inhibitor
- Generally well-tolerated

Disadvantages
- Potential for serious or life-threatening drug interactions (see Table 4)
- Might accelerate clearance of certain drugs, including oral contraceptives (requiring alternative or additional contraceptive measures for women taking these drugs)
- Can cause severe hyperlipidemia, especially hypertriglyceridemia
- GI (e.g., diarrhea) events common

ALTERNATE EXPANDED REGIMENS

Basic regimen plus one of the following:

- **Atazanavir (Reyataz®; ATV) ± ritonavir (Norvir®; RTV)**

Preferred dosing
- ATV: 400 mg once daily, unless used in combination with TDF, in which case ATV should be boosted with RTV, preferred dosing of ATV 300 mg + RTV: 100 mg once daily

Dosage forms
- — ATV: 100, 150, and 200 mg capsules
- — RTV: 100 mg capsule

Advantages
- — Potent HIV protease inhibitor
- — Convenient dosing – once daily
- — Generally well tolerated

Disadvantages
- — Hyperbilirubinemia and jaundice common
- — Potential for serious or life-threatening drug interactions (see Table 4)
- — Avoid coadministration with proton pump inhibitors
- — Separate antacids and buffered medications by 2 hours and H2-receptor antagonists by 12 hours to avoid decreasing ATV levels
- — Caution should be used with ATV and products known to induce PR prolongation (e.g., diltiazem)

- **Fosamprenavir (Lexiva®; FOSAPV) ± ritonavir (Norvir®; RTV)**

Preferred dosing
- — FOSAPV: 1400 mg twice daily (without RTV)
- — FOSAPV: 1400 mg once daily + RTV 200 mg once daily
- — FOSAPV: 700 mg twice daily + RTV 100 mg twice daily

Dosage form
- — FOSAPV: 700 mg tablets
- — RTV: 100 mg capsule

Advantages
- — Once daily dosing when given with ritonavir

Disadvantages
- — Tolerability: GI side effects common
- — Multiple drug interactions. Oral contraceptives decrease fosamprenavir concentrations
- — Incidence of rash in healthy volunteers, especially when used with low doses of ritonavir. Differentiating between early drug-associated rash and acute seroconversion can be difficult and cause extraordinary concern for the exposed person

- **Indinavir (Crixivan®; IDV) ± ritonavir (Norvir®; RTV)**

Preferred dosing
- — IDV 800 mg + RTV 100 mg twice daily without regard to food

Alternative dosing
- — IDV: 800 mg every 8 hours, on an empty stomach

Dosage forms
- — IDV: 200 mg, 333, and 400 mg capsule
- — RTV: 100 mg capsule

Advantages
- — Potent HIV inhibitor

Disadvantages
- — Potential for serious or life-threatening drug interactions (see Table 4)
- — Serious toxicity (e.g., nephrolithiasis) possible; consumption of 8 glasses of fluid/day required
- — Hyperbilirubinemia common; must avoid this drug during late pregnancy
- — Requires acid for absorption and cannot be taken simultaneously with ddI, chewable/dispersible buffered tablet formulation (doses must be separated by ≥1 hour)

- **Saquinavir (Invirase®; SQV) + ritonavir (Norvir®; RTV)**

Preferred dosing
- — SQV: 1,000 mg (given as Invirase) + RTV 100 mg, twice daily
- — SQV : five capsules twice daily + RTV: one capsule twice daily

Dosage forms
- — SQV (Invirase): 200 mg capsule
- — RTV: 100 mg capsule

Advantages
- — Generally well-tolerated, although GI events common

Disadvantages
- — Potential for serious or life-threatening drug interactions (see Table 4)
- — Substantial pill burden

- **Nelfinavir (Viracept®; NFV)**

Preferred dosing
- — NFV: 1,250 mg (2 x 625 mg or 5 x 250 mg tablets), twice daily with a meal

Dosage forms
- — NFV: 250 or 625 mg tablet

Advantages
- — Generally well-tolerated

Disadvantages
- — Diarrhea or other GI events common
- — Potential for serious and/or life-threatening drug interactions (see Table 4)

- **Efavirenz (Sustiva®; EFV)**

Preferred dosing
- — EFV: 600 mg daily, at bedtime

Dosage forms
- — EFV: 50, 100, 200 capsules
- — EFV: 600 mg tablet

Advantages

— Does not require phosphorylation before activation and might be active earlier than other antiretroviral agents (a theoretic advantage of no demonstrated clinical benefit)

— Once daily dosing

Disadvantages

— Drug associated with rash (early onset) that can be severe and might rarely progress to Stevens-Johnson syndrome

— Differentiating between early drug-associated rash and acute seroconversion can be difficult and cause extraordinary concern for the exposed person

— Central nervous system side effects (e.g., dizziness, somnolence, insomnia, or abnormal dreaming) common; severe psychiatric symptoms possible (dosing before bedtime might minimize these side effects)

— Teratogen; should not be used during pregnancy

— Potential for serious or life-threatening drug interactions (see Table 5)

ANTIRETROVIRAL AGENTS GENERALLY NOT RECOMMENDED FOR USE AS PEP

- **Nevirapine (Viramune®; NVP)**

Disadvantages

— Associated with severe hepatotoxicity (including at least one case of liver failure requiring liver transplantation in an exposed person taking PEP)

— Associated with rash (early onset) that can be severe and progress to Stevens-Johnson syndrome

— Differentiating between early drug-associated rash and acute seroconversion can be difficult and cause extraordinary concern for the exposed person

— Drug interactions: can lower effectiveness of certain antiretroviral agents and other commonly used medicines

- **Delavirdine (Rescriptor®; DLV)**

Disadvantages

— Drug associated with rash (early onset) that can be severe and progress to Stevens-Johnson syndrome

— Multiple drug interactions

- **Abacavir (Ziagen®; ABC)**

Disadvantages

— Severe hypersensitivity reactions can occur, usually within the first 6 weeks

— Differentiating between early drug-associated rash/hypersensitivity and acute seroconversion can be difficult

- **Zalcitabine (Hivid®; ddC)**

Disadvantages

— Three times a day dosing

— Tolerability

— Weakest antiretroviral agent

ANTIRETROVIRAL AGENT FOR USE AS PEP ONLY WITH EXPERT CONSULTATION

- **Enfuvirtide (Fuzeon™; T20)**

Preferred dosing

— T20: 90 mg (1 ml) twice daily by subcutaneous injection

Dosage forms

— T20: Single-dose vial, reconstituted to 90 mg/ml

Advantages

— New class

— Unique viral target; to block cell entry

— Prevalence of resistance low

Disadvantages

— Twice-daily injection

— Safety profile: local injection site reactions

— Never studied among antiretroviral-naïve or HIV-negative patients

— False-positive EIA HIV antibody tests might result from formation of anti-T20 antibodies that cross-react with anti-gp41 antibodies

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MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports September 30, 2005 / Vol. 54 / No. RR-9

Continuing Education Activity Sponsored by CDC

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

EXPIRATION — September 30, 2007

You must complete and return the response form electronically or by mail by **September 30, 2007**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 1.5 hours Continuing Medical Education (CME) credit; 0.15 Continuing Education Units (CEUs); or 1.9 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

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1. Read this *MMWR* (Vol. 54, RR-9), which contains the correct answers to the questions beginning on the next page.
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6. Submit your answers no later than **September 30, 2007**
7. Immediately print your Certificate of Completion for your records.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This report provides recommendations regarding clinical practice for managing occupational exposures to HIV in health-care settings, including appropriate use of HIV postexposure prophylaxis (PEP). The goal of this report is to provide recommendations for guiding clinical practice in managing PEP for health-care personnel (HCP) with occupational exposure to HIV. Upon completion of this educational activity, the reader should be able to a) describe occupational exposures for which exposure management is appropriate; b) describe the appropriate selection of HIV PEP; c) describe the appropriate use of HIV PEP; d) describe the follow-up evaluation of exposed HCP; e) describe the follow-up counseling of exposed HCP; and f) list situations for which expert consultation in the management of occupational exposures is recommended.

To receive continuing education credit, please answer all of the following questions.

1. Contact with which body fluid(s) poses a risk for HIV transmission in health-care settings? (*Indicate all that apply.*)

A. Blood.
B. Urine.
C. Sweat.
D. Amniotic fluid.
E. A and D.
F. B and C.

2. What is the recommended duration of HIV PEP for occupational exposures to HIV? (*Choose the one correct answer.*)

A. 7 days.
B. 14 days.
C. 21 days.
D. 28 days.
E. 2 months.

3. What is the recommended time to initiation of HIV PEP after exposure when PEP is indicated? (*Choose the one correct answer.*)

A. 2 days.
B. 24–48 hours.
C. As soon as possible (preferably within hours).

4. Follow-up after occupational exposures to HIV should include which of the following? (*Choose the one correct answer.*)

A. Serologic follow-up for HIV infection.
B. Monitoring for adverse effects of HIV postexposure prophylaxis if taken.
C. Monitoring for acute seroconversion illness.
D. Counseling on adherence with HIV PEP and the emotional stress of dealing with exposures.
E. All of the above.

5. The potential for interactions with other medications is greatest for which of the antiretroviral drug classes recommended for HIV postexposure prophylaxis? (*Choose the one correct answer.*)

A. Reverse transcriptase inhibitors (nucleoside analogues).
B. Nonnucleoside reverse transcriptase inhibitors.
C. Protease inhibitors.
D. A and B.
E. B and C.
F. A and C.

6. Which antiretrovirals are not currently recommended for use by pregnant HCP? (*Indicate all that apply.*)

A. Efavirenz.
B. Zidovudine.
C. Nelfinavir.
D. Tenofovir.

7. Resistance testing of the source-patient after an exposure should always be performed to help in selection of HIV postexposure prophylaxis regimens.

A. True.
B. False.

8. Adverse effects of antiretroviral HIV postexposure prophylaxis are uncommonly reported by HCP.

A. True.
B. False.

9. Which types of exposure pose a risk for HIV transmission in health-care settings? (*Indicate all that apply.*)

A. Intact skin exposure to blood.
B. Mucous membrane splash of urine.
C. Needlestick injury after phlebotomy.
D. Splash of blood on abraded skin.
E. C and D.
F. A and B.

10. A 12-month serologic follow-up after an occupational exposure to HIV is recommended in which situation(s)? (*Indicate all that apply.*)

A. Any percutaneous exposure to an HIV-infected source.
B. If the exposed worker takes HIV postexposure prophylaxis.
C. If the exposure source is coinfected with HIV and HCV and becomes HCV-infected.
D. None of the above.

11. Which best describes your professional activities:

A. Physician.
B. Nurse.
C. Health educator.
D. Office staff.
E. Other.

12. I plan to use these recommendations as the basis for …(*Indicate all that apply.*)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

13. Overall, the length of the journal article was…

A. much too long.
B. a little too long.
C. just right.
D. a little too short.
E. much too short.

14. After reading this report, I am confident I can describe occupational exposures for which exposure management is appropriate.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

15. After reading this report, I am confident I can describe the appropriate selection of HIV PEP.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe the appropriate use of HIV PEP.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe the follow-up evaluation of exposed HCP.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe the follow-up counseling of exposed HCP.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can list situations for which expert consultation in the management of occupational exposures is recommended.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

20. The learning outcomes (objectives) were relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

21. The instructional strategies used in this report (text, tables, boxes, and appendix) helped me learn the material.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

22. The content was appropriate given the stated objectives of the report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

***MMWR* Response Form for Continuing Education Credit**
September 30, 2005/Vol. 54/No. RR-9

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

To receive continuing education credit, you must
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2. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E		17. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
3. [ ] A	[ ] B	[ ] C				18. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
4. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E		19. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
5. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F	20. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
6. [ ] A	[ ] B	[ ] C	[ ] D			21. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
7. [ ] A	[ ] B					22. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
8. [ ] A	[ ] B					23. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
9. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F	24. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
10. [ ] A	[ ] B	[ ] C	[ ] D			25. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
11. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E		26. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
12. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E		27. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E
13. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E		28. [ ] A	[ ] B			
14 [ ] A	[ ] B	[ ] C	[ ] D	[ ] E		29. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E [ ] F
15. [ ] A	[ ] B	[ ] C	[ ] D	[ ] E						

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EXHIBIT 16

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Effectiveness of Postinoculation (*R*)-9-(2-Phosphonylmethoxypropyl) Adenine Treatment for Prevention of Persistent Simian Immunodeficiency Virus SIV_{mne} Infection Depends Critically on Timing of Initiation and Duration of Treatment

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(*R*)-9-(2-Phosphonylmethoxypropyl)adenine (PMPA), an acyclic nucleoside phosphonate analog, is one of a new class of potent antiretroviral agents. Previously, we showed that PMPA treatment for 28 days prevented establishment of persistent simian immunodeficiency virus (SIV) infection in macaques even when therapy was initiated 24 h after intravenous virus inoculation. In the present study, we tested regimens involving different intervals between intravenous inoculation with SIV and initiation of PMPA treatment, as well as different durations of treatment, for the ability to prevent establishment of persistent infection. Twenty-four cynomolgus macaques (*Macaca fascicularis*) were studied for 46 weeks after inoculation with SIV. All mock-treated control macaques showed evidence of productive infection within 2 weeks postinoculation (p.i.). All macaques that were treated with PMPA for 28 days beginning 24 h p.i. showed no evidence of viral replication following discontinuation of PMPA treatment. However, extending the time to initiation of treatment from 24 to 48 or 72 h p.i. or decreasing the duration of treatment reduced effectiveness in preventing establishment of persistent infection. Only half of the macaques treated for 10 days, and none of those treated for 3 days, were completely protected when treatment was initiated at 24 h. Despite the reduced efficacy of delayed and shortened treatment, all PMPA-treated macaques that were not protected showed delays in the onset of cell-associated and plasma viremia and antibody responses compared with mock controls. These results clearly show that both the time between virus exposure and initiation of PMPA treatment as well as the duration of treatment are crucial factors for prevention of acute SIV infection in the macaque model.

We recently used the simian immunodeficiency virus (SIV)-infected macaque model to evaluate the efficacy of (*R*)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), which is an acyclic nucleoside phosphonate analog and a potent antiretroviral compound (1, 2) in the setting of acute retroviral infection (23). In that study, PMPA prevented SIV infection even when treatment was started 24 h after intravenous virus inoculation (23). The increased antiretroviral efficacy of PMPA in SIV-challenged macaques (23), compared with that of other nucleoside analogues such as zidovudine (AZT) (15, 24, 29), may be related to ease of phosphorylation and the longer intracellular half-life for active phosphorylated metabolites of acyclic nucleoside phosphonates than for other nucleoside analogs (1). Although PMPA is highly potent when administered during de novo or early in SIV infection, the optimal treatment regimen of PMPA for preventing establishment of persistent SIV infection has not yet been determined. Therefore, we undertook the present study to determine the impact of increasing intervals between virus inoculation and initiation of PMPA treatment and varying the duration of treatment on the effectiveness of treatment in preventing the establishment of persistent infection.

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MATERIALS AND METHODS

Macaques. The subjects were 24 cynomolgus macaques (*Macaca fascicularis*), 12 males and 12 females, 2.5 to 3.5 years old. All animals were determined to be clinically healthy and free of type D retrovirus and SIV before virus inoculation. The macaques were assigned to study groups as summarized in Table 1 and Fig. 1 to 3. Treatment regimens are described in detail below. Care and husbandry were in strict conformance with federal guidelines. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Washington.

Virus inoculum. Virus used for inoculation was derived from the cell culture supernatant of uncloned SIV_{mne} propagated in HuT 78 cells (3). The cell supernatant was filtered (0.45-μm-pore-size filter; Nalgene, Rochester, N.Y.) and frozen in aliquots in liquid nitrogen. The titer of this virus stock was 10^5 tissue culture infectious doses per milliliter as determined in human T-cell lines. The stock was diluted immediately before inoculation. All macaques were inoculated intravenously with 1.0 ml of 10^3 tissue culture infectious doses, which is equivalent to 10 times the 50% animal infectious dose (25). Such a dose results in 100% infectivity in macaques. Intravenous inoculation was used to minimize potential differences between animals in transmission across mucosal barriers.

PMPA preparation and treatment regimen. PMPA was dissolved in water, and the pH was adjusted to 7.0 with 0.1 N NaOH. The volume of the solution was adjusted with distilled water to a PMPA concentration of 30 mg/ml and filter sterilized (0.2-μm-pore-size filter; Nalgene). The macaques were divided into six groups of four animals each (groups A, B, C, D, E, and F) and inoculated intravenously with 10 times the 50% animal infectious dose of SIV_{mne}. The four

TABLE 1. Summary of virological and immunological status following various treatment regimens

Group	Determination	No. positive at indicated wk p.i./no. tested											
		1	2	3	4	6	8	12	16	20	24	32	46
A (mock-treated control; macaques 95012, 95023, 95032, 95041)	PBMC viremia[a]	0/4	4/4	3/4	3/4	3/4	3/4	4/4	4/4	3/4	3/4	4/4	3/4
	Plasma SIV RNA	4/4	4/4	4/4	4/4	4/4	4/4	4/4	3/4	4/4	3/3	3/3	3/4
	PCR-viral DNA[b]	3/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	3/4	ND[c]	ND	4/4
	SIV antibodies	0/4	0/4	0/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
B (24-h postexposure, 28-day treatment; macaques 95025, 95044, 95054, M94312)	PBMC viremia	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	Plasma SIV RNA	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	PCR-viral DNA	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	SIV antibodies	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4	1/4
C (48-h postexposure, 28-day treatment; macaques 95026, 95035, 95043, 95059)	PBMC viremia	0/4	0/4	0/4	0/4	2/4	3/4	3/4	1/4	1/4	1/4	1/4	1/4
	Plasma SIV RNA	0/4	0/4	0/4	0/4	2/4	4/4	3/4	3/4	3/4	3/4	2/4	2/4
	PCR-viral DNA	0/4	0/4	0/4	0/4	2/4	3/4	2/4	2/4	2/4	ND	ND	4/4
	SIV antibodies	0/4	0/4	0/4	0/4	1/4	2/4	3/4	4/4	4/4	4/4	4/4	4/4
D (72-h postexposure, 28-day treatment; macaques 95017, 95038, 95061, M95033)	PBMC viremia	0/4	0/4	0/4	0/4	1/4	2/4	2/4	2/4	2/4	2/4	2/4	2/4
	Plasma SIV RNA	0/4	0/4	0/4	0/4	3/4	3/4	3/4	4/4	2/4	2/4	2/4	2/4
	PCR-viral DNA	0/4	0/4	0/4	0/4	2/4	3/4	3/4	3/4	1/4	ND	ND	2/4
	SIV antibodies	0/4	0/4	0/4	0/4	2/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
E (24-h postexposure, 10-day treatment; macaques 95016, 95020, 95033, 95053)	PBMC viremia	0/4	0/4	0/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4
	Plasma SIV RNA	0/4	0/4	1/4	1/4	2/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4
	PCR-viral DNA	0/4	0/4	0/4	1/4	2/4	0/4	2/4	2/4	1/4	ND	ND	1/4
	SIV antibodies	0/4	0/4	0/4	0/4	0/4	2/4	2/4	2/4	2/4	2/4	2/4	3/4
F (24-h postexposure, 3-day treatment; macaques 95015, 95030, M95018, 95052)	PBMC viremia	0/4	0/4	1/4	3/4	1/4	1/4	2/4	2/4	2/4	2/4	2/4	2/4
	Plasma SIV RNA	1/4	3/4	3/4	4/4	3/4	2/4	2/4	3/4	2/4	3/4	2/4	2/4
	PCR-viral DNA	0/4	0/4	1/4	4/4	3/4	4/4	4/4	3/4	2/4	ND	ND	2/4
	SIV antibodies	0/4	0/4	0/4	3/4	3/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4

[a] PBMC were titrated from 10^6 to 10^1 cells and then cocultured with C8166 cells to isolate infectious virus in this in vitro assay.
[b] A nested PCR was used to detect SIV long terminal repeat DNA in 10^6 PBMCs.
[c] ND, not determined.

macaques in group A served as an infection control group: after inoculation they were mock treated with sterile, physiological saline for 28 days. The macaques in groups B to F were treated with PMPA beginning 24, 48, or 72 h postinoculation (p.i.). PMPA (30 mg/kg) was administered once daily via the subcutaneous route for 3, 10, or 28 days. The treatment regimens for macaque groups A to F are summarized in Table 1.

Clinical observations. The macaques were observed daily for general physical condition including appetite, stool consistency, activity level, and appearance. At specific intervals they were anesthetized with ketamine for thorough physical examination. At these times, weight and body temperature were recorded and blood was drawn for complete blood counts, serum biochemistry, virology, and lymphocyte subset analyses. Blood draws were performed weekly during PMPA treatment (i.e., the first 4 weeks p.i.), every 2 weeks for the next 6 weeks, and then once a month until the end of the study (46 weeks p.i.). The data obtained from the physical examinations and blood analyses were used to monitor the course of SIV infection, SIV-induced disease, and potential drug toxicity.

Processing of blood samples. EDTA-anticoagulated blood was collected as described above, and the course of SIV infection was followed for 46 weeks. The EDTA-anticoagulated blood obtained from the femoral vein was centrifuged to separate plasma and buffy coats. Plasma was aliquoted and used for assays of SIV RNA, anti-SIV immunoglobulin G (IgG) antibodies, and immunoblotting. Peripheral blood mononuclear cells (PBMC) were separated from the buffy coat by centrifugation through Ficoll-Hypaque density gradients (Pharmacia, Piscataway, N.J.).

SIV RNA in plasma (plasma-associated virus). Virus-associated SIV RNA in plasma was quantified via a real-time reverse transcriptase (RT)-mediated PCR (RT-PCR) assay as described in detail elsewhere (22). Briefly, plasma virion-associated RNA was extracted with commercial reagents (Purescript; Gentra Systems, Minneapolis, Minn.). After a random-primed reverse transcription, real-time quantitative PCR analysis was performed with primers to a highly conserved region of SIV *gag* sequence and a fluorochrome-labeled internally hybridizing oligonucleotide probe (22). Duplicate RT-PCRs were performed for each sample, along with a reaction in which no RT was included as a control to detect any DNA contamination of the test samples. The nominal threshold sensitivity for the assay was 300 copy eq/ml of plasma.

Assessment of virus infectivity. The frequency of infected cells was measured by cocultivation of serial 10-fold dilutions (10^6 to 10^1) of PBMC or lymph node mononuclear cells (LNMC) prepared from biopsied lymph nodes with target cells (C8166) in 24-well tissue culture plates or cell culture flasks for virus isolation (23, 26). The cells were maintained in RPMI 1640 medium to which were added 2 mM L-glutamine, 50 μg of gentamicin per ml, and 10% heat-inactivated fetal calf serum. Cultures were examined twice weekly for syncytial cytopathic effects, and culture supernatants were sampled weekly for detection of SIV p27 antigens by antigen capture assay (Coulter, Hialeah, Fla.). All cultures were maintained for 4 weeks by weekly passage of culture on to fresh target cells. The results of virus isolation and detection were used for estimating the frequency of infectious cells or the level of cell-associated virus. For example, 10^6 PBMC or LNMC needed for detection of SIV were determined as one infectious cell frequency; 10^5 and 10^4 PBMC that yielded a positive SIV were expressed as 10 and 100 infectious cells per 10^6 PBMC, or 1- to 2-log-higher levels of cell-associated virus.

Virus isolation from PBMC or LNMC. Approximately 10^6 PBMC were cultured for 2 days in RPMI 1640 containing 5 μg of phytohemagglutinin (Sigma) per ml for activation of T lymphocytes. The supernatant of culture was removed, and the cell pellets were resuspended in RPMI 1640 medium supplemented with 8 U of human interleukin-2 (Boehringer Mannheim) per ml and cocultivated with C8166 cells. The basic methods for cell culture and virus isolation were the same as those described for infectivity assays described above. Culture supernatants were sampled for measuring the levels of SIV p27 antigen by the use of a capture enzyme-linked immunosorbent assay (Coulter).

PCR for SIV DNA in PBMC. PCR detection of SIV nucleic acid sequences was performed on DNA extracted from PBMC, using a nested set of oligonucleotide primers specific for SIV long terminal repeat regions as described previously (23, 24). Briefly, 1 μg of PBMC DNA was amplified in each reaction mixture containing 0.2 mM deoxynucleoside triphosphates, 2.0 mM $MgCl_2$, Amplitaq buffer, 2.5 U of *Taq* polymerase (Amplitaq; Perkin-Elmer Cetus, Norwalk, Conn.), and 10 nM primers (National Bioscience, Plymouth, Mass.). Samples were amplified with external primers, the products were diluted 1:100, and the internal nested primers were used to amplify a fragment of 850 bp. Specific DNA bands were detected on ethidium bromide-stained agarose gels. Analysis was done for PBMC collected at multiple time points from 1 to 46 weeks p.i.

Antibody determination. Anti-SIV IgG antibody titers in plasma were detected by an immunofluorescence antibody (IFA) assay (25, 27) and expressed as the reciprocal of the highest twofold dilution (duplicate per dilution) that gave positive immunofluorescence staining. Briefly, plasma from experimental macaques was diluted 1:20 to 1:40,960 in phosphate-buffered saline. SIV-infected C8166 cells attached to Teflon-coated slides (Cel-Line Associates, Newfield, N.J.) were used as target cells for binding SIV antibodies from the diluted plasma. After incubation and washing, fluorescein-conjugated goat anti-monkey IgG (Organon Teknika Cappel, Malvern, Pa.) was added. Cells showing fluorescence were considered to be positive for the presence of SIV antibody. The lower limit of the IFA assay for anti-SIV IgG antibody titer was 1:20. SIV-specific antibodies to viral proteins were detected by Western blotting (3, 4) using a 0.45-μm-pore-size Immobilon membrane (Millipore, Bedford, Mass.). Briefly, 1,000-fold-concentrated SIV was separated on sodium dodecyl sulfate–10 to 20% polyacrylamide electrophoresis gradient gels and transferred by electrophoresis as described

previously (3) except that a 0.45-μm-pore-size Immobilon membrane (Millipore) was used instead of nitrocellulose. On Western immunoblots, each strip contained approximately 10 μg of viral proteins.

Lymphocyte subset analysis. $CD4^+$ and $CD8^+$ lymphocyte data were obtained from all macaques before, during, and after PMPA treatment. Specific lymphocyte subsets were determined by incubating EDTA-anticoagulated blood samples with a panel of mouse anti-human monoclonal antibodies that react with macaque lymphocytes (23, 26). Specific $CD4^+$ cells and other lymphocyte subsets were analyzed by flow cytometry using a FACScan (Becton Dickinson, San Jose, Calif.). Absolute cell numbers were calculated from total and differential leukocyte counts and the percentage of lymphocytes with T-cell markers.

Statistical analysis. Data obtained from virologic, immunologic, and hematologic studies were analyzed by χ^2 and analysis of variance.

RESULTS

Virologic and serologic studies. All macaques were monitored at predetermined intervals for levels of plasma virion-associated SIV RNA, PBMC-associated virus, PCR SIV DNA in PBMC, and SIV antibody responses. The summary and outcome of the various PMPA treatments are shown in Table 1. To facilitate comparison of data for individual macaques described in the text, the study groups and the macaque numbers in each group are shown in the same order in Fig. 1 to 3 and in Table 1. Comparisons of virologic data between group A (the mock-treated control) and groups B (treated starting 24 h p.i.), C (treated starting 48 h p.i.) and D (treated starting 72 h p.i.) demonstrate the effects of the time interval between intravenous virus inoculation and the initiation of PMPA treatment. Similarly, the differences between group A and groups B, E, and F demonstrate the effects of various durations of PMPA treatment (28, 10, and 10 days, respectively). In addition to the virologic status shown in Table 1, detailed data for PBMC-associated SIV (Fig. 2), plasma-associated virus (Fig. 1), and SIV antibody responses (Table 1 and Fig. 3) were used as criteria for determining SIV infection.

All four of the mock-treated macaques in group A developed persistent infection as determined by plasma viremia (17,000 to 130,000 copy eq of SIV RNA/ml of plasma) by week 1 p.i. (Fig. 1), by PBMC-associated virus (100 to 1,000 infectious cells per 10^6 PBMC, except in macaque 95041, which had 1 infectious cell per 10^6 PBMC) starting at week 2 p.i. (Table 1 and Fig. 2), and by the presence of anti-SIV IgG antibodies (antibody titers ranging from 1:640 to 1:1,280) beginning at week 4 p.i. The SIV infection and antibody response in the control macaques persisted throughout the 46-week study. However, in macaque 95041 these levels were 1 to 2 logs lower than in other control macaques.

When PMPA treatment was initiated 24 h p.i. and continued for 28 days (group B) (Table 1 and Fig. 1 to 3), three of the four macaques showed no evidence of SIV infection by virologic and serologic detection throughout the 46-week observation period. The fourth macaque (M94312) had a very low titer (1:40) of antibody at week 24 p.i. with no increase in the scope of antigen specificity or titer of antibody at week 46, despite negative virus isolation from PBMC and lymph node biopsies, negative PCR SIV DNA, and undetectable plasma SIV RNA.

When PMPA treatment was initiated 48 h p.i. and continued for 28 days (group C) (Table 1 and Fig. 1 to 3), all four macaques showed no evidence of infection over the first 4 weeks p.i. during PMPA treatment. Upon withdrawal of PMPA, however, two macaques (95026 and 95043) showed transient viremia as determined by PBMC-associated virus (1 infectious cell per 10^6 PBMC) at 6 to 12 weeks p.i. (Fig. 2) and by measurable plasma viral RNA levels (1,000 to 22,000 copy eq/ml, respectively) at 8 to 12 weeks p.i. (Fig. 1); thereafter, their PBMC and plasma no longer showed any evidence of virus. These two macaques also had low levels of SIV-specific antibodies to viral proteins detectable by immunoblotting beginning at week 16 p.i. The other two macaques in this group (95059 and 95035) developed persistent infection. Macaque 95059 had continuously high levels of both PBMC-associated virus (10 to 100 infectious cells per 10^6 PBMC) and plasma viral RNA (mean of 1,630,000 copy eq/ml of plasma) and high titers (1:10,240) of anti-SIV IgG antibody. Likewise, macaque 95035 had moderately high titers (1:2,560 to 1:5,120) of anti-SIV IgG antibody beginning 8 weeks p.i. and lasting until the end of the observation period. In the first 2 weeks after discontinuation of PMPA, plasma SIV RNA went from undetectable to 90,000,000 copy eq/ml and then decreased in the post-acute phase of infection, equilibrating at approximately 200,000 copy eq/ml during weeks 24 to 46 (Fig. 1).

When PMPA treatment was initiated 72 h p.i. and continued for 28 days (group D) (Table 1 and Fig. 1 to 3), the four macaques did not show any evidence of viral replication during the treatment period. Macaque M95033 did not show evidence of infection in any of the virologic assays performed throughout the 46-week study but had very low levels of antibody (1:40) detectable by IFA and immunoblotting beginning 8 weeks p.i.; antibody persisted at a titer of 1:80 from weeks 24 through 46 p.i. Macaques 95017 and 95061 became persistently infected, showing high levels of PBMC-associated virus (10 to 100 infectious cells per 10^6 PBMC) and plasma viral RNA and increasing antibody titers from 6 weeks p.i. until the end of the study. Interestingly, macaque 95038 had only transiently detectable viremia as determined by plasma SIV RNA (37,000 copy eq/ml) only at week 6 p.i. and by PBMC-associated virus (1 infectious cell per 10^6 PBMC) only at week 10 p.i.; thereafter the PBMC and plasma no longer showed any detectable virus. However, this macaque had a measurable anti-SIV antibody (1:640 to 1:1,280) beginning 8 weeks p.i. and persisting to the end of the observation period.

When PMPA treatment was initiated 24 h p.i. and continued for only 10 days (group E) (Table 1 and Fig. 1 to 3), three of the four macaques showed no signs of persistent viremia by virologic detection. Of these three animals, macaque 95053 had very low levels of anti-SIV IgG antibody, with titers of 1:40 beginning 8 weeks p.i. and 1:80 from weeks 24 through 46. This macaque had a very low level of plasma SIV RNA (600 copy eq/ml) only at week 6 p.i. Macaque 95020 had an even lower antibody titer (1:40) beginning 24 weeks p.i., detectable by a very weak band for SIV gp120 on immunoblotting. Macaque 95033 had no detectable antibody throughout the 46-week study. However, one macaque (95016) had a persistent infection as determined by increasing plasma SIV RNA beginning at week 3 p.i. (1,700 copy eq/ml of SIV RNA), by increasing PBMC-associated virus beginning at week 4 p.i. (1 infectious cell per 10^6 PBMC), and by increasing antibody response beginning at week 8 p.i. (anti-SIV IgG titer of 1:640). By the end of the study, this macaque had 31,000,000 copy eq of SIV RNA/ml of plasma, 10 to 100 infectious cells per 10^6 PBMC of PBMC-associated virus, and 1:40,960 titer of anti-SIV antibody.

When PMPA treatment was initiated 24 h p.i. and continued for only 3 days (group F) (Table 1 and Fig. 1 to 3), two macaques (95030 and M95018) apparently had transient infection with detectable plasma SIV RNA levels (6,000 to 730,000 copy eq/ml in macaque 95030 and 2,400 to 25,000 copy eq/ml in macaque M95018) beginning 1 to 2 weeks p.i. By 8 weeks p.i., plasma SIV RNA was undetectable in these two animals. It remained undetectable in macaque M95018 through the end of the study, but low levels (1,400 to 2,000 copy eq/ml) were detectable in macaque 95030 at 16 and 24 weeks p.i. Interestingly, macaque M95018 had no evidence of viral infection by

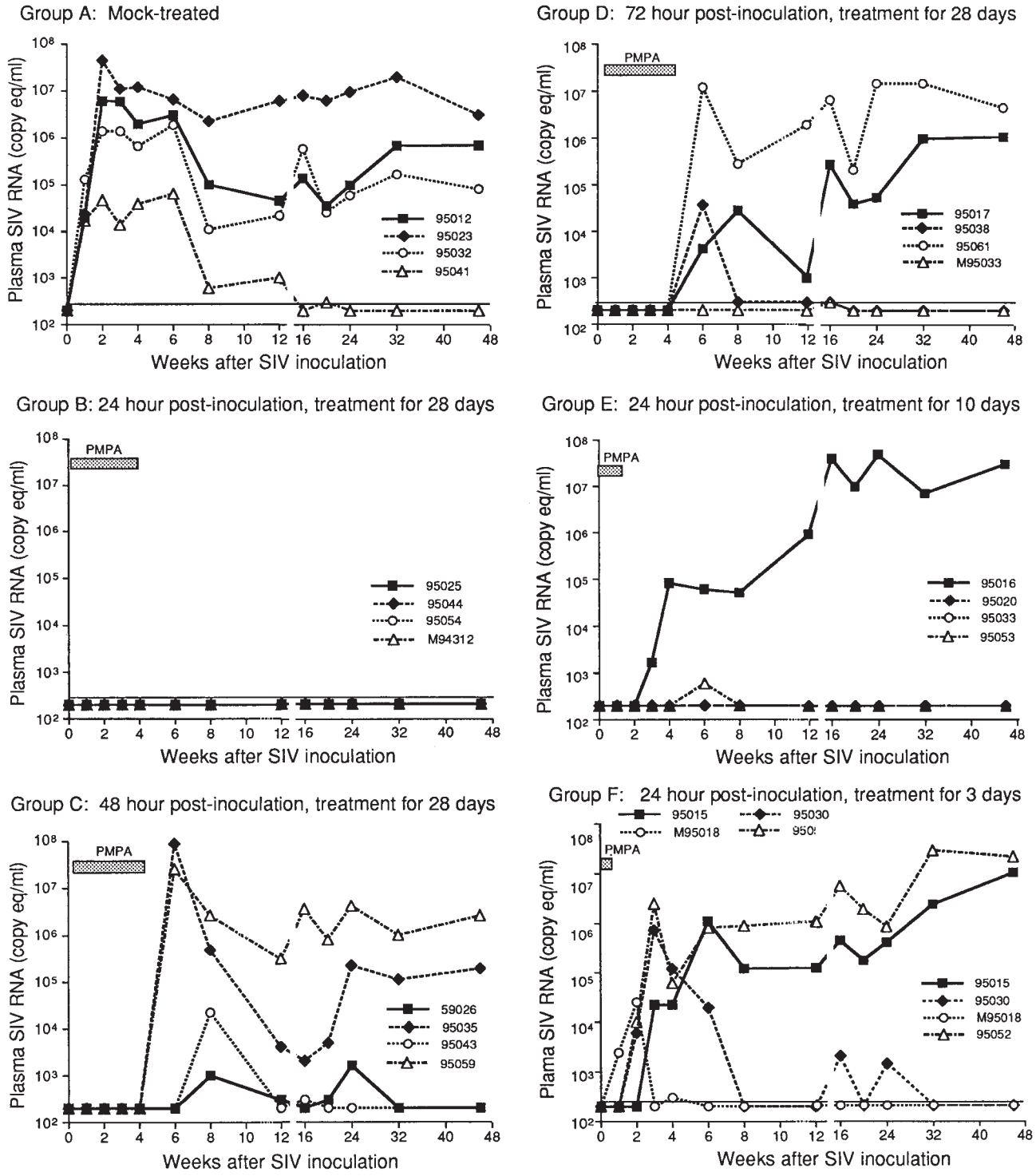

FIG. 1. Plasma viral load levels in mock-treated and PMPA-treated macaques after intravenous inoculation with uncloned SIV_{mne}. SIV RNA levels in plasma were measured by a sensitive quantitative competitive RT-PCR assay as described in the text. Threshold sensitivity for the assay was 300 copy eq/ml of plasma.

PBMC-associated virus isolation and showed only low titers (1:80) of antibody throughout the study. Macaque 95030 showed a persistent antibody response (antibody titer of 1:640 to 1:1,280) beginning 6 weeks p.i. and lasting to the end of the study. The two remaining macaques (95015 and 95052) had a persistent infection as determined by plasma SIV RNA beginning 2 to 3 weeks p.i. (10,000 to 22,000 copy eq/ml) and by PBMC-associated virus (1 to 10 infectious cells per 10^6 PBMC) beginning 4 weeks p.i.; the infection lasted through the end of the study. At 46 weeks p.i., the mean level of infection in these two macaques was 17,000,000 copy eq of SIV RNA/ml of plasma and 10 to 100 infectious cells per 10^6 PBMC. Both

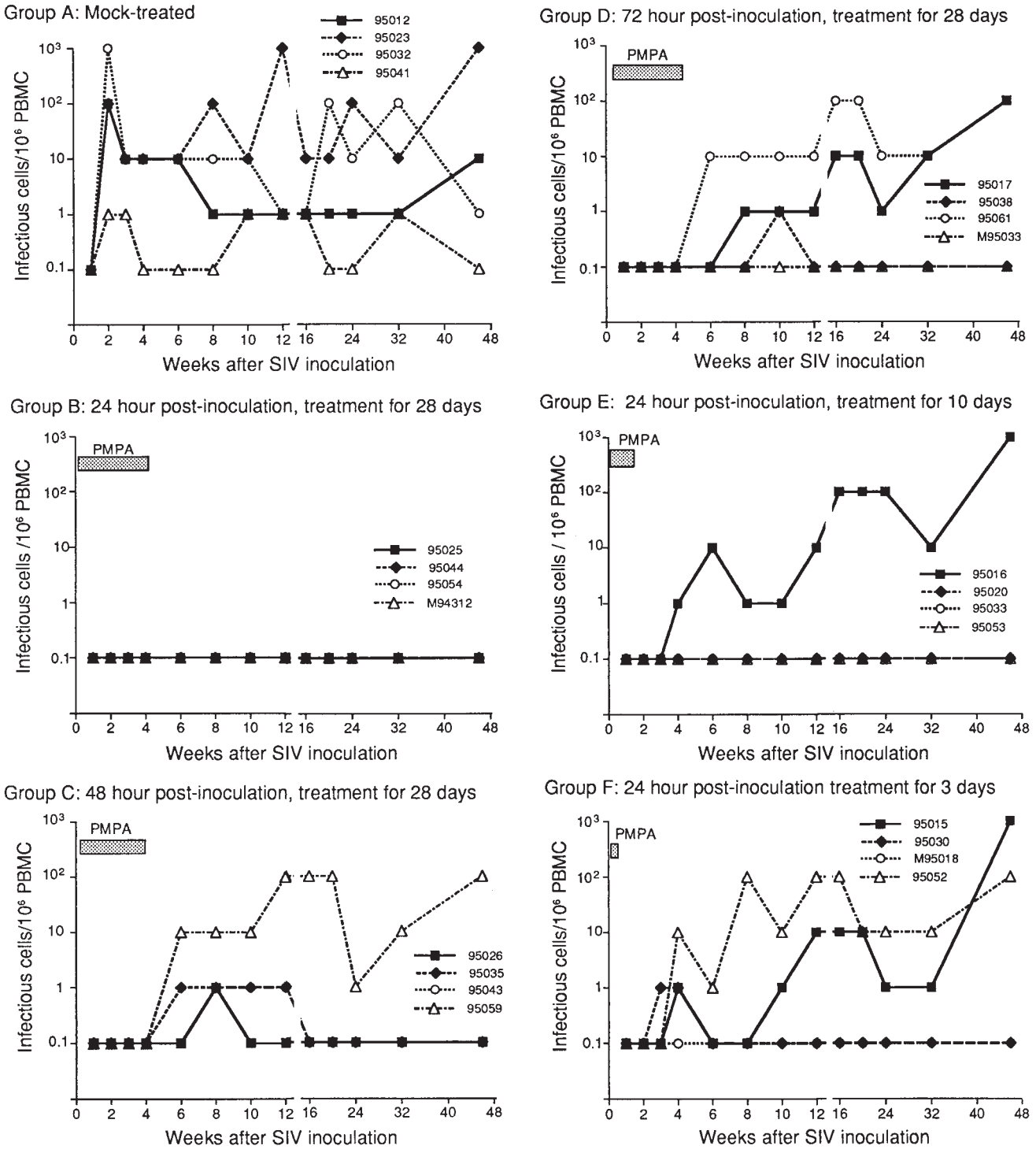

FIG. 2. Frequencies of infectious cells in PBMC from macaques. The frequency of infectious cells was measured by cocultivation of serial dilutions of PBMC with target cells for detection of viral replication as described in the text.

macaques also had persistent antibody responses beginning 4 to 8 weeks p.i. (antibody titer of 1:640) and lasting through the end of the study (antibody titer of 1:20,480 to 1:40,960 at 46 weeks p.i.).

Clinical status and drug toxicity. None of the PMPA-treated macaques showed signs of toxic side effects throughout the maximum duration of treatment (28 days); there were no abnormalities in complete blood counts, serum chemistry and biochemistry profiles, general physical condition, or neurobehavioral activities. However, 8 of the 16 PMPA-treated macaques (groups B to E) showed transient decreases of serum phosphorus during treatment (the first 4 weeks p.i.). Of these eight macaques, one (95035) had a severe decrease (1.1 to 2.5 mg/dl) and seven had a mild decrease (2.9 to 3.5 mg/dl) of

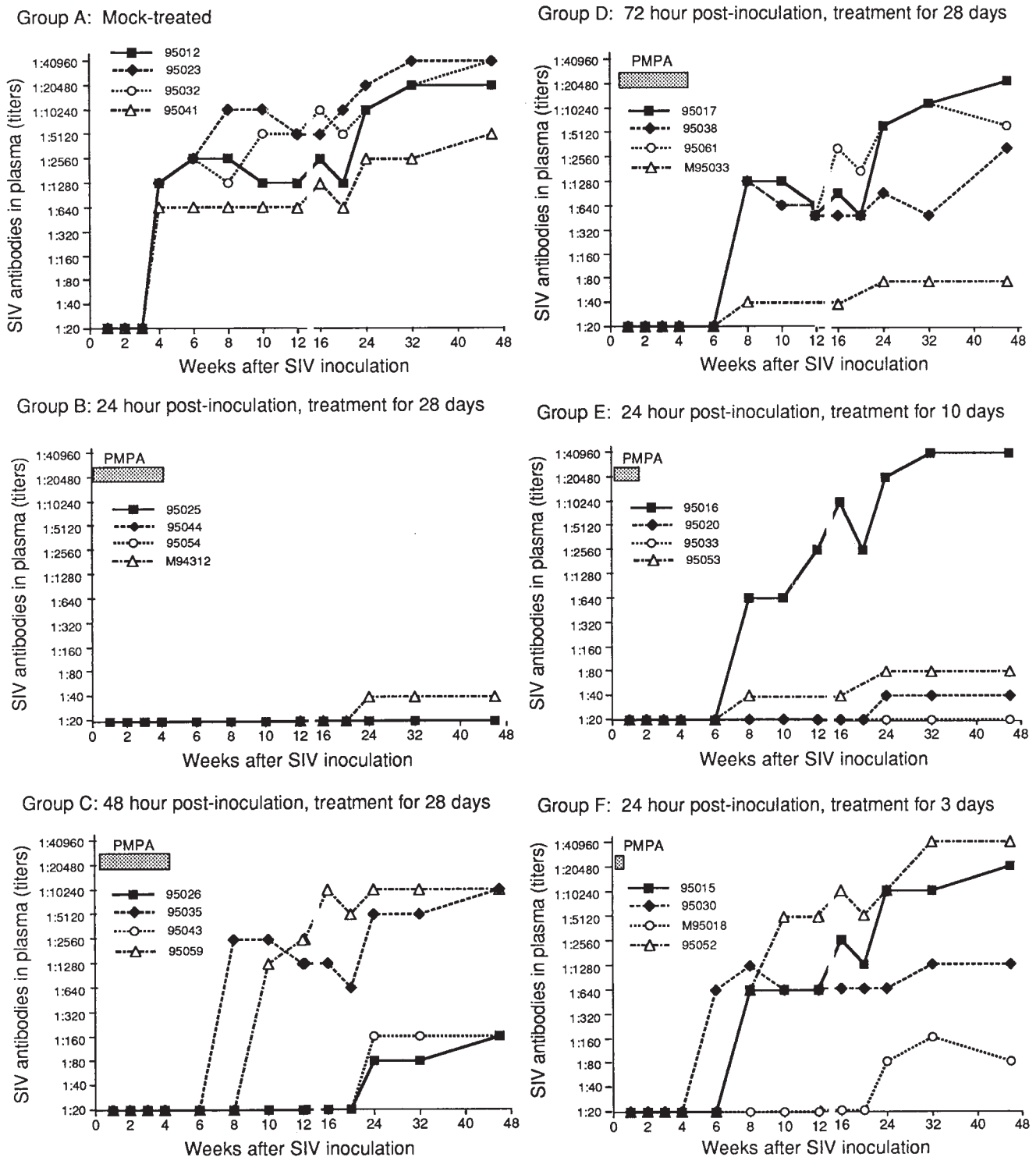

FIG. 3. Anti-SIV IgG antibody response in mock-treated and PMPA-treated macaques after intravenous inoculation with uncloned SIV_{mne}. Titers were expressed as the reciprocal of the highest dilution that yielded positive immunofluorescent staining. The lowest titer of SIV-positive antibody in this assay was 1:40.

serum phosphorus. In contrast, untreated controls (group A) and macaques treated with PMPA for only 3 days (group F) showed normal values of serum phosphorus ranging from 4.0 to 6.4 mg/dl (mean, 4.99 ± 0.49) and from 4.1 to 6.1 mg/dl (mean, 5.24 ± 0.23), respectively. All four mock-treated macaques showed a transient mild decrease in leukocyte counts at 2 weeks p.i., and three showed a moderate lymphadenopathy at 4 weeks p.i. Beginning 10 weeks p.i., mock-treated macaques with high viral load (i.e., based on levels of plasma SIV RNA and infectious cells per 10^6 PBMC) developed persistent lymphadenopathy and recurrent skin rashes.

Of the 20 PMPA-treated macaques, seven showed no clini-

cal signs of SIV infection and six showed only transient clinical evidence of infection. The remaining seven PMPA-treated macaques, which had persistently high viral loads, exhibited recurrent rashes and/or lymphadenopathy similar to those observed in the mock-treated macaques.

Two mock-treated macaques with high viral load had severe thrombocytopenia beginning 46 weeks p.i. Similarly, four PMPA-treated macaques with persistent viremia and high viral loads also developed moderate to severe thrombocytopenia beginning 46 weeks p.i.

Lymphocyte subsets. To determine whether the antiviral effect of PMPA treatment also improves responses of $CD4^+$ and $CD8^+$ lymphocytes in PBMC, the PMPA-treated macaques were grouped according to the level of viremia and then compared with mock-treated macaques. The mock-treated macaques ($n = 4$) showed a decrease in the mean $CD4^+$ cells from 2,300 ± 446 cells/mm^3 at virus inoculation to 1,585 ± 461 cells/mm^3 over the course of 20 weeks p.i. The PMPA-treated macaques that were virus negative ($n = 7$) and only transiently iremic ($n = 6$) showed slight increases in the mean $CD4^+$ cells, from 2,015 ± 693 cells/mm^3 at virus inoculation to 2,436 ± 310 cells/mm^3 by week 20 p.i. The PMPA-treated, persistently viremic macaques ($n = 7$) showed a slight decrease in the mean $CD4^+$ cells from 2,073 ± 497 cells/mm^3 before inoculation to 1,515 ± 186 cells/mm^3 by week 20 p.i.; this was similar to the level of the mock-treated macaques. There was no significant difference in the $CD4^+/CD8^+$ ratios between PMPA-treated macaques and mock-treated macaques before week 32 p.i. (data not shown). However, beginning at week 46 p.i., two of the four mock-treated macaques showed further decreases in $CD4^+$ cells (range, 572 to 583 cells/mm^3; mean, 578 ± 8 cells/mm^3) as well as $CD4^+/CD8^+$ ratios (range, 0.31 to 0.63; mean, 0.47 ± 0.23). Similarly, six of seven PMPA-treated, persistently viremic macaques showed further decreases in $CD4^+$ cells (range, 665 to 1,288 cells/mm^3; mean, 985 ± 266 cells/mm^3) as well as $CD4^+/CD8^+$ ratios (range, 0.33 to 0.76; mean, 0.45 ± 0.18). The remaining two mock-treated macaques, seven PMPA-protected macaques, and six PMPA-treated, transiently viremic macaques had normal or slightly increased levels of $CD4^+$ cells and CD4/CD8 ratios. Approximately 50% of both mock-treated controls and PMPA-treated macaques showed an intermediate to persistent increase in CD20 cell counts (or B cells).

Evaluation of efficacy. On the basis of virologic, immunologic, and clinical results, we confirmed our previous finding that PMPA at a dose of 30 mg/kg once daily by subcutaneous injection for 28 days is safe and well tolerated. PMPA treatment that was begun 24 h after viral inoculation and continued for 28 days completely prevented the establishment of persistent SIV_{mne} infection throughout the 46-week study. PMPA treatment for the same duration (28 days) but not begun until 48 or 72 h p.i. was less efficacious. Furthermore, reducing the duration of treatment from 28 days to 10 days diminished protection in one of the four macaques on this regimen, and limiting the duration to 3 days further reduced the efficacy of PMPA against acute SIV_{mne} infection. However, all the macaques that did become infected in the PMPA-treated groups showed delays in PBMC-associated virus, plasma viremia, and antibody responses compared with mock controls.

DISCUSSION

Previously, we showed that PMPA treatment at 30 mg/kg daily for 28 days completely prevented detectable acute SIV infection and establishment of persistent infection in macaques, even when therapy was started 24 h after intravenous virus inoculation (23). In the present study, we explored the temporal parameters of postinoculation PMPA treatment, with three major aims: (i) to understand the impact of increasing delays between inoculation and onset of treatment, as well as the impact of various durations of treatment on antiviral effectiveness; (ii) to identify the most effective regimen for postinoculation PMPA treatment in *M. fascicularis* inoculated intravenously with SIV_{mne}; and (iii) to gain insight into basic aspects of early SIV viral replication following intravenous inoculation.

Our results show that a 4-week regimen of PMPA completely protects macaques from acute SIV infection and establishment of persistent infection if treatment is initiated within 24 h p.i. but provides less protection if treatment is begun 48 or 72 h p.i. The highest efficacy achieved when treatment was begun 24 h p.i. indicated that the level of virus infection established within 24 h after intravenous inoculation was still low enough to be preventable by an effective (28-day) regimen of antiretroviral treatment, plus perhaps a contribution from immune responses. The antiretroviral effect of PMPA treatment most probably involved blocking the spread of virus from those $CD4^+$ cells already infected by the time treatment was initiated and then maintaining the blockade until this population of cells had decreased through death and clearance, thereby precluding reemergence of extensive viral replication after drug treatment was withdrawn. The failure of similar 28-day treatment regimens beginning 48 or 72 h p.i. implies that within 2 to 3 days of systemic exposure, the virus can establish a level or type of infection that does not decay sufficiently over a 28-day treatment period to preclude reemergence upon withdrawal of treatment. Overall, there seems to be a short temporal window during which postinoculation PMPA treatment can block establishment of persistent infection. After this time, PMPA treatment may dramatically decrease viral replication but cannot prevent or eradicate persistent infection (16, 28, 30).

The duration of postinoculation PMPA treatment also was critical in blocking the establishment of persistent SIV infection. Even when started within 24 h p.i., a 3-day course of PMPA treatment was largely ineffective and a 10-day course protected only half of the macaques tested, while a 28-day course was 100% effective. These results clearly establish that the mechanism of postinoculation PMPA treatment effects is not through the blockade of initial infection by the inoculating virus and provide insight into the size and life span of the infected cell population established in the period between inoculation and the initiation of treatment. The average clearance half life of the productively infected cells contributing the majority of virions to the plasma virus pool in SIV-infected macaques is estimated at less than 2 days (16), similar to values for human immunodeficiency virus (HIV)-infected humans (11, 17, 18, 32). Assuming that complete blockade by PMPA of new infections occurs, the pool of such cells will decay at this rate during the treatment period. In this model, the effectiveness of a given treatment regimen will thus depend on the size of the infected cell pool at the initiation of treatment and on whether the duration of treatment provides a sufficient number of clearance half-lives for the pool of infected cells to decay below the threshold required for reemergence of virus upon discontinuation of treatment. In this model, back-calculation for the number of treatment half-lives comprised by different treatment durations allows provisional estimation of the pool size of productively infected cells present at the initiation of treatment. This depends on assumptions about the pool size of residual productively infected cells required for reemergence of measurable plasma virus following discontinuation of treatment.

One additional factor contributing to differences in the reemergence of virus upon discontinuation of treatment in identically inoculated animals receiving identical PMPA treatment regimens likely involves differences in the size or nature of the infected cell pool present at the initiation of treatment (10, 13, 31). Marked differences in viral replication patterns were observed between identically inoculated mock-treated control animals, similar to other reports (10, 13, 31), with comparable or greater variability in the heterogeneity of viral replication patterns in identically inoculated, identically PMPA-treated animals, except for the uniform protection observed in those that received 28-day treatment beginning 24 h p.i. (group B).

Infection of longer-lived cells may also play a role in the results obtained. Thus, although the majority of virus in the plasma compartment is derived from productively infected cells with a clearance half-life of less than 2 days (16), decay characteristics of the plasma virus compartment with sustained antiretroviral treatment indicate the presence of additional compartments with decay half-lives on the order of approximately 14 to 40 days (14, 17, 18). This compartment may reflect contributions both from virus produced by longer-lived cells such as macrophage lineage cells and from the activation of viral replication from latently infected cells. Recent studies indicate that this latently infected cell compartment can persist for prolonged periods, even in the face of continuous effective antiretroviral treatment that suppresses viral replication to below detectable levels (8, 9, 33). However, the time when this compartment is first established has not been determined. This factor, which is critical for understanding retroviral pathogenesis and designing effective treatment for HIV infection, may also help determine the effectiveness of different postinoculation treatment regimens. Given the prolonged lifetime of these cells, short-term antiretroviral treatment is unlikely to prevent establishment of persistent infection if initiated after the establishment of such a latently infected cell compartment. Identification of the time interval during which this compartment is first established, and evaluation of its contribution to the type of results that we observed, will be important objectives for future studies.

In this study, we also investigated the time kinetics of viral infection, including antibody responses, in macaques that became infected in the face of incompletely protective PMPA treatment. In saline-treated macaques, evidence of productive viral infection developed within 1 to 2 weeks p.i. No such evidence was observed in macaques that received 4 weeks of PMPA treatment starting 24 h p.i. For macaques that achieved incomplete protection, the main effect of PMPA treatment was to delay the onset of viral infection and antibody response until 1 to 3 weeks after PMPA treatment ended. PMPA likely delayed the spread of infection by preventing de novo infection from cells already infected at the initiation of treatment to new uninfected targets. Stopping PMPA treatment before the end of 4 weeks of treatment presumably resulted in the resumption of virus spread from infected cells whose life span exceeded our treatment period, such as latently infected cells with proviral DNA or perhaps infected cells sequestered in sites that are functionally inaccessible to PMPA treatment. However, these PMPA-treated, SIV-infected macaques had markedly different patterns of viral replication, as reflected by plasma SIV RNA measurements, than did mock-treated controls, including 50% of macaques in which plasma SIV RNA was detectable only transiently following the withdrawal of PMPA. These macaques also showed lower antibody responses, consistent with lower levels of viral replication, than did macaques with persistent infection. In these cases, PMPA treatment may have suppressed early virus replication sufficiently to allow development of immune responses capable of holding viral replication comparatively in check upon withdrawal of treatment. The present study did not include a rechallenge with infectious virus of those macaques manifesting only apparently transient infection, to determine whether such transient viral replication was associated with induction of protective immune responses. However, it is intriguing to speculate that such protection, if it occurs, may be similar to the apparent increased resistance to HIV infection and demonstrable immune responses to HIV, seen in some seronegative subjects with repeated exposures, consistent with prior abortive or transient infection (19–21).

There is a need for a regimen of antiretroviral treatment that completely inhibits de novo viral infection and eliminates the long-lived infected cells in HIV type 1 (HIV-1)-infected patients (6, 8, 9, 18). Such a regimen would be clinically beneficial and could prevent the development of drug-resistant viruses. Current regimens can prevent viral replication, but the long-lived infected cells remain a formidable challenge. In this study we found that a 4-week regimen of PMPA treatment beginning 24 h after virus exposure seems to be effective against acute SIV in macaques presumably because it suppresses viral spread during the period usually associated with the initial burst of acute viral replication, allowing decay of the infected cell pool already established by the time treatment is initiated. Unlike PMPA, AZT given postexposure is incompletely effective against acute SIV infection in macaques (15, 24, 29). The greater efficacy of PMPA compared with AZT may be related to the rapid intracellular formation and long half-life of PMPA's active metabolites in macaques (9a).

The course of acute SIV infection in macaques as well as primary HIV-1 infection in humans suggests that the first week after virus exposure is a critical time during which antiviral therapy can be most effective. Unfortunately, it is not always possible to know when exposure has occurred among the general population. Among the infant population, however, it can be assumed that neonates born to HIV-infected mothers have been exposed to the virus. Epidemiological studies suggest that about 65 to 70% of infants with congenital HIV-1 infection became infected shortly before or during delivery (5, 7, 12). Beginning PMPA treatment regimen within 24 h after birth could have a significant role in reducing the risk of maternal transmission of HIV-1 infection to these infants.

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EXHIBIT 17

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Efficacy of Postexposure Prophylaxis after Intravaginal Exposure of Pig-Tailed Macaques to a Human-Derived Retrovirus (Human Immunodeficiency Virus Type 2)

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Postexposure prophylaxis (PEP) after intravaginal exposure to human immunodeficiency virus (HIV) was investigated using the HIV type 2 (HIV-2)/pig-tailed macaque transmission model. PEP for 28 days with the reverse transcriptase inhibitor (*R*)-9-(2-phosphonylmethoxypropyl)adenine (PMPA; tenofovir) was initiated 12 to 72 h following HIV-2 exposure. Systemic infection was not evident in the 12- and 36-h groups, as defined by plasma viremia, cell-associated provirus, antibody responses, and lymph node virus. Breakthrough infection in the 72-h group was detected at week 16 post-virus exposure. These results demonstrate for the first time using a vaginal transmission model that early intervention after high-risk sexual exposures may prevent infection.

Reducing exposure to human immunodeficiency virus (HIV) through behavior modification remains the primary and most accepted method for preventing infection. Administering postexposure prophylaxis (PEP) with antiretrovirals following a high-risk sexual exposure to HIV remains controversial (5). Human studies addressing PEP efficacy for sexual exposure remain difficult to implement because of the required sample size for meaningful evaluation as well as ethical considerations regarding placebo control (7, 10). Therefore, only minimal anecdotal clinical evidence of PEP efficacy currently exists.

To date, systematic PEP investigations involving nonhuman primate models have shown promise for preventing infection under certain conditions (1). However, most studies have utilized intravenous (i.v.) exposures with simian retroviruses and, like for studies of human needlestick exposures (3, 4), the validity of extrapolating results to sexual exposures remains unclear. There are important variables related to viral dissemination patterns after a vaginal exposure and the effective window for prophylaxis initiation that may impact PEP efficacy. This investigation represents the first efforts to address the potential efficacy of early antiretroviral prophylaxis following HIV exposure mimicking heterosexual contact, the major mode for worldwide transmission (12).

In this study, 16 naïve female pig-tailed macaques, ages 3 to 5 years and weighing 5.5 to 8.5 kg (Charles Rivers Laboratories, San Antonio, Tex.), were used in accordance with the recommendations of the Centers for Disease Control and Prevention Animal Care and Use Committee. An inoculum of HIV type 2 (HIV-2) strain GB122 (previously shown to infect pig-tailed macaques [18, 19]) was generated by limited propagation of the original AIDS patient isolate onto a mixture of phytohemagglutinin-(p)-activated peripheral blood mononuclear cells (PBMC) from four source macaques. The titer of this challenge stock was determined by standard techniques (8, 9) and consisted of approximately 10^4 tissue culture infectious doses per ml or at least 10^2 pig-tailed macaque i.v. infectious doses. All virus exposures involved atraumatic inoculation of cell-free virus into the vaginal pouch via a sterile gastric feeding tube. Anesthetized macaques remained recumbent and were intravaginally inoculated three times over 2 h, with each exposure and absorption period separated by ~1 h.

Longitudinal blood specimens were collected and processed as described previously (19). Cervicovaginal lavage (CVL) specimens were obtained by instilling 4 ml of sterile phosphate-buffered saline directed at the cervical os. Cervicovaginal cells were separated from CVL supernatants by mild centrifugation (15 min at 400 × *g*) and whole inguinal lymph node (ILN) biopsy specimens were harvested during the course of study. Routine cell sieving procedures (Cellector tissue sieve; E-C Apparatus, St. Petersburg, Fla.) were used to generate ILN total cell suspensions. Half of each ILN suspension was used to derive a direct cellular lysate for duplicate DNA PCR analysis, while remaining cells were either cocultured for virus isolation or cryopreserved.

Nested DNA PCR was used to detect HIV-2 provirus in PBMC or ILN cells as described previously (19). Virus isolations from ~10^7 viable purified PBMC or whole cells recovered from ILN biopsy specimens were attempted using the PM-1 T-cell line ($CD4^+$ $X4^+$ $R5^+$) by standard coculturing techniques (8, 18, 19). Culture supernatants were monitored for core antigen levels through at least 4 weeks. Detection of virus-specific antibody was achieved as described previously (18, 19). Virion-associated HIV-2 RNA (vRNA) was quantitatively measured in plasma or cell-free CVL supernatants by a reverse transcriptase-mediated PCR (RT-PCR) prototype assay system similar in design to that detailed by Mulder et al. (16) and more recently described by Nkengasong et al. (17). Assay sensitivity was determined to be ~100 copies per ml.

All macaques in this study received three doses (3 ml each) of the HIV-2_{GB122} stock by the intravaginal route during a 2-h period (total inoculum, ~10^5 tissue culture infectious doses), thus producing a high infection rate (75%) in control ma-

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TABLE 1. HIV-2-specific provirus detection in PBMC and serologic status

Study group and macaque	Detection[a]/status[b] at wk post-virus exposure									
	0	1	2	3	4	8	12	16	20	24
Untreated controls										
53-422	−/−	−/−	+/−	+/+	+/+	+/+	+/+	+/+	+/+	+/+
53-443	−/−	−/−	+/−	+/+	+/+	+/+	+/+	+/+	+/+	+/+
83-306	−/−	−/−	+/−	+/−	+/+	+/+	+/+	+/+	+/+	+/+
83-310	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−
12-h PEP										
83-268	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
83-283	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
83-308	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
83-297[d]	−/−	−/−	−/−	−/−	−[c]/−	NT	NT	NT	NT	NT
36-h PEP										
52-121	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
83-267	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
83-269	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
83-273	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
72-h PEP										
72-34	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
83-285	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	−/−	−/−	−/−
83-305	−/−	−/−	−/−	−/−	−[c]/−	−/−	−/−	+/+	+/+	+/+
83-303[d]	−/−	−/−	−/−	NT	NT	NT	NT	NT	NT	NT

[a] +, nested DNA-PCR amplification and detection of HIV-2 protease gene sequences; −, no HIV-2-specific signal was detected; NT, not tested.
[b] +, confirmed HIV-2-specific seroconversion; −, lack of seroresponse; NT, not tested.
[c] DNA PCRs and virus isolation results were also negative for ILN biopsy specimens.
[d] Longer-term follow-up was not possible due to unanticipated death.

caques not receiving PEP (Table 1; Fig. 1). In these animals, rising plasma vRNA levels were observed, with peak viral loads occurring at week 2 or 3 postinoculation (p.i.). Quantifiable levels of vRNA were also observed in cell-free supernatants derived from CVL specimens collected longitudinally from all infected macaques and, in most cases, were the earliest signs of infection. All infected control animals showed a typical acute phase of HIV-2 infection for this species, characterized by early peaks of plasma viremia, early establishment of chronic provirus in PBMC, the ability to readily isolate virus from PBMC (data not shown), and a classic antibody response beginning at 3 or 4 weeks p.i. In most cases, plasma virus became undetectable by week 12 to 16 p.i. Interestingly, macaque 83-310 (classified as exposed, uninfected) had detectable vRNA in CVL specimens only at weeks 1 and 3 p.i. (Fig. 1), with no other indication of productive infection.

Groups of HIV-2-exposed macaques ($n = 4$ each) were subsequently treated with (*R*)-9-(2-phosphonylmethoxypropyl)adenine (PMPA) (tenofovir; Gilead Sciences, Foster City, Calif.) by subcutaneous injection of 30 mg/kg of body weight daily for 28 days, starting 12, 36, or 72 h after the last viral inoculation. None of the four macaques in the 12-h group showed any indication of systemic infection (Fig. 2A). While plasma viremia was not observed, vRNA was observed in early CVL specimens (weeks 1 and 2) from a single macaque in this group. HIV-2 provirus was not detected in PBMC, attempts of virus isolation from PBMC were not

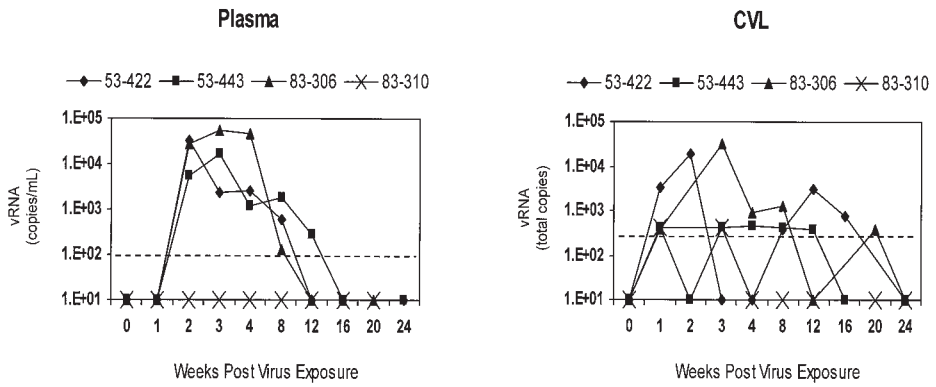

FIG. 1. HIV-2 load in plasma and CVL specimens through 24 weeks after intravaginal virus exposure in untreated control macaques ($n = 4$). Plasma vRNA levels are reported as $\log_{10}$ copies per milliliter and virus levels in CVL supernatants are indicated as $\log_{10}$ total copies per lavage specimen. The sensitivity limits are 100 copies/ml for plasma and 400 total copies for CVL supernatants with a 50-μl sample equivalent input into the assay system (dashed line).

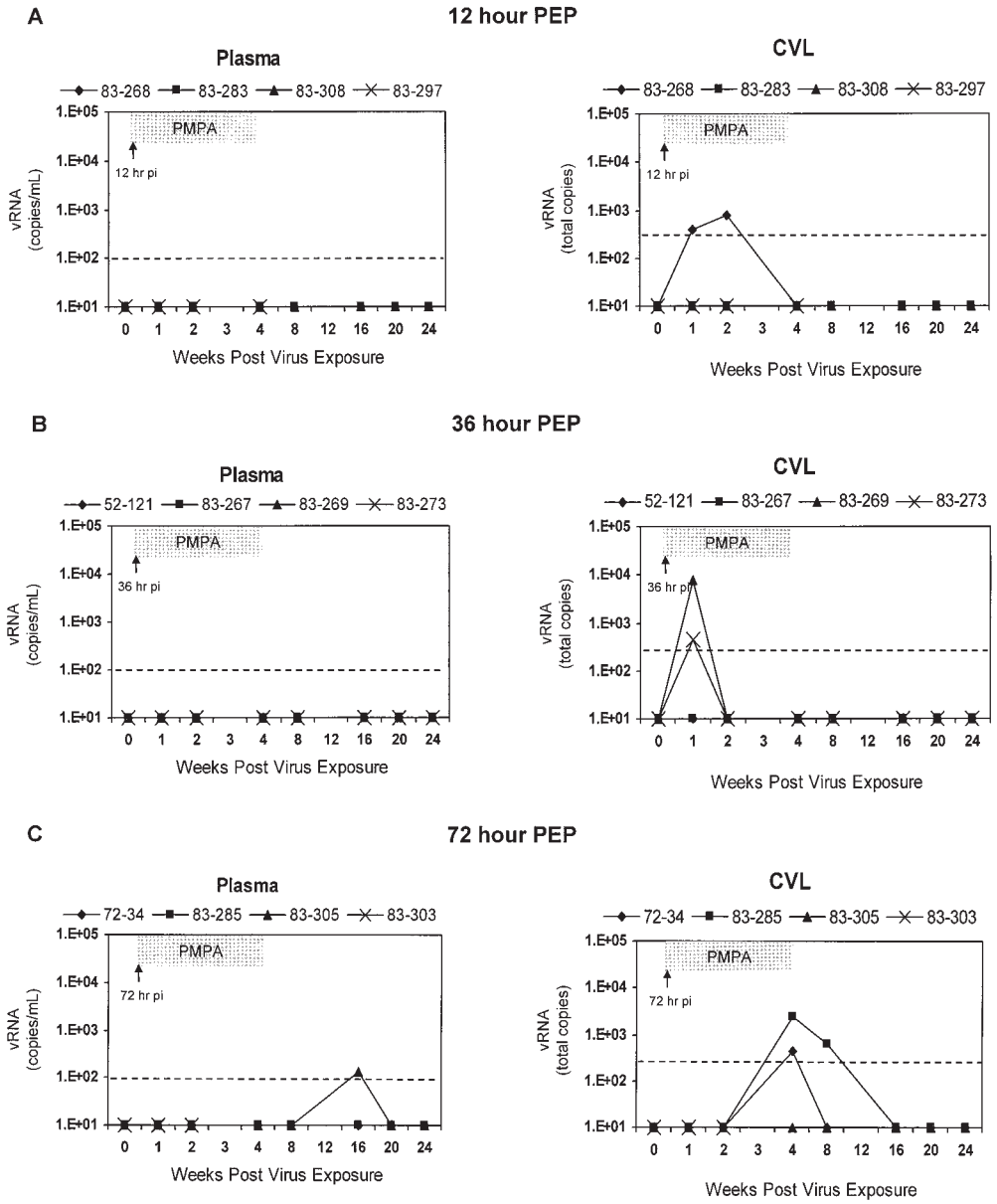

FIG. 2. Longitudinal HIV-2 vRNA levels in plasma versus CVL supernatants after intravaginal virus exposure in experimental macaque groups (n = 4 each) receiving PEP with PMPA at the indicated times. Results are reported as in Fig. 1.

successful (data not shown), and virus-specific antibody responses remained negative for each macaque in the 12-h group (Table 1). Also, ILN tissues harvested from each macaque on the final day (day 28) of PMPA treatment were virus negative, as assessed by nested PCR for provirus and virus isolation. One macaque (83-297) in the 12-h group was found dead at week 5 p.i. as a result of circumstances unrelated to any experimental procedure. Postmortem tissues were PCR negative for proviral DNA (not shown).

Similarly, those macaques (n = 4) receiving PEP at 36 h post-virus exposure were also protected from systemic infection and remained negative by virologic and serologic parameters through 24 weeks p.i. (Table 1; Fig. 2B). Furthermore, ILN specimens collected from all four macaques in the 36-h group were provirus and virus isolation negative. In this group, transient vRNA signals were also observed in early CVL specimens collected from two animals.

Macaques (n = 4) receiving PMPA treatment at 72 h post-exposure also showed a lack of systemic infection through the first 12 weeks p.i. by all parameters (Fig. 2C). Once again, vRNA in some CVL specimens was detectable; however, these signals were seen later than in the other treatment groups. One macaque had a low-level signal at week 4 p.i., while another had higher vRNA titers detectable at weeks 4 and 8 p.i. One macaque in the 72-h group (83-303) died at week 2 p.i. from unrelated causes. One confirmed seroconversion in the 72-h group was observed at week 16 p.i., indicating delayed, systemic infection and PEP failure (Table 1). A low level of plasma viremia was detected and circulating PBMC were provirus positive, although vRNA was not observed in CVL spec-

imens. The other two macaques in the 72-h group remained uninfected by all systemic parameters through 6 months postvirus exposure. Further follow-up data, up to 1 year after virus exposure for all macaques receiving PEP, remained identical to those results shown for week 24.

The novel aspects of this experimental design involve (i) the use of intravaginal exposure, (ii) the evaluation of a timing strategy for prophylaxis which would be realistic following a potential high-risk human heterosexual contact, (iii) the use of a human-derived-retrovirus (HIV-2) vaginal transmission model, and (iv) direct assessment of CVL supernatant virus levels. The results demonstrated that early intervention with a potent antiretroviral regimen in response to a vaginal retrovirus exposure significantly reduced the establishment of systemic infection in macaques treated 36 h or sooner after exposure (zero of eight infected) compared with untreated controls (three of four infected; $P = 0.018$ by Fisher's exact test). However, the regimen did not protect all macaques in which PMPA treatment was initiated 72 h after virus exposure, a finding consistent with previous animal data derived using i.v. exposures to simian immunodeficiency virus (SIV) (1).

Elegant macaque studies (13, 14) have linked the efficiency of vaginal transmission to the extent with which a virus strain replicates in vivo after i.v. inoculation. It still remains unclear as to how much linkage, if any, exists between viral virulence and mucosal transmission efficiencies (20). The intravaginal transmission method detailed in this study served to model high-risk vaginal exposures resulting in an extremely high infection rate (75%) compared with that suggested by human data (0.1 to 0.2% risk per receptive vaginal episode) (11).

The most dramatic protection reported in macaque PEP studies has followed the use of the nucleotide analog RT inhibitor PMPA (23–27). Initiation of PMPA treatment no later than 24 h after i.v. SIV challenge, with continued prophylaxis for 28 days, was the most effective regimen in those studies. Delaying prophylaxis initiation (48 or 72 h postexposure) or shortening treatment to 10 or 3 days reduced PMPA efficacy (23). Different exposure routes and a possible requirement for localized replication prior to systemic dissemination most likely contributed to the differences between the findings of these previous studies and those of our investigation. PMPA treatment following oral SIV exposure in newborns has also been reported (26); however, treatment that was started up to 5 days after inoculation led to alterations in rapid disease course outcomes rather than preventing systemic infection. Furthermore, the optimal effective duration for PEP remains unknown and has not been fully explored (3, 6), even in animal studies. Böttiger et al. (2) demonstrated a dramatic protective effect (12 of 12 macaques) with only a 3-day regimen using another RT inhibitor (BEA-005) when administered 1 to 8 h following i.v. inoculation with SIV.

The lack of evidence for systemic infection until 16 weeks p.i. for the breakthrough animal, even in ILN specimens on the final day of PMPA therapy, is intriguing and perhaps indicates the presence of an early low-level infection, possibly localized to the site of exposure. The observation of this delayed infection in our model (~3 months later than in untreated controls) and recent human evidence (21) further support the need for adequate follow-up periods after PEP administration to monitor for delayed seroconversions.

Evaluation of CVL supernatant virus levels in this study was highly informative and provided some suggestive evidence for possible localized virus production. The detectable cervicovaginal virus signals noted in some macaques during treatment may be a consequence of PMPA's inability to suppress all virus activity localized to the exposure site. Indeed, successful PEP prevention of a systemic infection may occur at the level of virus dissemination events.

The important issue of localized virus replication at a mucosal exposure site in the absence of an overt systemic infection has also been raised by intriguing investigations into transient infections of drug-naïve macaques resulting from both intrarectal and intravaginal SIV transmissions (15, 22). Although virus detection in genital mucosal compartments was not included, the investigations' results indicated a potential for inducing a transient infection state within a virus-exposed macaque. This phenonemon seems unlikely in our study due to the consistent lack of systemic virus detection up to a full year after virus exposure in those animals protected by PEP; however, tissue reservoirs harboring low levels of virus cannot be ruled out by our present findings.

In summary, our findings indicate that early intervention with a potent antiretroviral regimen may be successful in preventing infection via vaginal exposure to a human-derived retrovirus. The data provide additional insight into the critical timing related to PEP initiation for maximum effectiveness and have generated a proof of concept for the use of antiretroviral agents following a high-risk heterosexual exposure to HIV in humans.

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EXHIBIT 18

Preexposure Prophylaxis for HIV
Unproven Promise and Potential Pitfalls

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An estimated 11 000 new human immunodeficiency virus (HIV) infections occur worldwide per day and approximately 4 million individuals are infected with HIV per year.[1] Although behavior change has likely led to substantial reductions in HIV incidence in some populations and risk-reduction counseling will likely remain the cornerstone of HIV prevention programs, new HIV prevention strategies are urgently needed to further reduce incident infections. Preexposure chemoprophylaxis (PrEP) has emerged as a promising new biomedical strategy for preventing HIV infection,[2] and clinical trials are planned or under way[3] to evaluate the safety and efficacy of this approach. Because many antiretroviral drugs are licensed in the United States, PrEP could become available for use as a prevention tool more quickly than other experimental prevention strategies, such as an HIV vaccine.

Recent interest in PrEP as a prevention strategy has been based in part on encouraging preclinical data on combination PrEP[4] and also on an announcement from the Centers for Disease Control and Prevention (CDC)[5,6] about a switch in antiretroviral agent for the PrEP trial in Botswana from single agent tenofovir to combination emtricitabine/tenofovir (FTC/TDF). This attention[5] appears to have created increased interest in PrEP, as well as potential confusion in community laypersons and clinicians about how PrEP is different from postexposure prophylaxis (PEP) and which antiretroviral medications are being evaluated in the current PrEP trials. Meanwhile, there have been anecdotal reports of off-label and unapproved PrEP use occurring in the community outside clinical trials. The current interest in PrEP could result in increased use of this strategy despite the lack of proven safety and efficacy for preventing HIV infection.

This commentary will provide background on and context for the recent developments in the PrEP field by clarifying the concept of PrEP by distinguishing PEP from PrEP, providing an update on the current PrEP clinical trials and implications of recent changes in the trials, discussing anecdotal reports of off-label PrEP use and potential individual and community harms associated with this practice, and providing recommendations to clinicians for discussing PrEP with their patients.

PEP vs PrEP

Unlike PEP, which is a 28-day course of antiretroviral therapy taken shortly after a high-risk exposure, PrEP refers to HIV-negative individuals taking a daily dose of antiretroviral therapy started before HIV exposure and continuing throughout periods of risk. PrEP has several theoretical advantages over PEP as a prevention tool. Although both PEP and PrEP have prevented simian immunodeficiency virus acquisition in nonhuman primate models,[7-10] data from animal studies suggest that higher levels of protection may be achieved when antiretroviral medications are given before exposure (PrEP) rather than after exposure (PEP). In addition, PEP may be challenging to implement effectively in humans because of the difficulty individuals have in accurately self-identifying high-risk exposures[11] and the numerous operational challenges in providing PEP to patients as soon as possible after high-risk exposure.[12]

In contrast to PEP, PrEP dosing is unlinked to sexual practice, does not require individuals to identify high-risk exposures, and does not need to be initiated within a critical period after exposure. Because many seroconverting individuals have multiple risk episodes during periods of risk,[13] PrEP taken continuously may be a more successful strategy than PEP in reducing infection rates globally, if proven both safe and effective.

PrEP Clinical Trials

Several clinical trials are under way to evaluate daily oral tenofovir disoproxil fumarate (TDF) as PrEP in various HIV-negative populations. These first-generation PrEP studies are randomized, double-blind, placebo-controlled trials designed to evaluate the safety and efficacy of PrEP in high-risk heterosexual men and women in Botswana and injection drug users in Thailand and the biological and behavioral safety of PrEP in men who have sex with men in the United States (San Francisco and Atlanta).[3] One of the authors (R.M.G.) is the principal investigator of a planned National Institutes of Health–funded efficacy trial of PrEP involving men who have sex with men in Peru.[3] These studies will also collect data on antiretroviral resistance in seroconverting individuals, adherence patterns, and whether taking PrEP affects risk behavior. Although data from these

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trials will not be available for the next few years, preliminary data may be reported later this year from a recently completed PrEP trial in 400 high-risk women in Africa.[3] Waiting for results from the full complement of PrEP trials before recommending its use is important because this single study will not provide definitive efficacy data. Also, extrapolating from one population to another will be difficult because patterns of PrEP use, tolerability, and toxicity; route and patterns of HIV exposure; and drug levels in target tissues may be different across different risk groups.

Questions have been raised about the need for combination PrEP, arising in part from recently presented data[4] involving an evaluation of a daily combination of FTC/TDF in macaques. Although promising, these data do not provide direct comparisons of the safety, tolerability, or efficacy of single vs combination therapy. More important, data from small numbers of animals in an artificial challenge system cannot be used to predict human experience with chemoprophylaxis. In response to emerging information, the recently initiated Botswana study and the planned Peru study will involve evaluation of the FTC/TDF combination, whereas the US and Thailand studies, which are further along in enrollment, will continue with TDF alone. This complement of clinical trials will provide an evaluation of the safety and efficacy of both regimens and may help determine the optimal number of drugs needed for PrEP. Similar to the strategy for tuberculosis, the number of drugs needed for HIV chemoprophylaxis may be less than that needed for effective treatment.

Off-label and Unapproved PrEP Use

It has been suggested that PrEP use may be occurring outside clinical trials.[14,15] These reports describe physicians prescribing off-label PrEP to selected high-risk HIV-negative patients and describe use of tenofovir at circuit parties, sex clubs, or bathhouses in combination with "club drugs" such as ecstasy and sildenafil.[14,15] Studies are needed to rigorously evaluate the prevalence of community PrEP use and to monitor patterns and trends in use.

As investigators of the TDF PrEP trial in San Francisco, which began enrollment in February 2005 and is under way, we are concerned about possible off-label or unmonitored PrEP use in the community. The currently available information is not sufficient to recommend PrEP use. Physicians should become familiar with the objectives and limitations of the current PrEP trials and be prepared to discuss with patients the risks of unmonitored use of this unproven practice.

The use of PrEP could result in an increase in the frequency or types of risk behavior in individuals who believe that PrEP is protecting them, despite the lack of efficacy data. In PrEP clinical trials, study participants receive proven prevention interventions, including condoms and risk-reduction counseling, and are told that PrEP's efficacy is unknown. Trial participants also do not know whether they are receiving placebo (which has no protective benefit) or TDF (which has no known protective benefit). If PrEP use is unblinded and unlinked to other prevention strategies in clinical practice, PrEP may be used as a justification for increasing the frequency or types of risk-taking behaviors, which could result in higher rates of sexually transmitted infections and fuel HIV transmission. Findings from the current generation of research are essential for determining how best to counsel PrEP users about risks and benefits. Additional research designed to optimize risk-reduction counseling for PrEP users will be needed if safety and efficacy are demonstrated.

PrEP use could also lead to antiretroviral resistance on the individual and community level, especially if antiretroviral agents are continued after infection occurs. This may be a particular problem if PrEP is taken episodically or even as a single-dose "evening before" or "morning after" pill, resulting in suboptimal plasma and intracellular concentrations. Rapid emergence of drug-resistant simian immunodeficiency virus with the K65R mutation has been documented in macaques with high viral loads early after treatment with tenofovir monotherapy.[16] In addition, drug resistance has occurred when PEP was given to an individual who had a detectable viral load at baseline.[17]

Although the frequency and patterns of resistance in the setting of PrEP failure are unknown and will be evaluated in current PrEP trials, infection with acquired or transmitted virus harboring the K65R or M184V mutations could limit treatment options. In these situations, treatment may require use of drugs with greater potential for toxicity or more difficult dosing schedules. For example, the use of the soon-to-be-approved single-pill regimen containing TDF, FTC, and efavirenz would not be appropriate for patients with these mutations. To minimize the risk of drug resistance in PrEP clinical trials, HIV testing is performed frequently to minimize the risk that PrEP therapy will be started for individuals who are already infected and to help ensure that PrEP therapy is promptly stopped for those who may become infected. Such frequent monitoring for HIV infection is not typically available in current clinical practice.

In addition, unmonitored antiretroviral use could result in serious adverse events for HIV-negative individuals. Although uncommon, nephrotoxicity has occurred with use of TDF when combined with other antiretroviral medications in some HIV-infected patients, and renal function should be closely monitored with use.[18-20] Although also potentially uncommon when used only sporadically, small losses in bone mineral density have also been observed during TDF therapy in individuals with HIV infection, although early bone loss may stabilize and no associated fractures have been reported.[21] Further, TDF and FTC are active against hepatitis B virus,[22,23] and hepatitis B flares have occurred after drug use is discontinued.[24,25] Individuals who begin or stop taking these drugs should have liver function and hepatitis B status monitored. In addition, little is known about potential interaction between antiretroviral drugs and recreational drugs, if taken simultaneously. Drugs acquired from nonprescription sources may also harm individuals taking the drugs because quality control cannot be ensured if drugs

are purchased illicitly. Furthermore, if drugs are obtained through drug sharing from HIV-positive individuals, this practice may result in suboptimal dosing and possible regimen failure in HIV-positive individuals. Many of these important safety issues in HIV-negative individuals will be evaluated in current clinical trials.

Conclusions

PrEP is an unproven but promising new HIV prevention strategy that is being evaluated in clinical trials. Off-label PrEP use may be occurring and could lead to individual and community harm. Treatment and research communities can work together to mitigate these potentially harmful effects of unmonitored PrEP use. First, physicians and other health professionals should be aware that PrEP use is not recommended, because insufficient information on safety and efficacy of this strategy is available. The CDC has issued recommendations for nonoccupational PEP to be used in certain situations, and clinicians should provide patient education about the availability of PEP after high-risk exposures.[26] In engaging patients in discussions about PrEP, the importance of using standard prevention strategies for HIV infection should be emphasized, and appropriate linkages to prevention services should be provided. Clinicians, health departments, and community-based organizations can develop educational campaigns to inform community members about the current status of clinical trials and potential harms associated with PrEP use. Community forums have been held in several US cities, including one organized by the Community HIV/AIDS Mobilization Project.[27]

PrEP clinical trials should proceed quickly to provide the evidence required for informed counseling about PrEP. While the results of these trials are eagerly awaited, optimism for the future should not replace currently available and proven prevention strategies.

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EXHIBIT 19

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Effectiveness of Prevention Strategies to Reduce the Risk of Acquiring or Transmitting HIV

There are now more options than ever before to reduce the risk of acquiring or transmitting HIV. Using medicines to treat HIV, using medicines to prevent HIV, using condoms, having only low-risk sex, only having partners with the same HIV status, and not having sex can all effectively reduce risk. Some options are more effective than others. Combining prevention strategies may be even more effective. But in order for any option to work, it must be used correctly and consistently.

The following tables provide the **best estimates** of effectiveness for various strategies to prevent HIV acquisition or transmission. Each estimate was identified from the published scientific literature and represents the effectiveness of each strategy **when used optimally**. Available measures of optimal use vary by strategy. The principles for prioritizing measures and findings that were most relevant can be found here. A description of each prevention strategy, corresponding effectiveness estimate, and a summary of the evidence is provided below.

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Antiretroviral Therapy (ART) for HIV-Positive Persons to Prevent Sexual Transmission

Population	Effectiveness Estimate	Source	Interpretation
"Optimal Use" (Taking ART daily as prescribed and achieving and maintaining viral suppression)			

Population	Effectiveness Estimate	Source	Interpretation
Heterosexual Men and Women	100%	Cohen, 2016 Rodger, 2016	For HIV-positive heterosexual men and women, taking ART regularly greatly reduces the risk of HIV transmission to an HIV–negative partner. For persons who achieve and maintain viral suppression, there is *effectively no risk* of transmitting HIV to their HIV–negative sexual partner. This translates to an effectiveness estimate of 100%† for taking ART regularly as prescribed and achieving and maintaining viral suppression. Effectiveness is lower, and there is a risk of transmitting HIV, when persons do not take ART as prescribed or stop taking ART, if viral suppression is not achieved, or if viral suppression is not maintained.
Men who have sex with men (MSM)	100%	Rodger, 2016 Bavinton, 2018 Rodger, 2019	For HIV-positive MSM, taking ART regularly greatly reduces the risk of HIV transmission to a negative partner. For persons who achieve and maintain viral suppression, there is *effectively no risk* of transmitting HIV to their HIV-negative sexual partner. This translates to an effectiveness estimate of 100%† for taking ART regularly as prescribed and achieving and maintaining viral suppression. Effectiveness is lower, and there is a risk of transmitting HIV, when persons do not take ART as prescribed or stop taking ART, if viral suppression is not achieved, or if viral suppression is not maintained.

† Data are not available from these studies to calculate a combined confidence interval for the effectiveness estimate of 100%; however, confidence intervals for transmission rate estimates from each study are presented below. A recent review of many studies, including these, reported a combined HIV transmission risk estimate, across populations, while the HIV-positive person was virally suppressed of 0.00 (95% CI: 0.00 – 0.07) per 100 couple-years (Vernazza, 2019).

Evidence Supporting Effectiveness Estimates:

- **Effectiveness estimates based on suppressive ART ("Optimal Use" of ART) as indicated by achieving and maintaining viral suppression:**
  - Optimal use of ART is defined as taking ART daily as prescribed and achieving and maintaining a suppressed viral load (or viral suppression).
  - Four key studies provide evidence for the effectiveness of ART, *when used optimally*, on preventing the sexual transmission of HIV. These studies – HPTN052 (Cohen, 2016), PARTNER (Rodger, 2016), Opposites Attract (Bavinton, 2018), and PARTNER2 (Rodger, 2018) – observed zero linked sexual transmissions among HIV-discordant couples with viral suppression.
    - Each of these studies followed HIV-discordant couples while the HIV-positive partners were treated with ART with the intent of suppressing HIV replication. The follow-up assessments, at frequencies typical of what experts recommend for clinical care, included regular measurement of plasma HIV RNA concentrations and HIV testing of the HIV-negative partner. In each study, new HIV infections in the uninfected partners were assessed phylogenetically to determine whether they were genetically linked to their HIV-positive partner in the study.
    - The **HPTN052 study (Cohen, 2016)** followed 1,763 HIV-discordant couples (97% heterosexual; 3% MSM) for a median of 5.5 years. Zero genetically linked transmissions were observed while the HIV-positive partner was virally suppressed, defined as <400 copies/mL of plasma, resulting in a transmission rate estimate of 0.00 per 100 couple-years and an effectiveness estimate of 100%, if calculated (not reported in study). The confidence intervals for the effectiveness and transmission rate estimates were not reported and could not be calculated from data reported. The authors reported six partner infections that occurred during the study period where linkage could not be determined due to the inability to amplify HIV RNA; these infections were excluded from all analyses. Although linked infection could not be definitively ruled out, epidemiologic investigation strongly suggested most were not linked (Eshleman, 2017). Reported condom use was high (93%) among couples (Cohen, 2011) and likely contributed to the observed reduction in HIV transmission risk.
    - The **PARTNER study (Rodger, 2016)** followed 1,166 HIV-discordant couples (62% heterosexual; 38% MSM) for a median of 1.3 years while the HIV-positive partner was treated with ART and virally suppressed at baseline. During the 1,238 couple-years of follow-up time included in the analysis, where nearly 900 couples engaged in over 58,000 condomless sex acts, the HIV-negative partner did not use PrEP or PEP, and the HIV-positive partner was virally suppressed, defined as VL <200 copies/mL of plasma, zero genetically linked transmissions were observed. The resulting transmission rate

estimate per 100 couple-years was 0.00, with a 95% confidence interval (CI) = (0.00, 0.30). The upper 95% confidence limit varied by risk group and sexual behavior due to the range of couple-years observed across the subgroups. For example, the estimate for the sexual transmission rate of HIV among discordant couples while the HIV-positive partner was virally suppressed was:

- 0.00 (0.0 – 0.46) per 100 couple-years during **any condomless sex** among **heterosexual men and women**
- 0.00 (0.0 – 0.89) per 100 couple-years during **condomless anal sex** among **MSM**

- The **Opposites Attract study (Bavinton, 2018)** followed 343 HIV-discordant male-male couples for a median of 1.7 years while the HIV-positive partner was treated with ART, with most taking ART at baseline (80%). During the 232 couple-years of follow-up time included in the analysis, where the HIV-positive partner was virally suppressed (defined as <200 copies/mLof plasma) and couples reported over 12,000 episodes of any condomless anal sex acts and no PrEP use, there were zero genetically linked transmissions observed. This translates to a transmission rate estimate of:
  - 0.00 (0.00 – 1.59) per 100 couple-years during **condomless anal sex** among **MSM**
- The **PARTNER2 study (Rodger, 2019)** was an extension of the PARTNER study that recruited more HIV-discordant male-male couples and extending the follow-up time for those enrolled in the PARTNER study, totaling 972 HIV-discordant male-male couples enrolled in PARTNER2. The final analysis included almost 800 couples followed for a median of 2.0 years. Over nearly 1,600 couple-years of follow-up while the HIV-positive partner was on ART and virally suppressed, defined as <200 copies/mL of plasma, and couples reported no PrEP use and over 76,000 episodes of condomless anal sex, zero genetically linked transmissions were observed. This translates to a transmission rate estimate of:
  - 0.00 (0.00 – 0.23) per 100 couple-years during **condomless anal sex** among **MSM**

◦ Additional supporting evidence beyond the four individual studies includes:

- Combining over 2,600 couple-years of follow-up and more than 125,000 episodes of sex without a condom or PrEP while the HIV-positive partner was virally suppressed, from the PARTNER, PARTNER2, and Opposites Attract studies, results in a combined HIV transmission risk estimate for condomless and PrEP-less sex among heterosexual or MSM couples of 0.00 (0.00 – 0.14) per 100 couple-years (https://www.cdc.gov/hiv/pdf/risk/art/cdc-hiv-art-viral-suppression.pdf (https://www.cdc.gov/hiv/pdf/risk/art/cdc-hiv-art-viral-suppression.pdf)).
- A recent review at the 2019 CROI conference combined the four studies above along with several previous observational studies, accumulating over 4,000 couple-years of follow-up, and reported a combined HIV transmission risk estimate while the HIV-

positive person was virally suppressed, excluding unconfirmed viral loads, of 0.00 (0.00 – 0.07) per 100 couple-years (Vernazza, 2019).
    - No cases of linked HIV transmission to sexual partners when the person with HIV was virally suppressed have been documented.

- **Earlier effectiveness estimates based on original RCT study:**
    - Cohen (2011) was the first published RCT examining the protective benefits of ART for reducing HIV transmission. This paper reported the interim analysis of the HPTN 052 study, a randomized controlled trial (RCT) of providing early ART, compared with delayed ART, among 1,763 mostly heterosexual, serodiscordant couples followed for a median of 1.7 years. The effectiveness estimate for ART was 96%, based on the ITT results using verified linked cases of HIV.
        - Typically, findings from the primary analysis within an RCT include many participants assigned to the intervention strategy but not necessarily using the strategy. In this study, however, most participants in the "early ART" arm were ***taking ART consistently*** as evidenced by a high level of adherence to ART (79% had at least 95% adherence via pill count) and a high rate of viral suppression (89% were virally suppressed by 3 months). Given that this ITT analysis included time periods where the HIV-positive person was not taking ART or not virally suppressed, this effectiveness estimate for consistent use of ART is not an accurate estimate for optimal use of ART, where the HIV-positive person would be taking ART as prescribed and would have achieved viral suppression.
        - The 96% effectiveness of taking early ART, as well as a significant reduction in morbidity and mortality among HIV-positive participants, led to ending the RCT and offering all couples ART. Cohen and colleagues have continued to follow participants from this original study and offer ART to participants in both arms (thereby turning the study from an RCT to an observational design, although they continue also to analyze participants per their original random assignment) (Cohen, 2016). By the end of the study, 96% of HIV-positive persons in the "delayed ART" arm had started ART. The final HPTN 052 study ITT effectiveness estimate, including more than 5 years of follow-up, was 93% comparing "early ART" vs "delayed ART" (Cohen, 2016). Given that essentially all participants in both arms has started ART by the end of the study, this finding is not a better estimate of the effectiveness of taking ART (versus not taking ART) on reducing HIV transmission.
        - Based on the HPTN 052 RCT (Cohen, 2011), the best estimate for the overall effectiveness of ***taking ART consistently*** among heterosexuals is 96%. There are no comparable RCTs for MSM or PWID.

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Oral Daily Pre-Exposure Prophylaxis (PrEP)† for HIV-Negative Persons

Population	Effectiveness Estimate	Source	Interpretation
"Optimal or Consistent Use"[a] (Taking PrEP daily or at least 4 times per week)			

Population	Effectiveness Estimate	Source	Interpretation
Men who have sex with men (MSM)	~99%	Grant, 2014 Liu, 2015 McCormack, 2015 Volk, 2015 Marcus, 2017	When taking PrEP daily or consistently (*at least 4 times per week*), the risk of acquiring HIV is reduced by about 99% among MSM. While daily use is recommended in the U.S., taking PrEP consistently (*at least 4 times per week*) appears to provide similar levels of protection among MSM. The effectiveness of oral PrEP is highly dependent on PrEP adherence. When taking oral PrEP daily or consistently, HIV acquisition is extremely rare and has not been observed in any of the studies described below. In clinical practice, a few cases of new HIV infections have been confirmed while HIV-negative individuals were on PrEP with verified adherence.
Heterosexual Men and Women	~99%	*N/A*	There is evidence for the effectiveness of PrEP when used recently[b] (based on detecting TFV in plasma), which is estimated to be 88 – 90% as described below. There is no effectiveness estimate of PrEP when taken daily or consistently among heterosexuals; however, it is likely to be greater than the estimates corresponding to recent use and similar to what has been observed for MSM. The effectiveness of oral daily PrEP is highly dependent on PrEP adherence, with maximum effectiveness when taking PrEP daily and lower effectiveness when not taken consistently.

Population	Effectiveness Estimate	Source	Interpretation
Persons Who Inject Drugs (PWIDs)	74 – 84%	Choopanya, 2013 Martin, 2015	PWID face HIV risks from both injecting and sex behaviors. Studies on the effectiveness of PrEP when taken daily among PWID are limited. However, when taking PrEP consistently, the risk of acquiring HIV is reduced by an estimated 74 – 84% among PWID. These estimates are based on tenofovir alone and among a subset of PWID taking PrEP consistently, as verified by directly observed therapy or daily diary plus monthly pill count. The effectiveness of two-drug oral therapy has not been assessed among PWID but may be higher. The effectiveness of oral daily PrEP is highly dependent on PrEP adherence, with maximum effectiveness when taking PrEP daily and lower effectiveness when missing doses.

† The guidelines for PrEP use in the U.S. recommends daily oral PrEP (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf) and daily dosing is the only Food and Drug Administration (FDA)-approved schedule for taking PrEP to prevent HIV. Therefore, this summary evidence table refers to the science behind optimal or consistent use of daily PrEP and does not currently include on-demand PrEP. Although not included above, evidence also demonstrates that on-demand PrEP provides effective protection during sex for MSM as described below in the IPERGAY Trial and IPERGAY OLE.

[a] Optimal use of oral daily PrEP is defined as taking PrEP daily. In studies, optimal or daily PrEP use has been determined by levels of TFV-DP detected in dried blood spots equivalent to 7 pills/week. Consistent use is defined as taking PrEP at least 4 pills/week, and has been measured in studies by levels of TFV-DP detected in dried blood spots or other objective adherence measures, consistent with at least 4 pills/week.

[b] Recent use of oral PrEP is determined by detecting any amount of TFV in plasma.

Evidence Supporting Effectiveness Estimates[c]:

- **Effectiveness estimates based on "Optimal or Consistent Use" of oral daily PrEP.**

- The effectiveness of oral daily PrEP is highly dependent on PrEP adherence (Riddell, 2018). The effectiveness estimate of PrEP, when taken daily or consistently, is presented here. The effectiveness estimates of PrEP as assigned within a trial or when used recently are presented below.
- When taking oral PrEP daily or consistently, it is extremely effective in preventing HIV and HIV acquisition is extremely rare. Only three cases of seroconversion have been confirmed to date worldwide, while HIV-negative individuals were on PrEP with verified adherence (http://www.thebody.com/content/80972/has-anyone-gotten-hiv-when-they-were-on-prep.html (http://www.thebody.com/content/80972/has-anyone-gotten-hiv-when-they-were-on-prep.html))
- The US Preventive Services Task Force (USPSTF) provides a Grade A recommendation for oral daily PrEP in preventing HIV acquisition in persons at high risk. The USPSTF also concludes with high certainty that the benefit of oral PrEP is substantial, but that adherence to PrEP is central to maximizing its benefit (USPSTF, 2019).
- **MSM:** Several studies evaluated the effectiveness of PrEP use among MSM. These studies vary in study design methods (e.g. RCT, observational) as well as how PrEP adherence is measured; but all provide evidence for the effectiveness of PrEP when taken daily or consistently.
  - **iPrEx OLE Study** (Grant, 2014). This open-label extension (OLE) cohort study enrolled 1,603 MSM and transgender women previously enrolled in three PrEP trials (ATN 082; iPrEx; and US Safety Study) and followed participants for 72 weeks. All were offered free daily oral PrEP (TDF/FTC or *Truvada*), and 1,225 elected to take PrEP. PrEP adherence was measured by drug concentration of TFV-DP in dried blood spots. No new HIV infections were observed among MSM taking PrEP where drug levels indicated they had taken 4 or more doses per week.
    - Among those with the highest drug concentrations indicating daily PrEP use, as verified by drug level of TFV-DP in dried blood spots of ≥1250 fmol/punch (equivalent to ~7 pills/week), there were no new HIV infections. This resulted in a risk reduction estimate of 100% when compared to the previous placebo group from the iPrEx trial or the concurrent group of participants not on PrEP.
    - In addition, among those with drug concentration levels indicating at least 4 pills/week (>700 fmol/punch), there were no new HIV infections, which resulted in a risk reduction estimate of 100% when compared to either comparison group.
  - **DEMO Project** (Liu, 2015). This open-label observational study enrolled 557 MSM and transgender women in 2 STI clinics and a community health center in 3 U.S. cities and offered free daily oral PrEP (TDF/FTC) for 48 weeks. PrEP adherence was measured by drug concentration of TFV-DP in dried blood spots in a large sample of participants at all

follow-up visits. At the end of follow-up, 527 had at least 1 follow-up visit, providing a total of 481 person-years of follow-up. Most of the participants (ranging from 80% to 86% of participants across the follow-up visits) of those assessed for PrEP adherence had drug levels considered protective (consistent with ≥4 pills/week). At the end of the study, 2 participants acquired HIV infection; however, both participants had drug levels indicative of < 2 doses/week or BLQ (below the limit of quantification) throughout the study. This means no new HIV infections were observed among those with protective levels of PrEP use.

- **PROUD Study** (McCormack, 2015). The PROUD study was a randomized-control trial (RCT) evaluating immediate daily oral PrEP (TDF/FTC) vs delayed PrEP among HIV-negative MSM patients in 13 clinics in England from 2012-2014. A total of 554 MSM were randomized, 275 to immediate PrEP and 269 to the delayed group. After an interim analysis, the trial stopped early and all deferred patients were offered PrEP. More than 90% of the patients in each group were retained at the end of the study, providing ~500 person-years of follow up. The mITT results from the trial are reported below. Although there were 3 new HIV infections among those assigned to the immediate PrEP group, there were no HIV infections observed among those actually taking PrEP. All 3 new HIV infections in the immediate PrEP group, based on clinical indications, attendance, and prescription info, were not taking PrEP near the time of seroconversion – 2 never started taking PrEP and 1 infection was identified over 40 weeks after last clinic visit (where 90 PrEP pills were provided).
- **Kaiser Permanente Observational Study** (Volk, 2015; Marcus, 2017). This observational study followed 1,045 Kaiser Permanente (KP) patients, mostly MSM (98-99%), who were referred to a specialized PrEP program in KP San Francisco during 2012-2015, and then later extended through February 2017. PrEP use was measured based on pharmacy refill data. Among the 2,107 patients never starting PrEP, there were 22 new HIV infections. Among the 4,991 who started PrEP, although we don't know how many were always taking PrEP daily, there were no new HIV infections while PrEP prescriptions were filled (over 12.4 months; 5,104 person-years on PrEP). Of the 1,303 patients who stopped PrEP (prescription not re-filled), 11 new HIV infections were later observed after stopping PrEP, by the end of the follow-up.
- In summary, the effectiveness of PrEP among MSM when used daily or consistently is estimated to be 100% in studies. However, a few cases of new HIV infections have been reported with PrEP verified adherence, indicating that the risk has not been completely eliminated and that the effectiveness of PrEP cannot be exactly 100%. Given the number of persons on PrEP worldwide (prepwatch.org (http://www.prepwatch.org)), the risk reduction (or effectiveness of PrEP) would likely need to be very high and close to100%

to observe only three confirmed cases of PrEP failure (new HIV infection despite taking PrEP daily or consistently) to date. To represent the protective value of PrEP while also acknowledging the small number of failures, we indicate the effectiveness of PrEP is about 99%.

- **Transgender women:** The **iPrEx OLE** cohort study (Grant, 2014) enrolled mostly MSM, but included 175 transgender women previously enrolled in three PrEP trials (ATN 082; iPrEx; and US Safety Study) and offered free daily oral PrEP (TDF/FTC or *Truvada*) for 72 weeks. PrEP adherence was measured by drug concentration of TFV-DP in dried blood spots. One transgender woman seroconverted while receiving PrEP and one seroconversion occurred in a woman who elected not to use PrEP. No new HIV infections were observed among transgender women who were taking PrEP where drug levels indicated they had taken 4 or more doses per week. However, the iPrEx trial results described below show no benefit of PrEP among transgender women, likely due to low PrEP adherence (Deutsch, 2015).
- **Heterosexual men and women:** There is no effectiveness estimate of PrEP when taken daily or consistently among heterosexuals. There is evidence for the effectiveness of PrEP when used recently, which is estimated to be 88 – 90%, as described below. These estimates come from subset analyses among heterosexual men or women with evidence of taking PrEP recently (based on detecting TFV in plasma). These subset analyses likely include people who vary in PrEP adherence, including those who used PrEP recently but not consistently, used PrEP consistently but not daily (e.g. ~4 times/week), or used PrEP daily. Given that the effectiveness of PrEP is highly dependent on PrEP adherence, the effectiveness of PrEP when taking PrEP daily or consistently is likely to be greater than when taking PrEP recently; therefore, likely to be greater than 90% and similar to what is observed for MSM. Data show that it takes longer (~13 days longer) to reach a maximum drug level of PrEP in vaginal tissue as compared to rectal tissue (CDC, 2018), but once maximum drug levels are reached, the effectiveness of PrEP in preventing acquisition during sex should be similar for vaginal or anal sex, and for men or women.
- **PWID:** The **Bangkok Tenofovir Study (BTS)** (Choopanya, 2013) was an RCT evaluating oral daily PrEP use (TDF alone) against placebo among HIV-negative persons who inject drugs (PWID).
  - When taking PrEP (TDF) nearly daily, as verified by TFV detected in plasma and directly observed therapy (DOT) (with at least 70% of days were DOT, with no gaps of >2 days without DOT; equivalent to ~5 days/week), the risk of HIV acquisition was reduced by 74% among HIV-uninfected injecting drug users (subset analysis; BTS; Choopanya, 2013).

- When taking PrEP (TDF) nearly daily, when defined as 97.5% adherence, based on daily diary (most often confirmed daily by DOT staff) and monthly pill count, the risk of HIV acquisition was reduced by about 84% (subset analysis; BTS; Martin, 2015). This study also showed a dose-response between adherence and protection from PrEP, with greater adherence resulting in a greater effectiveness estimate for PrEP.
- This BTS study evaluated TDF (Tenofovir) rather than the combination drug TDF/FTC (Truvada). The effectiveness of two-drug oral therapy has not been assessed among PWID but may be higher than TDF alone. TDF alone had been shown to have a slightly lower efficacy than TDF/FTC, although not statistically different, among heterosexual HIV-discordant couples in the Partners PrEP study (Baeten, 2012; Baeten, 2014). In addition, since the measures used in the BTS study for assessing PrEP adherence included those taking PrEP nearly daily but not daily, the effectiveness of daily PrEP use may in fact be greater.
- Note that TDF (Tenofovir) is recommended in the U.S. as an alternative to TDF/FTC (Truvada) among PWID (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf)

- **Effectiveness estimates based on "Recent Use" of oral daily PrEP.**
  - Recent use of oral PrEP is measured based on drug detected, typically detecting FTC or TFV, in plasma. All effectiveness estimates presented here come from subset analyses within larger RCTs restricting to participants with drug detected in plasma indicating recent use of PrEP. These estimates do not reflect optimal or consistent use of PrEP, which resulted in greater effectiveness estimates among MSM and PWID as described above.
  - **MSM:** The **iPrEx Trial** (Grant, 2010) was an RCT evaluating oral daily PrEP use (TDF/FTC) against placebo among MSM. The findings from a case/control sub-analysis show that effectiveness of PrEP, when recently used, was estimated to be 92%. This measure of recent use of PrEP was based on detecting FTC or TFV in plasma or detecting FTC-TP or TFV-DP in PBMC.
  - **Heterosexual men and women:** The **Partners PrEP Study** (Baeten, 2012) was an RCT with three arms, evaluating oral daily PrEP use as TDF/FTC and as TDF alone against a placebo arm, among HIV-discordant heterosexual men and women.
    - The effectiveness of PrEP (TDF/FTC), when used recently, was estimated to be 88% – 90%, which comes from two separate sub-analyses from the Partners PrEP Study.
    - A case/control sub-analysis reported the effectiveness of PrEP, when used recently (based on detecting TFV in plasma), was estimated to be 90% among HIV-uninfected heterosexual men and women (Baeten, 2012).
    - Another restricted analysis of the same study was based on TFV drug levels in plasma. When taking PrEP (TDF/FTC) recently, as defined by >40 ng/ml of TFV in plasma

(unknown equivalent pills/week), the risk of HIV acquisition was reduced by 88% among HIV-uninfected heterosexual men and women (Donnell, 2014). Given these levels of TFV in plasma do not translate to a known level of PrEP adherence or known number of pills/week, this finding more accurately corresponds to those taking PrEP recently rather than daily or consistently.

- **PWID:** The **Bangkok Tenofovir Study (BTS)** (Choopanya, 2013) was an RCT evaluating oral daily PrEP use (TDF alone) against placebo among HIV-negative persons who inject drugs (PWID).
  - A case/control sub-analysis reported the effectiveness of PrEP (TDF), when used recently (based on detecting TFV in plasma), was estimated to be 70% among PWID.
  - This BTS study evaluated TDF (Tenofovir) rather than the combination drug TDF/FTC (Truvada). The effectiveness of two-drug oral therapy has not been assessed among PWID but may be higher than TDF alone. TDF alone has been shown to have a slightly lower efficacy than TDF/FTC when compared to placebo, although not statistically different, among heterosexual HIV-discordant couples in the Partners PrEP study (Baeten, 2012; Baeten, 2014).
  - Note that TDF (Tenofovir) is recommended in the U.S. as an alternative to TDF/FTC (Truvada) among PWID (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf)

- **Effectiveness estimates based on modified intent-to-treat (mITT) analyses in trials, regardless of level of PrEP use:**
  - **MSM:**
    - **The iPrEx Trial** (Grant, 2010) was an RCT designed to evaluate the efficacy of oral daily PrEP (TDF/FTC) versus placebo in preventing HIV acquisition among 2,499 HIV-uninfected MSM and transgender women. After a median of 1.2 years of follow-up, the risk of HIV acquisition was reduced by 44% among HIV-uninfected MSM assigned to daily PrEP (TDF/FTC) (mITT analysis). This estimate includes all participants assigned to take daily PrEP, regardless of actual use.
    - The **PROUD Study** (McCormack, 2015) was an RCT evaluating immediate daily oral PrEP (TDF/FTC) versus delayed PrEP among HIV-negative patients in 13 clinics in England from 2012-2014. A total of 554 MSM were randomized, 275 to immediate PrEP and 269 to the delayed group. After an interim analysis, the trial stopped early and all deferred patients were offered PrEP. More than 90% of the patients in each group were retained at the end of the study, providing ~500 person-years of follow-up.
      - RCT results (mITT analysis) – At the end of interim analysis, 3 new HIV infections were observed in the immediate PrEP group and 20 in delayed group, resulting in a risk reduction estimate of 86%.

- There were no HIV infections observed among those taking PrEP. All 3 new HIV infections in immediate PrEP group, based on clinical indications, attendance, and prescription information, were not taking PrEP near the time of seroconversion – 2 never started taking PrEP and 1 infection was identified over 40 weeks after last clinic visit (where 90 PrEP pills were provided).

- The **IPERGAY Trial** (Molina, 2015) was an RCT evaluating the efficacy of "on-demand" PrEP (TDF/FTC) regimen (defined as taking 2 pills 2-24 hours before sex, 1 pill 24 hours later, and a 4th pill 24 hours after the 3rd) versus placebo among 400 MSM. At the interim analysis of the trial, after 1 year of follow-up, the efficacy of "on-demand" PrEP was estimated to be 86% in the mITT analysis and 82% in the ITT analysis. By measured plasma drug levels in a subset of those randomized to TDF/FTC, 86% had TDF levels consistent with having taken the drug during the previous week.
  - The **IPERGAY OLE** (Molina, 2017) study. Following the interim analysis where the efficacy of "on-demand" PrEP was determined, the placebo group was discontinued, all study participants were offered TDF/FTC in an OLE phase of the study, and 361 enrolled. Although not part of the trial, the **IPERGAY OLE** study reported the risk of HIV acquisition was reduced by 97% when comparing the MSM taking PrEP as part of the OLE cohort to the placebo arm of the IPERGAY trial (Molina, 2017). Seventy-one percent of those in the OLE cohort had TDF levels consistent with having taken the drug during the previous week.
  - Two participants in the "on-demand" PrEP arm of the RCT seroconverted after enrollment and 1 participant in the OLE cohort seroconverted during follow-up. In all three cases, study records showed that the participants were not taking PrEP at the time of the diagnosis (no drug detected in plasma and all had returned all or most of their PrEP pills at the most recent visit). No new HIV infections were observed among participants taking PrEP.
  - A small sub-study of the IPERGAY trial reported high effectiveness of on-demand PrEP among those MSM participants with less frequent sexual intercourse (Antoni, 2017). This subset analysis reported an estimated 100% reduction in HIV incidence among a subset of participants reporting less frequent sexual intercourse (median of 5 sex acts/month) when reportedly taking on-demand PrEP, about 9.5 pills/month (or ~2-3 pills/week), compared to placebo.
  - Daily dosing is the only Food and Drug Administration (FDA)-approved schedule for taking PrEP to prevent HIV. However, the International Antiviral Society-USA supports the "off-label" but evidence-based use of on-demand PrEP, as an alternative to daily PrEP, for gay, bisexual and other men who have sex with men with infrequent sexual exposures (Saag, 2018). Given limited data on the effectiveness of on-demand

PrEP for heterosexual men and women, PWID, and transgender persons, IAS-USA does not currently recommend on-demand PrEP for these populations. Several health departments have developed guidance on off label use of on demand PrEP for MSM, including the New York City Department of Health (https://www1.nyc.gov/assets/doh/downloads/pdf/ah/prep-on-demand-dosing-guidance.pdf (https://www1.nyc.gov/assets/doh/downloads/pdf/ah/prep-on-demand-dosing-guidance.pdf)) and the San Francisco Department of Public Health (http://www.gettingtozerosf.org/wp-content/uploads/2018/11/HIVUpdate_02122019_v2.pdf (http://www.gettingtozerosf.org/wp-content/uploads/2018/11/HIVUpdate_02122019_v2.pdf))

- **Transgender women:** A follow-up sub-analysis of the **iPrEx Trial** evaluated the effectiveness of PrEP (TDF/FTC) versus placebo among 339 transgender women (Deutsch, 2015). No benefit of PrEP was identified (HR=1.1, 95% CI: 0.5 – 2.7); however the transgender women appeared to have lower PrEP adherence than MSM within iPrEx.
- **Heterosexual men and women:**
  - The **Partners PrEP study** was an RCT among 4747 HIV-discordant heterosexual couples assessing the efficacy of oral daily PrEP by comparing three treatment arms – TDF/FTC (Truvada), TDF alone, and placebo. The risk of HIV acquisition was reduced by 75% among HIV-uninfected heterosexual men and women assigned to TDF/FTC (Truvada) compared to placebo (mITT analysis; Baeten, 2012). This estimate included all participants assigned to take daily PrEP, regardless of actual use.
  - The **TDF2 study** was an RCT among 1219 HIV-negative heterosexual men and women comparing TDF/FTC (Truvada) to placebo and found the risk of HIV acquisition was reduced by 62% (mITT analysis; Thigpen, 2012). This estimate included all participants assigned to take daily PrEP, regardless of actual use. An as-treated analysis, restricting to those participants taking PrEP recently based on self-reported PrEP use in last 30 days, found the risk of HIV acquisition was reduced by 78%. This, however, was based on self-report and not an objective measure of recent use.
  - There are additional PrEP trials among women reported in the literature not summarized here. Riddell (2018) and the USPSTF (2019) reviewed the trial findings for PrEP and described additional trials among women showing no significant effects of PrEP, primarily due to extremely low adherence among women in the studies.
- **PWIDs:** The **Bangkok Tenofovir Study (BTS)** was an RCT evaluating oral daily PrEP use (TDF alone) against placebo among HIV-negative persons who inject drugs. This trial showed the risk of HIV acquisition was reduced by 49% among HIV-uninfected injecting

drug users assigned to oral daily PrEP (TDF) (mITT analysis; Choopanya, 2013). This estimate included all participants assigned to take daily PrEP, regardless of actual use.

c The effectiveness estimate for PrEP is estimating the percentage reduction in HIV risk due to PrEP. It is not estimating the risk of HIV acquisition among those on PrEP, but is estimating the relative reduction in that risk due to PrEP. An effectiveness estimate of "about 99%" results in an extremely small estimated risk of HIV acquisition for those taking oral PrEP daily or consistently.

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Male Condom Use

Population	Effectiveness Estimate	Source	Interpretation
"Optimal Use" (Used consistently and correctly during every sex act)			

Population	Effectiveness Estimate	Source	Interpretation
MSM or Heterosexual Men and Women	Not Avail	Not Avail	Condoms provide an impermeable barrier to HIV. FDA quality control standards and laboratory studies indicate leaks due to product failure are extremely rare. In practice, it is difficult, *if not impossible*, to measure optimal use of condoms during sex. No studies have been able to provide accurate estimates for the effectiveness of condoms in preventing HIV, when used consistently and correctly, in practice. However, such an estimate is likely to be greater than the estimates provided in studies where participants self-reported consistent condom use during sex.
"Consistent Use" (Always used during sex per self-report)			
Heterosexual Men and Women	80%	Weller, 2002	Always using condoms, based on self-report, during sex with an HIV-positive partner reduces the risk of HIV acquisition by an estimated 80% among heterosexual men and women. Self-report may not be entirely accurate, resulting in an underestimate of the true effectiveness for consistent condom use. Condom effectiveness is also likely to be higher when condoms are used correctly every time during sex.
MSM, Receptive Anal Sex	72-91%	Smith, 2015 Johnson, 2018	Always using condoms, based on self-report, during receptive anal sex with HIV-positive partners reduces the risk of HIV acquisition by an estimated 72% (Smith, 2015) and an estimated 91% (Johnson, 2018) among HIV-negative MSM. Self-report may not be entirely accurate, resulting in an underestimate of the true effectiveness for consistent condom use. Condom effectiveness is also likely to be higher when condoms are used correctly every time during sex.

Population	Effectiveness Estimate	Source	Interpretation
MSM, Insertive Anal Sex	63%	Smith, 2015	Always using condoms, based on self-report, during insertive anal sex with HIV-positive partners reduces the risk of HIV acquisition by an estimated 63% among HIV-negative MSM. Self-report may not be entirely accurate, resulting in an underestimate of the true effectiveness for consistent condom use. Condom effectiveness is also likely to be higher when condoms are used correctly every time during sex.

Evidence Supporting Effectiveness Estimates:

- **Effectiveness Estimates based on "Optimal Use" of Condoms.**
  - Optimal use of condoms is defined here as both consistent and correct use during every sex act.
  - Laboratory studies show that (latex-based, polyurethane, or other synthetic material-based) condoms provide an impermeable barrier to passage of HIV. Even during optimal use, however, condoms may not offer complete protection all the time due to the rare chance of product failure.
  - Measures are in place to ensure high quality control on product development. Condoms are regulated as class II medical devices by the U.S. Food and Drug Administration (FDA). FDA requires every condom to be tested electronically for holes and weak spots before it is packaged and released for sale. In addition, samples of condoms undergo a series of additional laboratory tests for leakage, strength, and other factors. Condom samples must be at least 99.6% effective in laboratory "water leak" tests, which means that at least 996 out of every 1000 condoms sampled must pass the test. (Warner, 2018; FDA link below)
  - Other laboratory testing has estimated that the worst-case product failure would lead to less than 0.01% of volume leakage during sex. In other words, the worst-case scenario would still eliminate about 99.99% of volume exposure during sex, in the event of product failure. (Carey, 1992)
- **Effectiveness Estimates based on "Consistent Use" of Condoms.**
  - *Although rare, and not easily measured, condoms may break, slip, or leak during use, even if used correctly. In addition, not using condoms correctly (user failure) increases the risk of breakage, slippage, leakage, or incomplete coverage which can increase exposure to HIV and, thus, may decrease condom effectiveness. Because male condoms are applied by the*

user during sex, user error or failure is an ongoing risk during each sexual episode. User error is difficult to eliminate; however, over time, as the user becomes more experienced, it is minimized. In addition, not using condoms consistently, meaning during every sex act, may further increase potential exposure to HIV and decrease effectiveness even more. Below are effectiveness estimates for consistently using condoms in practice as measured in observational studies.

- **Heterosexual Men and Women:** The Weller 2002 Cochrane review of 13 longitudinal cohort studies among HIV discordant heterosexual couples reported results comparing those reporting "Always" vs "Never" using condoms during vaginal sex from 5 of the 13 studies with data available at the longest follow-up. Vaginal versus anal and insertive versus receptive sex were not distinguished in these analyses. Always using condoms, based on self-report, during sex with an HIV-positive partner reduces the risk of HIV acquisition per person-year of follow-up by an estimated 80% among heterosexual men and women. This measure does not account for the possibility of different numbers of sex acts over time between condom users and non-users.
- **MSM:** Two recent studies have estimated the effectiveness of consistent condom use on HIV risk among HIV-negative MSM having sex with HIV-positive men.
  - The Smith 2015 study combined data from two longitudinal studies among MSM (EXPLORE & Vax004) and compared HIV-negative MSM who reported "Always" vs "Never" using condoms during receptive anal sex, during insertive anal sex, and during any anal sex, with HIV-positive partners.
    - **MSM, Receptive Anal Sex —** Always using condoms, based on self-report, during receptive anal sex with HIV-positive partners reduced the risk of HIV acquisition per person-year by an estimated 72% among MSM.
    - **MSM, Insertive Anal Sex** — Always using condoms, based on self-report, during insertive anal sex with HIV-positive partners reduced the risk of HIV acquisition per person-year by an estimated 63% among MSM. This analysis does not take into account whether HIV-negative MSM also engaged in receptive anal sex, with or without condoms, which could affect this estimate.
    - **MSM, Any Anal Sex —** Always using condoms, based on self-report, during any (insertive or receptive) anal sex with HIV-positive partners reduced the risk of HIV acquisition per person-year by an estimated 70% among MSM.
    - These measures do not account for the possibility of different numbers of sex acts over time between condom users and non-users.
  - The Johnson 2018 study examined condom effectiveness per partner in four cohorts of MSM (EXPLORE, Vaxx004, JumpStart, and Vaccine Preparedness Study) by comparing those "Always" using condoms versus "Not always" using condoms, based on self-report,

throughout the sexual partnerships. Among HIV-uninfected MSM engaging in receptive anal sex with their HIV-positive partner, always using condoms during receptive anal sex throughout the partnership reduced the risk of HIV acquisition per partner by an estimated 91%. This measure does not account for the possibility of different numbers of sex acts per partner between condom users and non-users.

- The estimates provided here likely underestimate the effectiveness of condoms when used consistently and correctly in practice due to measurement error regarding both aspects of condom use – *consistent use and correct use*.
  - These estimates for "*consistent use*" are based on observational cohort studies because no RCTs exist, due to ethical and feasibility concerns with assigning a no condom use arm. In addition, only subjective measures of condom use (*self-report*) are available in studies with HIV as an outcome, which may overestimate actual condom use, resulting in underestimating condom effectiveness. Therefore, the effectiveness of consistent condom use is likely greater.
  - These studies also did not measure whether condoms were used *correctly*. If used incorrectly, condoms may break, slip, leak, or not provide complete coverage, which may increase exposure to HIV. The studies among MSM, however, did ask MSM to count "breakage" and "slippage" as "not using a condom" in an attempt to account for user failure – but this relies on knowledge of failure and self-report and likely underestimates true failure. If these analyses included any data where condoms were used incorrectly but misclassified as consistent and correct use, then these estimates are likely underestimating condom effectiveness when used correctly, and the effectiveness of correct condom use is likely greater.

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Circumcision of Adult Males

Population	Effectiveness Estimate	Source	Interpretation
MSM, Insertive Anal Sex	Inconclusive	Wiysonge, 2011; Sanchez, 2011; Doerner, 2013	Based on observational studies of circumcision among adult males, there is insufficient evidence at this time to conclude that male circumcision reduces the risk of the insertive partner acquiring HIV during anal sex among MSM.
MSM, Receptive Anal Sex	Inconclusive	Wiysonge, 2011; Schneider, 2012	Based on observational studies of circumcision among adult males, there is insufficient evidence at this time to conclude that male circumcision (*of the insertive partne*r) reduces the risk of the receptive partner acquiring HIV during anal sex among MSM.
Heterosexual Men	50%	Siegfried, 2009	Based on trials of circumcision among adult males, male circumcision reduces the risk of heterosexual men acquiring HIV during sex by 50%.
Heterosexual Women	Inconclusive	Wawer, 2009; Weiss, 2009; Baeten, 2010	Based on several trials and observational studies of circumcision among adult males, there is insufficient evidence at this time to conclude that male circumcision reduces the risk of heterosexual women acquiring HIV during sex.

Strengths and Limitations of Effectiveness Estimates:

- Most of the evidence is based on observational studies and circumcision status is primarily based on self-report; only some studies are based on medical exam (objective measure of exposure).
- MSM Insertive Anal Sex – A Cochrane review of 7 observational studies among MSM reporting mainly or only "insertive" sex reports a significant protective effect of circumcision on acquiring HIV through insertive anal sex, 73% risk reduction (Wiysonge 2011). Exposure (circumcision) was primarily measured via self-report (subjective measure), although genital

exams occurred in some studies. Two more recently published observational studies show non-significant effects of circumcision on HIV acquisition during insertive anal sex (Sanchez, 2011; Doerner, 2013). With conflicting results, the evidence is inconclusive and an updated meta-analysis is needed.

- MSM Receptive Anal Sex – A Cochrane review of 3 observational studies among MSM reporting primarily "receptive" sex reports a non-significant effect estimate for circumcision (*of the insertive partner*) on HIV acquisition during receptive anal sex, with exposure measured by self-report (Wiysonge 2011). A more recently published observational study reports a significant effect of circumcision (based on self-report) on HIV acquisition during receptive anal sex among MSM (Schneider, 2012). With conflicting results, the evidence is inconclusive, and an updated meta-analysis is needed.
- Heterosexual Men – A Cochrane review of 3 RCTs synthesizes ITT results on the effects of circumcision on risk of HIV acquisition during sex among HIV-negative heterosexual men (Siegfried, 2009).
- Heterosexual Women – A meta-analysis (including one RCT and several observational studies) reports that there is insufficient evidence to conclude that male circumcision reduces the risk of HIV acquisition during sex among HIV-negative heterosexual women (Weiss, 2009). Two more recent reports, 1 RCT and 1 observational study, also show non-significant effects of male circumcision (confirmed by medical exam) on HIV acquisition in women among HIV-discordant heterosexual couples (Baeten, 2010; Wawer, 2009). The evidence is inconclusive, and an updated meta-analysis is needed.

Source:

- Baeten JM, Donnell D, Kapiga SH, et al. Male circumcision and risk of male-to-female HIV-1 transmission: a multinational prospective study in African HIV-1-serodiscordant couples. AIDS 2010;24(5):737-44.
- Doerner R, McKeown E, Nelson S, Anderson J, Low N, Elford J. Circumcision and HIV infection among men who have sex with men in Britain: The insertive sexual role. Archives of sexual behavior. 2013; 42:1319–1326.
- Sanchez J, Sal YRVG, Hughes JP, et al. Male circumcision and risk of HIV acquisition among MSM. AIDS 2011;25:519-23.
- Schneider JA, Michaels S, Gandham SR, et al. A protective effect of circumcision among receptive male sex partners of Indian men who have sex with men. AIDS and Behav 2012;16: (2)350-9.
- Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men (Review). Cochrane database of systematic reviews. 2009 (2):CD003362.

- Wawer MJ, Makumbi F, Kigozi G, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomized controlled trial. Lancet 2009;374(9685):229-37.
- Weiss HA, Hankins CA, Dickson K. Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis. Lancet Infect Dis 2009;9:669–77.
- Wiysonge CS, Kongnyuy EJ, Shey M, et al. Male circumcision for prevention of homosexual acquisition of HIV in men. Cochrane database of systematic reviews. 2011(6):CD007496.

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