Optimal HIV Postexposure Prophylaxis Regimen Completion With Single Tablet Daily Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine Compared With More Frequent Dosing Regimens

Kenneth H. Mayer, MD,* †‡§ Daniel Jones, MSN, RN,* Catherine Oldenburg, ScD, MPH,§ Sachin Jain, MD, MPH, Marcy Gelman, RN, MSN, MPH, Shayne Zaslow, MA, MS,* Chris Grasso, MPH,* and Matthew J. Mimiaga, ScD, MPH**

**PREVENTION RESEARCH**

Structure: The study evaluated elvitegravir/cobicistat/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (“Quad pill”) for postexposure prophylaxis (PEP).

Background: HIV-exposed individuals may benefit from PEP, but completion rates have been suboptimal because of regimen complexity and side effects. Newer antiretroviral combinations coformulated as single daily pills may optimize PEP adherence.

Setting: One hundred HIV-uninfected individuals who presented to a Boston community health center after an acute HIV sexual exposure were enrolled and initiated PEP with the daily, single-pill combination Quad pill for a 28-day course.

Methods: Side effects and medication completion rates from study participants were compared with historical controls who had used PEP regimens consisting of TDF/FTC daily and raltegravir twice daily, or earlier regimens of twice daily zidovudine (AZT)/lamivudine (3TC) and a protease inhibitor, using \( \chi^2 \) tests for independence.

Results: Of the 100 participants who initiated the Quad pill for PEP after a high-risk sexual exposure, 71% completed the 28-day Quad pill regimen, which was significantly greater than historical controls who used TDF/FTC and raltegravir (57%, \( P < 0.05 \)) or AZT/3TC plus a protease inhibitor (39%, \( P < 0.001 \)). The most common side effects reported by Quad pill users were as follows: abdominal discomfort or pain, gas or bloating (42%), diarrhea (38%), fatigue (28%), nausea or vomiting (28%), headache (14%), or dizziness or lightheadedness (6%). Most symptoms were mild, limited, and did not result in medication discontinuation. No participants became HIV infected.

Conclusions: Fixed-dose combination of elvitegravir/cobicistat/TDF/FTC was safe and well tolerated for PEP, with higher regimen completion rates than more frequently dosed PEP regimens.

Key Words: postexposure prophylaxis, HIV prevention, integrase strand transfer inhibitors, men who have sex with men

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INTRODUCTION

Over the past decades, multiple studies have indicated that the use of antiretroviral medication can prevent HIV transmission in high-risk individuals when given as pre-exposure prophylaxis (PrEP).\(^ {1–4} \) However, many individuals may not anticipate being exposed to HIV, and thus postexposure prophylaxis (PEP) is still recommended.\(^ {5,6} \) Because of the relative inefficiency of HIV transmission,\(^ {7} \) and the premise that the use of PEP is often a one-time event, there are no human randomized control studies to justify the practice. However, there are multiple animal studies that suggest that postexposure dosing of antiretrovirals can protect against HIV acquisition.\(^ {8–13} \)

In addition, the US Centers for Disease Control and Prevention conducted a retrospective analysis of health care workers occupationally exposed to HIV and found that those who had used zidovudine (AZT) within 72 hours of exposure to a known HIV-infected source achieved significantly greater protection against HIV compared with those who did not use prophylaxis.\(^ {14} \) However, many of the earlier PEP regimens were not well tolerated because triple antiretroviral regimens were usually used that included early generation reverse transcriptase agents, such as zidovudine or stavudine and/or protease inhibitors. This led to regimen completion rates that were often suboptimal, occasionally resulting in seroconversions.\(^ {15,16} \) More recently, newer medications have been developed that are better tolerated. The use of tenofovir disoproxil fumarate (TDF) instead of AZT as part of a PEP
regimen has been associated improved tolerability and higher completion rates, offering the promise of fewer seroconversions.17,18

The development of integrase strand transfer inhibitor (INSTI) agents offers a novel opportunity for highly potent PEP formulations. In a series of 100 patients followed at a Boston community health center, tolerance of daily tenofovir (TDF)–emtricitabine (FTC) coformulated with the addition of raltegravir given twice daily was extremely well tolerated, but completion rates were suboptimal with only 57% completing as prescribed and 28% stopping or modifying the regimen.19 The availability of single coformulated pills containing INSTI and other antiretrovirals that can be given once a day, which have demonstrated favorable tolerability in HIV treatment trials,20 provides a unique opportunity for more convenient PEP. Furthermore, recent studies have demonstrated a protective benefit in macaques using integrase inhibitors for PEP.21,22

With this in mind, our study team decided to evaluate the safety, tolerability, and acceptability of elvitegravir/cobicistat/TDF/FTC (known as the “Quad Pill”) as a single-tablet regimen for PEP after sexual or parenteral exposures to HIV and compare the findings with data from previous PEP studies conducted at this center.

METHODS

The participants for the study were recruited at a Boston community health center specializing in the care of sexual and gender minority populations.23 Because of engagement in a number of HIV prevention research studies, over more than 2 and a half decades, the health center had developed a PEP hotline and was able to recruit participants initially for observational studies and subsequently for evaluating the use of TDF/FTC for PEP and later the use of TDF/FTC and raltegravir.17,19 Participants in the study had to identify a high-risk exposure, which constituted either condomless receptive or insertive penile–anal or penile–vaginal intercourse, from a source that was either HIV infected or whose serostatus was unknown. The exposure had to occur within 72 hours of the time where PEP could be administered. Individuals opting out of study participation were connected to other care services for PEP treatment access.

The research nurse conducted a medical history and contraindicated medication review to ensure safety after informed consent and enrollment procedure. Rapid HIV I/II antibody screening and additional sexual risk assessment were conducted to rule out current possible infection. Participants were provided half of the total 28-day regimen and scheduled for follow-up appointments at 14 days after the determination of safety and seronegative status. Screening and treatment referrals for sexually transmitted infections and viral hepatitis, supportive counseling, education, and connection to other care services were provided as needed were identified. Participants were screened for safety laboratories, and if renal function tests were abnormal (ie, creatinine clearance less than 70 cc/mL), then they were referred for other PEP regimens. Screening for hepatitis B infection was performed; active infection was exclusionary, which would have result in stopping study drug (however, this did not occur in this protocol). Participants returned for a 2-week visit to assess for symptoms of potential seroconversion, medication-related side effects or adverse events, and medication administration experiences. A third visit was conducted at 30 days after exposure, after completion of PEP regimen for rapid HIV antibody screening, and review of regimen safety, tolerability, and acceptability. The final and fourth visit was conducted at 90 days after exposure. Rapid HIV antibody and fourth-generation antibody/antigen testing with counseling was conducted. Surveys assessing side effects and sexual behavior were administered during these visits.

SAS 9.4 was used to analyze data, where statistical significance was determined at the alpha 0.05 level.24 The general analytic strategy was to compare side effects and regimen completion rates among those in the current study taking a fixed-dose once-daily combination of elvitegravir/cobicistat/TDF/FTC compared with historical controls who used PEP regimens consisting of TDF/FTC daily and raltegravir twice daily, or earlier regimens of twice daily zidovudine (AZT)/lamivudine (3TC) and a protease inhibitor, using χ² tests for independence.

RESULTS

Between May 2013 and November 2015, 100 participants were enrolled (Table 1). The participants’ age ranged

<table>
<thead>
<tr>
<th>TABLE 1. Demographic and Behavioral Profile of Quad PEP Users at Fenway Health, Boston, 2000–2015</th>
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<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>AZT/3TC/PI* (N = 119)</td>
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<tr>
<td>Recruited</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>White, %</td>
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<tr>
<td>Latino, %</td>
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<tr>
<td>Black, %</td>
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<tr>
<td>Asian/PI, %</td>
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<td>Gay or bisexual, %</td>
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<td>College degree or higher, %</td>
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*AZT/3TC/PI, zidovudine/lamivudine/protease Inhibitor.
†TDF/FTC + RAL, tenofovir disoproxil fumarate coformulated with emtricitabine plus raltegravir bid.
‡Quad pill, tenofovir disoproxil fumarate, emtricitabine, elvitegravir, and cobicistat coformulated.
§Data not systematically recorded before tenofovir-based clinical trials.
¶Total column % may exceed 100% because individuals could report more than one sexual behavior when presenting for PEP.
from 19 to 62, with a mean age of 34 years and a median of 31 years. Almost all (98%) of the participants identified as male at birth, and none identified as transgender; 81% of the participants identified as gay, 5% as heterosexual, 8% as bisexual, 3% as other, and 3% declined to answer. The most common mode of sexual risk exposure was male-to-male sexual exposure through condomless anal intercourse (43% of the participants), with 13 participants having a known HIV-infected source. An additional 15 participants noted that they were exposed to ejaculate of the partner when engaging in condomless sex, 3 with an HIV-infected source, and 12 with a partner whose serostatus was unknown. Almost half (43%) reported engaging in anal intercourse which included a condom, and 20 with a known HIV-infected source. One participant presented after being exposed through condomless receptive vaginal intercourse with exposure to ejaculate; 10 participants presented after exposure through oral intercourse.

The study protocol included follow-up safety evaluations at 14, 30, and 90 days after initiation of study medication. The aggregate retention rate for the protocol was 93%, with 98% of participants coming for their first follow-up visit, but with subsequent attenuation over the course of the study. Seven participants discontinued study product during the trial. One participant was taken off the study product because of elevated creatinine at baseline. Another participant discontinued the study product because of side effects, but later revealed that he had also taken TDF/FTC and efavirenz before enrollment. Another participant described a localized, pruritic, nonurticarial, maculopapular rash, which could have possibly been related to study medication. Another participant was taken off the study product after experiencing loose stools, excessive gas, weakness, dizziness, decreased appetite, and acid reflux that could have possibly been related to study medication. Another participant complained of palpitations, nervousness, headaches, and nausea. One participant discontinued medication because of adherence challenges, and another received study medication, but did not return for study visits.

Almost all the participants (91%) reported at least one adverse event during study participation that was considered probably or possibly related to study product. Gastrointestinal symptoms, which included loose stools, nausea, and/or flatulence, were most commonly reported (121 times) by Quad pill users, but 88% of the symptoms were categorized as mild, and generally did not result in product discontinuation. Diarrhea was reported by 38% of participants using Quad PEP, compared with 21% of TDF/FTC and raltegravir PEP recipients ($P < 0.01$) and 58.8% of those who used AZT/3TC and protease inhibitor regimens ($P < 0.01$) (Table 2). Fatigue or exhaustion was described by 28% of the Quad pill users at least once, but 90% described it as mild, which was more common than it being described by TDF/FTC and raltegravir PEP users ($P < 0.05$), but less common than historical controls who used AZT/3TC and a protease inhibitor ($P < 0.01$). The prevalence of nausea and vomiting was comparable between the Quad pill regimen and the TDF/FTC and raltegravir regimen (around 28%), but significantly less than those who used AZT/3TC and protease inhibitor-based regimens ($P < 0.001$). The prevalence of headache was similar across the groups between 11.8% and 15%. Dizziness and lightheadedness was relatively uncommon (6%) with the Quad pill regimen and comparable to the TDF/FTC and raltegravir regimen (10%) and the AZT/3TC and protease inhibitor regimens (8.4%). Muscle joint aches, pain, and overall discomfort were reported by only 2% of the PEP participants who used the Quad pill regimen (2%), significantly less common than those who used TDF/FTC and raltegravir (8%, $P < 0.05$) or AZT/3TC and a protease inhibitor (10.9%, $P < 0.01$). No participants reported negative social impacts as part of study participation.

Of the hundred participants enrolled in the study, only 29% of participants missed any doses of study medication; the other 71% of Quad PEP users indicated that they took all their study medication. Thirty-seven of the reported missed doses were due to forgetfulness, and 5 were due to the medication being temporarily displaced. Four were ascribed to difficulties in swallowing. Four participants reported feeling sick with a cold and not willing to take other medication when ill. Two missed pills were reported as due to anorexia; 2 missed doses were ascribed to other non-specified side effects. Ten doses were stopped by participants without explanation, and one participant complained of a late start schedule and was not able to return home to finish completing study medication. None of the participants in the course of the study had a documented HIV seroconversion.

Among those who were not fully adherent to the study protocol, 15% either stopped or modified the regimen, and 14% were lost to follow-up by the last study visit (Table 3). In comparison, of the series of individuals who received TDF/FTC and raltegravir for PEP, only 57% were able to complete study visits. Eighty percent of Quad pill users indicated that they took all their study medication. Thirty-seven of the reported missed doses were stopped by participants without explanation, and one participant complained of a late start schedule and was not able to return home to finish completing study medication. None of the participants in the course of the study had a documented HIV seroconversion.

| TABLE 2. Most Commonly Reported Adverse Events Among Quad Pill PEP Participants Versus Those Using Other PEP Regimens, Fenway Health, Boston, 2000–2015 |
|-------------|-------------|-------------|-------------|
| **AZT/3TC/PI** | **TDF/FTC + RAL** | **Quad Pill** |
| **(N = 119)** | **(N = 100)** | **(N = 100)** |
| **% (N)** | **% (N)** | **% (N)** |
| Diarrhea | 58.8 (70|$^*$) | 21.0 (21|$^*$) | 38.0 (38) |
| Fatigue | 48.5 (54|$^*$) | 14.0 (14|$^*$) | 28.0 (28) |
| Nausea/vomiting | 58.8 (70|$^*$) | 27.0 (27) | 28.0 (28) |
| Headache | 11.8 (14) | 15.0 (15) | 14.0 (14) |
| Dizziness/lightheadedness | 8.4 (10) | 10.0 (10) | 6.0 (6) |
| Body/muscle/joint pain or aches and/or overall discomfort | 10.9 (13|$^*$) | 8.0 (8|$^*$) | 2.0 (2) |

*AZT/3TC/PI, zidovudine/lamivudine/protease inhibitor.
†TDF/FTC + RAL, tenofovir disoproxil fumarate coformulated with emtricitabine plus raltegravir bid.
‡Quad pill, tenofovir disoproxil fumarate, emtricitabine, elvitegravir, and cobicistat coformulated.
¶Includes abdominal cramping, excessive gas, upset stomach, and stomach ache.

Quad pill, referent.
TABLE 3. Regimen Completion Rates Among Quad Pill PEP Participants Versus Those Using Other PEP Regimens, Fenway Health, Boston, 2000–2015

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Recruited</th>
<th>Completed as prescribed</th>
<th>Stopped or modified</th>
<th>Lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT/3TC/PI*</td>
<td>January 2000–March 2004</td>
<td>38.8 (46§)</td>
<td>14.0 (17)</td>
<td>47.3 (56¶)</td>
</tr>
<tr>
<td>TDF/FTC + RAL†</td>
<td>March 2008–November 2010</td>
<td>57.0 (57)</td>
<td>28.0 (28)§</td>
<td>15.0 (15)</td>
</tr>
<tr>
<td>Quad Pill‡</td>
<td>May 2013–November 2015</td>
<td>71.0 (71)</td>
<td>15.0 (15)</td>
<td>14.0 (14)</td>
</tr>
</tbody>
</table>

*AZT/3TC/PI, zidovudine/lamivudine/protease inhibitor.
†TDF/FTC + RAL, tenofovir disoproxil fumarate coformulated with emtricitabine plus raltegravir bid.
‡Quad pill, tenofovir disoproxil fumarate, emtricitabine, elvitegravir, and cobicistat coformulated.
§P < 0.05.
¶P < 0.001.

The advent of newer regimens that are better tolerated, using a tenofovir backbone, as well as INSTIs, has been associated with high levels of medication tolerability. Other promising regimens include those that are single-tablet, daily regimens with TAF and FTC. There may be other iterations that could optimize PEP provision in the future. The development of tenofovir alafenamide (TAF), which seems to be less nephrotoxic and osteotoxic than TDF, may offer enhanced safety features. However, given that PEP use is only for 28 days, the differences and long-term benefits between TAF and TDF may be negligible, particularly if generic TDF/FTC offers a cost advantage in the near term. Another promising regimen is the new INSTI, bictegravir, which has been coformulated with TAF and FTC. Given that this INSTI does not require a metabolic booster such as cobicistat or ritonavir, while still providing a safe and well-tolerated once-daily PEP pill.

Part of the emerging importance of providers being aware of PEP and providing this to appropriate patients in a timely manner is the reality that many individuals who present for PEP continue to engage in recurrent HIV risk behaviors. These individuals could be excellent candidates for PrEP, and optimally managing the PEP–PrEP transition should be an important part of ongoing clinical education for successful HIV prevention. By determining the likelihood of recurring risk, providers can use a satisfactory PEP experience as an opportunity to educate their patients about the need for consistent adherence if the patients are to transition to a PrEP regimen that will need to be taken over a sustained period of time to be effective for long-term protection against HIV.

In summary, this study found that the fixed-dose combination of elvitegravir/cobicistat/TDF/FTC, as known as “the Quad pill,” was well tolerated with high completion rates. This type of regimen, a single pill once a day, offers great promise as an effective regimen for PEP and may enable clinicians to identify individuals who may subsequently benefit from PrEP.

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REFERENCES


