ORIGINAL ARTICLE

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

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ABSTRACT

BACKGROUND

Antiretroviral preexposure prophylaxis has been shown to reduce the risk of human immunodeficiency virus type 1 (HIV-1) infection in some studies, but conflicting results have been reported among studies, probably due to challenges of adherence to a daily regimen.

METHODS

We conducted a double-blind, randomized trial of antiretroviral therapy for preexposure HIV-1 prophylaxis among men who have unprotected anal sex with men. Participants were randomly assigned to take a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) or placebo before and after sexual activity. All participants received risk-reduction counseling and condoms and were regularly tested for HIV-1 and HIV-2 and other sexually transmitted infections.

RESULTS

Of the 414 participants who underwent randomization, 400 who did not have HIV infection were enrolled (199 in the TDF-FTC group and 201 in the placebo group). All participants were followed for a median of 9.3 months (interquartile range, 4.9 to 20.6). A total of 16 HIV-1 infections occurred during follow-up, 2 in the TDF-FTC group (incidence, 0.91 per 100 person-years) and 14 in the placebo group (incidence, 6.60 per 100 person-years), a relative reduction in the TDF-FTC group of 86% (95% confidence interval, 40 to 98; P=0.002). Participants took a median of 15 pills of TDF-FTC or placebo per month (P=0.57). The rates of serious adverse events were similar in the two study groups. In the TDF-FTC group, as compared with the placebo group, there were higher rates of gastrointestinal adverse events (14% vs. 5%, P=0.002) and renal adverse events (18% vs. 10%, P=0.03).

CONCLUSIONS

The use of TDF-FTC before and after sexual activity provided protection against HIV-1 infection in men who have sex with men. The treatment was associated with increased rates of gastrointestinal and renal adverse events. (Funded by the National Agency of Research on AIDS and Viral Hepatitis [ANRS] and others; ClinicalTrials.gov number, NCT01473472.)

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The prevention of infection with human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) remains a major public health challenge.[1] Owing to the lack of an effective HIV vaccine, consistent condom use remains the cornerstone of prevention, but biomedical interventions such as male circumcision and the use of antiretroviral drugs for the treatment of HIV infection represent additional prevention strategies.[2-5] Among the promising interventions is preexposure prophylaxis, in which antiretroviral drugs are started in HIV-negative persons before potential exposure to the virus. Daily oral preexposure prophylaxis with either tenofovir disoproxil fumarate (TDF) or the combination of TDF and emtricitabine (FTC) has been shown to provide protection against HIV-1 infection among men who have sex with men, heterosexual men and women, intravenous drug users, and HIV-1–negative partners in serodiscordant couples.[6-9] However, two recent trials involving heterosexual women did not show a benefit of daily oral preexposure prophylaxis, most likely because of low adherence.[10,11] In high-income countries, the HIV-1 epidemic is concentrated in high-risk groups, among whom men who have sex with men are disproportionately affected.[12-14] To date, the Preexposure Prophylaxis Initiative (iPrex) trial,[6] the only efficacy trial of preexposure prophylaxis among such men, showed a moderate relative reduction of 42% in HIV-1 incidence with daily use of TDF-FTC.[6]

A Quick Take is available at NEJM.org

In a multicenter study called the Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY), we assessed the efficacy and safety of sexual activity–dependent preexposure prophylaxis with TDF-FTC among high-risk men who have sex with men in France and Canada on the basis of the hypothesis that the rate adherence (and thus efficacy) might be higher than that with a daily regimen.

Methods

Protocol and Study Population

The protocol was approved by public health authorities and by ethics committees in France (Comité de Protection des Personnes Ile de France IV) and Canada (Comité d'Ethique de la Recherche de Montreal). All participants provided written informed consent. Full details with respect to the study design can be found in the study protocol, available with the full text of this article at NEJM.org.

Inclusion criteria were HIV-negative status, an age of at least 18 years, and male or transgender female sex among participants who have sex with men and who are at high risk for HIV infection (defined as a history of unprotected anal sex with at least two partners during the past 6 months). Exclusion criteria included positive results on testing for hepatitis B surface antigen, chronic infection with hepatitis C virus, a creatinine clearance of less than 60 ml per minute (as assessed by means of the Cockroft–Gault equation), an alanine aminotransferase level of more than 2.5 times the upper limit of the normal range, and glycosuria or proteinuria of more than 1+ on urine dipstick testing.

Randomization and Study Procedures

Randomization was performed by means of a fixed-size block of 4 and stratified according to country. At enrollment, eligible HIV-negative participants were assigned in a 1:1 ratio to receive either either TDF-FTC or placebo. The use of a placebo was deemed to be justified because of the inconsistent efficacy of preexposure prophylaxis in previous trials and the moderate efficacy of preexposure prophylaxis in the iPrex trial among men who have sex with men.

TDF-FTC was given as a fixed-dose combination of 300 mg of TDF and 200 mg of FTC per pill. Participants were instructed to take a loading dose of two pills of TDF-FTC or placebo with food 2 to 24 hours before sex, followed by a third pill 24 hours after the first drug intake and a fourth pill 24 hours later. In case of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse and then to take the two postexposure pills. When resuming preexposure prophylaxis, participants were instructed to take a loading dose of two pills unless the last drug intake was less than 1 week earlier, in which case they were instructed to take only one pill.

Study visits were scheduled 4 and 8 weeks after enrollment and every 8 weeks thereafter. Each visit included drug dispensation with enough pills to cover the daily use of TDF-FTC or placebo between visits, pill count and adher-

ence counseling, serum testing for HIV-1 and HIV-2, and biochemical analyses. Before each visit, participants were asked to complete at home a computer-assisted structured interview to collect information about sociodemographic characteristics, use of alcohol and recreational drugs, sexual behavior, and adherence to preexposure prophylaxis during their most recent sexual intercourse.

STANDARD PREVENTION INTERVENTIONS

At every scheduled visit, participants were offered a comprehensive package of prevention services, including patient-centered, interactive counseling according to the RESPECT risk-reduction model performed by a peer community member, free condoms and gel, and diagnosis and treatment of sexually transmitted infections.[15] Peer counselors were also available between visits to address participants' needs and reinforce adherence to study medications. Vaccination against hepatitis A and B was offered to all participants who were at risk for these infections. At enrollment and every 6 months thereafter, participants were screened for syphilis (on serologic analysis) and for chlamydia and gonorrhea (by means of a specific polymerase-chain-reaction [PCR] assay performed on anal and throat swabs and urine samples). Treatment of incident sexually transmitted infections was provided according to the protocol recommendations. Postexposure prophylaxis was readily available at study sites in case of unprotected exposure to a possibly HIV-infected partner.

PRIMARY END POINT

The primary end point was the diagnosis of HIV-1 infection, which was defined as the first evidence of HIV antibodies or p24 antigen in serum with the use of a fourth-generation enzyme-linked immunosorbent assay (ELISA) for HIV-1 and HIV-2 combined or HIV-1 RNA in plasma on PCR assay. At most of the sites, investigators used the Architect HIV Ag/Ab Combo assay (Abbott) for ELISA and the RealTime HIV-1 assay (Abbott) or Cobas TaqMan HIV-1 Test, version 2.0 (Roche), for HIV RNA PCR. Genotypic testing for drug resistance was performed on the sample obtained at the time of diagnosis to detect major resistance mutations at positions 184, 65, and 70 of the reverse transcriptase gene.[16]

ANALYSIS OF ADHERENCE

Pill count was the first measure of adherence. Participants were asked to return their study-drug bottles at each visit, and a pill count of unused medication was performed. We also measured drug levels in plasma in the first participants who were enrolled. Plasma was tested for the presence of tenofovir and FTC with the use of a validated liquid chromatography–tandem mass spectrometry method with a limit of detection of 0.1 ng per milliliter for tenofovir and 0.4 ng per milliliter for FTC. This plasma assay was able to detect drugs up to 9 days after intake.[17]

Adherence to the study regimen during the most recent sexual intercourse was also assessed by means of computer-assisted structured interviews that were completed before each visit. Three categories of adherence were defined: correct use of preexposure prophylaxis (at least one pill taken within 24 hours before sex and one pill taken within 24 hours after sex), no use of preexposure prophylaxis (no pills taken within 48 hours before and after sex), and suboptimal use of preexposure prophylaxis (i.e., any other use).

SAFETY

All participants who received at least one dose of TDF-FTC or placebo were included in the safety analyses. Adverse events were recorded at each visit, regardless of the perceived association with the medication. Toxicity was graded according to the scale of the severity of adverse events in adults used by the France Recherche Nord et Sud Sida-HIV et Hépatites (National Agency of Research on AIDS and Viral Hepatitis [ANRS]).[18]

STUDY OVERSIGHT

The conduct of the trial at each study site was monitored by the Service Commun 10–Unité de Service 19 (a clinical trial center) of INSERM. Gilead Sciences donated the study medications and provided funding for the pharmacokinetics analysis but had no role in data collection, data analysis, or manuscript preparation. All the authors vouch for the completeness and accuracy of the data reported and adherence to the study protocol.

STATISTICAL ANALYSIS

We calculated that 64 HIV-1 seroconversion events would provide a power of 80% to detect a 50%

relative reduction in the incidence of HIV-1 infection in the TDF-FTC group, as compared with the placebo group, at a two-sided alpha level of 0.05. The expected incidence of HIV-1 infection in the placebo group was 3 cases per 100 person-years. We determined that a sample size of 1900 participants would be required to achieve the target number of study end points, with 12 to 36 months of follow-up for each participant and a rate of loss to follow-up of 15 per 100 person-years.

We used a modified intention-to-treat approach for the primary analysis, in that we excluded data only from participants who were found to have HIV-1 infection before receiving the first dose of study medication or who were lost to follow-up or withdrew consent between randomization and enrollment and did not receive study medication. All participants who underwent randomization were included in an intention-to-treat analysis.

We used the Kaplan–Meier method to estimate the cumulative probability of HIV-1 infection per group and used the log-rank test to perform between-group comparisons. To assess sexual behavior over time in the two study groups, probit mixed models and binomial mixed models were used.

The study data were reviewed every 6 months by an independent data and safety monitoring board. On October 23, 2014, just after the early discontinuation of another trial of preexposure prophylaxis involving men who have sex with men, called the Preexposure Option for Reducing HIV in the UK: An Open-Label Randomization to Immediate or Deferred Daily Truvada for HIV-Negative Gay Men (PROUD) in the United Kingdom,[19] the data and safety monitoring board asked for a first unblinded interim analysis of the data and subsequently recommended that the placebo group be discontinued and that all the study participants be offered on-demand preexposure prophylaxis. The present analysis includes data collected during the double-blind phase of the study up to January 27, 2015. The study is now ongoing with an open-label design.

All analyses were conducted with the use of Stata/SE software, version 12.1 (StataCorp), and SAS software, version 9.2 (SAS Institute). All P values and confidence intervals are two-sided.

RESULTS

STUDY PARTICIPANTS

From February 22, 2012, through October 23, 2014, we screened 445 participants at seven study sites (six in France and one in Canada), which were opened sequentially during the study. Of the 414 participants who underwent randomization, 400 who subsequently tested negative for HIV infection were enrolled and followed during the study period (Fig. 1). Baseline characteristics of study participants were similar in the two groups (Table 1). Of the 400 participants, 56 (14%) (31 in the TDF-FTC group and 25 in the placebo group, P=0.37) received postexposure prophylaxis during the study period.

Retention was good during the study period, with premature study discontinuation by 49 participants (12%), for a total of 431.3 person-years of follow-up for the assessment of the incidence of HIV-1 infection after enrollment, with a median follow-up of 9.3 months (interquartile range, 4.9 to 20.6).

ADHERENCE TO STUDY MEDICATION

Participants took a median number of 15 pills (interquartile range, 11 to 21) per month in the TDF-FTC group and 15 pills (interquartile range, 9 to 21) per month in the placebo group (P=0.57) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Individual patterns of pill use showed large interpatient and intrapatient variability over time (Fig. 2).

We also measured tenofovir and FTC levels in plasma for the first 113 participants who were enrolled (Fig. S2A and S2B in the Supplementary Appendix). In the TDF-FTC group, the rates of detection were 86% for tenofovir and 82% for FTC, respectively, a finding that was consistent with receipt of each drug within the previous week. Tenofovir and FTC were also detected in 8 participants in the placebo group, 3 of whom were receiving postexposure prophylaxis.

Finally, we used computer-assisted structured interviews to analyze self-reports of the use of preexposure prophylaxis during the most recent

sexual intercourse. Overall, 28% of participants did not take TDF-FTC or placebo, 29% took the assigned drug at a suboptimal dose, and 43% took the assigned drug correctly (Table S1 in the Supplementary Appendix).

SEXUAL BEHAVIOR

Sexual practices did not change overall among the participants during the study period as compared with baseline (Fig. S3 in the Supplementary Appendix). There were no significant between-group differences in the total number of episodes of sexual intercourse in the 4 weeks before visits (P=0.07), in the proportion of episodes of receptive anal intercourse without condoms (P=0.40), or in the proportion of episodes of anal sex without condoms during the most recent sexual intercourse (P=0.90). However, there was a slight but significant decrease in the number of sexual partners within the past 2 months in the placebo group as compared with the TDF-FTC group (7.5 and 8, respectively; P=0.001). The proportions of participants with a new sexually transmitted infection (of the throat, anus, and urinary tract combined) during follow-up were similar, with 41% in the TDF-FTC group and 33% in the placebo group (P=0.10). Most of the sexually transmitted infections (39%) were rectal infections. Overall, 81 participants (20%) acquired chlamydia infections during follow-up, 88 (22%) gonorrhea, 39 (10%) syphilis, and 5 (1%) hepatitis C virus. No participant acquired hepatitis B virus infection.

EFFECT OF TDF-FTC ON HIV-1 ACQUISITION

Overall, HIV-1 seroconversion was observed in 19 participants, of whom 3 acquired HIV-1 between randomization and enrollment. In the modified intention-to-treat analysis, 16 HIV-1 infections developed after enrollment: 2 in the TDF-FTC group (incidence of 0.91 per 100 person-years) and 14 in the placebo group (incidence of 6.60 per 100 person-years), indicating a relative reduction in the incidence of HIV-1 acquisition in the TDF-FTC group of 86% (95% confidence interval [CI], 40 to 98; P=0.002) (Fig. 3). In the intention-to-treat analysis, the relative reduction in the incidence of HIV-1 acquisition was 82% (95% CI, 36 to 97; P=0.002). The 2 participants

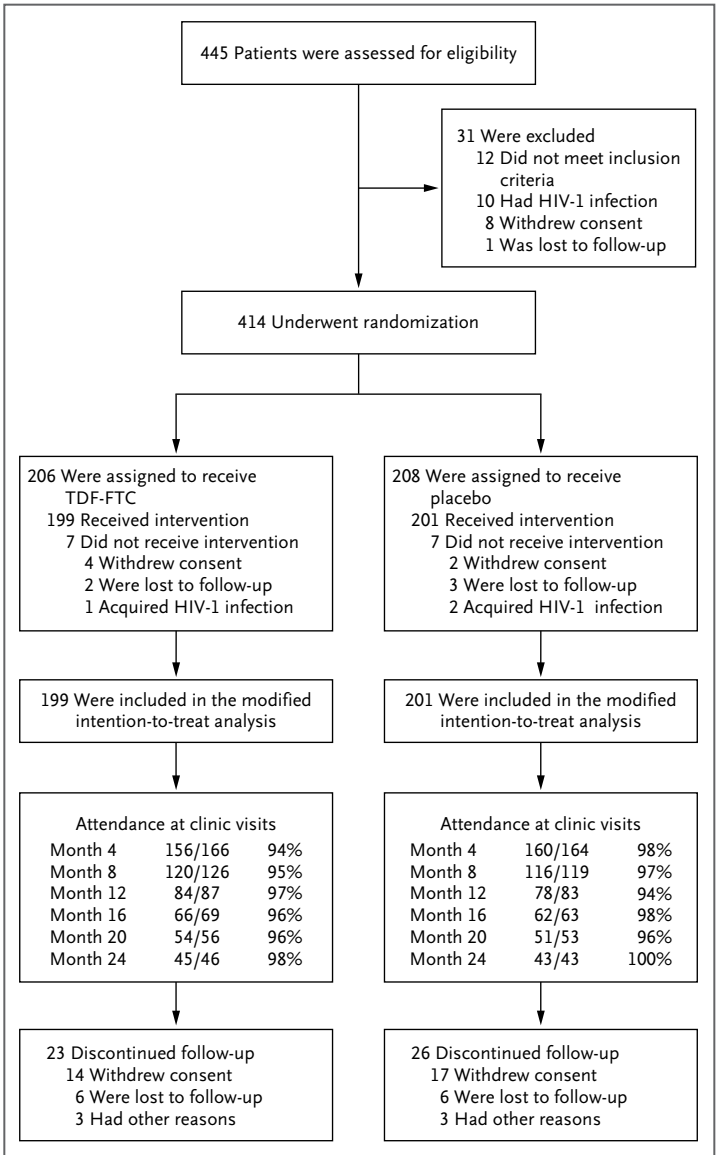

Figure 1. Enrollment and Follow-up of the Study Participants.

The most common reasons for ineligibility were ongoing HIV-1 infection and laboratory abnormalities. Only 2 participants met one of the noninclusion criteria of a creatinine clearance of less than 60 ml per minute, glycosuria, or proteinuria, all of which were designed to minimize potential renal toxic effects from exposure to tenofovir disoproxil fumarate (TDF). A total of 14 participants (3 with HIV-1 infection, 6 who withdrew consent, and 5 who were lost to follow-up) underwent randomization but were not enrolled, and their data were not included in the primary modified intention-to-treat analysis. Attendance at clinic visits is shown on a quarterly basis for all participants who remained in the study. Study visits were scheduled 4 and 8 weeks after enrollment and every 8 weeks thereafter. FTC denotes emtricitabine.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	TDF-FTC (N=199)	Placebo (N=201)	P Value
Male sex — no. (%)	199 (100)	201 (100)	
Median age (IQR) — yr	35 (29–43)	34 (29–42)	0.56
Age group — no. (%)			0.87
18–24 yr	31 (16)	27 (13)	
25–29 yr	26 (13)	30 (15)	
30–39 yr	72 (36)	73 (36)	
40–49 yr	50 (25)	55 (27)	
≥50 yr	20 (10)	16 (8)	
White race — no. (%)†	188 (94)	178 (89)	0.04
Relationship status — no. (%)			0.55
Not in a couple	144 (72)	149 (74)	
In a couple with HIV-1–positive partner	19 (10)	13 (6)	
Other	36 (18)	39 (19)	
Postsecondary education — no. (%)	146 (73)	141 (70)	0.51
>5 Alcoholic drinks per day in past month — no. (%)	49 (25)	42 (21)	0.40
Use of recreational drugs — no. (%)‡	85 (43)	92 (46)	0.45
Site of enrollment — no. (%)			0.65
France			
Paris	96 (48)	105 (52)	
Lyon	47 (24)	36 (18)	
Nice	13 (7)	18 (9)	
Tourcoing	13 (7)	14 (7)	
Nantes	9 (5)	6 (3)	
Montreal	21 (11)	22 (11)	
Sexual-risk factors at screening			
Median no. of partners in past 2 mo (IQR)	8 (5–17)	8 (5–16)	0.47
Median no. of episodes of sexual intercourse in past 4 wk (IQR)	10 (6–18)	10 (5–15)	0.08
Circumcision — no. (%)	38 (19)	41 (20)	0.75
Sexually transmitted infection diagnosed at screening — no. (%)§	49 (25)	62 (31)	0.17
Hepatitis B virus status — no. (%)¶			0.12
Susceptible	46 (23)	38 (19)	
Immune from natural infection	18 (9)	31 (15)	
Immune from vaccination	135 (68)	132 (66)	

* FTC denotes emtricitabine, IQR interquartile range, and TDF tenofovir disoproxil fumarate.
† Race was reported by investigators.
‡ Recreational drugs that were reported in the past 12 months included ecstasy, crack cocaine, cocaine, crystal, speed, and γ-hydroxybutyric acid or γ-butyrolactone.
§ Infections included syphilis (as detected on serologic testing by means of rapid plasma reagin confirmed with the use of a treponema-specific assay) and gonorrhea and chlamydia (as detected on polymerase-chain-reaction assay of urine samples and throat and anal swabs).
¶ Status with respect to hepatitis B virus was based on detection of anti–hepatitis B surface antibodies and anti–hepatitis B core total antibodies in the absence of hepatitis B surface antigen and was determined as follows: immune from natural infection (both antibodies detected), immune from vaccination (only anti–hepatitis B surface antibodies detected), or susceptible (no antibodies detected).

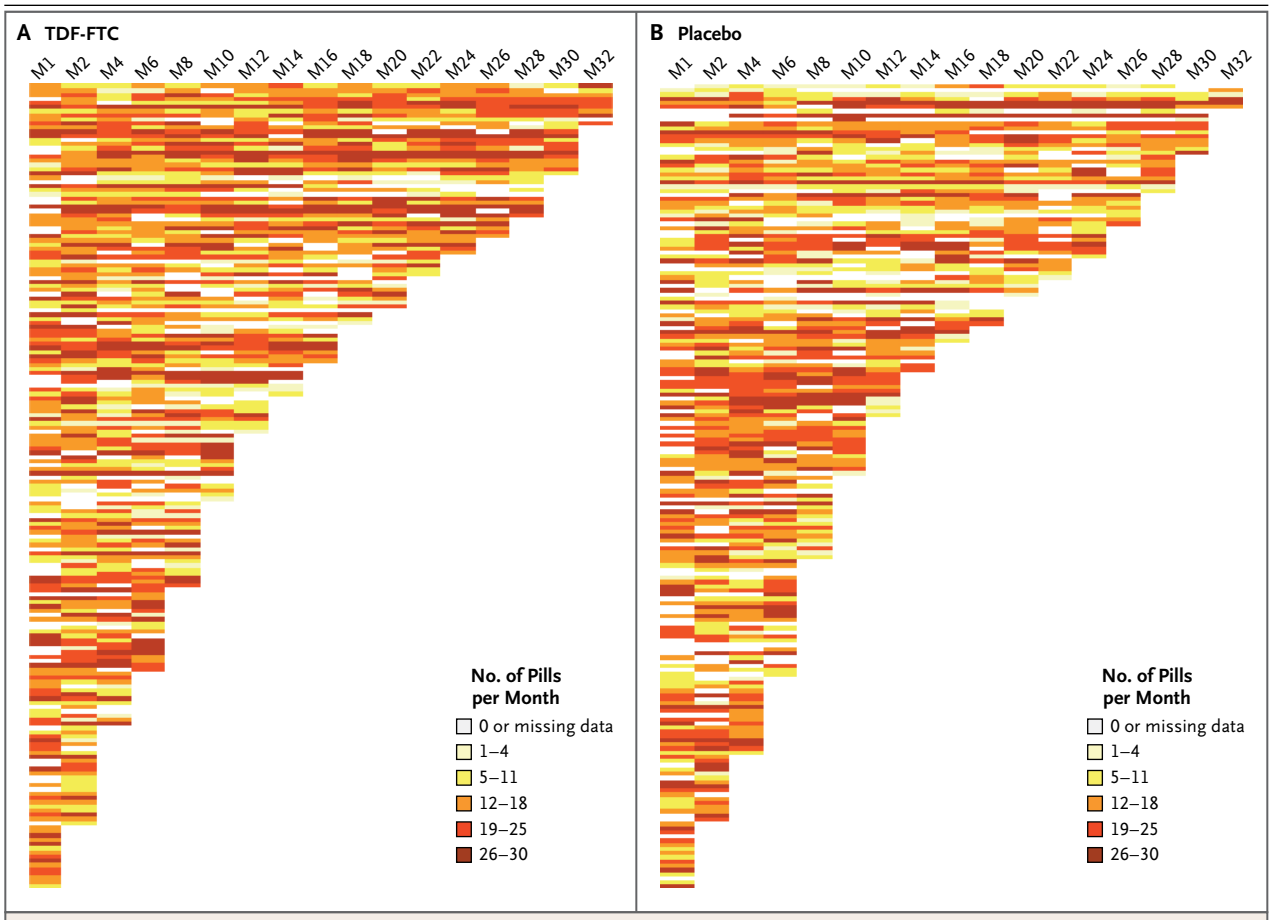

Figure 2. Patterns of Pill Use on the Basis of Clinic Visits during the Study Period.

Shown are the number of doses of TDF-FTC (Panel A) and placebo (Panel B) that were taken during the 32-month study period (M1 through M32). Six categories of pill use per month were defined at each visit: no pill use or missing data, 1 to 4 pills, 5 to 11 pills, 12 to 18 pills, 19 to 25 pills, and 26 to 30 pills. Each colored bar represents a single patient; the length of follow-up varies according to the time of enrollment.

in the TDF-FTC group in whom HIV-1 infection was diagnosed at scheduled visits returned 60 and 58 pills out of 60, respectively, at these visits and were therefore deemed to be nonadherent to preexposure prophylaxis. Study drugs were not detected in plasma samples obtained from these 2 participants at the time of HIV-1 diagnosis. None of the 16 participants who acquired HIV-1 infection after enrollment had resistance mutations to study medications.

SAFETY AND ADVERSE EVENTS

There were no significant between-group differences in the frequency of serious adverse events or grade 3 or 4 adverse events, and there were no deaths during the study (Table 2, and Table S2 in the Supplementary Appendix). Only one participant in the TDF-FTC group discontinued the study drug because of a suspected drug–drug interaction with dabigatran when he presented with a relapse of deep venous thrombosis. Drug-related gastrointestinal adverse events (nausea, vomiting, diarrhea, abdominal pain, and other gastrointestinal disorders) were seen more commonly in the TDF-FTC group than in the placebo group (14% vs. 5%, $P=0.002$).

Elevations in serum creatinine levels were seen in 35 participants (18%) in the TDF-FTC

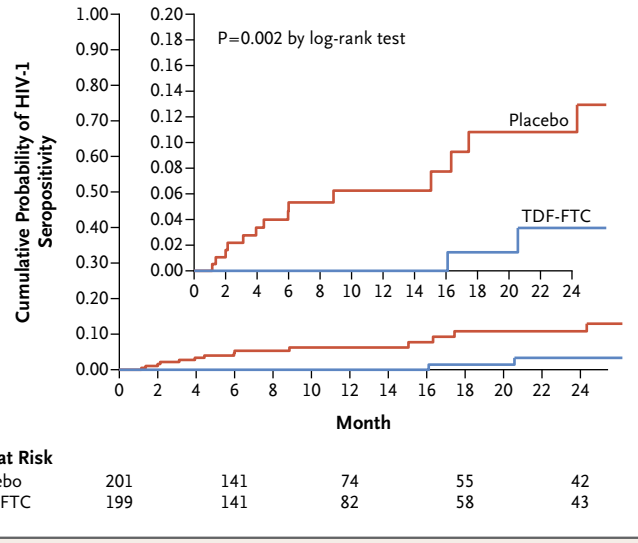

Figure 3. Kaplan–Meier Estimates of the Probability of HIV-1 Infection.

The cumulative probability of HIV-1 acquisition is shown for the two study groups in the modified intention-to-treat analysis. The inset shows the same data on an enlarged y axis.

group and 20 participants (10%) in the placebo group (P=0.03). All but one of these events were grade 1 (Table 2), and none led to study-drug discontinuation. Only 2 participants (1%), both of whom were in the TDF-FTC group, had a transient decrease in creatinine clearance to below 60 ml per minute.

DISCUSSION

In this study involving high-risk men who have sex with men, sexual activity–dependent preexposure prophylaxis with TDF-FTC was associated with a relative reduction of 86% in the risk of HIV-1 infection. This finding is among the highest risk reductions that have been reported to date, but the short follow-up for our study may have increased the likelihood of an exaggerated estimate of efficacy due in part to high initial adherence.[19] In the iPrex trial involving young men who have sex with men, in which overall adherence to daily preexposure prophylaxis on the basis of drug testing was only 51%, the relative reduction in the risk of HIV-1 infection was 42% in the intention-to-treat analysis but increased to 92% in a case–control subgroup of participants with detectable levels of tenofovir in their blood.[6] However, participants might not need continuous exposure to antiretroviral drugs to be protected from infection, especially when they are not exposed to HIV-1. In macaques, intermittent oral preexposure prophylaxis with TDF-FTC was shown to be at least as effective as daily prophylaxis.[20,21] On the basis of data from studies in animals, we hypothesized that preexposure prophylaxis taken at the time of sexual activity would provide adequate protection against HIV-1, while improving convenience and adherence to the drug regimen. Post hoc analyses from the open-label extension of the iPrex study have suggested that there were no incident HIV-1 infections among participants with an intracellular level of tenofovir diphosphate that was associated with continuous receipt of at least 4 tablets of TDF-FTC per week.[22] This finding is consistent with the efficacy reported in our study, in which participants took a median of 15 pills per month. On the other hand, our results cannot be extrapolated to persons taking a lower number of pills per month.

Assessing adherence to sexual activity–dependent preexposure prophylaxis is challenging and represents another limitation of our study. Measures of plasma drug levels revealed that a high proportion of participants in the TDF-FTC group were exposed to TDF-FTC. However, using self-administered questionnaires to assess the use of preexposure prophylaxis at the time of the most recent sexual intercourse, we found that 28% of participants reported no use of such prophylaxis, suggesting that they were able to discern when to use preexposure prophylaxis on the basis of their own assessment of risk.

It was reassuring that there was no obvious increase in behavior associated with heightened risk during follow-up in our study, a finding that was echoed in previous trials of preexposure prophylaxis.[6,19] The use of TDF-FTC was associated with gastrointestinal symptoms and transient increases in creatinine, both of which were consistent with previous reports.[6] We were unable to assess the potential of long-term toxicity of TDF-FTC, and ultimately safety concerns will have to be balanced against potential benefits from HIV-1 prevention.

In conclusion, our study showed a reduced incidence of HIV-1 infection with sexual activity–

Table 2. Adverse Events.*

Adverse Events	TDF-FTC (N = 199)	Placebo (N = 201)	P Value
	no. of patients (%)		
Any adverse event	186 (93)	181 (90)	0.21
Any serious adverse event	20 (10)	17 (8)	0.58
Death	0	0	1.00
Any grade 3 or 4 event	19 (10)	15 (7)	0.45
Treatment discontinuation due to adverse event	1 (1)	0	
Gastrointestinal adverse event†	28 (14)	10 (5)	0.002
Nausea	16 (8)	2 (1)	
Vomiting	3 (2)	0	
Abdominal pain	13 (7)	3 (1)	
Diarrhea	8 (4)	6 (3)	
Other gastrointestinal disorder	1 (1)	2 (1)	
Bone fracture	3 (2)	6 (3)	0.51
Confirmed laboratory event			
Elevated plasma creatinine			
Any grade	35 (18)	20 (10)	0.03
Grade 1	35 (18)	19 (9)	
Grade 2	0	1 (<1)	
Proteinuria ≥2+	11 (6)	9 (4)	0.63
Glycosuria ≥2+	1 (1)	0	0.50
Elevated alanine aminotransferase			
Any grade	33 (17)	26 (13)	0.30
Grade 1	24 (12)	17 (8)	
Grade 2	8 (4)	5 (2)	
Grade 3	0	1 (<1)	
Grade 4	1 (1)	3 (1)	

* Listed are the numbers of participants who had at least one event from the time of the study initiation until the end of their participation in the double-blind phase of the study, when participants were switched to open-label TDF-FTC.
† Investigators made the determination that these gastrointestinal events were related to either TDF-FTC or placebo.

dependent preexposure prophylaxis with TDF-FTC among high-risk men who have sex with men and who engage in unprotected anal sex. Given that participants took a median of 15 pills per month, the results of this study cannot be extrapolated to men who have sex with men who have less frequent sexual intercourse and thus would be taking TDF-FTC on a more intermittent regimen. While we wait for an effective vaccine against HIV, the use of such preexposure prophylaxis with TDF-FTC among high-risk men could contribute to a reduced incidence of HIV infection.[23]

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APPENDIX

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REFERENCES

1. UNAIDS. The gap report (http://www.unaids.org/en/resources/documents/2014/20140716_UNAIDS_gap_report).
2. Hammer SM, Sobieszczyk ME, Janes H, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. N Engl J Med 2013;369:2083-92.
3. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med 2005;2(11):e298.
4. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493-505.
5. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173-80.
6. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587-99.
7. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med 2012;367:423-34.
8. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2013;381:2083-90.
9. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012;367:399-410.
10. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med 2015;372:509-18.
11. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med 2012;367:411-22.
12. Le Vu S, Le Strat Y, Barin F, et al. Population-based HIV-1 incidence in France, 2003-08: a modelling analysis. Lancet Infect Dis 2010;10:682-7.
13. Lavoie E, Alary M, Remis RS, et al. Determinants of HIV seroconversion among men who have sex with men living in a low HIV incidence population in the era of highly active antiretroviral therapies. Sex Transm Dis 2008;35:25-9.
14. Beyrer C, Sullivan P, Sanchez J, et al. The increase in global HIV epidemics in MSM. AIDS 2013;27:2665-78.
15. Kamb ML, Fishbein M, Douglas JM Jr, et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. JAMA 1998;280:1161-7.
16. Descamps D, Delaugerre C, Masquelier B, et al. Repeated HIV-1 resistance genotyping external quality assessments improve virology laboratory performance. J Med Virol 2006;78:153-60.
17. Fonsart J, Loze B, Morel S, et al. Tenofovir and emtricitabine pharmacokinetics in plasma and saliva following a single dose of TDF 600 mg/FTC 400 mg: implications of on demand PrEP (ANRS Ipergay). Presented at the 20th International AIDS Conference, Melbourne, VIC, Australia, July 20–25, 2014. abstract.
18. ANRS scale to grade the severity of adverse events in adults. Version 1.0 4. November 2008 (http://www.anrs.fr/Rubriques-transversales/Outils-pour-la-recherche).
19. McCormack S, Dunn DT, Desai M, et al. Preexposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2015 September 9 (Epub ahead of print).
20. García-Lerma JG, Otten RA, Qari SH, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. PLoS Med 2008;5(2):e28.
21. García-Lerma JG, Cong ME, Mitchell J, et al. Intermittent prophylaxis with oral Truvada protects macaques from rectal SHIV infection. Sci Transl Med 2010;2:14ra4.
22. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis 2014;14:820-9.
23. Youle M, Wainberg MA. Could chemoprophylaxis be used as an HIV prevention strategy while we wait for an effective vaccine? AIDS 2003;17:937-8.