Raltegravir, Tenofovir DF, and Emtricitabine for Postexposure Prophylaxis to Prevent the Sexual Transmission of HIV: Safety, Tolerability, and Adherence

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Abstract: Antiretroviral drugs have been recommended for postexposure prophylaxis (PEP) after high-risk sexual exposures for more than a decade. Three drug regimens could offer the highest levels of protection, particularly if the infectious source is taking medication, but drug intolerance has often led to suboptimal adherence. The current study evaluated a novel 3-drug PEP regimen, consisting of raltegravir, tenofovir DF, and emtricitabine. Of 100 participants enrolled in this study at a Boston community health center that has had a comprehensive PEP program for more than a decade, 85 were evaluable at 3 months and none became HIV infected. Fifty seven percent of those enrolled completed the regimen as prescribed, and 27% took their medicine daily, but sometimes missed the second daily dose of Raltegravir. The most common side effects reported included nausea or vomiting (27%), diarrhea (21%), headache (15%), fatigue (14%), abdominal symptoms (including pain, gas, or bloating) (16%), and myalgias or arthralgias (8%), all of which were mild and tended to be self-limited, not resulting in drug discontinuation. The side effects were significantly less common than those reported by historical controls, who used a 3-drug PEP regimen including zidovudine, lamivudine, and a ritonavir-boosted protease inhibitor. Raltegravir, tenofovir DF, and emtricitabine may be useful as a 3-drug regimen for PEP.

Key Words: postexposure prophylaxis, raltegravir, tenofovir-emtricitabine, HIV prevention

(*J Acquir Immune Defic Syndr* 2012;59:354–359)

INTRODUCTION

The use of antiretroviral medication for nonoccupational postexposure prophylaxis (NPEP) has become an accepted modality to prevent HIV transmission after sexual exposure to HIV, based on US Public Health Service guidelines.[1] Although the efficacy of NPEP has not been demonstrated by a randomized controlled trial, these recommendations are based on biological plausibility, supported by animal model data,[2–6] a retrospective case–control study of occupational postexposure prophylaxis (PEP),[7] and the findings of multiple different studies, utilizing several antiretroviral regimens.[8–11]

However, the incidence of adverse events related to PEP regimens may be more than 60%, when 3-drug regimens have been used,[12,13] and more than 30% for 2-drug regimens containing zidovudine, the original standard.[14] Although these adverse effects are generally not severe, experience from occupational and nonoccupational settings suggests that a substantial proportion of individuals for whom PEP is recommended fail to complete their prescribed regimen. A regimen that is simple and well tolerated could potentially improve the acceptability of NPEP, resulting in improved adherence, which might lead to greater utilization and increased effectiveness of this intervention.[15]

Because of the relative inefficiency of HIV transmission and the ethical responsibility to provide active medication for anyone presenting for prophylaxis, it is unlikely that data from randomized controlled trials will be forthcoming supporting recommendations for use of specific 2 versus 3 antiretroviral medications in a PEP regimen, or the choice or specific agents. Currently, 3-drug PEP regimens are recommended when the source is known to be HIV infected and the exposure is particularly high risk, with some discretion left to providers in the choice of the number of drugs when the source's HIV status is unknown, and/or the exposure may be associated with a lower but nonzero risk of HIV transmission. Three-drug regimens for PEP include 2 nucleoside or nucleotide reverse transcriptase agents combined with a ritonavir-boosted protease inhibitor, resulting in increased pill burden and often associated with gastrointestinal adverse effects. The risks and benefits of 2 versus 3 drug regimens for PEP have been analyzed in a decision analysis model.[16] The main arguments in favor of a 2-drug PEP regimen have been improved tolerance and simplicity, which positively correlate with improved medication adherence and likelihood of completing the prescribed regimen. However, a simple well-tolerated and effective 3-drug NPEP regimen could obviate the need to make difficult (and potentially arbitrary) decisions between using 2 drugs or 3 drugs for PEP.

Received for publication May 26, 2011; accepted January 5, 2012.

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Supported by unrestricted investigator-initiated research grant from Merck, Inc to support the costs of the trial, and provision of Raltegravir; Gilead Sciences provided tenofovir DF-emtricitabine.

Presented at International AIDS Society meeting, 2009, Capetown, South Africa.

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Fenway Health is the largest ambulatory care center serving sexual and gender minority populations in New England and has had a specialized program to provide NPEP after high-risk sexual exposures for more than a decade.[17] This work was supported initially by a grant from the Centers for Disease Control and Prevention and subsequently has been supported to conduct Phase IV studies of novel post-exposure prophylaxis agents by industry.[17] Since the start of the NPEP program at Fenway, more than 600 individuals have called the 24-hour hotline that Fenway Health maintains to handle emergencies, with an average of approximately 1 call per week, for exposures that might require NPEP. With recent data demonstrating the safety, efficacy, and excellent tolerability of the first Food and Drug Administration–approved integrase inhibitor, raltegravir, for the treatment of HIV,[18,19] Fenway researchers decided to evaluate the combination of raltegravir and the fixed-dose combination, tenofovir DF and emtricitabine (Truvada) and raltegravir for NPEP to create a regimen with great potency and excellent tolerability to prevent HIV transmission after high risk exposures.

METHODS

Study Design

Participants were HIV-uninfected people, at least 18 years of age, who contacted Fenway Health and presented within 72 hours after a potential sexual exposure to HIV-1, including anal, vaginal, oral, or other mucosal exposure to ejaculate cervicovaginal secretions or rectal secretions from an HIV-infected partner or high-risk partner of unknown HIV status. This study was explained to potential participants, who provided written informed consent (per the approved protocol of the Fenway Health Institutional Review Board). All participants received the standardized counseling messages from trained Fenway Research staff, who educated them about potential signs and symptoms of adverse events and those of acute HIV infection. Participants were given a printed card, which instructed them on how they could reach study personnel 24 hours a day. At each scheduled study visit, participants were interviewed by trained clinical staff who used a printed checklist to ensure that participants' pre-exposure prophylaxis experiences were collected in a standardized manner. Pill counts were performed at 14 and 28 days. Anyone who declined participation in the study, but sustained an exposure warranting PEP, was offered access to nonstudy medication and routine monitoring. Participants were not provided any monetary compensation for their enrollment in this study.

Data Collection

After making contact with the specially trained Fenway clinician, who was available 24 hours a day by pager, participants who reported exposure that qualified for NPEP were asked to come to the clinic. After giving informed consent, participants were interviewed about their exposures and completed a survey that asked them about specific demographic variables, risk behaviors at the time of exposure, and the source of their exposure. After being educated about NPEP, participants received study medication and were given a diary for collecting adverse experiences. This diary was reviewed with study staff at follow-up visits, which occurred at days 10–14/week 2 and day 28/week 4. If the participants complained of symptoms, a medical provider performed a focused physical examination. HIV antibody testing was done by an enzyme-linked amino acid assay HIV ½ enzyme immunoassay test at baseline and at days 28 and 84, and positive results were confirmed by Western Blot. If symptoms suggestive of acute retroviral syndrome were present, HIV RNA testing was also performed to identify early infections.

Data Analysis

The primary data are presented as summary statistics of the participants' experience with the tenofovir-emtricitabine-raltegravir regimen. Demographic, clinical, and behavioral data from the current study participants were compared with data obtained from individuals enrolled in an earlier Fenway protocol studying tenofovir and emtricitabine administered as a single fixed-drug combination pill for NPEP and contemporaneous historical controls who used regimens containing zidovudine, lamivudine, and a protease inhibitor.[17] Participants in the earlier studies were enrolled between January 2000, and May 2004. The distribution and range of each variable was assessed; descriptive statistics were calculated for demographic, clinical, and behavioral data. The χ^2 global tests of independence and Fisher exact tests were used to examine independent associations between variables. SAS version 9.1.3 statistical software was used to analyze data, where statistical significance was determined at the alpha 0.05 level.[20] The study was powered to detect a 10% or greater difference in symptoms between groups based on the sample size of 100 in the tenofovir disoproxil fumarate–emtricitobine-raltegravir group.

RESULTS

Between March 2008 and March 2010, 131 individuals called the Fenway Health hotline because of a high-risk sexual exposure, and 100 were enrolled in the current study. Ninety-eight of the participants were male, and 2 were female. Most of the participants (83%) were men who had sex with men; 10 identified as bisexual and 5 as heterosexual. The mean age of the participants was 33 years old, with a standard deviation of approximately 10 years. Seventy-six percent of the participants were white, 11% were African American/black, 3% identified as Asian, with 10% described other racial identities, and 16% of the whole sample identified as Latino (Table 1). More than 70% of the participants had a college degree (45%) or further advanced education (26%). The demographics for this sample were comparable with participants in earlier NPEP studies, with the exception that those in the raltegravir-tenofovir-emtricitabine group were more likely to be male ($P < 0.05$).

More than one-third (37%) of the participants indicated that they knew that they were exposed to an HIV-infected partner. Fifty-seven percent reported unprotected anal sex, either because of not using condoms or because of condom breakage, with 21% reported known exposure to ejaculate. A

TABLE 1. Demographic Profile of NPEP Users, Fenway Health

	TDF-FTC-Ral (n = 100)	TDF/ Emtricitabine (n = 44)	AZT/ Lamivudine + 1* (n = 119)
Age range	18–61	20–57	18–59
Mean age (SD)	33.3 (9.69)	32.9 (8.94)	31.8 (8.72)
White	76.0%	84.0%	74.8%
Hispanic/Latino	16.0%	11.4%	12.6%
Black	11.0%	2.3%	7.6%
Asian/PI	3.0%	2.3%	2.5%
Male†	98%	100%	73.9%
Gay or Bisexual	92.0%	93.2%	N/A
College degree or higher	71.0%	70.5%	N/A

TDF, tenofovir disoproxil fumarate; TDF-FTC, tenofovir disoproxil fumarate-emtricitobine.

*AZT/lamivudine + 1 = 3 drug combination NPEP.

†TDF-FTC-Ral pts were more likely to be male compared with historical control ($P < 0.01$).

larger number (42%) reported unprotected anal insertive sex. Four individuals who presented for NPEP reported insertive or receptive vaginal intercourse. Additionally, 67% of the participants reported oral receptive sex without a condom, including 16% reporting oral exposure to ejaculate.

Eighty-five percent of the participants were seen at 3 months, and none had become HIV infected. The most commonly reported symptoms among the participants who used raltegravir-tenofovir DF-emtricitabine, were nausea and/or vomiting (27%); diarrhea (21%); headache (15%); fatigue (14%); abdominal discomfort, including pain, gas or bloating (16%); and/or myalgias or arthralgias (8%) (Table 2). Participants who used raltegravir-tenofovir DF-emtricitabine for NPEP reported mild adverse events in 71.4% of the episodes of diarrhea, 93.8% of abdominal discomfort, 78.6% of fatigue, 88.9% of nausea and/or vomiting, and 86.7% of those with headache. Only 1 participant indicated that he had severe fatigue, which remitted without any medical intervention.

In terms of completion rates, 57% of those who used raltegravir-tenofovir DF-emtricitabine for NPEP completed the full course of 28 days of the regimen as prescribed and 27% completed a modified regimen. One participant stopped treatment after he discovered that his exposure partner was not HIV infected, and 15 participants were lost to follow-up. The most common modification of the prescribed course of raltegravir-tenofovir DF-emtricitabine for NPEP was failure to consistently take the second daily dose of raltegravir, but all these participants reported adherence to the daily use of the tenofovir DF-emtricitabine dose, and the raltegravir dose that was taken at the same time. The completion rates of this regimen were comparable with that of historical controls who took tenofovir DF-emtricitabine alone, and were superior to the completion rates of those who used azidothymidine-lamivudine and a protease inhibitor (Table 3). For the participants for whom there was a follow-up visit at 4 weeks, 67% of them reported 100% adherence and 7% greater than 95% adherence to this regimen.

TABLE 2. Most Commonly Reported Symptoms by NPEP Users: Fenway Health

	TDF-FTC-Ral (n = 100) % (n)	TDF/ Emtricitabine (n = 100) % (n)	AZT/ Lamivudine + 1* (n = 119) % (n)
Diarrhea	21.0 (21)	47.5 (21)†	58.8 (70)†
Fatigue	14.0 (14)	30.0 (13)‡	48.5 (54)†
Abdominal discomfort, pain, gas, or bloating	16.0 (16)	47.5 (21)†	2.9 (3)†
Nausea/vomiting	27.0 (27)	22.5 (10)	58.8 (70)†
Headache	15.0 (15)	22.5 (10)	11.8 (14)
Dizziness/ Lightheadedness	10.0 (10)	20.0 (9)	8.4 (10)
Body/muscle/joint pain or aches and/or overall discomfort	8.0 (8)	25.0 (11)†	10.9 (13)

TDF, tenofovir disoproxil fumarate; TDF-FTC, tenofovir disoproxil fumarate-emtricitobine.

*AZT/lamivudine + 1 = triple antiretroviral NPEP.

Reference group: TDF-FTC-Ral.

†$P < 0.01$.

‡$P < 0.05$.

DISCUSSION

Although the CDC first issued guidelines for the use of antiretrovirals for occupational PEP more than 20 years ago,[21] the use of NPEP after high-risk exposures has been limited.[22] To some extent, the uptake of NPEP has been hindered by the frequent inability of at risk persons to know that they have been exposed to HIV because of their partners' ignorance of their own serostatus or unwillingness to disclose,[11] and the relative lack of awareness of the utility of PEP after sexual exposure.[22] Some of the limitations in NPEP uptake may also stem from perceptions that antiretroviral therapies may have undesirable toxicities that may need to be endured for those who are infected, but would not be sufficiently tolerable for HIV-uninfected persons, particularly for those who knew that the per contact risk of HIV transmission after 1 sex act was relatively inefficient.[23] Yet, over the past year, the field of antiretroviral chemoprophylaxis has been transformed with

TABLE 3. Regimen Completion Rates of NPEP Users: Fenway Health

	TDF-FTC-Ral (n = 100) % (n)	TDF/ Emtricitabine (n = 44) % (n)	AZT/ Lamivudine + 1* (n = 119) % (n)
Completed as prescribed	57 (57)	72.7 (32)—NS	38.8 (46)†
Stopped or modified	28 (28)	13.65 (6)—NS	14 (17)†
Lost to follow-up	15.0 (15)	13.65 (6)—NS	47.3 (56)‡

TDF-FTC-Ral = referent.

NS, not significantly different; TDF, tenofovir disoproxil fumarate; TDF-FTC, tenofovir disoproxil fumarate-emtricitobine.

*$P < 0.05$.

†$P < 0.01$.

‡$P < 0.001$.

the first proof in humans that the use of vaginal tenofovir gel or the oral use of tenofovir-DF-Emtricitabine decreased the transmission of HIV to South African women and an international sample of men who had sex with men, respectively.[24,25]

Although in animal models, the use of antiretrovirals before exposure has been particularly protective, postexposure prophylaxis has also conferred high levels of protection, particularly when administered soon after an exposure and continued for a 4-week course.[7,26–28] The challenge of administering antiretrovirals to HIV-uninfected humans has been that the frequent development of adverse reactions to the first recommended PEP regimens. Adherence to the recommended 3-drug regimen as follows: zidovudine-lamivudine and a ritonavir-boosted protease inhibitor has been often associated with nonadherence and early medication discontinuation.[29,30]

Because adherence is essential if a PEP regimen is to be effective, assessment of better-tolerated alternatives has been needed. In clinical trials involving several thousand HIV-infected patients, tenofovir DF had demonstrated excellent tolerability, with a side-effect profile comparable with placebo.[31–35] The most common adverse events seen were mild to moderate gastrointestinal side effects,[31] which led to drug discontinuation in less than 1% of patients.[36] Its bioavailability and long half-life allow for once-daily dosing, desirable for optimal adherence. In prior studies of NPEP conducted at Fenway Health, the combinations of tenofovir DF and lamivudine or the coformulated tenofovir DF-emtricitabine were each found to be associated with fewer adverse events and greater completion rates than historical controls who used regimens containing azidothymidine-lamivudine and a ritonavir-boosted protease inhibitor.[17]

Due to the relative inefficiency of HIV transmission and the hope that PEP will be an infrequent experience for those who use it, if concomitant counseling can result in subsequent reductions in risk taking,[37] randomized clinical trials of different PEP regimens are not feasible. Moreover, it has not been certain if 3-drug regimens would offer enhanced protection against HIV acquisition, compared with 2-drug regimens, because of frequent discontinuations due to adverse events.[38] The most commonly used third drug in a PEP regimen has been a ritonavir-boosted protease inhibitor because of unacceptable hepatotoxicity in immunocompetent hosts using nevirapine[39] and central nervous system side effects with efavirenz.[40] Yet, there are clearly times when using 3 drugs targeting at least 2 stages in the HIV life cycle are preferable, particularly when the source is known to be HIV infected, and antiretroviral treatment experienced, especially if nonadherent.

The current study is the first to evaluate an integrase inhibitor, raltegravir, as the third active agent in a PEP regimen. The rationale was based on the findings that this drug has been shown to be extremely well tolerated, with potent antiretroviral activity,[18] and 3-drug regimens are most likely to be most efficacious in preventing HIV transmission if they are well tolerated. The use of an integrase inhibitor makes great sense for HIV prevention because these compounds prevent HIV from becoming established in latent reservoirs of susceptible cells, inhibiting a different cellular target than the reverse transcriptase inhibitors most commonly used for PEP. In the current study, we found that raltegravir with tenofovir DF and emtricitabine was extremely well tolerated for NPEP with high completion rates. Because of small sample sizes and unmeasured biases that may occur when historical controls are compared, it is not appropriate to make definitive conclusions about the 2 versus 3-drug regimens containing tenofovir disoproxil fumarate-emtricitobine, but the data suggest that the addition of raltegravir did not result in an increase in adverse events and that tenofovir-containing regimens seemed to be better tolerated than 3-drug regimens containing zidovudine and a protease inhibitor.

The major form of nonadherence in the current study was that a subset of participants missed taking 1 of 2 daily doses of the drug, whereas the adherence with the tenofovir DF-emtritabine moiety, which was administered once daily, was excellent. Recent data suggested that raltegravir dosed twice daily as part of a treatment regimen was superior to using a double dose once daily.[41] Because the optimal dose of raltegravir for prophylactic use is unknown, this raises some challenging questions because it is not known whether the same drug exposure is needed for chemoprophylaxis as treatment in infected persons with billions of virions already in their body. Thus, it is not clear whether 800 mg of raltegravir given once daily in combination with tenofovir DF-emtricitabine could be sufficient for PEP, if nonadherence to twice daily dosing would be high. Alternatively, clinicians prescribing PEP might want to emphasize the importance of the second daily raltegravir dose as part of their initial counseling and might use the conversation with their patients to think of strategies to enhance adherence to the second dose.

The current study had some limitations, including the reliance on self-reports to measure adherence. Although participants were assured continued study participation and services whether they were fully adherent or not, social desirability bias could lead to elevated reports of medication adherence. A larger sample would have greater power to detect smaller differences more definitively. The study population was almost exclusively male, reflecting the demographics of people who call Fenway's hotline after an acute sexual exposure, and thus further studies of this PEP regimen for women will be needed. Another concern is the use of historical controls, which may have received different care during an earlier period. The use of the controls was not intended to provide a definitive assessment of the comparable tolerability or efficacy of tenofovir disoproxil fumarate–emtricitobine-raltegravir compared with earlier regimens, but because the same clinical protocols were used at the same research center, it is hoped that they could indicate the range of adverse events seen with earlier regimens. The primary finding of this article is the high level of tolerability of tenofovir disoproxil fumarate–emtricitobine-raltegravir as a 3-drug PEP regimen.

This study was the first in humans to demonstrate that an integrase inhibitor can be a well tolerated as part of an HIV chemoprophylactic regimen. Raltegravir had a very low rate of adverse events, with the most common side effects being mild headache, nausea, dizziness, and diarrhea. It has a favorable safety profile in both preclinical and human studies, with no evidence of mutagenicity or significant

toxicity. Raltegravir is primarily metabolized by glucuronidation and is not a potent inhibitor of the hepatic cytochrome P-450 system. Therefore, significant drug–drug interactions are not expected and were not seen. The study was not powered to demonstrate efficacy for HIV prevention, but the lack of incident HIV infections and high level of tolerability for this drug in high-risk HIV-uninfected participants when used in combination with tenofovir DF-emtricitabine was reassuring. Other studies are underway evaluating the use of integrase inhibitors as a topical microbicides alone and coformulated with other antiretroviral drugs,[42] and other integrase inhibitors are currently being studied for therapeutic use, so the optimal ways in which this potent new class of antiretroviral agents could be used to prevent HIV transmission will take some time to elucidate. However, the current study provides some new data to suggest that raltegravir should be considered as a useful third drug for postexposure chemoprophylaxis.

ACKLNOWEDGMENTS

The authors would like to recognize the contributions of Pam McMorrow; Rodney VanDerwarker; Steven Boswell, Jackie White, Susan Johnson, Mark Fallon, Andrea Karis, and the entire medical staff at Fenway Health.

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