DOI: 10.1111/hiv.12075

HIV Medicine (2014), **15**, 13–22

ORIGINAL RESEARCH

Raltegravir–emtricitabine–tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence*

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Objectives

Three-drug nonoccupational post-exposure prophylaxis (NPEP) typically includes co-formulated emtricitabine-tenofovir (FTC-TDF) and a protease inhibitor. However, protease inhibitors can cause significant toxicities, can interact with prescribed and illicit drugs, and work late in the viral cycle. Agents that act before viral integration into host DNA may have efficacy advantages. Raltegravir (RAL) is a good candidate for NPEP as it has few side effects or drug interactions and acts prior to HIV integration. The objective of this study was to investigate the use of RAL in 3-drug NPEP in terms of safety, adherence and tolerability.

Methods

We evaluated 28 days of RAL-FTC-TDF treatment in 86 men and FTC-TDF treatment in 34 men eligible for three- and two-drug NPEP, respectively. We assessed adherence (compared between groups and with nonstudy controls) and clinical and adverse events at weeks 1, 2 and 4, and efficacy at week 12. Analyses were by intention to treat, excluding from the adherence analysis subjects who ceased NPEP because their source was HIV-uninfected.

Results

No participant became infected with HIV. For RAL-FTC-TDF and FTC-TDF, regimen completion rates were 92% and 91% and medication adherence rates were 89% and 90%, respectively. Eight (9%) RAL recipients developed mild myalgias, with four developing transient grade 4 elevations in creatine kinase (two developed both), all of which improved to grade 2 or less by week 4 without RAL discontinuation. Eight prescribed and 37 potential illicit drug interactions with a protease inhibitor were avoided by use of RAL.

Conclusions

RAL-FTC-TDF is well tolerated as NPEP, results in high levels of adherence and avoids potential drug–drug interactions. Patients and clinicians should be aware of the potential for acute muscle toxicity when RAL is used as NPEP.

Keywords: HIV, post-exposure prophylaxis, raltegravir

Accepted 3 July 2013

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*Presented in part at the 23rd Annual Australasian Society for HIV Medicine, Canberra, Australia, 26–28 September 2012.

Introduction

Antiretroviral therapy (ART) is widely used as HIV post-exposure prophylaxis (PEP) in occupational (OPEP) and nonoccupational (NPEP) settings [1–4] on the basis of the findings of studies in other primates; studies on the prevention of mother-to-child HIV transmission; a retrospective, case–control study of OPEP in health care workers; a

randomized study of ART as pre-exposure prophylaxis in men who have sex with men (MSM); and a randomized trial of ART as prevention in HIV-serodiscordant, heterosexual couples [5–9].

PEP does not always prevent HIV transmission [10–12]. Longer time to first PEP dose, incomplete PEP adherence, continued HIV risk behaviour and primary ART drug resistance have each been linked to failure [11,12]. In seven PEP studies published since 2001, 51% of the total 1009 participants reported at least one adverse event (AE) and around 20% failed to complete the 28-day course [13–19].

The use of three antiretroviral agents in PEP is common [1–4] but based solely on standard-of-care treatment of HIV infection. The most commonly used third drug is a protease inhibitor [1–4]. Protease inhibitors prevent mature HIV protein formation within cells in which HIV is already integrated into host-cell DNA. Agents that act before viral integration may have efficacy advantages by preventing rather than limiting infection. In addition, some prescribed and proscribed drugs have potentially dangerous interactions with protease inhibitors.

Raltegravir (RAL) is an HIV integrase strand transfer inhibitor. The potency of RAL and its safety record, ease of use (infrequent side effects, low pill burden, small tablets, and dosing independently of food), short time from administration to maximum plasma concentration (T_{max}), high tolerability, mode of action prior to HIV integration and low potential for drug interactions make it an attractive candidate for PEP [20–22]. It does, however, require twice-daily dosing and has rarely been associated with muscle toxicity [23]. Mayer *et al.* reported good tolerability of RAL-based NPEP in 100 men [24], but did not specifically assess for muscle toxicity or report biochemical safety, and found a surprisingly low rate of NPEP completion (57%).

The key objectives of the present study were to investigate RAL in terms of safety, adherence and tolerability when used in combination with co-formulated emtricitabine-tenofovir (FTC-TDF) as a three-drug NPEP regimen, and compare outcomes with those with two-drug NPEP (FTC-TDF) for lower risk exposure and with our standard three-drug NPEP (FTC-TDF-stavudine).

Methods

Participants

Participants were HIV-negative MSM aged 18 years or over who presented following a potential sexual exposure to HIV, defined as unprotected insertive or receptive anal intercourse with an HIV-positive source or a source of unknown HIV status or receptive oral intercourse with ejaculation from a known HIV-positive source.

After providing written, informed consent, potential participants were screened for eligibility in two stages. At stage 1, potential participants were ineligible if they were using any medicine contraindicated with the study medications, were known to have chronic active or treated hepatitis B virus (HBV) infection or had received NPEP containing RAL in the past.

At stage 2 (3–5 days after NPEP commencement), participants with serology consistent with established or possible primary HIV infection, serum hepatic transaminases > 5 times the upper limit of normal, an estimated glomerular filtration rate (eGFR) of < 60 mL/minBSAc, or serology consistent with chronic active HBV infection were deemed to have failed the second stage screening phase, and so ceased study medication. These individuals were subsequently managed according to Australian standard-of-care guidelines for NPEP or newly diagnosed HIV infection [4,25].

MSM presenting for NPEP during the study period who received standard-of-care NPEP provided written, informed consent to demographic and risk event data collection to our HIV database.

Study settings

The study was conducted in two centres between 1 July 2010 and 31 May 2012. At St Vincent's Hospital, participants were recruited in the Emergency Department on Saturdays and Sundays. At Sydney Sexual Health Centre, participants were recruited during business hours. All patients had all follow-up study visits at the HIV ambulatory care unit in St Vincent's Hospital. The study protocol was approved by the institutional review boards of St Vincent's and Prince of Wales Hospitals. The study protocol was registered at ClinicalTrials.gov (NCT01087840).

Interventions

This was a nonrandomized, open-label, prospective cohort study. Study three-drug NPEP was RAL 400 mg twice-daily plus FTC 200 mg-TDF 300 mg once-daily for 28 days, and study two-drug NPEP was FTC-TDF once-daily for 28 days. MSM eligible for NPEP but who declined study participation (or were ineligible) received standard-of-care three-drug NPEP (FTC-TDF-stavudine) or two-drug NPEP (FTC-TDF).

Participants were reviewed at weeks 1, 2, 4, 5 and 12. Data regarding subjective AEs were collected at each visit and graded according to the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (Version 1.0) [26]. NPEP adherence was measured by pill count at weeks 2, 4 and 5 and calculated by dividing

the number of doses returned by the number of doses dispensed, expressed as the percentage of doses taken. Data were collected at each visit regarding any concomitant drug use.

All participants were managed by and received standardized education (including written information) from a single experienced nurse consultant regarding potential NPEP side effects, signs and symptoms of primary HIV infection, the need for 100% adherence and what to do in the event of a missed medication dose. All participants had 24-hour contact with the same nurse consultant by mobile phone, received appointment reminders by SMS and were subject to proactive recall if an appointment was missed.

Assessments

Blood was sampled and tested at baseline (pre-NPEP), week 2, week 4 (end of NPEP) and week 12. Study-specific testing included: fourth-generation HIV-1, HIV-2 and p24 antigen screening (HIV antigen/antibody combo screen; Abbott Diagnostics, Chicago, IL) at baseline, week 4 and week 12; hepatitis B serology at baseline; and measurement of electrolytes, urea, creatinine, inorganic phosphate, calcium, alanine and aspartate aminotransferases, glucose, amylase, lipase, creatine kinase and lactate, and a full blood count, at baseline, week 2 and week 4. Lactate was measured in a rested state with the tourniquet removed and the lactate sample was collected last in the blood draw. The estimated glomerular filtration rate was derived using the Modification of Diet in Renal Disease (MDRD) equation.

Freshly voided urine was collected at baseline, week 2 and week 4 for dip-stick analysis using Multistix®10 (SG Siemens Healthcare Diagnostics Inc., Malvern, Pennsylvania, USA).

The 2006 Australian NPEP guidelines recommend testing for HIV at 4 to 6 weeks, 12 weeks and 24 weeks post-exposure [27]. These were in a process of review at the time the study commenced. In keeping with these draft guidelines, testing for HIV post-NPEP in the study concluded at 12 weeks post-exposure [4]. There are no definite cases of delayed HIV seroconversion (beyond week 12) in occupational and nonoccupational PEP settings. The fourth-generation HIV-1, HIV-2 and p24 antigen screening assay used in our study would be expected to identify cases of HIV seroconversion within 12 weeks of HIV infection.

Sample size and data analysis

Based on an envisaged recruitment period of 2 years, we aimed to recruit 125 subjects, of whom at least 90 would receive RAL-FTC-TDF and 30 would receive FTC-TDF, with the unequal group sizes explained by the predominance of three-drug NPEP prescribed in our local area. Our NPEP completion rate for our current three-drug NPEP regimen is 74%. For an anticipated higher completion rate of 90%, a sample of 90 subjects would provide a 95% confidence interval (CI) of 82 to 95%; a much larger sample of 200 subjects with 90% completion would yield only a slightly smaller 95% CI (85 to 93%).

All participants who were eligible for NPEP (who met the eligibility criteria and whose source partner was not subsequently known to be HIV-uninfected) were included in the adherence analyses. All participants were included in the analysis of AEs as all received at least one dose of drug.

Descriptive statistics were obtained and tests of significance (Pearson's χ^2 and Fisher's exact tests for independent proportions and two-sample *t*-test for independent means) were performed using the SPSS statistics package, version 19 (IBM, New York, NY). Significance was set at 0.05 and CIs at 95%.

Results

Demographics

Between July 2010 and May 2012 there were 524 MSM presenting for NPEP to St Vincent's Hospital. Of those, 51% (267 of 524) were assessed for the study and 102 (19%) consented to participate and were enrolled. A further 21 MSM were recruited through Sydney Sexual Health Centre (Fig. 1). Two hundred and fifty-five MSM received standard-of-care NPEP through St Vincent's Hospital NPEP service and the remaining 144 patients were referred to NPEP services within their areas of residence. There was no difference in mean age between those who participated in the study and those who did not, or between the two study arms, or between study participants by recruitment site (Table 1). Because the two- or three-drug regimen was allocated according to the relative risk of HIV acquisition, no participant in the FTC-TDF arm had an exposure to an HIV-infected source or had receptive anal intercourse as their NPEP event. The commonest reasons given for non-participation were the intensity and/or frequency of the study visits. The commonest reason ($n = 52$) for study ineligibility was MSM who were visiting from overseas or interstate.

Treatment outcomes

Ninety-one MSM were prescribed RAL-FTC-TDF, of whom five stopped NPEP for the following reasons: HIV-positive at baseline ($n = 2$); eGFR < 60 mL/minBSAc ($n = 1$);

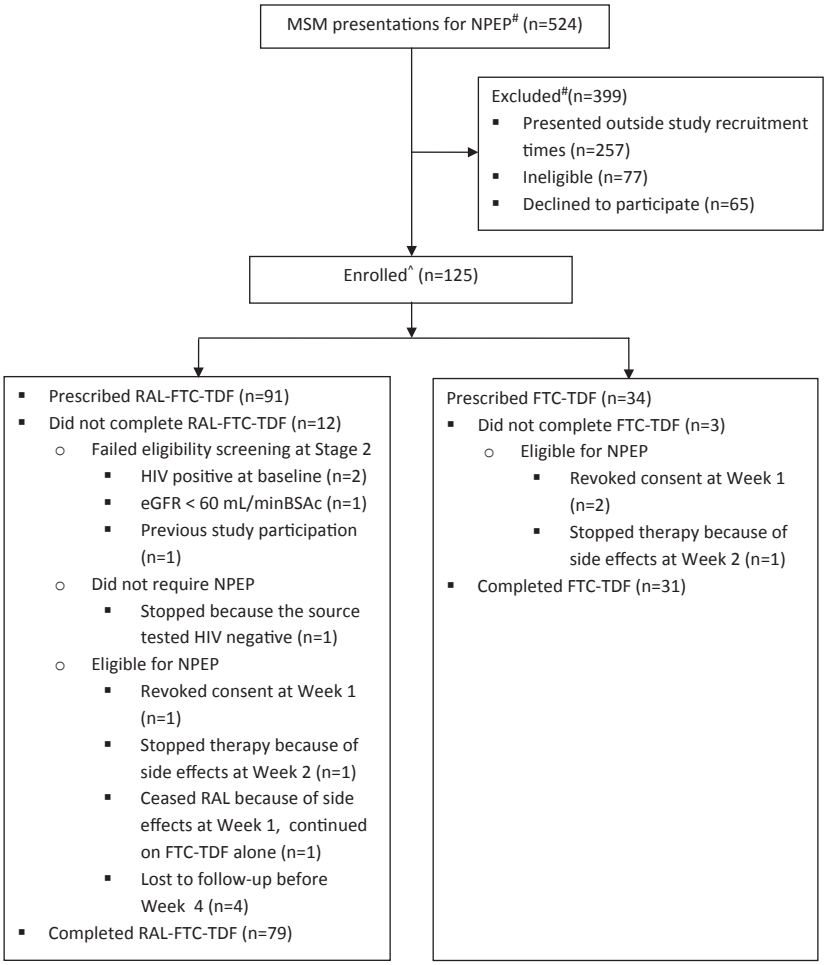

Fig. 1 Participant enrolment and follow-up. eGFR, estimated glomerular filtration rate; FTC, emtricitabine; MSM, men who have sex with men; NPEP, nonoccupational post-exposure prophylaxis; RAL, raltegravir; TDF, tenofovir. #St Vincent's Hospital data. ^Includes 23 participants recruited through Sydney Sexual Health Centre.

Table 1 Demographic and risk event profile for study participants *vs.* nonstudy participants and three-drug study participants *vs.* two-drug study participants

	Nonstudy NPEP (n = 399)	SVH participants (n = 102)	SSHC participants (n = 23)	RAL-FTC-TDF (n = 91)	FTC-TDF (n = 34)
Age (years) [mean (SD)]	32 (8)	34 (7)	32 (11)	33 (8)	35 (8)
Receptive anal sex (%)	66	62	80	87	0
Insertive anal sex (%)	27	37	22	13	97
Receptive oral sex (%)	5	1	0	1	0
Other sexual event (%)	3	0	0	0	0
Known HIV-positive source (%)	30	24	43	37	0
Previous NPEP (%)	35	40	17	36	35

FTC, emtricitabine; NPEP, nonoccupational post-exposure prophylaxis; RAL, raltegravir; SD, standard deviation; SSHC, Sydney Sexual Health Centre; SVH, St Vincent's Hospital; TDF, tenofovir.

previous enrolment in the study (n = 1); and the 'source' sexual partner was found to be HIV-uninfected (n = 1). Seventy-nine of the remaining 86 participants (92%) completed 28 days of RAL-FTC-TDF treatment (Table 2).

Thirty-four MSM were prescribed FTC-TDF alone, of whom 31 (91%) completed 28 days of treatment. The difference in completion rates was not significant between the two arms (P = 0.90).

Table 2 Treatment outcomes

Outcome	RAL-FTC-TDF (n = 86)	FTC-TDF (n = 34)	P-value*
Completed 28 days of NPEP [n (%)]	79 (92)	31 (91)	0.90
Revoked consent [n (%)]	1 (1)	2 (6)	0.19
Stopped or modified regimen because of side effects [n (%)]	2 (2)	1 (3)	1.00
Lost to follow-up before week 4 [n (%)]	4 (5)	0	0.57
Regimen adherence (%) [mean (SD)]	89 (28)	90 (29)	0.79
Achieved 100% regimen adherence (%)	52	74	0.03

FTC, emtricitabine; NPEP, nonoccupational post-exposure prophylaxis; RAL, raltegravir; SD, standard deviation; TDF, tenofovir.
*χ^2 or Fisher's exact test for differences in proportions between groups.

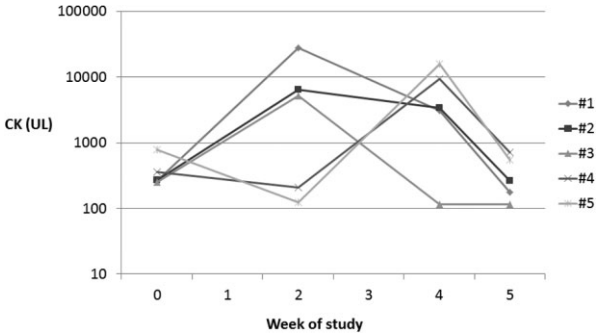

Fig. 2 Time-course of grade 4 creatine kinase (CK) elevations. The upper limit of normal for creatine kinase was 130 U/L. A grade 4 creatine kinase elevation is defined as at least 20 times the upper limit of normal (2600 U/L).

Including the seven subjects in the RAL-FTC-TDF group and the three subjects in the FTC-TDF group who ceased NPEP prematurely, mean regimen adherence in the RAL-FTC-TDF group was 89% [standard deviation (SD) 28%] *vs.* 90% (SD 29%) in the FTC-TDF group (P = 0.79). The FTC-TDF group was significantly more likely to be 100% adherent than the RAL-FTC-TDF group [74% *vs.* 52%, respectively; odds ratio (OR) 1.9; 95% CI 1.0–3.8; P = 0.03]. The 48% of RAL-FTC-TDF recipients with < 100% adherence missed a median of 2 doses [range 1–32; interquartile range (IQR) 1–5] and the 26% of FTC-TDF recipients with < 100% adherence missed a median of 1 dose (range 1–21; IQR 1–4). During the study period, 82 MSM received standard-of-care three-drug NPEP (FTC-TDF-stavudine) and 173 MSM received standard-of-care two-drug NPEP (FTC-TDF). The study three-drug NPEP recipients were significantly more likely to complete the 28-day regimen than the standard-of-care three-drug NPEP recipients (OR 2.5; 95% CI 1.2–5.2; P = 0.001). Similarly, the study two-drug NPEP recipients were significantly more likely to complete 28 days of FTC-TDF than the standard-of-care FTC-TDF recipients (OR 8.7; 95% CI 1.2–62.1; P = 0.005).

No participant seroconverted to HIV over the duration of the study.

Muscle-related adverse events

Eight patients (9%) in the RAL-FTC-TDF group and no patient in the FTC-TDF group reported myalgias after baseline (P = 0.10). No patient reported muscle weakness, although more patients receiving RAL reported fatigue (37% *vs.* 26% in the FTC-TDF group; P = 0.25).

For the 115 study participants who had at least one creatine kinase measurement on NPEP, 6% (seven of 115) developed a grade 1 or 2 creatine kinase elevation (three on FTC-TDF alone and four on RAL-FTC-TDF). There was no significant difference in the development of a creatine kinase elevation (any grade) between the FTC-TDF and RAL-FTC-TDF recipients (P = 1.00).

Grade 4 creatine kinase elevations occurred in five subjects on RAL-FTC-TDF and no subjects on FTC-TDF alone (P = 0.16). These events were most commonly seen at week 2 (SD 7 days; range 8–26 days) (Fig. 2). Three participants with grade 4 creatine kinase elevations had presentations consistent with acute muscle toxicity: two reported myalgia and one had microscopic haematuria by dipstick urinalysis. No other study participant had microscopic haematuria.

No participant ceased treatment or had their regimen changed. All patients with grade 4 creatine kinase elevations were exercising at the gym and all were advised to desist from exercise and to increase their oral fluid intake (Table 3). All grade 4 events resolved to a grade 2 or less by a mean of day 26 (SD 6 days; range 16-32 days) without changes to study medication.

Following a second HIV risk event at week 5, one of the five participants with a grade 4 creatine kinase elevation recommenced RAL-FTC-TDF NPEP with residual study medication. Four days later, without exercise, his serum creatine kinase was 2770 U/L. He was asymptomatic with normal renal function and no myoglobinuria. His only concomitant medication was citalopram. RAL was ceased and FTC-TDF continued. His creatine kinase returned to normal without any further intervention.

Other clinical adverse events

All 125 study participants reported at least one AE, with 333 AEs overall (Table 4). The 91 RAL-FTC-TDF recipients reported 260 AEs (mean 2.9/person) and the 34 FTC-TDF recipients reported 73 AEs (mean 2.1/person). Two study participants (one in each arm) ceased NPEP at week 2 because of side effects and a further participant in the

Table 3 Grade 4 increases in creatine kinase

Case number	Maximum creatinine kinase value (U/L) (day)	Symptoms	Signs	Exercising	Outcome
1	5220 (day 12)	Nil	Nil	Yes	Grade 2 by day 26
2	6350 (day 17)	Myalgias	Nil	Yes	Grade 1 by day 27
3	9330 (day 26)	Nil	Nil	Yes	Grade 1 by day 32
4	15 600 (day 21)	Myalgias	Muscle tenderness	Yes	Grade 1 by day 28
5	29 294 (day 8)	Nil	Microscopic haematuria	Yes	Grade 1 by day 16

Table 4 Frequency and severity (grade 1–2)* of subjective adverse events occurring in ≥ 5% of participants during treatment

Adverse event	RAL-FTC-TDF (n = 91)	FTC-TDF (n = 34)	Total (n = 125)	$P^{\dagger}$
Systemic [n (%)]				
Fatigue	34 (37)	9 (26)	43 (34)	0.25
Sweating	5 (5)	1 (3)	6 (5)	1.00
Thirst	9 (10)	0 (0)	9 (7)	0.11
Decreased libido	5 (5)	2 (6)	7 (6)	1.00
Infection [n (%)]				
Pharyngitis	6 (6)	2 (6)	8 (6)	1.00
Skin [n (%)]				
Pimples	5 (5)	0 (0)	5 (4)	0.32
Gastrointestinal [n (%)]				
Nausea	22 (24)	6 (18)	28 (22)	0.43
Bloating	15 (16)	7 (21)	22 (18)	0.59
Abdominal cramps	19 (21)	4 (12)	23 (18)	0.24
Flatulence	22 (24)	7 (21)	29 (23)	0.67
Diarrhoea	23 (25)	12 (35)	35 (28)	0.26
Decreased appetite	7 (8)	2 (6)	9 (7)	1.00
Increased appetite	6 (7)	1 (3)	7 (6)	0.67
Neurological [n (%)]				
Vivid dreams	14 (15)	4 (12)	18 (14)	0.77
Insomnia	5 (5)	2 (6)	7 (6)	1.00
Headache	14 (15)	7 (21)	21 (17)	0.48
Depression	9 (10)	1 (3)	10 (8)	0.28
Feeling vague	7 (8)	2 (6)	9 (7)	1.00
Impaired concentration	5 (5)	2 (6)	7 (6)	1.00
Dizziness	7 (8)	0 (0)	7 (6)	0.18
Paraesthesiae (face, scalp and/or fingers)	8 (9)	1 (3)	9 (7)	0.44
Alcohol intolerance	5 (5)	1 (3)	6 (5)	1.00
Musculoskeletal [n (%)]				
Myalgias	8 (9)	0 (0)	8 (6)	0.10

FTC, emtricitabine; RAL, raltegravir; TDF, tenofovir.
*There were no grade 3–4 subjective adverse events.
$^{\dagger}\chi^2$ or Fisher's exact test for differences in proportions between groups.

RAL-FTC-TDF arm modified his regimen because of side effects by stopping RAL at week 1 and continuing on FTC-TDF alone.

All subjective AEs were either grade 1 or 2 and 82% were possibly, probably or definitely related to study drug. Gastrointestinal AEs predominated. There was no significant difference in the proportions of any reported subjective AEs between the RAL-FTC-TDF and FTC-TDF groups.

Other laboratory adverse events

The frequency and severity of other laboratory AEs are detailed in Table 5. There was no grade 3 or 4 laboratory AE in the FTC-TDF alone recipients *vs.* nine grade 3 or 4 laboratory AEs in the RAL-FTC-TDF recipients (P = 0.11).

Grade 1–2 elevations in alanine and aspartate aminotransferases occurred in 28 (22%) study participants but grade 3 or 4 was rare (2%) and included two patients with possible rhabdomyolysis. The grade 3 or 4 transaminitis events resolved as both the participants' creatine kinase levels returned to normal.

Two (2%) of the RAL-FTC-TDF recipients and five (15%) of the FTC-TDF recipients experienced grade 1 or 2 hyperlactataemia (mean 3.6 mmol/L; reference range 2.4–5.6 mmol/L) at a mean 23 days (range 12–28 days). All

Table 5 Frequency and severity of laboratory adverse events occurring in ≥ 1% of patients during treatment

	RAL-FTC-TDF (*n*=91)		FTC-TDF (*n* = 34)		Total (*n*=125)		
Adverse event	G1–2	G3–4	G1–2	G3–4	G1–2	G3–4	*P**
Chemistries [*n* (%)]							
Alanine aminotransferase	17 (19)	1(1)	2 (6)	0 (0)	19 (15)	1 (1)	0.97
Aspartate aminotransferase	8 (9)	2 (2)	1 (3)	0 (0)	9 (7)	2 (2)	0.28
Bilirubin	2 (2)	0 (0)	1 (3)	0 (0)	3 (2)	0 (0)	1.00
Creatine kinase	4 (4)	5 (5)	3 (9)	0 (0)	7 (6)	5 (4)	1.00
Hypophosphataemia	2 (2)	0 (0)	1(3)	0 (0)	3 (2)	0 (0)	1.00
Hyperlactataemia	2 (2)	0 (0)	5 (15)	0 (0)	7 (6)	0 (0)	0.01
Amylase	4 (4)	0 (0)	1 (3)	0 (0)	5 (4)	0 (0)	1.00
Lipase	2 (2)	1 (1)	1 (3)	0 (0)	3 (2)	1 (1)	1.00
Urinalysis [*n* (%)]							
Proteinuria	3 (3)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)	0.56
Haematuria	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1.00

FTC, emtricitabine; G1–2, grade 1–2; G3–4, grade 3–4; RAL, raltegravir; TDF, tenofovir.
*χ^2 or Fisher's exact test for differences in proportions between groups.

were asymptomatic and all completed 28 days of NPEP. These elevations in serum lactate resolved after treatment with the study drug ceased.

Concomitant licit and illicit drug use

Almost half (46%) of the study participants were taking at least one other prescribed medication regularly. These medicines included antipsychotics, antidepressants, hypnotics, benzodiazepines, opiates, corticosteroids, anticonvulsants, proton pump inhibitors, anti-histamines, beta blockers, calcium channel blockers, angiotensin-converting-enzyme inhibitors, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and phosphodiesterase type 5 (PDE5) inhibitors. We identified eight potential drug interactions in eight study participants in the three-drug arm where, had a protease inhibitor been the third component of the regimen, concomitant protease inhibitor use would have been an absolute contraindication in two cases (simvastatin and St John's Wort) or a relative contraindication in six [phenytoin, sildenafil (two participants), vardenafil, carbamazepine and budesonide].

Of the 125 study participants, 121 (97%) provided a substance use history, of whom 89 (74%) indicated regular drug use. Seventy-three of these (82%) used alcohol and 37 (42%) used at least one illicit, 'recreational' drug (Fig. 3). Of these, 18 (49%), nine (24%) and seven (19%) were using methamphetamine (ice), gamma-hydroxybutyrate (GHB) and 3,4-methylenedioxy-*N*-methylamphetamine (ecstasy), respectively.

Discussion

In this population of young men receiving RAL-FTC-TDF as NPEP, 92% completed 28 days of treatment, very similar to the percentage who completed 28 days of FTC-TDF treatment (91%). The use of RAL rather than a protease inhibitor avoided eight known prescribed drug interactions, and 37 potential interactions with illicit drugs. However, 9% of patients receiving RAL-FTC-TDF developed a grade 4 creatine kinase elevation, of whom three had a clinical presentation consistent with a degree of rhabdomyolysis, although none developed renal impairment or ceased RAL as a result.

When we compared completion rates for study regimen recipients with those for our clinic standard-of-care three-drug and two-drug NPEP recipients, we found that study three-drug recipients and study two-drug recipients were both significantly more likely to complete 28 days of their allocated regimen than were nonstudy three- and two-drug NPEP recipients. Our completion rate of 92% with RAL-TDF-3TC is also greater than the 57% reported by Mayer *et al.* in a study of 100 adults (98% male, 92% MSM and 76% White; mean age 33 years) [24]. Twenty-eight per cent of participants in that study stopped or modified RAL-TDF-3TC, 15% were lost to follow-up, 67% of those who completed therapy took 100% of their doses and approximately a quarter consistently missed their second dose of RAL.

There may be several reasons for the differences seen among these three groups (i.e. our study drug recipients, our nonstudy NPEP recipients, and Mayer *et al.*'s study drug recipients). First, our study participants received a high level of support, including management by a single nurse consultant with extensive experience in NPEP, frequent clinical review, 24-hour contact with the nurse consultant by mobile phone, appointment reminders by SMS messaging and proactive recall following a missed appointment. Secondly, we provided specific and frequent adherence education. Thirdly, 36% of the RAL-FTC-TDF group and 35% of the FTC-TDF group had previously

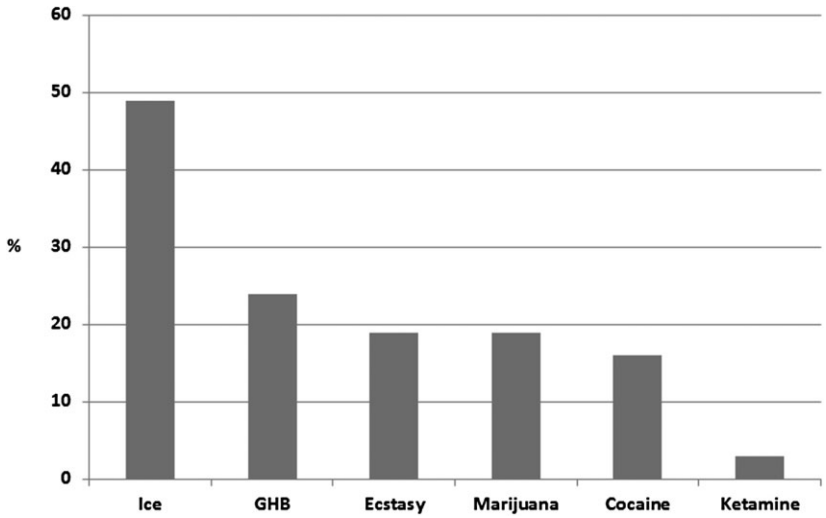

Fig. 3 Recreational drug use in study participants. GHB, gamma-hydroxybutyrate; ice, methamphetamine.

received NPEP containing FTC-TDF at least once with previous adherence education, so may have been selected for better FTC-TDF tolerability. Fourthly, we possibly introduced a social desirability bias by the explicit expectation of 100% adherence as measured by participant-anticipated pill counting. Overall, the different adherence rates in our study, in the study by Mayer *et al.* and in our clinic controls suggest that implementation of more intensive education and support may yield improvements in adherence above and beyond any gains achieved with simpler NPEP. Whether other NPEP regimens that can be taken once-daily can result in improved medication adherence needs exploration, although the potential margin for improvement seems small.

Five study participants (all on RAL-FTC-TDF) developed a grade 4 creatine kinase elevation (median 72 times the upper normal limit). Of these five participants, two reported myalgias and one had microscopic haematuria. All five cases were confounded by concurrent exercise (although none of the participants was receiving a statin) and no participant ceased NPEP as a result. In a recent overview, grade 3 or 4 creatine kinase elevations were reported in 5 to 13% of HIV-infected adults commencing treatment with an integrase inhibitor, although cases of myopathy or rhabdomyolysis were rare [23]. Our data show that this can occur within 4 weeks in HIV-uninfected adults.

We can also report additional experience with RAL used as NPEP outside of the study protocol. During the study period, a healthy, 32-year-old medical officer received 28 days of RAL-FTC-TDF as OPEP. His creatine kinase was normal at baseline testing, had increased to 18 300 U/L by day 19 and peaked at 46 400 U/L on day 21. He was symptomatic with significant myalgia and his urine was positive for myoglobin. He was exercising at the gym (which he ceased) and was taking no other medicines. He completed his 28 days of RAL-FTC-TDF and his creatine kinase returned to normal within 7 days of completing NPEP.

The New York State Department of Health AIDS Institute recently listed RAL-FTC-TDF as its preferred OPEP regimen [28]. Because of the potential muscle toxicity we observed, it is not clear whether RAL-FTC-TDF should be a preferred NPEP regimen. If RAL-FTC-TDF is used as NPEP, we would recommend: inquiry about concomitant medications associated with rhabdomyolysis, for example statins; patient education about the possible link between rhabdomyolysis, exercise and PEP containing RAL; the need for patients to report and providers to ask about myalgia; baseline measurement of serum creatine kinase with at least one other measurement during the course of treatment if myalgias or weakness develops, and clinical examination for proximal muscle weakness.

Subjective AEs in our study were common (mean 2.7 per subject, predictable and mild or moderate in severity. MSM receiving NPEP with RAL-FTC-TDF or FTC-TDF alone should be warned about the nature and frequency of probable AEs but be reassured that these are, in the main, tolerable.

We found high rates of 'recreational drug use' but, given that our participants were young (mean age 34 years), the high rate of prescribed co-medication was unexpected. Raltegravir is not a cytochrome P450 substrate, inducer or inhibitor and so P450-related drug interactions between RAL and licit or illicit drugs are not a concern. Eight (6%)

of our study participants used prescribed drugs that could adversely interact with a protease inhibitor or cobicistat and 37 (41%) were using illicit, 'recreational' substances including the stimulants ecstasy, amphetamine and cocaine, and the depressant GHB. There is virtually no research in this area, although there have been case reports of death and near-fatal reactions between ecstasy and ritonavir and GHB and saquinavir/ritonavir [29–31].

Our study has limitations. It was confined to White MSM and performed at only two sites. Our data cannot be extrapolated, therefore, to injecting drug users, women, non-White men or children. We compared NPEP regimen completion rates with those of clinic controls, but unmeasured biases limit any conclusion concerning equivalence or superior tolerability. Announced pill counts may result in an overestimation of adherence because social desirability can result in 'pill dumping' before a scheduled visit [32]. However, when used to assess adherence in HIV-positive patients on antiretroviral treatment, pill counts have been shown to correlate with electronic drug monitoring and HIV viral load and provide an objective measure of adherence [33]. Finally, our study was nonrandomized with a relatively small sample size and therefore inadequately powered to determine the clinical significance of the muscle-related AEs seen in the RAL-FTC-TDF arm.

In summary, RAL-FTC-TDF was well tolerated with high rates of on-drug adherence and treatment completion. Its use (as opposed to a protease inhibitor) avoided potentially dangerous drug interactions in a substantial number of our patients. The muscle-related AEs, while of unclear clinical significance, raise a cautionary note concerning its unmonitored use in PEP. Larger, multicentre randomized trials adequately powered to assess both adherence to and safety of various three-drug NPEP regimens in more diverse patient populations are required.

Acknowledgements

The authors would like to recognize the 125 men who participated in the study and committed themselves to frequent clinical visits and blood sampling, the assistance from Robyn Richardson and Nicola Mackenzie with site and data management, and helpful comments from Dr Sarah Pett.

Conflicts of interest: JM, AM, WWYT and AI report no conflict of interest. PR has received financial support to attend educational conferences from MSD, ViiV Healthcare, Janssen, BMS, BI and Gilead Sciences. He has also received honoraria for noncommercial educational presentations from MSD and Janssen. AC has received research funding from Baxter, Gilead Sciences and MSD; has received consultancy fees and lecture and travel sponsorships from Gilead Sciences, MSD, Serono and ViiV Healthcare; and has served on advisory boards for Gilead Sciences, MSD, and ViiV Healthcare.

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