Randomised controlled trial of the tolerability and completion of maraviroc compared to Kaletra® in combination with Truvada® for HIV post-exposure prophylaxis (MiPEP Trial)

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Short Title: Maraviroc for HIV post-exposure prophylaxis

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ABSTRACT

Objectives: Post-exposure prophylaxis (PEP) for HIV is often poorly tolerated, and not completed. Alternative PEP regimens may improve adherence and completion, aiding HIV prevention. We conducted an RCT of a maraviroc-based PEP regimen compared to a standard-of-care regimen using ritonavir–boosted lopinavir.

Methods: Patients attending 5 UK sexual health clinics, meeting criteria for PEP were randomized, to Truvada® (TVD) 200/245mg OD plus Kaletra® 400/100mg or maraviroc 300mg BD. The composite primary end point was completion of 28 days of the allocated PEP regimen without grade 3 or 4 clinical or laboratory adverse events (AEs) related to the PEP medication.

Results: 213 individuals were randomised (107 to maraviroc; 106 toritonavir-boosted lopinavir). Follow-up rates were high in both groups. There was no difference in the primary end point (p=0.36) completed PEP without grade 3 or 4 AEs. Discontinuation of PEP was the same (18%) in both groupsThere were no grade 3 or 4 clinical AEs in either arm, but more grade 1 or 2 clinical AEs in the ritonavir-boosted lopinavir arm (91% vs. 70%; p< 0.001). There were somewhat more grade 1 or 2 laboratory abnormalities in the ritonavir-boosted lopinavir arm (64% vs 49%; p=0.056). Antidiarrhoeal medication use was higher in the ritonavir-boosted lopinavir arm (67% vs 25%; p< 0.001). There were no HIV seroconversions in the study period.

Conclusion: The completion rate in the absence of grade 3 or 4 adverse events was similar with both regimens. Maraviroc-based PEP was better tolerated, supporting its use as an option for non-occupational PEP.

Introduction

HIV post-exposure prophylaxis (PEP) is a well-established prevention strategy in the UK and most of the developed world. The current United Kingdom National Guideline for the Use of HIV Post-Exposure Prophylaxis Following Sexual Exposure (PEPSE) recommends triple combination therapy for 28-days, to be started as soon as possible after exposure, preferably within 24 hours, but it can be offered up to 72 hours after [1]. PEP should be considered when other strategies for preventing HIV infection have not been used or failed, and requires a risk-benefit assessment to be undertaken for each individual presenting following an exposure event.

A prospective randomised-controlled trial to determine the efficacy of post-exposure prophylaxis following sexual exposure has been precluded due to the high number of participants that would be required for such a study. In addition the evidence from observational studies in favour of efficacy has led to a lack of the necessary equipoise. A case-control study conducted in healthcare workers suggested that the use of zidovudine (AZT) for post-exposure prophylaxis (PEP) after percutaneous exposure to HIV-infected blood was associated with a significant decrease in the risk of HIV transmission [2]. In addition mother to child transmission studies where only the neonate received antiretroviral therapy have also demonstrated a protective effect [3, 4]. Animal models mimicking sexual exposure either vaginally or rectally also show protective benefits of the use of antiretroviral therapy and demonstrate that time to initiation and duration of PEP influence outcome of PEP, with delays and shorter courses reducing effectiveness [5].

However studies also suggest that PEP is often poorly tolerated, with individuals frequently reporting side effects and poor completion rates [6]. As delayed initiation and non-completion of PEP are likely to reduce efficacy, it is important to actively manage side-effects and to choose regimens that are likely to be better tolerated.

The UK guideline for the use of post-exposure prophylaxis for HIV following sexual exposure [7], at the time of initiation of our study, recommended tenofovir (TDF) and emtricitabine (FTC) as the fixed dose combination Truvada® (TVD) and ritonavir-boosted lopinavir (LPV/r - Kaletra®) for 28 days as

standard of care. In non-randomised comparisons PEP regimens containing TDF combined with lamivudine (3TC) or FTC were associated with improved completion rates and fewer treatment discontinuations due to adverse events, than regimens containing zidovudine (ZDV) [8,9]. The combination of TDF and FTC has also been shown to prevent acquisition of HIV infection when used as pre-exposure prophylaxis (PrEP) [10-12].

The choice of third agent is less clear and depends on consideration of short term tolerability. It is well recognized that ritonavir-boosted protease inhibitors (rPI) including LPV/r are commonly associated with gastrointestinal side effects and elevations in blood lipids [13]. In the ABT-730 study conducted in HIV positive participants, 37% experienced grade 3 or 4 adverse events and laboratory abnormalities in the LPV/r arm [14]. LPV/r also inhibits cytochrome p450 CYP3A and therefore has the potential for drug-drug interactions.

Maraviroc (MVC), a CCR5 antagonist has been shown to be an effective antiretroviral agent in the MOTIVATE and MERIT studies [15-18]. In MERIT the percentage of patients achieving HIV-1 RNA < 50 copies/mL was comparable to those receiving efavirenz where they had CCR5-tropic virus at baseline. Also, MVC does not inhibit any of the major P450 enzymes at clinically relevant concentrations and appears to have fewer drug-drug interactions than LPV/r. Furthermore the observed frequency of grade 3 or 4 adverse events was low (20%) in the MERIT study.

MVC acts pre-integration which may have theoretical advantages for use in both PrEP and PEP. Animal data demonstrates that the use of a CCR5 inhibitor reduced the likelihood of macaques acquiring SIV following vaginal exposure [19]. MVC has also been demonstrated to penetrate the male and female genital tract well and achieve high rectal tissue concentrations [20, 21].

We conducted an open-label, randomised controlled trial designed to determine whether a MVC-based PEP combination was superior to a LPV/r-based combination. The comparison was based on the proportion of patients who complete a full PEP course in the absence of clinically important treatment-related toxicities.

Methods

Study design and participants

We conducted a parallel-group randomised controlled open-label trial to compare tolerability of MVC-based PEP relative to a LPV/r-based combination. We enrolled participants attending 5 sexual health clinics in England. Eligible participants were adults aged 18 years or older who were considered eligible for PEP for non-occupational exposure according current UK national guidelines; participants had to report unprotected anal or vaginal intercourse with a known HIV positive partner, or a partner at high risk for HIV. Patients with a positive HIV antibody test result at screening, currently receiving medication with known interactions with MVC or LPV/r, pregnant or possibly pregnant were not eligible. If the source was known to have multi-drug resistant HIV and therefore more likely to have CXCR 4-tropic virus, these participants were also excluded.

Ethics

The protocol was reviewed and approved by the London-Riverside Research Ethics Committee (REC reference number: 11/LO/1333) and by the Medicines and Healthcare products Regulatory Agency. All participants provided written informed consent. The trial was registered with the International Standard Randomised Controlled Trial Number registry (number ISRCTN63350011).

Randomisation

Randomisation occurred on the day the patient attended the clinic requesting PEP. Participants were randomly assigned (1:1) to TVD, one tablet once daily in addition to either a) MVC (300 mg), one tablet twice daily (experimental arm) or b) LPV/r (lopinavir 200 mg, ritonavir 50 mg), two tablets twice daily (control arm) for 28 days. Block randomisation was undertaken, with blocks of varying size, stratified by centre. Randomisation was performed online; treatment allocation was open label.

Procedures

All trial participants started their allocated medication on the randomisation day (baseline visit) and were followed according to the trial schedule which included study visits at baseline, days 14 and 28 and month four. Study medication was dispensed at baseline and again at the day 14 visit for an individual to complete the full course of 28 days of PEP, according to usual clinical practice. Adherence to the PEP regimen was measured by self-reported completion and a count of tablets remaining at day 14 and day 28 visits. All clinical and laboratory adverse events were graded according to the Division of AIDS table for Grading the Severity of Adult and Paediatric adverse events (Version 2.0, November 2014) by investigators and reported to the coordinating centre following standard ICH GCP Guidance. Review of any serious adverse events was carried out by an independent clinical reviewer who was blinded to the study allocation.
Switching between study arms was not allowed, but participants could be switched to alternative PEP regiments for safety and tolerability reasons.

Outcomes

The primary outcome was a composite end point of completion of 28 days of the allocated PEP regimen without grade 3 or 4 clinical or laboratory adverse events (excluding lipid abnormalities) related to PEP. The secondary outcomes included completion rates of 28 days of allocated PEP regimen, rates of grade 1, 2, 3 or 4 clinical adverse events and laboratory abnormalities; adherence to the allocated PEP regimen; number of doses of antidiarrhoeal and/or antiemetic medication taken; rates of HIV seroconversion at month 4 after exposure; number of sexual partners and unprotected anal/vaginal intercourse in i) while receiving PEP and ii) in the three months after completion of PEP with a potentially serodiscordant partner. Rates of sexually transmitted infections (gonorrhoea, chlamydia, lymphogranuloma venereum, syphilis, hepatitis B and C) were also examined at baseline and follow-up. For testing clinical adverse events were grouped by organ and laboratory adverse events by system.

For the purposes of this study, completion of allocated PEP combination to day 28 (or 14) was defined as not stopping the PEP combination by day 28 (or 14), irrespective of whether some doses were missed.

Sample size

We calculated that with 140 patients recruited per arm, allowing for a 75% follow-up rate, 105 patients would provide the primary outcome in each arm. This sample size provided 80% power to demonstrate the superiority of MVC based PEP relative to LPV/r based PEP if in the experimental arm the prevalence of the primary outcome (completion of 28 days of PEP without grade 3 or 4 toxicity) was 20% higher (70%) than the estimated rate in the control arm (50%). The sample size also provided 80% power if under MVC the prevalence was 79% and in the LPV/r arm it was 60%. Though this was not formally designed as a non-inferiority trial and no choice of non-inferiority margin was made, we also calculated that this sample size would provide over 80% power to demonstrate the non-inferiority of MVC relative to LPV/r if the prevalence of the primary outcome was 60% under MVC and 50% under LPV/r, or 69% under MVC and 60% under LPV/r, if non-inferiority is defined as a prevalence not more than 10% lower than in the LPV/r arm.

Primary and secondary outcome analyses

All primary comparisons of the two PEP treatments were made according to the randomisation arm (intention-to-treat, ITT). All effect measures are presented with 95% confidence intervals, with p-values based on 2-sided tests; a 5% significance level was used.

Adjustment was made for recruiting centre and for any factors for which an imbalance between arms was seen at baseline or which were seen to be linked to differential loss to follow up between arms. Regression analysis was used; standard logistic regression for binary outcomes and ordinal

logistic regression for ordinal outcomes. The effect measures are odds ratios, presented with 95% confidence intervals; primary comparisons of arms are based on the adjusted odds ratios.
All analyses were conducted using Stata SE version 12.0; Stata Corporation, College Station, TX, USA.

Missing data

All analyses are presented for complete cases only, except for analysis of the primary outcome measure which was repeated multiply imputing missing outcome values. Missing data in the primary outcome were anticipated, arising if a patient attended the 14 day visit and reported PEP compliance to that time and no grade 3 or 4 laboratory or clinical adverse events attributable to PEP, but then drops out. Imputation was based on data from similar patients who do not drop out after the 14 day visit, and conducted separately by randomisation arm. Imputation was also conducted separately for the two components of the primary outcome (completion of PEP, absence of grade 3 or 4 adverse events attributable to PEP) based on logistic regression models including age as a predictor, as it was seen to be related to the primary outcome. Age (as a continuous variable) and site (3 categories) were also then adjusted for in all analyses.

Results

Between August 2012 and December 2014, 213 participants were recruited; 107 were randomised to TVD/MVC and 106 to TVD/LPV/r. Recruitment was discontinued early because the national recommended standard of care regimen for PEP was changed to TVD/raltegravir [1].

The primary outcome was observed for 98 participants (92% of those randomised) in each arm, and attendance at each study visit is displayed in Figure 1. Baseline characteristics (shown in Table 1) were similar between study groups. The study population was mainly male (98%), white (84%), and with a mean age of 33.9 (SD 9.56) years. Overall, 94% of participants were MSM. A third of the study population (33%) had received PEP previously. All study participants were prescribed PEP following high risk sexual exposure with a potentially seropositive partner.

There was no difference in the combined primary endpoint between study arms: 71% and 65% in the MVC and LPV/r arms respectively at day 28 (p=0.357). Multiple imputation of the primary outcome was conducted because of missing data and this provided very similar results (73% and 67%; p=0.330). The completion rate of PEP in the MVC arm was 82% compared to 77% in the LPV/r arm (p=0.350) (Table 2). By day 28 of follow-up, there were no SAEs or grade 3 or 4 clinical adverse events in the study population. However, there were 123 grade 1 or 2 clinical adverse events in the MVC arm and 175 in the LPV/r arm. Participants randomised to MVC had a significantly lower rate of gastro-intestinal adverse events (OR= 0.23; 95%CI= 0.22-0.42; p<0.0001) (Table 3). Therefore, a lower proportion of participants in the MVC arm were prescribed antidiarrhoeal medication (OR=0.15; 95%CI= 0.08-0.28; p<0.001) and there was somewhat lower use of antiemetic medication (OR=0.68; 95%CI=0.39-1.16; p=0.158) (Table 2).

A total of 127 and 158 grade 1, 2 or 3 laboratory adverse events were observed in patients randomised to the MVC and the LPV/r arm respectively by day 28. Most grade 3 laboratory adverse events were related to renal function measurements. 13 participants had grade 3 hypophosphatemia, but with no difference between randomisation arms. There were 57 participants with hypercholesterolaemia with a significant difference between randomisation arms (17 and 40 in patients randomised to MVC and LPV/r respectively; p<0.0001) but the only grade 3 hypercholesterolaemia reported by day 28 was in a participant in the MVC arm, this patient had persistent hypercholesterolaemia during the entire study period including month 4 visit, which suggests that this was a pre-existing condition not related to study medication (no baseline cholesterol measurement was available). Laboratory abnormalities reflecting metabolic disturbances (lipids and glucose) were less frequently observed in participants on MVC (OR=0.27; 95%CI=0.14-0.50; p<0.0001), and predominantly due to grade 1-2 hypertriglyceridaemia. The distribution of laboratory adverse events are summarised in Table 4. By 4 months after starting PEP, 93% of grade 2, 3 and 4 laboratory adverse events were documented as having resolved.

Attendance at study visits was high in both groups with 80% of participants in the MVC arm and 81% in the LPV/r arm attending the day 28 study visit. Adherence to the allocated PEP regimen at day 28 was similar in both arms with 27% of participants reporting missing at least one dose of TVD, whereas 22% of participants missed at least one dose of MVC or LPV/r. There was no difference between arms in the number of days absent from work, or in the number of additional clinic visits during the course of PEP (Table 2).

67% and 53% of participants in the MVC and LPV/r arms, respectively, attended their month 4 study visits. By the end of the study follow up there were no HIV seroconversions reported.

At the baseline visit 12% of participants were diagnosed with a sexually transmitted infection (STI). At the day 28 visit, when all participants were screened for STIs again, 13% were diagnosed with an STI (Table 5). During the study period participants randomised to both groups showed similar sexual behaviour patterns. By the day 14 visit 55% and 62% in the MVC and LPV/r arms respectively ($p=0.344$) reported no sexual activity since PEP initiation (Table 6). Combining study arms we see that 15% of participants reported ≥3 sexual partners since baseline by day 28 and 37% reported ≥3 sexual partners since baseline by 4 months. The proportion of participants reporting unprotected sex since baseline was 8% at day 28 and 26% at 4 months.

Discussion

The completion rate of PEP was high in both arms of this trial, and did not differ between arms. Furthermore, there were no differences observed in the rate of PEP completion in the absence of grade 3 or 4 clinical and laboratory adverse abnormalities comparing MVC vs. LPV/r-based combinations. This was the combined primary endpoint of the trial.

The favourable MVC tolerability and safety profile, demonstrated in previous studies both in treatment and prevention make it an attractive option to be considered as part of a PEP regimen [15-18, 22]. In this study the benefit of using MVC was limited to fewer mild to moderate gastrointestinal side effects in the MVC-arm (OR= 0.23; 95%CI= 0.22-0.42; $p<0.0001$). The excess of

gastrointestinal symptoms in the LPV/r-arm led to increased use of anti-diarrhoeal and anti-emetic medication. Low completion rates of PEP have been reported in many settings; therefore PEP regimens with a more favourable tolerability profile may help in this regard [23-26]. Recent data suggest that another ritonavir-boosted PI, darunavir, may be better tolerated [27]. However all ritonavir-boosted PI-based combinations have a higher risk for drug-drug interactions than alternatives such as raltegravir or rilpivirin [28, 29].

We did not observe any serious clinical adverse events. Laboratory abnormalities were mild to moderate grade 1 to 3, mostly reflecting hypertriglyceridemia and hypophosphatemia. Laboratory abnormalities associated with PEP exposure were transient and returned to normal after cessation of PEP.

It was decided not to include lipids in the primary end point because hyperlipidaemia is a recognized effect of LPV/r, which would be transient and with no clinically significant sequelae in the context of short-term treatment.

The results of the study indicate that when using TVD and MVC the routine prescription of antiemetic or antidiarrhoeal drugs is not necessary. Where LPV/r is used, routine provision of antiemetic and antidiarrhoeal drugs is standard practice in the UK and this study suggests that this should continue to be considered.

Although proximal renal tubular dysfunction and Fanconi's syndrome are well reported in HIV-positive individuals on TDF-based ART [30], these have not been reported in the setting of PEP and were not seen in this study.

We recruited a high-risk population, of whom a high proportion had received PEP previously, the majority more than once. This may in part explain the high rate of treatment completion and adherence we observed. We also observed high rates of STIs, both at baseline and during the follow-up period, but no HIV seroconversions, consistent with previous reports [31]. High risk individuals may be suitable candidates for pre-exposure prophylaxis rather than repeated courses of PEP [32].

The strengths of this trial are the low withdrawal and lost-to-follow up rates and the design being representative of routine clinical care. Potential limitations include the restriction of the study population to those at risk from sexual exposure, and almost all MSM. There were no occupational exposure cases. The fact that many of the participants had received PEP previously, and were seeking PEP again means that those who had had more severe adverse effects of current PEP regimens may have been less likely to be seek PEP again, and so be less likely to be included in the study. Previous users of these medications may also have a different perception of the adverse effects. Although at the close of recruitment 213 participants out of an initial planned sample size of 280 had been enrolled, due to a change in the standard of care regimen, we had a better than expected follow-up rate. We had 196 participants who provided data for the primary outcome, which is only just short of the planned 210 and did not therefore materially compromise the power of the study.

In conclusion, MVC-based PEP has demonstrated advantages in comparison with a LPV/r-based PEP regimen in terms of tolerability, even if that did not translate into a significant increase in completion rates in this trial.

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We thank all patients and staff from all the centres participating in the MiPEP trial.

Paul Benn was MiPEP Trial Chief Investigator until January 2014, and is now employed by ViiV Healthcare.

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†Professor Martin Fisher died in April 2015 – he made a significant contribution to this study and our speciality as a whole – he is greatly missed.

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Transparency declarations

P. B. was MiPEP Trial Chief Investigator until January 2014. Between January 2014 and December 2015, P. B. was employed full time by Gilead Sciences UK, in the HIV franchise; from January 2016 onwards, he was employed full time by ViiV Healthcare. All other authors: none to declare.

Author contributions

P. B., R. G., A. A. P., A. Copas and A. M. designed the study. A. M., A. A. P., P.B. and R. G. co-ordinated and oversaw the study. N. B. and A. Copas did the statistical analysis. All authors interpreted data. A.

M., P. B., A. A. P., N.B., A. Copas and R. G. drafted the report. All the authors provided input into the report and approved the final version of the report.

Disclaimer

The views and opinions expressed herein are those of the authors.

Contributors

PB, RG, AAP, AC and AM designed the study. AM, AAP, PB and RG coordinated and oversaw the study. NB and AC did the statistical analysis. All authors interpreted data. AM, PB, AAP, NB, AC and RG drafted the report. All the authors provided input into the report and approved the final version of the report.

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Figure 1: Trial profile

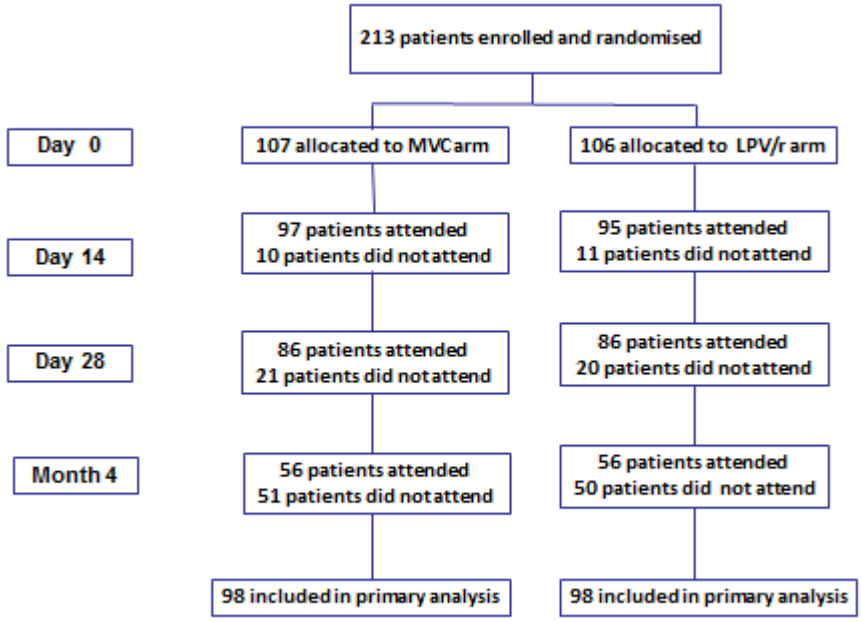

Table 1: Baseline demographic and sexual behaviour characteristics of the sample

Characteristics, n (%) or mean (SD)		**MVC arm N=107**	**LPV/r arm N=106**
Age in years, mean (SD)		33.6 (9.15)	34.4 (10.0)
Sex	Female	4(4)	1(1)
	Male	103(96)	105(99)
Ethnicity	Black	4 (4)	3 (3)
	South Asian	1 (1)	4 (4)
	Other/mixed	10 (10)	10 (10)
	White	86 (85)	85 (83)
Sexual orientation	Bisexual	12(12)	10(10)
	Heterosexual	6(6)	4(4)
	Homosexual	83(82)	89(86)
Number of sex partners in the last 3 months	No Sex	0(0)	0(0)
	1	9(9)	20(20)
	2	17(17)	19(19)
	3-9	42(43)	34(34)
	10+	30(31)	26(27)
Previous PEP	No	70(69)	62(60)
	Yes	32(31)	41(40)
Number of times had PEP previously	1	16(50)	25(61)
	2+	16(50)	16(39)
Had STI screen at baseline	No	71(68)	57(54)
	Yes	33(32)	48(46)
Any STIs at baseline visit if screened	No	29(88)	42(88)
	Yes	4(12)	6(13)
Syphilis at baseline if tested	No	29(100)	28(97)
	Yes	0(0)	1(3)

Table 2: Outcome measures, summary statistics and odds ratios (OR) comparing MVC with LPV/r arm

Outcome measure, N=denominator across arms		MVC arm n(%),N=107	LPV/r arm n(%),N=106	[1]p-value	Unadjusted [2] OR (95% CI)	[3]Adjusted [2] OR (95% CI)
Primary: completion of 28 days of allocated PEP regimen without grade 3 or 4 clinical or laboratory adverse event related to PEP, N=196	No Yes	28(29) 70(71)	34(35) 64(65)	0.357	*p=0.357* 1.33 (0.73-2.43)	*p=0.254* 1.44 (0.77-2.70)
Primary after imputation: completion of 28 days of allocated PEP regimen without grade 3 or 4 clinical or laboratory adverse event related to PEP, N=213	No Yes	27% 73%	33% 67%	0.350	*p=0.330* 1.35 (0.74-2.46)	*p=0.262* 1.43 (0.77-2.65)
Completion of 28 days of allocated PEP regimen, N=193	No Yes	17(18) 80(82)	22(23) 74(77)	0.351	*p=0.352* 1.40 (0.69-2.84)	*p=0.309* 1.46 (0.70-3.04)
Laboratory abnormalities, highest grade reported, N=196	0 1 2 3	37(37) 29(29) 20(20) 13(13)	23(24) 30(31) 31(33) 13(12)	0.108	*p=0.056* 0.61 (0.37-1.01)	*p=0.079* 0.63 (0.38-1.05)
Grade 3+ laboratory abnormality related to PEP, N=196	No Yes	87 (88) 12(12)	85 (88) 12(12)	0.957	*p=0.957* 0.98 (0.42-2.30)	*p=0.911* 0.95 (0.39-2.29)
Clinical adverse events, highest grade reported, N=196	0 1 2	30(30) 59(60) 10(10)	9(9) 69(71) 19(20)	0.001	*p<0.001* 0.32 (0.17-0.59)	*p<0.001* 0.32(0.17-0.59)
Number of missed doses of TVD over 14 days, if completed 14 days of allocated PEP regimen, N=184	0 1+	89(95) 5(5)	83(92) 7(8)	0.493	*p=0.502* 0.67 (0.20-2.18)	*p=0.514* 0.67 (0.20-2.22)

Number of missed doses of TVD over 28 days, if completed 28 days of allocated PEP regimen, N=154	0 1+	68(85) 12(15)	68(92) 6(8)	0.178	*p=0.190* 2.00 (0.71-5.64)	*p=0.123* 2.31 (0.80-6.68)
Number of missed doses of LPV/r or MVC over 14 days if completed 14 days of allocated PEP regimen, N=184	0 1 2+	80(85) 12(13) 2(2)	73(81) 11(12) 6(7)	0.865	*p=0.409* 0.72 (0.33-1.56)	*p=0.384* 0.71 (0.33-1.54)
Number of missed doses of LPV/r or MVC over 28 days, if completed 28 days of allocated PEP regimen, N=154	0 1 2+	62(78) 8(10) 10(12)	58(78) 9(12) 7(10)	0.853	*p=0.829* 1.09 (0.51-2.32)	*p=0.867* 1.07 (0.50-2.28)
Number of doses of antidiarrheal medication taken over 28 days, N=196	0 1-5 6+	74(75) 18(18) 7(7)	32(33) 28(29) 37(38)	<0.001	*p<0.001* 0.16 (0.09-0.28)	*p<0.001* 0.15 (0.08-0.28)
Number of doses of antiemetic taken over 28 days, N=196	0 1-5 6+	58(59) 22(22) 19(19)	49(51) 20(21) 28(29)	0.059	*p=0.157* 0.68 (0.39-1.16)	*p=0.158* 0.68 (0.39-1.16)
Number of days absent from work or college over 28 days (not including days absent for clinic visits), N=173	0 1-5 6+	77(87) 5(6) 7(8)	73(87) 6(7) 5(6)	0.843	*p=0.905* 1.05 (0.44-2.53)	*p=0.863* 1.08 (0.45-2.61)
HIV seroconversion 4 months after exposure, N=119	No Yes	66(100) 0(0)	53(100) 0(0)	1.000	-	-
Additional Visits, N=196	No Yes	88(90) 10(10)	91(93) 7(7)	0.446	*p=0.449* 1.48 (0.54-4.05)	*p=0.338* 1.67 (0.58- 4.90)

[1]Chi squared, Fisher exact and Mann-Whitney tests were used as appropriate.
[2] Odds ratios based on logistic regression for binary outcome or ordinal logistic regression assuming proportional odds for ordinal outcome.
[3]Adjusted for age (continuous) and site

Table 3: Clinical Adverse events (CAE) by the highest grade at 28 days visit, by study arm

CAE type	MVC arm n(%),N=99			LPV/r arm n(%),N=97			[1]OR (95% CI), p-value
Grade	0	1	2	0	1	2	
CNS	**85(86)**	**12(12)**	**2(2)**	**79(81)**	**17(18)**	**1(1)**	**0.68 (0.31-1.48), p=0.330**
Headache	89(90)	8 (8)	2 (2)	83(86)	13(13)	1(1)	
Sleeping disorder	93 (94)	6 (6)	0(0)	91 (94)	6 (6)	0(0)	
Other CNS	97 (98)	2 (2)	0(0)	96 (99)	1(1)	0(0)	
GI	**46(47)**	**46(47)**	**6(6)**	**14(14)**	**68(70)**	**15 (16)**	**0.32 (0.18-0.56), p<0.0001**
Nausea/vomiting	69(70)	27(27)	3(3)	59 (61)	31 (32)	7 (7)	
Diarrhoea	80(81)	18(18)	1(1)	25(26)	61(63)	11(11)	
Constipation	95(96)	3(3)	1(1)	95(98)	2(2)	0(0)	
Other GI	83(84)	15(15)	1(1)	60(62)	30(31)	7(7)	
Skin	**96 (97)**	**3 (3)**	0(0)	**88(91)**	**8 (8)**	**1 (1)**	**0.36 (0.09-1.38) p=0.135**
Rash	97(98)	2(2)	0(0)	89(92)	7(7)	1(1)	
Other skin	98(99)	1(1)	0(0)	96(99)	1(1)	0(0)	
Tiredness, fatigue, etc.	**63 (64)**	**30 (30)**	**6 (6)**	**59 (61)**	**35 (36)**	**3 (3)**	**1.05 (0.58-1.87) p=0.882**
Other	**81 (82)**	**14 (14)**	**4 (4)**	**70 (72)**	**24 (25)**	**3 (3)**	**0.59(0.30-1.16) p=0.128**

[1] OR for MVC arm relative to LPV/r. Ordered Logistic regression assuming proportional odds for GI (grade 0, 1, 2). Logistic regression for CNS, Skin, Tiredness, Other (binary outcome grade 1+)

Table 4: Laboratory Adverse events (LAE) by the highest grade at 28 days visit, by study arm.

LAE type	MVC arm n(%), N=99				LPV/r arm n(%), N=97				[2]OR (95% CI), p-value
Grade	0	1	2	3	0	1	2	3	
Renal	**45(45)**	**23(23)**	**19(19)**	**12(12)**	**46(47)**	**21(22)**	**19(20)**	**11(11)**	**1.06 (0.63-1.78), p=0.820**
Sodium	94(96)	4(4)	1(1)	0(0)	95(98)	2(2)	0(0)	0(0)	
Urea	92(93)	0(0)	0(0)	7(7)	9598)	0(0)	0(0)	2(2)	
Creatinine	98(99)	1(1)	0(0)	0(0)	97(100)	0(0)	0(0)	0(0)	
[1]Phosphate (see notes)	66(67)	13(13)	16(1)	4(4)	56(58)	14(14)	18(19)	9(9)	
UPCR	82(83)	14(14)	2(2)	1(1)	89(86)	9(9)	2(2)	0(0)	
Liver	**83(84)**	**13(13)**	**2(2)**	**1(1)**	**82(85)**	**12(12)**	**3(3)**	0(0)	**1.05(0.49-2.27), p=0.894**
Bilirubin	89(90)	8(8)	1(1)	1(1)	88(91)	7(7)	2(2)	0(0)	
ALT	93(94)	5(5)	1(1)	0(0)	90(93)	6(6)	1(1)	0(0)	
Metabolic	**76(77)**	**20(20)**	**1(1)**	**2(2)**	**47(49)**	**28(29)**	**21(22)**	**1(1)**	**0.27(0.14-0.50), p<0.0001**
Glucose	95(96)	4(4)	0(0)	0(0)	89(92)	7(7)	1(1)	0(0)	
Total cholesterol	82(83)	14(14)	2(2)	1(1)	57(59)	20(21)	20(21)	0(0)	
LDL	90(91)	8(8)	0(0)	1(1)	78(80)	12(12)	6(6)	1(1)	
Triglyceride	94(95)	5(5)	0(0)	0(0)	73(75)	22(23)	2(2)	0(0)	
Bone	**65(66)**	**14(14)**	**16(16)**	**4(4)**	**55(57)**	**15(15)**	**18(19)**	**9(9)**	**0.66 (0.38-1.15), p=0.145**
[1]Phosphate	66(67)	13(13)	16(16)	4(4)	56(58)	14(14)	18(19)	9(9)	
Calcium	98(99)	1(1)	0(0)	0(0)	95(99)	2(2)	0(0)	0(0)	

[1] Phosphate results contribute to both Renal and Bone groups [2] OR for MVC arm relative to LPV/r. Ordered Logistic regression assuming proportional odds for Renal (grade 0, 1, 2, 3), Metabolic (grade 0, 1, 2+), Bone (grade 0, 1, 2+). Logistic regression for liver (binary outcome grade 1+)

Table 5: [1]STIs - rates of testing and infection, by study arm

Variables		MVC arm n(%)	LPV/r arm n(%)
Had STI screen at 14 days, n=191	No	28(29)	29(30)
	Yes	69(71)	66(70)
Any STIs at 14 days visit if screened, n=134	No	57(84)	57(86)
	Yes	11(16)	9(14)
Syphilis at 14 days if tested, n=52	No	26(100)	26(100)
	Yes	0(0)	0(0)
Had STI screen at 28 days, n=172	No	57(67)	54(64)
	Yes	28(33)	31(36)
Any STIs at 28 days visit if screened, n=59	No	23(82)	28(90)
	Yes	5(18)	3(10)
Syphilis at 28 days if tested, n=49	No	23(100)	26(100)
	Yes	0(0)	0(0)
Had STI screen at 4 moths, n=120	No	28 (42)	32(59)
	Yes	38(58)	22(41)
Any STIs at 4 months visit if screened, n=60	No	38(100)	22(100)
	Yes	0(0)	0(0)
Syphilis at 4 months if tested, n=25	No	12(100)	10(8)
	Yes	0(0)	3(23)

[1]STI screen may include at least one of the following tests: Chlamydia Trachomatis (CT) (up to 3 sites), gonococcus (GC) (up to 3 sites), Lymphogranuloma venereum (LGV) (up to 3 sites), herpes, human papilloma virus (HPV), bacterial vaginosis (BV), non-specific urethritis (NSU), and syphilis.

Table 6: Sexual behaviour characteristics at follow up visits, by study arm

Variables		MVC arm MVC arm n(%)	LPV/r arm LPV/r arm n(%)
Number of sex partners since baseline reported at 14 days visit, n=188	No sex	53(55)	57 (62)
	1	3 (31)	25 (27)
	2	7(7)	5(5)
	3-9	5(5)	5(5)
	10+	1(1)	0(0)
Number of sex partners since baseline reported at 28 days visit, n=172	No sex	35(41)	44(51)
	1	32(37)	24(28)
	2	6(7)	6(7)
	3-9	12(14)	11(13)
	10+	1(1)	1(1)
Number of sex partners since baseline reported at 4 months days visit, n=125	No sex	13(19)	12(23)
	1	21(30)	14(25)
	2	9 (13)	10(18)
	3-9	15(21)	12(22)
	10+	12(17)	7(13)
Unprotected sex since baseline reported at 14 days, n=191	No	88 (92)	88(93)
	Yes	8(8)	4(4)
	Don't know	0(0)	3(3)
Unprotected sex since baseline reported at 28 days, n=172	No	78(91)	80(93)
	Yes	8(9)	6(7)
	Don't know	0(0)	0(0)
Unprotected sex since baseline reported at 4 months, n=126	No	49(70)	43(77)
	Yes	21(30)	12(21)
	Don't know	0(0)	1(2)