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Excellent HIV Post-Exposure Prophylaxis Regimen Completion with Single Tablet Daily Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine Compared to More Frequent Dosing Regimens

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Abstract

Structure—The study evaluated elvitegravir/cobicistat/tenofovir disiproxil fumarate(TDF)/emtricitabine(FTC) (“Quad pill”) for post-exposure 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 co-formulated as single daily pills may optimize PEP adherence.

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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 to 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-square 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: 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 elvitegravir/cobicistat/TDF/FTC was safe and well-tolerated for PEP, with higher regimen completion rates than more frequently dosed PEP regimens.

Keywords

Post-exposure prophylaxis; HIV prevention; integrase strand transfer inhibitors; men who have sex with men

INTRODUCTION

Over the past decade 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 post-exposure 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 post-exposure dosing of antiretrovirals can protect against HIV acquisition (8–13).

Additionally, the US Centers for Disease Control and Prevention conducted a retrospective analysis of healthcare 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 to those who did not use prophylaxis (14). However, many of the earlier PEP regimens were not well tolerated, since triple antiretroviral regimens were usually used that included early generation reverse transcriptase agents, such as zidovudine or stavudine, and 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 agents (INSTI) offers a novel opportunity for highly potent PEP formulations. In a series of one hundred patients followed at a Boston community health center, tolerance of daily tenofovir(TDF)-emtricitabine (FTC) co-formulated 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 co-formulated 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 inibitors for PEP (21, 22).

With this in mind, our study team decided to evaluate the safety, tolerability, and acceptability of Elvitegravir/cobicistat/ tenofovir disoproxil fumarate (TDF)/ emtricitabine (FTC) (known as the “Quad Pill”) as a single tablet regimen for PEP following sexual or parenteral exposures to HIV, and compare the findings with data from prior 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 two 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 following informed consent and enrollment procedure. Rapid HIV I/II Antibody screening and additional sexual risk assessment was 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 following 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 needs were identified. Participants were screened for safety laboratories, and if renal function tests were abnormal (i.e., 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 post-exposure, following 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 post exposure. Rapid HIV antibody and 4th 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. 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 to 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 chi-square tests for independence.

RESULTS

Between May 2013 and November 2015 one hundred participants were enrolled (Table 1). The participants' age ranged from nineteen to sixty-two years of age, with a mean age of thirty-four years and a median of thirty-one 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, 20 with a known HIV-infected source. One participant presented after being exposed through condomless receptive vaginal intercourse with exposure to ejaculate; and ten participants presented after exposure through oral intercourse.

The study protocol included follow-up safety evaluations at 14, 30, and 90 days after initial presentation for PEP. 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 prior to enrollment. Another participant described a localized, pruritic, non-urticarial, 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 of 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 to 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 was 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 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 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 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.

Amongst 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 the regimen as prescribed ($p <0.05$), and that was primarily because a substantial number stopped or modified the dose regimen. In the majority of cases their dosage modification was due to the discontinuation of the afternoon dose of raltegravir. Completion rates were substantially lower among historical controls who used an AZT/3TC and protease inhibitor regimen ($p <0.001$). The loss to follow up rates were substantially less among those who used the QUAD pill or TDF/FTC and raltegravir for PEP compared to those who used AZT/3TC plus a protease inhibitor for PEP.

DISCUSSION

The use of PEP continues to have an important role in acute HIV prevention, being recommended by the WHO (5) and CDC (6), based on animal and human studies (8–14). However, some individuals who present to emergency rooms after sexual assault, or who have other high risk exposures, may not be retained in care, resulting in low PEP regimen completion rates (25). Socially disadvantaged high risk individuals who are less informed and/or have less access to HIV prevention services (e.g. PrEP) may present for acute medical attention after HIV exposures (26). These individuals can benefit from simple, well-tolerated PEP regimens, so that their initial experience with antiretroviral chemoprophylaxis is acceptable, since they might subsequently benefit from PrEP. When PEP was first recommended, some felt that using multi-drug regimens optimized the likelihood of aborting early HIV infection, particularly if the infected source was antiretroviral-experienced, but normative guidance has increasingly favored simpler, better tolerated regimens to optimize medication adherence (5, 6). One clinical effectiveness study modeling PEP completion rates, based on regimens using older drugs with increased side effects, suggested that the third drug (e.g. protease inhibitors) might increase non-adherence, so the use of two drug PEP (e.g. TDF/FTC) might be preferable because of the possibility of higher completion rates (27). The advent of newer regimens that are better tolerated, using a tenofovir backbone, as well as integrase strand transfer inhibitors (INSTI), has been associated with high levels of medication tolerability (17, 19, 28, 29). This helps to explain the higher regimen completion rates seen in the current study. In addition to better tolerated regimens, another goal of PEP is to make the regimens as simple as possible. In the current study, the demonstration that over 70% of individuals completed the once daily QUAD pill regimen as prescribed suggests this single tablet, daily regimens may be a successful way to provide PEP in the future. Compared to an earlier study using a raltegravir-based PEP regimen, there were higher rates of completion because up to a quarter of the earlier sample missed the afternoon dose of raltegravir (19). The simpler daily regimen might also be particularly attractive for patients who have insurance that requires co-payments for each additional pill.

There may be other iterations that could optimize PEP provision in the future. The development of tenofovir alafenamide (TAF), which appears to be less nephrotoxic and osteotoxic than tenofovir disoproxil fumarate (TDF) (30), 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 co-formulated with TAF and FTC (31). Given that this INSTI does not require a metabolic booster such as cobicistat or ritonavir, this would minimize the likelihood of drug interactions, 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 (32–37). 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 (33,38). 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 in order to be effective for long-term protection against HIV.

In summary, the present study found that the fixed dose combination of elvitegravir/cobicistat /TDF/FTC, a.k.a. “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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Table 1

Demographic and Behavioral Profile of Quad PEP Users at Fenway Health, Boston, 2000–2015

Demographics	**AZT/3TC/PI[1] (N=119)**	**TDF/FTC+RAL[2] (N=100)**	**QUAD Pill[3] (N=100)**
Recruited	**Jan 2000 – May 2004**	**Mar 2008 – Mar 2010**	**May 2013 – Nov 2015**
Male, %	73.9	100.0	98.0
White, %	14.8	76.0	73.0
Latino, %	4.1	11.0	9.0
Black, %	12.7	16.0	12.0
Asian/PI, %	2.5	3.0	8.0
Gay or Bisexual, %	92.4	96.0	89.0
College Degree or Higher, %	N/A[4]	71.0	72.0
Condomless sexual risk[4,5]			
Receptive anal	N/A	57.0	43.0
Insertive anal	N/A	42.0	43.0
Receptive oral	N/A	16.0	10.0
Receptive vaginal	N/A	2.0	2.0
Insertive vaginal	N/A	2.0	9.0

[1] AZT/3TC/PI = Zidovudine/Lamivudine/Protease Inhibitor

[2] TDF/FTC+RAL = Tenofovir disoproxil fumarate coformulated with emtricitabine plus raltegravir bid

[3] QUAD Pill = tenofovir disoproxil fumarate, emtricitabine, elvitegravir, cobicistat coformulated

[4] Data not systematically recorded prior to tenofovir-based clinical trials

[5] Total column % may exceed 100% because individuals could report more than one sexual behavior when presenting for PEP.

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[1] (N = 119) % (N)	TDF/FTC+RAL[2] (N = 100) % (N)	QUAD Pill[3] (N= 100) % (N)
Recruited	**Jan 2000 – May 2004**	**Mar 2008 – Mar 2010**	**May 2013 – Nov 2015**
Diarrhea	58.8 (70)[4]	21.0 (21)[4]	38.0 (38)
Fatigue	48.5 (54)[4]	14.0 (14)[5]	28.0 (28)
Nausea/vomiting	58.8 (70)[6]	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)[4]	8.0 (8)[5]	2.0 (2)

Quad Pill = referent

^Includes abdominal cramping, excessive gas, upset stomach, stomach ache

[1]AZT/3TC/PI = Zidovudine/Lamivudine/Protease Inhibitor

[2]TDF/FTC+RAL = Tenofovir disoproxil fumarate coformulated with emtricitabine plus raltegravir bid

[3]QUAD Pill = tenofovir disoproxil fumarate, emtricitabine, elvitegravir, cobicistat coformulated

[4]p<.05

[5]p<.01

[6]p<.001

Table 3

Regimen completion rates among Quad Pill PEP participants versus those using other PEP regimens, Fenway Health, Boston, 2000–2015

	AZT/3TC/PI[1] (N = 119) % (N)	TDF/FTC+RAL[2] (N = 100) % (N)	QUAD Pill[3] (N= 100) % (N)
Recruited	**Jan 2000 – May 2004**	**Mar 2008 – Mar 2010**	**May 2013 – Nov 2015**
Completed as prescribed	38.8 (46)[4]	57.0 (57)[5]	71.0 (71)
Stopped or modified	14.0 (17)	28.0 (28)[4]	15.0 (15)
Lost to follow-up	47.3 (56)[6]	15.0 (15)	14.0 (14)

Quad Pill = referent

[1] AZT/3TC/PI = Zidovudine/Lamivudine/Protease Inhibitor

[2] TDF/FTC+RAL = Tenofovir disoproxil fumarate coformulated with emtricitabine plus raltegravir bid

[3] QUAD Pill = tenofovir disoproxil fumarate, emtricitabine, elvitegravir, cobicistat coformulated

[4] $p<.05$

[5] $p<.01$

[6] $p<.001$