A Randomized Noninferiority Trial of Standard Versus Enhanced Risk Reduction and Adherence Counseling for Individuals Receiving Post-Exposure Prophylaxis Following Sexual Exposures to HIV

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Background. The National HIV/AIDS Strategy proposes to scale-up post-exposure prophylaxis (PEP). Intensive risk reduction and adherence counseling appear to be effective but are resource intensive. Identifying simpler interventions that maximize the HIV prevention potential of PEP is critical.

Methods. A randomized noninferiority study comparing 2 (standard) or 5 (enhanced) risk reduction counseling sessions was performed. Adherence counseling was provided in the enhanced arm. We measured changes in unprotected sexual intercourse acts at 12 months, compared with baseline; HIV acquisition; and PEP adherence. Outcomes were stratified by degree of baseline risk.

Results. We enrolled 457 individuals reporting unprotected intercourse within 72 h with an HIV-infected or at-risk partner. Participants were 96% male and 71% white. There were 1.8 and 2.3 fewer unprotected sex acts in the standard and enhanced groups. The maximum potential risk difference, reflected by the upper bound of the 95% confidence interval, was 3.9 acts. The difference in the riskier subset may have been as many as 19.6 acts. The incidence of HIV seroconversion was 2.9% and 2.6% among persons randomized to standard and enhanced counseling, respectively, with a maximum potential difference of 3.4%. The absolute and maximal HIV seroconversion incidence was 9.9% and 20.4% greater in the riskier group randomized to standard, compared with enhanced, counseling. Adherence outcomes were similar, with noninferiority in the lower risk group and concerning differences among the higher-risk group.

Conclusions. Risk assessment is critical at PEP initiation. Standard counseling is only noninferior for individuals with lower baseline risk; thus, enhanced counseling should be targeted to individuals at higher risk.

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The United States 2010 National HIV/AIDS Strategy includes scale-up of access to post-exposure prophylaxis (PEP) [1]. Despite uncertain efficacy in preventing infection, PEP with risk reduction and medication adherence counseling is recommended after potential sexual exposures to HIV [2–4]. Interventions that reduce HIV risk behaviors and support PEP adherence maximize the potential impact of PEP services. Although they appear to be effective, the 5-session HIV risk reduction counseling strategy and intensive adherence interventions previously evaluated are resource intensive [5, 6]. Developing simpler, effective interventions is a priority [7].

The minimum intensity of counseling required to support risk reduction and maximize PEP adherence after sexual exposures is not known. We conducted a randomized, controlled, noninferiority study comparing the impact of 2 versus 5 risk reduction counseling sessions. We also compared PEP adherence among individuals randomized to a single session of clinician-delivered adherence counseling with 2 additional counselor-delivered sessions. We further compared the impact of the interventions among participants reporting more and less previous sexual risk to determine whether different intervention intensity is indicated, depending on prior risk.

METHODS

This was a randomized, controlled, noninferiority study comparing 2 HIV risk reduction and PEP adherence counseling strategies in individuals after a potential sexual exposure to HIV. It was conducted at a clinical research facility affiliated with the University of California, San Francisco.

Participants

A volunteer sample of HIV-uninfected individuals >14 years of age were eligible if they had unprotected (no condom use or condom failure) receptive or insertive anal or vaginal intercourse or receptive oral intercourse with ejaculation or contact with a potentially infected body fluid on a mucous membrane or nonintact skin during the prior 72 h. The partner must have been HIV infected, a man who has sex with men, an injection drug user, a sex worker, or anonymous (previously not know to the person and not obviously in one of these groups). The Committee on Human Research at the University of California, San Francisco approved the study protocol. Each participant provided written informed consent.

Risk Reduction Counseling

Participants were randomized to receive standard (2 sessions) or enhanced (5 sessions) risk reduction counseling (see eMethods). The enhanced intervention was that used in the feasibility study [5]. The standard intervention included the first 2 sessions. 20–30-min sessions were individually tailored on the basis of social cognitive theory, motivational interviewing, and coping effectiveness training [8–10]. In session 1, the counselor and participant explored the details and context of the risk exposure, identified strategies to mediate risk behavior, and developed a written risk reduction plan, including identification of a support person. In session 2, the counselor provided the HIV test results. They reviewed risk behavior during the previous week and the effectiveness of the risk reduction plan and revised the plan accordingly.

Participants randomized to enhanced counseling had 3 additional weekly sessions. In session 3, the patient discussed difficulties in implementing the risk reduction plan. The plan was revised, and participants were guided in identifying what they wanted to take away from the experience. In sessions 4 and 5, the participant developed an increasingly personalized plan to prevent risk behavior by identifying factors (eg, settings, emotions, and substance use) that led to both low- and high-risk behavior. They discussed the degree of motivation to continue reducing risk.

PEP Medications and Adherence Counseling

We provided 2 nucleoside analogue reverse-transcriptase inhibitors (zidovudine plus lamivudine in combination, stavudine plus lamivudine, or stavudine plus didanosine), based on the source person's antiretroviral therapy history, for 28 days. A protease inhibitor, nelfinavir, was offered if the source partner reported recent detectable plasma HIV RNA while taking antiretroviral drugs directly to study staff or as described by the patient. The objective was to provide 2 antiretroviral drugs to which the virus was likely to be susceptible. Medication was dispensed at baseline (10-day supply) and at week 1 (18-day supply) in the standard arm and at baseline (10-day supply) and at weeks 1 (7-day supply) and 2 (11-day supply) in the enhanced arm. The clinician briefly reviewed dosing instructions, good times to take the medications, and adverse effect management with all participants before they saw the counselor. In the standard adherence arm, the counselor did not provide any additional counseling. In the enhanced arm, counselors asked participants to describe the treatment regimen and follow-up appointment schedules and reviewed the rationale (see eMethods). An individual needs assessment was completed by the counselor with use of a checklist to identify potential adherence problems. Subjects were taught to select regular daily activities, such as meals and television programs, to be medication cues. Counselors taught the participants to be alert to barriers and competing demands that could decrease adherence. Counselors provided social support. In addition to 3 study visits, they called the participants at week 3 to reinforce adherence. To address social network influence on adherence, we reframed adherence to be consistent with broader social norms and presented adherence as the smart thing to do [11].

HIV and Risk Behavior Measurements

The primary outcome was the change in the mean number of unprotected anal and vaginal sexual intercourse acts in the prior 6 months at 1 year after PEP initiation, compared with the 6 months before PEP initiation. Self-administered questionnaires addressed the number of sexual contacts, the type of sexual activity, condom use, and the HIV status of each partner during the previous 6 months at baseline and at months 6 and 12 after PEP initiation. Additional outcomes were the number of times a participant received or extended PEP (re-PEP) and HIV seroconversion in the year after PEP initiation.

Adherence Measurements

We documented completion of the PEP course, number of days of PEP completed, and the proportion of doses missed during the prior 4 days at the week 1 visit [7].

Laboratory Testing

HIV antibody testing was performed at baseline and at months 3, 6, and 12. We performed baseline and follow-up serologic testing for syphilis, herpes simplex virus type 2, hepatitis B, and hepatitis C. Urine, pharyngeal, and rectal specimens were tested for gonorrhea and chlamydia. Follow-up hepatitis serologic examination was performed at 1 year; all other tests were offered at 3, 6, and 12 months after study enrollment.

Statistical Analysis

The sample size was based on the change in the number of unprotected sex acts in the prior 6 months at 1 year after PEP initiation, compared with baseline. In the feasibility study, the mean change in number of unprotected acts during the 6 months after receipt of PEP minus the number of unprotected acts during the 6 months before PEP was −2.41, with a standard deviation of ±6.77 [7]. Standard counseling may be tolerable if it does not result in disinhibition (ie, mean change in unprotected acts of 0 or less). A mean change of 0 among those receiving standard counseling equates to a mean of 2.41 more acts than those receiving enhanced counseling. Thus, the 95% confidence interval (CI) for the difference between the change in the standard arm and the change in the enhanced arm should not exceed 2.41. If standard and enhanced counseling are equivalent, a sample size of 168 individuals per arm would provide a probability (power) of 0.90 that the upper boundary of the 95% CI for the difference between arms will not exceed 2.41 [12]. Allowing for up to 25% loss to follow-up, we required 224 participants per study arm.

The groups were compared for differences in the change in the number of unprotected sex acts 6–12 months after PEP, compared with 6 months before PEP initiation; 12-month cumulative incidence of repeated PEP, new HIV infections, and sexually transmitted infections (STIs); proportion completing the full 28-day PEP course; total number of days of PEP completed; number of doses of PEP not taken in the prior 4 days at the study visit 1 week after PEP initiation; and the proportion of doses missed in the prior 4 days at week 1. We used linear regression to estimate the effect of randomization group and baseline risk acts on 12-month risk behavior, Kaplan-Meier techniques to determine cumulative incidence, and noninferiority analyses to estimate 1-sided 95% CIs to determine the greatest (worst case) differences between groups. In secondary analyses, we stratified participants as more and less risky on the basis of the number of unprotected sex acts reported in the prior 6 months at the time of study enrollment (≤ 4 vs >4). Participants who did not return after baseline or missed the week 1 visit were assumed to be fully nonadherent. Participants without a week 4 visit were considered to have not completed the PEP course; the number of days of PEP taken was imputed as 7.

RESULTS

A total of 457 participants were randomized to standard ($n = 229$) or enhanced ($n = 228$) counseling from April 2001 through October 2002. Participants were mostly male (96%) and white (71%) and reported relatively high levels of education, income, and health insurance (Table 1). More than half (51%) reported unprotected receptive anal intercourse (Table 1). Forty percent knew that their sexual partner was HIV infected. Only 4 participants (0.8%) did not return for a study visit after the baseline visit; 27 (6%) did not return for the week 4 or later study visits.

Changes in HIV Risk Behavior

The mean and median numbers of reported sex acts at baseline were 5.5 and 1.0, respectively, for the standard group and 5.4 and 2.0, respectively, for the enhanced group. There was a reduction at 12 months in the number of unprotected sex acts, compared with baseline, with 1.8 and 2.3 fewer acts in the standard and enhanced groups, respectively (Table 2). The maximum potential risk difference, reflected by the upper bound of the 95% CI, was 3.9 acts. The difference between the counseling arms in the proportion of participants who repeated PEP was 6.8%, with a maximal potential difference of 13.8%. The cumulative incidence of seroconversion was 2.9% and 2.6% among participants randomized to standard and enhanced counseling, respectively. The difference in the cumulative incidence of HIV seroconversion was 0.3%, with a maximum potential difference of 3.4%.

For each outcome, the differences between the randomization arms differed by the degree of baseline risk (Table 2). For example, the less risksy group that was randomized to the standard counseling arm had a greater reduction of unprotected sex acts, compared with participants in the enhanced counseling arm. In contrast, the difference in the riskier group was 6.2 acts and may have been as much as 19.6 acts among persons randomized to the standard counseling arm, compared with those in the enhanced counseling arm. The pattern was similar with the cumulative incidence of repeated PEP, in which the riskier group had a difference of 14.5%, and up to 30.7%, between counseling arms. The cumulative incidence of HIV seroconversion was 9.9% greater in the riskier group that was randomized to standard counseling, compared with those who were randomised to enhanced counseling. This difference could have been as large as 20.4%. The differences in repeated PEP and seroconversion were much smaller between counseling arms for those who reported less risk at baseline.

Prevalent and Incident STIs

At baseline, 116 (25.8%) participants had serologic tests positive for herpese simplex virus type 2; 8 (1.8%) for syphilis; 24 (5.6%), 12 (3.2%), and 3 (0.7%) for rectal, pharyngeal, and urine gonorrhea; and 11 (2.5%) for urine chlamydia. Hepatitis C antibody

Table 1. Demographic and HIV Exposure Characteristics

Characteristic	Participants		
	Enhanced counseling, ($N = 228$)	Standard counseling, ($N = 229$)	All, ($N = 457$)
Median age (interquartile range)	34.7 (28.5–40.9)	33.0 (28.2–40.0)	33.9 (28.4–40.7)
Sex, no. (%)			
Male	220 (96.5)	220 (96.1)	440 (96.3)
Female	7 (3.1)	7 (3.1)	14 (3.1)
Ethnicity, no. (%)			
White	164 (71.9)	161 (70.3)	325 (71.1)
African American	7 (3.1)	15 (6.6)	22 (4.8)
Hispanic	26 (11.4)	31 (13.5)	57 (12.5)
Asian	18 (7.9)	11 (4.8)	29 (6.4)
Highest school completed, no. (%)			
Grades 7–11	4 (1.8)	4 (1.8)	8 (1.8)
Graduated from high school	17 (7.5)	23 (10.0)	40 (8.8)
Some college/Associates degree	55 (24.1)	66 (28.8)	121 (26.5)
Completed 4 years college	86 (37.7)	84 (36.7)	170 (37.2)
Completed graduate school	66 (29.0)	52 (22.7)	118 (25.8)
Yearly household income[a] in US$, no. (%)			
≤12,000 or less	26 (12)	29 (13.2)	55 (12.6)
12,001–36,000	60 (27.6)	63 (27.5)	123 (28.2)
36,001–75,000	64 (29.5)	58 (26.4)	122 (27.9)
>75,000	67 (30.9)	70 (31.8)	137 (31.4)
Have medical insurance, no. (%)			
Yes	168 (74.3)	159 (69.4)	327 (71.9)
No	58 (25.7)	70 (30.6)	128 (28.1)
HIV exposure, hierarchical[b], no. (%)			
Receptive anal intercourse	122 (53.5)	113 (49.3)	235 (51.4)
Insertive anal intercourse	71 (31.1)	60 (26.2)	131 (28.7)
Receptive vaginal intercourse	6 (2.6)	7 (3.1)	13 (2.8)
Insertive vaginal intercourse	8 (3.5)	18 (7.9)	26 (5.7)
Oral intercourse with ejaculation	11 (4.8)	16 (7.0)	27 (5.9)
Shared drug use equipment	2 (0.9)	4 (1.8)	6 (1.3)
Other sexual exposure[c]	8 (3.5)	11 (4.8)	19 (4.2)
HIV status of partner, no. (%)			
HIV-positive	85 (37.3)	98 (42.8)	183 (40.0)
Unknown	143 (62.7)	131 (57.2)	274 (60.0)
Anonymous partner, no. (%)	21 (9.2)	9 (3.9)	30 (6.6)

[a] Pretax.

[b] Hierarchical HIV exposure in the order listed. For example, if unprotected receptive anal intercourse and any other exposure were reported, the exposure is categorized as unprotected receptive anal intercourse; if unprotected receptive vaginal intercourse and any other exposure except unprotected receptive anal intercourse were reported, the exposure is categorized as unprotected receptive vaginal intercourse.

[c] Includes semen on non-intact skin or in eye, oral sex with blood or significant oral pathology, or rectal secretions on non-intact skin.

and hepatitis B surface antigen were each positive in 8 (1.8%) of participants. The cumulative incidence of new STIs is shown in Table 3; ~20% of persons in the entire cohort received a diagnosis of ≥1 STI during the 12 months after study enrollment. Hepatitis B is the only vaccine-preventable STI, and 6%–8.2% of this cohort had serologic evidence of new hepatitis B virus infection. The overall pattern of STIs between the randomization arms suggests that there was no substantial difference between the study groups. There was no statistical interaction between the low- and high-risk groups.

PEP Adherence

More than 79% of participants reported completing the full 28-day course. The difference between the standard and enhanced counseling arms was 2.3% and may have been as large as 8.8% (Table 4). The mean total number of days of PEP taken was >23, with a difference of 1 day between counseling arms. Fewer than 20% reported any missed doses in the prior 4 days at week 1. Of note, 29.6% of the riskier group that was randomized to standard counseling, compared with 14% of this group randomized to enhanced adherence counseling, did not complete the 28-day PEP course ($P = .078$).

Treatment was stopped before completion because the exposure source person was found to be HIV uninfected for 8 participants (1.8%). One participant (0.2%) tested positive for HIV at baseline and discontinued PEP. At weeks 1 and 4, 14 (13.0%) and 10 (2.2%) participants, respectively, reported stopping treatment because of adverse effects. There were no serious

Table 2. HIV Risk Outcomes Among Individuals Randomized to Standard or Enhanced Risk Reduction Counseling

Subjects	Risk Reduction Counseling Arm		Standard minus enhanced	Upper bound 95% CI
	Standard	Enhanced		
Change in no. unprotected sex acts at 12 months compared with baseline (no.)				
All	−1.8	−2.3	+0.5	+3.9
Less baseline risk[a]	−0.4	+1.2	−1.6	−0.2
More baseline risk[b]	−7.0	−13.2	+6.2	+19.6
12 month cumulative incidence of re-PEP (%)				
All	23.7	16.9	+6.8	+13.8
Less baseline risk	21.1	17.2	+3.9	+11.8
More baseline risk	31.5	17.1	14.5	+30.7
12 month cumulative incidence of HIV seroconversion (%)				
All	2.9	2.6	+0.3	+3.4
Less baseline risk	0.67	2.7	−2.1	+0.8
More baseline risk	12.3	2.4	+9.9	+20.4

[a] ≤ 4 baseline sex acts; $N = 305$ (78%).

[b] > 4 baseline sex acts; $N = 87$ (22%).

adverse events resulting in hospitalization or significant laboratory abnormalities. An additional 14 participants (3.0%) stopped PEP early because they believed that the number of pills taken already was adequate, lost interest, or decided HIV risk was small. In the standard group, 13 participants did not attend the week 1 visit or had stopped PEP; thus, 216 (94%) of 229 were provided enough PEP to complete a 28-day course regardless of study follow-up. In the enhanced group, 195 (86%) of 228 attended their week 2 visit and reported they were still taking PEP.

DISCUSSION

Although it is not widely available, PEP scale-up is included in the 2010 National HIV/AIDS Strategy [1, 13, 14]. Feasibility has been demonstrated, but the intensity of risk reduction and adherence counseling required to minimize the risk of acquiring HIV infection has not been described [4–6, 15–22]. In the present study, 2-session risk reduction counseling was not inferior in reducing risk behavior or HIV acquisition among persons reporting lower baseline sexual risk behavior. Among

Table 3. Cumulative Incidence of Sexually Transmitted Infections (STIs)

STIs	Standard	Enhanced	Standard minus enhanced	Upper bound 95% CI
Any	19.7	20.8	−1.1	6.4
Less baseline risk	18.6	19.9	−1.2	7.2
More baseline risk	24.1	25.2	−1.0	16.5
HSV-2	9.5	9.9	−0.3	6.3
Less baseline risk	10.8	9.7	1.2	8.8
More baseline risk	7.7	11.4	−3.7	12.0
Syphilis	2.0	3.0	0.9	2.0
Less baseline risk	1.7	2.4	−1.3	6.9
More baseline risk	3.7	5.0	−0.9	2.0
Rectal Gonorrhea	4.9	9.2	−4.3	1.7
Less baseline risk	2.5	9.0	−6.5	−0.2
More baseline risk	14.3	10.3	4.0	19.8
Urine gonorrhea	2.5	0.7	1.7	4.0
Less baseline risk	1.6	0	1.6	3.4
More baseline risk	3.5	3.1	0.3	7.9
Urine chlamydia	2.3	5.4	−3.1	0.5
Less baseline risk	2.3	6.3	−3.9	3.4
More baseline risk	0	2.8	−2.8	1.7
Hepatitis B	8.2	6.0	2.2	9.1
Less baseline risk	7.8	3.6	4.2	11.1
More baseline risk	6.7	20	−13.3	10.0
Hepatitis C	0.7	0	0.7	1.9
Less baseline risk	1.0	0	1.0	2.5
More baseline risk	0	0	0	NA

Table 4. PEP Adherence Outcomes Among Individuals Randomized to Standard or Enhanced Adherence Counseling

Subjects	Adherence counseling arm			
	Standard	Enhanced	Standard minus enhanced	Upper bound 95% CI
Proportion that did not complete 28-day course (%)				
All	21.0	18.7	+2.3	+8.8
Less baseline risk	16.8	19.9	−3.1	+4.2
More baseline risk	29.6	14.0	15.6	+29.9
Mean number of days of PEP completed				
All	23.6	24.7	−1.0	−2.3
Less baseline risk	24.4	24.2	0.2	−1.3
More baseline risk	22.1	26.2	−4.1	−6.8
Proportion fully adherent in prior 4 days at 1 week following PEP initiation (%) All	83.6	84.7	−1.1	−6.8
Proportion of missed doses in prior 4 days at 1 week following PEP initiation (%)				
All	4.6	5.6	−1.0	+1.8

those reporting higher risk, 2- and 5-session risk reduction counseling was not equivalent, as reflects by the upper bounds of the one-sided 95% CIs, which reflects lack of evidence for noninferiority. For riskier individuals the 3 additional sessions after the baseline HIV test results are provided may be necessary for risk behaviors to decrease. That experience can be used to design personalized risk reduction plans and to motivate change. After only 2 counseling sessions, the sense of relief associated with the negative baseline test result may reduce motivation to decrease subsequent risk.

Although increased risk-taking after PEP use is not common, seroconversion has been reported [4, 6, 21, 23]. A Brazilian study that described 10 seroconversions among non-PEP users and 1 among PEP users is often considered to be evidence of PEP efficacy [20]. However, PEP use may have reflected more PEP interest among individuals at less risk [15, 20]. The seroincidence in this cohort provided with PEP starter packs was 2.9 cases per 100 person-years. The expected seroincidence without PEP was 3.1 cases per 100 person-years ($P > .97$). We previously reported a 1% (95% CI, 0.4%–2%) seroconversion rate among 700 persons [4, 5]. A 2010 report from Amsterdam describes 5 seroconversions among 237 PEP users that were attributed to ongoing exposures [21]. Although it is difficult to determine with certainty when seroconversion results from prophylaxis failure or ongoing exposures, the effectiveness of each of these HIV prevention strategies, despite potential PEP efficacy, is questionable.

Cost-effectiveness analyses of PEP after nonoccupational exposures in the US suggest that PEP is cost-saving after receptive anal intercourse and cost-effective after the other moderate risk exposure types [24, 25]. The rate of seroconversion after PEP was derived from the occupational PEP seroconversion rate [3]. These analyses have not been updated. In France, PEP was cost-saving or cost-effective ~15% of the time because of frequent prescriptions for low risk exposures [16]. A 2009 systematic review noted limitations because of the efficacy assumption and concluded that nonoccupational PEP may be cost-effective in certain population subgroups [15]. Taken together, these analyses suggest that, at a minimum, PEP availability should be targeted to high and moderate risk exposures consistent with the inclusion criteria in this study [26].

Even if PEP is efficacious, the public health impact depends on the ability to scale-up the intervention. Although knowledge of PEP is moderate among individuals at high risk, PEP uptake remains relatively low [17–19, 27–29]. For example, among 1819 uninfected California men who have sex with men surveyed in 2006, 47% were aware of PEP but only 4% had used it [27]. Although this could reflect lack of availability, PEP awareness levels were equal in San Francisco, where PEP was widely advertised to facilitate study recruitment, and in other areas in California [13, 27]. Our PEP study recruitment took great effort despite increasing awareness to nearly 70% [5, 30]. We hypothesize that only a small proportion of individuals at risk will ever use PEP, because many are comfortable with or ambivalent about their current risk behavior.

The generalizability of our results is limited by several factors. Recent community discussion about pre-exposure prophylaxis or other temporal factors may influence the characteristics of individuals likely to use PEP. Second, tenofovir may be used more frequently than zidovudine and may be better tolerated [31]. We generally used 2 antiretroviral drugs, whereas the US guidelines recommend 3 drugs [1, 32]. Of most importance, our population of predominantly men who have sex with men reflects the San Francisco epidemiology but does not include all the populations at highest risk identified in the National HIV/AIDS Strategy (ie, African American and Latino populations). This study does not provide information about how much prior risk predisposes different populations to a higher risk of

seroconversion after PEP and, thus, should not be used to develop a risk assessment tool for all populations.

In the context of the National HIV/AIDS Strategy's call for combination approaches to HIV prevention, low PEP uptake despite moderate levels of awareness, and the uncertain efficacy of PEP, we believe that PEP is most likely to make a public health impact only if it is targeted, used as a tool to leverage additional interventions, and the lessons learned from this study are adopted [4, 20, 21]. A risk assessment must be conducted. For persons at higher risk, more intensive risk reduction and adherence counseling is necessary. PEP availability for their partners can be used to introduce a sexual risk discussion with HIV-infected clinic patients, facilitating the delivery of prevention-with-positive interventions [33, 34]. Comprehensive PEP programs that provide or refer individuals for prevention services can also be used in HIV testing and partner services settings. Without integration, PEP may make an individual impact but is unlikely to contribute to reducing the incidence of HIV infection.

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