

Dolutegravir with tenofovir disoproxil fumarate–emtricitabine as HIV postexposure prophylaxis in gay and bisexual men

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Objectives: Completion rates for HIV postexposure prophylaxis (PEP) are often low. We investigated the adherence and safety of dolutegravir (DTG; 50 mg daily) with tenofovir disoproxil fumarate–emtricitabine (TDF–FTC; 300/200 mg, respectively) as three-drug PEP in gay and bisexual men.

Design: Open-label, single-arm study at three sexual health clinics and two emergency departments in Australia.

Methods: In total, 100 HIV-uninfected gay and bisexual men requiring PEP received DTG and TDF–FTC for 28 days. The primary end point was PEP failure (premature PEP cessation or primary HIV infection through week 12). Additional end points were adherence by self-report ($n = 98$) and pill count ($n = 55$), safety, and plasma drug levels at day 28.

Results: PEP completion was 90% (95% confidence interval 84–96%). Failures (occurring at a median 9 days, interquartile range 3–16) comprised loss to follow-up (9%) and adverse event resulting in study drug discontinuation (headache, 1%). No participant was found to acquire HIV through week 12. Adherence to PEP was 98% by self-report and in the 55 participants with corresponding pill count data. The most common clinical adverse events were fatigue (26%), nausea (25%), diarrhoea (21%), and headache (10%). There were only four grade 3–4 subjective adverse events. The most common laboratory adverse event was raised alanine aminotransferase (22%), but there was no case of clinical hepatitis. At day 28, the mean estimated glomerular filtration rate decrease was 14 ml/min/1.73m² (SD 17, $P = 0.001$); an estimated glomerular filtration rate of less than 60 ml/min/1.73m² occurred in 3%.

Conclusions: DTG with TDF–FTC is a well tolerated option for once-daily PEP.

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Introduction

Condoms protect gay and bisexual men (GBM) from sexually acquired HIV infection but are at best 70% effective [1]. Antiretrovirals also reduce risk of HIV infection when used as either postexposure prophylaxis (PEP) or more recently as preexposure prophylaxis [2,3]. Nonhuman primate studies, studies of mother-to-child HIV transmission, a single case-control study of healthcare workers occupationally exposed to HIV, and cohort data all provide a supportive evidence base for use of PEP [4–7].

PEP can cause harm, including severe cutaneous toxicity and fulminant hepatitis with nevirapine, hypersensitivity with abacavir, and nephrolithiasis with indinavir [8–10]. Additionally, less severe side-effects can cause patients to stop PEP prematurely. In a meta-analysis, 33% of GBM ceased PEP prematurely; toxicity-driven discontinuation was more common with three-drug than with two-drug PEP (9% vs. 2%, respectively) [11].

Numerous guidelines recommend tenofovir (TNV) disoproxil fumarate (TDF) with either emtricitabine (FTC) or lamivudine 300 mg as the preferred nucleoside reverse transcriptase inhibitors in PEP, as TDF is better tolerated than zidovudine [12–15]. The WHO recommends three-drug PEP for all, but there is no consensus regarding the preferred third drug [2]. A systematic review found that PEP completion rates were highest for boosted darunavir/TDF-FTC (94%), raltegravir/TDF-FTC (75%), and lopinavir/TDF-FTC (71%) [15]. We found that TDF-FTC with raltegravir or rilpivirine resulted in 92% completion [16,17]. However, raltegravir requires twice-daily dosing and can rarely cause rhabdomyolysis and rilpivirine requires dosing with food.

In large studies of HIV-positive adults, the integrase inhibitor dolutegravir (DTG) was potent and well tolerated [18,19]. DTG has a short time to maximum plasma concentration (T_{max}), a long half-life, and is taken as one tablet, once daily with no dietary restrictions—all excellent characteristics for a PEP candidate. We evaluated the safety, tolerability, and adherence of three-drug, once-daily PEP containing DTG 50 mg with TDF-FTC.

Methods

Design

The trial was a multicenter, open-label, single-arm trial. In total, 100 eligible GBM were assigned to receive DTG 50 mg one tablet, once daily with TDF-FTC for 28 days according to Australian PEP guidelines for the use of three-drug PEP [12]. Participants attended for up to seven study visits over 12 weeks.

Study settings

The study was conducted in five centres at which GBM self-refer for PEP: St Vincent's Hospital, Sydney; Melbourne Sexual Health Centre; Sydney Sexual Health Centre; The Alfred Hospital, Melbourne and Clinic 16, Northern Sydney Sexual Health, Sydney. St Vincent's Hospital Human Research Ethics Committee granted ethical approval (approval number HREC/14/SVH/29). The protocol is registered on ClinicalTrials.gov, ID NCT02211690.

Eligibility criteria

GBM eligible for three-drug PEP were offered study participation. The study was restricted to GBM because they are the principal target group for PEP in Australia, account for almost all PEP use, and represent most incident HIV infections [20]. A two-stage eligibility screening process followed written, informed consent. Participants were ineligible if they were using any medicine contraindicated with study medications, had known chronic active or treated hepatitis B virus infection or had received PEP containing DTG in the past. Participants were also ineligible if at visit 2 (3–5 days after PEP commencement), baseline serology was consistent with established or possible primary HIV infection, serum alanine aminotransaminase (ALT) was greater than five times the upper limit of normal, the estimated glomerular filtration rate (eGFR) was less than 60 ml/min/1.73m², or serology was consistent with chronic active hepatitis B virus. These study participants ceased study medication and were managed as per usual site-specific protocols.

Assessments and outcome measures

Subjective adverse event were recorded at each subsequent visit and graded as previously described [16,17]. Drug adherence was measured by self-report and pill count at weeks 2, 4, and 5 (calculated by dividing the number of doses returned by the number of doses dispensed, expressed as the percentage of doses taken).

All participants received standardized education regarding potential subjective adverse effects and adherence. All participants received an short message service (SMS) reminder prior to each appointment and were contacted if an appointment was missed.

Blood was tested for HIV, hepatitis B, hepatitis C, and syphilis at screening. HIV and syphilis testing was repeated at weeks 4 and 12. Biochemistry, liver function tests, glucose, amylase, lipase, creatine kinase, and lactate were checked at baseline and weeks 2 and 4. Plasma was stored at baseline for HIV genotype/RNA testing in the event that baseline or subsequent HIV infection was demonstrated. Urinalysis was performed at baseline and week 4.

Plasma levels of DTG, FTC, and TNV were measured using high-performance liquid chromatographic separation

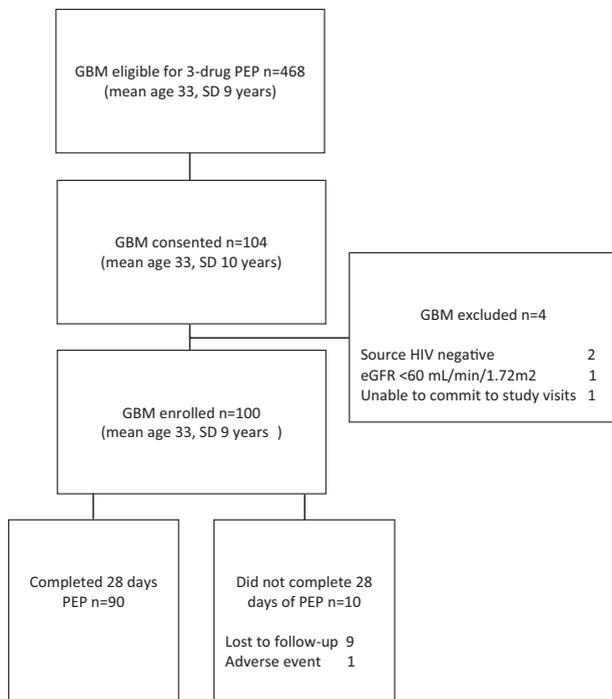


Fig. 1. Eligibility, enrollment and outcome. Consort Diagram eGFR, estimated glomerular filtration rate; GBM, gay and bisexual men; PEP, postexposure prophylaxis.

at week 4 while on PEP (PPD Laboratories 3230 Deming Way, Middleton, Wisconsin, USA). A plasma TNV level at least 40ng/ml indicates recent full adherence and a DTG level of at least 64ng/ml is associated with undetectable HIV viral load [21,22].

The primary end point was premature PEP cessation defined by cessation of PEP prior to day 28 (except if their 'source' partner was subsequently found to be HIV uninfected or the participant was found to be HIV positive at baseline) or primary HIV infection through week 12. Secondary end points were adherence (by self-report of doses missed, by pill count, and by plasma concentrations of DTG and TNV at week 4) and safety (clinical and laboratory adverse events, PEP cessation for adverse events).

Sample size and data analysis

For an estimated completion rate of 95%, 100 participants provided a 95% confidence interval (CI) of 90.7–99.3%. Analyses were performed on the intention-to-treat population unless otherwise stated. Descriptive statistics were calculated. Changes from baseline in laboratory parameters were tested for significance using the paired samples *t*-test. Significance was set at 0.05 and CIs at 95%.

Results

Baseline characteristics

Between 1 August 2014 and 30 October 2015, 468 men received three-drug PEP: 104 were consented and 100

were eligible (Fig. 1). The commonest reason for nonenrollment was presentation when study personnel were not available. As per protocol, four participants were withdrawn at day 3: two because the source partners were found to be HIV uninfected; one because of an eGFR less than 60 ml/min/1.73m² and one because he was unable to commit to study visits.

In total, 70% participants presented following condomless anal sex and the remainder after condom failure. In total, 40% exposure events occurred with an HIV-positive source and, of those, 10% and 8% reported an undetectable or detectable viral load, respectively. Forty-one percentage of participants reported the receipt of previous PEP (median 1 [interquartile range (IQR) 1–2, range 1–12] prior episodes).

Treatment outcomes

Of the 100 eligible study participants, PEP completion was 90% (95% CI 84–96). Failures comprised loss to follow-up (9%) and one adverse event resulting in PEP discontinuation (headache, 1%). Discontinuations occurred at a median 9 days (IQR 3–16). No participant was found to acquire HIV at week 4 ($n = 90$) or week 12 ($n = 77$). In total, 6% and 9% participants were diagnosed with *Chlamydia trachomatis* or *Neisseria gonorrhoea*, respectively, (four with both), 3% with primary anogenital herpes simplex virus infection, and one participant with infectious syphilis.

For the 98 participants with available data, self-reported medication adherence to all expected doses was 98% (SD 4%). Of the 55 participants with corresponding self-reported adherence and pill count data, adherence was also 98% (SD 3%). There was no reported or observed differential dosing for DTG vs. TDF+FTC.

In total, 85 participants had plasma DTG levels and 89 participants had TNV levels measured at week 4, a median of 16 h (IQR 11–22) after the last dose of medication. Of these, 94% had a DTG drug level at or greater than the protein-adjusted inhibitory concentration (IC₉₀) and 79% a TNV drug level at least 40ng/ml.

Safety

Subjective adverse events were predominantly gastrointestinal [nausea (25%), diarrhea (21%), flatus (9%), abdominal pain (9%), bloating (4%), and vomiting (2%)] or affecting the central nervous system [headache (10%), vivid dreams (7%), and dizziness (3%)]. There were four subjective adverse events graded 3–4 (vivid dreams, insomnia, headache, and fatigue). One patient ceased study medication at day 3 because of grade 3 headache. There was no unexpected adverse event or serious adverse event.

The most common laboratory adverse events are shown in Table 1. Transaminitis (raised ALT) was common (22%)

Table 1. Laboratory adverse events occurring in at least 1% of participants during treatment.

Laboratory test	Grade 1–2	Grade 3–4
Chemistries [<i>n</i> ^a (%)]		
Creatinine	10/93 (11)	
Glucose	1/91 (1)	
Hypophosphatemia	5/91 (5)	
Bilirubin	4/93 (4)	1/89 (1)
Alanine aminotransferase	21/96 (22)	
Creatine kinase	8/92 (9)	1/92 (1)
Lipase	7/92 (8)	1/84 (1)
Amylase	7/92 (8)	1/85 (1)
Lactate	8/91 (9)	1/89 (1)
Urinalysis [<i>n</i> (%)]		
Proteinuria	10/88 (11)	
Hematuria	1/88 (1)	
Glycosuria	2/88 (2)	

^aNot all patients had laboratory testing at visit 3 (day 12–14) and/or visit 4 (day 26–28).

Grade 1–4 laboratory adverse events were not counted if occurring at baseline with resolution by visit 3. Laboratory adverse events were counted if they escalated a grade at visit 3 or 4 or recurred at visit 4.

but universally grade 1–2. Three participants developed an eGFR less than 60 ml/min/1.73m²; the mean eGFR decrease at day 28 was 14 ml/min/1.73m² (SD 17, *P* = 0.001). Grade 1–2 proteinuria, grade 1–2 hematuria, and grade 1–2 glycosuria were noted in 11%, 1%, and 2% at day 28, respectively. Of the two participants with glycosuria, neither had hyperglycemia. No participant who developed an elevated serum creatine kinase had myalgia or reported muscle weakness. On follow-up testing of the three study participants who experienced an eGFR of less than 60 ml/min/1.73m², eGFR returned to prestudy baseline.

Discussion

In this population of GBM, 90% completed PEP with DTG/TDF–FTC, a rate similar to comparable studies of raltegravir or rilpivirine with TDF–FTC and superior to the reported third of GBM who fail to complete other PEP regimens [11,16,17].

Adherence (reported and observed) to DTG/TDF–FTC was high (estimated 98% of all doses taken). There was no evidence of differential dosing, but the discrepancy between the proportion with low DTG and TNV levels (6% and 21%, respectively) suggests that some participants may have taken more doses of DTG than of TDF–FTC. Pharmacokinetic differences seem less likely given that TDF has a longer half-life than DTG.

Subjective adverse events were common and largely grade 1–2. ALT changes were asymptomatic and not accompanied by hyperbilirubinemia. In large trials in HIV-positive adults, DTG was associated with ALT elevations to greater than three times the upper limit of normal in

2–5% (rates similar to those in comparator groups) that were rarely symptomatic [18,19]. Hepatitis and hepatic failure, particularly in patients with hepatitis B or C coinfection, is a rare potential adverse effect of DTG. It may be reasonable to screen for viral hepatitis and monitor ALT with PEP including DTG.

The decrease in eGFR we observed is consistent with the known benign DTG inhibition of the renal tubular organic cation transporter 2 (OCT2) receptor responsible for tubular secretion of creatinine; participants were, however, also taking TDF which is significantly associated with (usually modest) kidney disease in HIV-positive adults [22,23]. This confounding highlights the need to check renal function at baseline when initiating PEP with DTG and/or TDF and, in those found to have biochemical markers of decreased renal function, consider switching DTG and/or TDF to another agent not associated with artefactual or actual eGFR decreases.

Our study has limitations. The sample size is relatively small. The experience of non-GBM and women may differ. Almost half of participants had received PEP previously, the study was uncontrolled and open label, participants were warned about potential adverse events, received SMS reminders about clinic visits, and regular clinical review during the 28 days of PEP; all of these factors could positively or negatively affect adherence, regimen completion, and the reporting of adverse events, although perhaps less so for DTG.

In conclusion, DTG/TDF–FTC as daily PEP was well tolerated and resulted in high completion rates and levels of daily adherence. Baseline renal and liver function testing should precede the initiation of DTG/TDF–FTC as PEP.

Acknowledgements

J.W.M., A.C., and R.R. contributed equally to the study concept and study design. J.W.M. conducted the analysis. All authors contributed to writing the study manuscript.

Conflicts of interest

The work was supported in part by a ViiV Healthcare educational grant, including study drug provision. ViiV Healthcare had no input into the study design or analyses.

J.W.M. has received lecture fees and travel sponsorships from ViiV Healthcare. A.C. has received grants and research funding from Gilead Sciences and ViiV Healthcare, provision of study drug from ViiV healthcare, travel sponsorship from Gilead Sciences and ViiV Healthcare, payment of lecture fees from Gilead Sciences,

and is on the advisory boards for Gilead Sciences and ViiV Healthcare. For the remaining authors, no conflicts of interest are declared.

References

- Smith DK, Herbst JH, Zhang X, Rose CE. **Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States.** *J Acquir Immune Defic Syndr* 2015; **68**:337–344.
- Nathan Ford N, Mayer KH, World Health Organization Post-exposure Prophylaxis Guideline Development Group. **World Health Organization guidelines on postexposure prophylaxis for HIV: recommendations for a public health approach.** *Clin Infect Dis* 2015; **60** (Suppl 3):S161–S164.
- Grant RM, Lama JR, Anderson PL, McMahon V, Liu AY, Vargas L, *et al.*, iPrEx Study Team. **Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.** *N Engl J Med* 2010; **363**:2587–2599.
- Irvine C, Egan KJ, Shubber Z, Van Rompay KK, Beanland RL, Ford N. **Efficacy of HIV postexposure prophylaxis: systematic review and meta-analysis of nonhuman primate studies.** *Clin Infect Dis* 2015; **60** (Suppl 3):S165–S169.
- Wade NA, Birkhead GS, Warren BL, Charbonneau TT, French PT, Wang L, *et al.* **Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus.** *N Engl J Med* 1998; **339**:1409–1414.
- Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, *et al.* **A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for disease control and prevention Needlestick Surveillance Group.** *N Engl J Med* 1997; **337**:1485–1490.
- Thomas R, Galanakis C, Vezina S, Longpre D, Biossonnault M, Huchet E, *et al.* **Adherence to post-exposure prophylaxis (PEP) and incidence of HIV seroconversion in a major North American cohort.** *PLoS One* 2015; **10**:e0142534.
- Patel SM, Johnson S, Belknap SM, Chan J, Sha BE, Bennett C. **Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals.** *J Acquir Immune Defic Syndr* 2004; **35**:120–125.
- Easterbrook PJ, Waters A, Murad S, Ives N, Taylor C, King D, *et al.* **Epidemiological risk factors for hypersensitivity reactions to abacavir.** *HIV Med* 2003; **4**:321–324.
- van der Ende ME, Regez RM, Schreijff G, van der Meer JTM, Danner SA, Dutch PEP registration. **Postexposure prophylaxis.** *Int J STD AIDS* 2002; **13** (Suppl 2):30–34.
- Ford N, Irvine C, Shubber Z, Baggailey R, Beanland R, Vitoria M, *et al.* **Adherence to HIV postexposure prophylaxis: a systematic review and meta-analysis.** *AIDS* 2014; **28**:2721–2727.
- Australasian Society for HIV Medicine. **Post-Exposure prophylaxis after nonoccupational and occupational Exposure to HIV 2016;** <http://www.ashm.org.au/pep-guidelines>. [Accessed on 12 November 2016]
- British HIV Association. **UK National guideline for the use of HIV postexposure prophylaxis following sexual exposure (PEPSE) 2015;** <http://www.bhiva.org/PEPSE-guidelines.aspx>. [Accessed on 12 November 2016]
- Centers for Disease Control and Prevention. **Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016;** <http://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf>. [Accessed on 12 November 2016]
- Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, *et al.* **Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review.** *Clin Infect Dis* 2015; **60** (Suppl 3):S170–S176.
- McAllister J, Read P, McNulty A, Tong WWY, Ingersoll A, Carr A. **Raltegravir-emtricitabine-tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence.** *HIV Med* 2014; **15**:13–22.
- Foster R, McAllister J, Read TR, Pierce AB, Richardson R, McNulty A, Carr A. **Single-tablet emtricitabine-rilpivirine-tenofovir as HIV postexposure prophylaxis in men who have sex with men.** *Clin Infect Dis* 2015; **61**:1336–1341.
- Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, *et al.*, extended SPRING-2 Study Group. **Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naïve adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double blind, non-inferiority trial.** *Lancet Infect Dis* 2013; **13**:927–935.
- Walmsley SL, Antela A, Clumek N, Duiculescu D, Eberhard A, Gutiérrez F, *et al.*, SINGLE Investigators. **Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection.** *N Engl J Med* 2013; **369**:1807–1818.
- The Kirby Institute. **HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2015;** <http://kirby.unsw.edu.au/surveillance/Annual-Surveillance-Reports>. [Accessed on 12 November 2016]
- Hendrix CW, Andrade A, Bumpus NN, Kashuba AD, Marzinke MA, Moore A, *et al.* **Dose frequency ranging pharmacokinetic study of tenofovir-emtricitabine after directly observed dosing in healthy volunteers to establish adherence benchmarks (HPTN 066).** *AIDS Res Hum Retroviruses* 2016; **32**:32–43.
- Cottrell ML, Hadzic T, Kashuba AD. **Clinical pharmacokinetic, pharmacodynamic and drug-interaction profile of the integrase inhibitor dolutegravir.** *Clin Pharmacokinet* 2013; **52**:981–994.
- Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. **Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients.** *Clin Infect Dis* 2010; **51**:496–505.