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Pharmacology of boosted and unboosted integrase strand transfer inhibitors for two-dose event-driven HIV prevention regimens among men

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Abstract

Background: Event-driven HIV prevention strategies are a priority for users who do not require daily pre-exposure prophylaxis (PrEP). Regimens containing integrase strand transfer inhibitors (INSTIs) are under evaluation as alternatives to daily PrEP. To better understand INSTI distribution and inform dosing selection we compared the pharmacology of two-dose boosted elvitegravir and unboosted bictegravir regimens in MSM.

Materials and methods: Blood, rectal and penile secretions and rectal biopsies were collected from 63 HIV-negative MSM aged 18–49 years. Specimens were collected up to 96 h after two oral doses of tenofovir alafenamide and emtricitabine with elvitegravir boosted by cobicistat or unboosted bictegravir given 24 h apart. Antiretroviral drugs were measured by LC-MS.

Results: Mean bictegravir plasma concentrations remained above the 95% protein-adjusted effective concentration 96 h after dosing [273 (95% CI: 164–456) ng/mL] whereas elvitegravir plasma concentrations became undetectable 48 h after the second dose. Bictegravir and elvitegravir reached rectal tissues within 2 h after the first dose, and elvitegravir tissue

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Transparency declarations

J.G.G.-L. and W.H. are named in US Government patents on ‘Inhibition of HIV infection through chemoprophylaxis’. I.M., W.H. and J.G.G.-L. are named in a US Government patent on ‘HIV post-exposure prophylaxis’ and a patent application on ‘HIV pre-exposure prophylaxis’. All other authors: none to declare.

Disclaimer

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the US CDC or the Department of Health and Human Services.

Supplementary data

Figures S1 and S2 and Tables S1 to S3 are available as Supplementary data at *JAC* Online.

concentrations [1.07 (0.38–13.51) ng/mg] were greater than bictegravir concentrations [0.27 (0.15–0.70) ng/mg]. Both INSTIs became undetectable in tissues within 96 h. Elvitegravir and bictegravir were not consistently detected in penile secretions.

Conclusions: Whereas bictegravir plasma concentrations persist at least 4 days after a two-oral-dose HIV prophylaxis regimen, elvitegravir accumulates in mucosal tissues. Differing elvitegravir and bictegravir distribution may result in variable mucosal and systemic antiviral activity and can inform dosing strategies for event-driven HIV prevention.

Introduction

Current HIV pre-exposure prophylaxis (PrEP) options consist of daily oral dosing with the NRTIs emtricitabine and tenofovir prodrugs, either tenofovir disoproxil fumarate or tenofovir alafenamide, or a long-acting injectable formulation of the integrase strand transfer inhibitor (INSTI) cabotegravir.[1–6] Oral PrEP efficacy is highly dependent on individual adherence to daily dosing strategies, and long-acting injectable agents require administration by healthcare providers.[7,8] Therefore, identifying event-driven PrEP modalities that better adapt to different needs among users remains a critical priority. Event-driven PrEP modalities are being explored to provide additional options for persons who do not want or require daily PrEP. One event-driven PrEP strategy (2-1-1) consisting of two doses of emtricitabine and tenofovir disoproxil fumarate taken 24 h prior to sexual activity followed by additional doses taken 24 and 48 h after sex was shown to reduce the risk of HIV infection by 86% among MSM.[9,10] However, a dosing strategy involving one or two doses of potent antiretroviral drugs around sexual exposure can simplify event-driven PrEP and make it more desirable.

Although NRTIs provide potent options to limit virus replication, they are most effective when taken prior to or immediately after virus exposure.[11] Potent INSTIs acting at later stages of the viral replication cycle could allow for more flexible dosing options around virus exposure while preventing the establishment of infection. *In vitro* studies showed INSTIs can prevent infection when provided up to 10 h after virus exposure in cell culture.[12,13] A previous study in pigtail macaques demonstrated vaginal gels containing INSTIs could provide protection when administered up to 3 h after vaginal virus exposure.[13] Two recent studies in rhesus macaques demonstrated oral combinations of antiretroviral drugs including INSTIs could prevent infection following rectal virus exposure. A single-dose regimen containing emtricitabine and tenofovir alafenamide in combination with the integrase inhibitor elvitegravir boosted with cobicistat provided protection when given shortly before or up to 6 h after rectal virus exposure.[14] However, protection with a single dose waned when given 24 h after virus exposure but could be improved with a second dose given 48 h after virus exposure. A similar study using a combination of emtricitabine and tenofovir alafenamide with the unboosted integrase inhibitor bictegravir demonstrated that a two-dose strategy given 12 and 36 h after rectal virus exposure could also provide protection.[15] Together, these studies suggest two-dose oral regimens containing boosted or unboosted integrase inhibitors might provide event-driven HIV prevention options.

Although dosing regimens containing elvitegravir or bictegravir have shown promise in preclinical models, data regarding the pharmacology of two-dose strategies in humans are lacking. We sought to provide clinical data for two-dose oral regimens containing a boosted or unboosted integrase inhibitor given 24 h apart to better understand mucosal and systemic drug distribution and inform dosing modalities for HIV prevention. In this study, we evaluated the two-dose pharmacology of approved formulations of emtricitabine and tenofovir alafenamide in combination with the cobicistat-boosted integrase inhibitor elvitegravir or the unboosted integrase inhibitor bictegravir in MSM.

Methods

Study design

This study analyzed specimens collected from 63 male participants in three clinical trials registered at clinicaltrials.gov and conducted at the Emory Hope Clinic in Atlanta, Georgia. All trials were funded by CDC and approved by Emory University and CDC Institutional Review Boards. All study participants gave written informed consent, and the trials conform to the US Federal Policy for the Protection of Human Subjects. Participants were self-selected volunteers recruited from existing Emory University study databases, between the ages of 18 and 49, reported receptive anal intercourse with another man in the previous 6 months and were confirmed HIV-negative using the Chembio Sure Check HIV 1/2 test (Chembio Diagnostics Systems, Inc., Hauppauge, NY, USA) prior to dosing. There were no attempts to randomize participants from the eligible pool of volunteers.

In the first study, 15 male participants were sequentially assigned for convenience to study arms to receive a single-dose formulation containing 200 mg emtricitabine, 10 mg tenofovir alafenamide, 150 mg elvitegravir and 150 mg cobicistat as well as a single 800 mg dose of darunavir (NCT03472963). Participants provided specimens at 2 and 24 h post-dose ($n = 10$); or 4 and 24 h post-dose ($n = 5$). In the second study, 24 male participants were sequentially assigned for convenience to study arms to receive two doses of a single formulation containing 200 mg emtricitabine, 10 mg tenofovir alafenamide, 150 mg elvitegravir and 150 mg cobicistat (NCT03976752) given 24 h apart. Participants provided specimens at 26 and 72 h post first dose ($n = 8$); 28 and 96 h post first dose ($n = 8$); or 48 and 120 h post first dose ($n = 8$). In the third study, 24 male participants were sequentially assigned for convenience to study arms to receive two doses of a single formulation containing 200 mg emtricitabine, 25 mg tenofovir alafenamide and 50 mg bictegravir given 24 h apart, and provide biological specimens at specified study visits (NCT04039217). Participants provided specimens at 2, 48 and 72 h post-dose ($n = 12$); 4, 26 and 120 h post-dose ($n = 8$); or 24, 28 and 72 h post-dose ($n = 4$). Sampling for rectal secretions and tissue biopsies was performed at only one study visit per participant. Tenofovir and emtricitabine measures for one participant receiving bictegravir and one participant receiving elvitegravir were excluded from analysis because the participants were determined to have been taking tenofovir and emtricitabine prior to study enrollment.

Peripheral blood specimens were collected in sodium citrate cell preparation tubes (CPT) (Becton Dickinson, Franklin Lakes, NJ, USA). Plasma was collected from CPT tubes following centrifugation. Rectal secretions were collected via rigid sigmoidoscopy by

inserting a polyester Puritan applicator (Puritan Medical Products, Guilford, ME, USA) through the scope and rotating clockwise around the bowel wall for 3 to 5 s. An enema was not used prior to collection of rectal secretions. An anorectal swab and urine were collected at one time point per participant to test for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* by nucleic acid amplification (Aptima 2 Combo Assay, Marlborough, MA, USA). No urine specimens tested positive for *N. gonorrhoeae* or *C. trachomatis*, and one anorectal swab tested positive for *C. trachomatis*. Urethral secretions were collected by inserting a polyester Puritan miniature applicator 2 to 4 cm into the urethra and slowly rotating clockwise for 2 to 3 s. Glans surfaces were sampled by prewetting a polyester Puritan applicator in PBS and rolling the applicator around the head of the penis and underneath the foreskin, if present. Urine was collected in sterile specimen containers (Thermo Fisher Scientific, Waltham, MA, USA). All specimens were stored at −70°C prior to analysis.

Laboratory measurements

Concentrations of tenofovir, emtricitabine, elvitegravir and bictegravir were measured in all specimens using HPLC tandem MS (Sciex, Foster City, CA, USA; Shimadzu Scientific Instruments, Durham, NC, USA) as previously described.[14] Mass transitions (Q1→Q3) were monitored in positive multiple reaction monitoring mode following two transitions for each analyte [tenofovir (288.0/176.31 m/z and 288.0/159.11 m/z), emtricitabine (248.0/130.11 m/z and 248.0/113.11 m/z), elvitegravir (448.2/344.11 m/z and 448.2/143.11 m/z), bictegravir (450/289 m/z and 450/145 m/z) and tenofovir alafenamide (477.30/270.20 m/z and 477.30/176.20 m/z)]. Drug concentrations were estimated from a standard curve with a range of 0.5–2000 ng/mL and analysed using Analyst software version 1.7.1 (Sciex). Standard curves for plasma and urine specimens were generated in normal human plasma and urine, respectively. Standard curves for urethral, glans and rectal swabs were generated by spiking antiretroviral drugs (ARVs) onto dry applicators in a range of 0.5–2000 ng/swab. Standard samples were treated in like manner as the differing matrices required. The lower limit of quantification (LLOQ) and limit of detection (LOD) for this study was 1 ng/sample for urethral, glans and rectal swabs as well as tissue biopsies, and 10 ng/mL for plasma and urine. Tenofovir diphosphate and emtricitabine triphosphate concentrations were measured in PBMCs and rectal tissue biopsies as previously described with an LLOQ and LOD of 100 fmol/sample for tenofovir diphosphate and 500 fmol/sample for emtricitabine triphosphate.[14]

Estimates for average material collected on swabs were performed by comparing average precollection and postcollection weight of 25 swabs. Estimated material collected was 50 mg/swab for rectal swabs, 5 mg/swab for glans surface swabs and 2 mg/swab for urethral swabs. The 95% protein-adjusted inhibitory concentration ($PAIC_{95}$) of elvitegravir was 45 ng/mL, and the 95% protein-adjusted effective concentration ($PAEC_{95}$) of bictegravir was 162 ng/mL according to previous reports.[16,17] Intracellular EC_{50} of tenofovir diphosphate and emtricitabine triphosphate was 37 fmol/10^6 cells and 30 fmol/10^6 cells, respectively, based on a previous report.[18] Pharmacokinetic parameters were calculated using non-compartmental analysis using Phoenix WinNonlin version 8.3 (Certara, Princeton, NJ, USA). AUC measures were calculated using the sparse sampling function and linear

trapezoidal rule. Statistical calculations were performed using Prism 8 software (GraphPad Software, San Diego, CA, USA). Comparisons between study arm concentrations were calculated using a Mann–Whitney test, and comparisons between AUCs were calculated using Welch's *t*-test. Mean concentrations were calculated as geometric mean values. Measurements below the LLOQ were assigned a value of one-half the LLOQ for statistical calculations. A tissue-to-fluid density of 1 g/mL was used to compare tissue and plasma drug concentrations.

Results

Study participants

Sixty-three HIV-negative MSM study participants with a median age of 26 years (range: 18–46 years) were included in this analysis. Participants receiving bictegravir were significantly older than those receiving elvitegravir (Table 1). Study participants were primarily Black (67%) or White (21%), and most study participants (84%) were circumcised.

Comparison of plasma concentrations

Mean plasma elvitegravir concentrations peaked at 28 h, 4 h after the second dose, but rapidly declined to undetectable concentrations by 72 h (Figure 1). In contrast, mean plasma bictegravir concentrations peaked 2 h after the first dose yet remained above the $PAEC_{95}$ (162 ng/mL) for at least 96 h after the second dose. Persistence of plasma bictegravir concentrations resulted in an $AUC_{0–120h}$ more than twice that of elvitegravir ($P < 0.005$) (Table 2). Mean emtricitabine plasma concentrations peaked at 26 h for those receiving elvitegravir boosted with cobicistat, and at 2 h for those receiving bictegravir (Figure S1; available as Supplementary data at *JAC* Online). Plasma emtricitabine declined to undetectable concentrations by 72 h, 48 h after the second dose, and emtricitabine $AUC_{0–120h}$ among persons receiving elvitegravir boosted with cobicistat was more than twice that of those receiving bictegravir ($P = 0.002$) (Table S1). Tenofovir was below the LLOQ in plasma specimens collected during this study.

Comparison of mucosal concentrations

Mean rectal tissue elvitegravir concentrations peaked at 4 h, over 10 times greater than peak bictegravir concentrations at 2 h after the first dose ($P = 0.016$) (Figure 2A). Mean tissue elvitegravir concentrations were more than 10 times greater than the $PAIC_{95}$ (45 ng/mL) until 96 h, 72 h after the second dose, whereas mean tissue bictegravir concentrations did not reach more than twice the $PAEC_{95}$ at any time point. Tissue concentrations were highly variable; however, mean elvitegravir tissue $AUC_{0–120h}$ was more than 20 times greater than bictegravir tissue $AUC_{0–120h}$ ($P = 0.235$) (Table 3). The ratio of rectal tissue $AUC_{0–120h}$ to that of plasma was 10.6 for elvitegravir compared with 0.2 for bictegravir. Mean tissue emtricitabine concentrations among all participants peaked at 4 h, with concentrations among men also receiving elvitegravir boosted with cobicistat being greater than among those receiving bictegravir ($P = 0.032$) (Figure S2A, Table S2). Tissue emtricitabine $AUC_{0–120h}$ among men receiving elvitegravir boosted with cobicistat was more than 4 times greater than among men receiving bictegravir (Table S2) ($P = 0.117$). Tenofovir was only detected in 7/29 rectal tissue specimens from men receiving elvitegravir boosted

with cobicistat and in 17/23 rectal tissue specimens from men receiving bictegravir, with concentrations being consistently less than 1 ng/mg of tissue (data not shown).

Mean elvitegravir concentrations on rectal swabs peaked at 48 h (1085 ng/swab, 95% CI: 408–2888 ng/swab), over 500 times greater than bictegravir concentrations (2.1 ng/swab, 95% CI: 0.7–6.4 ng/swab, $P = 0.029$) (Figure 2B). Estimated elvitegravir concentrations in rectal secretions remained above the $PAIC_{95}$ for at least 72 h after the second dose whereas concentrations for bictegravir (C_{max}: 42 ng/mL, 95% CI: 14–128 ng/mL) remained below the $PAEC_{95}$ throughout all specimen collection times. Both elvitegravir and bictegravir concentrations became undetectable in most rectal swabs by 120 h. Mean emtricitabine concentrations on rectal swabs peaked at 48 h and were greater among participants also receiving boosted elvitegravir (241 ng/swab, 95% CI: 83–698 ng/swab) compared with those also receiving bictegravir (57 ng/swab, 95% CI: 1–3367 ng/swab, $P = 0.023$) (Figure S2B). Mean tenofovir concentrations peaked on rectal swabs at 48 h (16 ng/swab, 95% CI: 6–32 ng/swab) and were not different between men receiving boosted elvitegravir and men receiving bictegravir. Neither elvitegravir (16%) nor bictegravir (4%) were reliably detected on urethral or glans surface swabs collected from study participants (Table 4). In contrast, emtricitabine and tenofovir were measured on 69% and 15% of urethral and glans surface swabs collected in this study, respectively (Table S3).

Elvitegravir was detected in only 5% of urine specimens. Although bictegravir was detected in 46% of urine specimens, mean urine bictegravir concentrations remained less than 1 μg/mL at all time points and were undetectable within 48 h after the second dose (Table 4). In contrast, tenofovir and emtricitabine were readily detected in nearly all urine specimens (273/276), and mean tenofovir and emtricitabine concentrations remained above 700 ng/mL and 1 μg/mL, respectively, even 96 h after the second dose (Table S3).

Intracellular tenofovir and emtricitabine concentrations

Mean intracellular emtricitabine triphosphate concentrations in PBMCs peaked at 26 h, and tenofovir diphosphate concentrations peaked at 28 h (Figure 3A, Table 5). Mean PBMC emtricitabine triphosphate and tenofovir diphosphate concentrations remained more than 20 times and 3 times, respectively, greater than reported EC_{50} concentrations for PrEP (emtricitabine triphosphate: 37 fmol/10^6 cells; tenofovir diphosphate: 30 fmol/10^6 cells) at 120 h.

Mean emtricitabine triphosphate (64.1 fmol/mg, 95% CI: 9.2–447.3 fmol/mg) and tenofovir diphosphate (15.3 fmol/mg, 95% CI: 3.5–67.3 fmol/mg) concentrations peaked in rectal tissue at 48 h after the first dose (Figure 3B). Rectal tissue emtricitabine triphosphate and tenofovir diphosphate concentrations remained measurable at least 96 h after the second dose. Tenofovir diphosphate and emtricitabine triphosphate concentrations in PBMCs and rectal tissues were not significantly different between men receiving boosted elvitegravir and unboosted bictegravir (data not shown).

Discussion

Simple oral dosing strategies with potent ARVs that can be used shortly before or after sexual activity may provide desirable event-driven HIV prevention options for persons who do not want or require daily dosing.[14] Unlike daily PrEP dosing regimens, which result in persistent effective steady-state drug concentrations, event-driven dosing strategies provide transient drug exposures aimed at preventing HIV acquisition. HIV infection through sexual exposure starts in rectal, vaginal or penile mucosal tissues before disseminating through lymph nodes, and pharmacological studies assessing both mucosal and systemic drug distribution are particularly important for event-driven PrEP regimen and dose selection.[19] Because INSTI-based regimens are primary candidates for event-driven PrEP, we compared in this study the distribution of the INSTIs elvitegravir and bictegravir given in two doses combined with tenofovir alafenamide and emtricitabine. We demonstrate that these INSTIs distribute differentially, with elvitegravir showing much greater penetration and persistence in rectal tissues than bictegravir. Elvitegravir attained concentrations far greater than the $PAIC_{95}$ in mucosal specimens, suggesting significant antiviral activity at the point of virus exposure and highlighting its advantage in preventing initial infection or early rounds of virus replication. We also show longer persistence of bictegravir in plasma reflecting extended systemic post-dosing anti-HIV activity.

The mucosal penetration and accumulation of elvitegravir has remained largely unstudied in humans, but non-human primate studies demonstrate a similar accumulation of elvitegravir in rectal tissues and secretions following oral administration.[20] Elvitegravir mucosal concentrations reported here were similar to those observed in a previous non-human primate study demonstrating efficacy of elvitegravir in event-driven HIV prevention.[14] The mechanisms behind rectal penetration and accumulation of elvitegravir are unclear yet appear to extend to vaginal tissues in non-human primates.[20] Elvitegravir is primarily metabolized by cytochrome P450 3A4 (CYP3A4) in the liver and intestines, and coadministration of elvitegravir with the CYP3A4 inhibitor, cobicistat, increases systemic exposure and reduces clearance of elvitegravir, which has advantages for maintaining low viral loads among people living with HIV.[21] Although cobicistat may contribute to mucosal penetration and accumulation of elvitegravir, a previous non-human primate study also observed mucosal accumulation in the absence of a CYP3A4 inhibitor, suggesting additional factors may be involved.[20] Additional factors such as the hydrophobic nature of elvitegravir may contribute to accumulation in mucosal tissues compared with plasma. Increased systemic and mucosal concentrations of emtricitabine were also observed in men receiving cobicistat, suggesting cobicistat may be a factor in boosting mucosal accumulation of elvitegravir and emtricitabine, affecting the efficacy in event-driven dosing strategies. However, potential drug–drug interactions between cobicistat and non-antiretroviral medications persist and may need to be considered in HIV prevention strategies.[22]

Persistent systemic concentrations of unboosted bictegravir were observed after two doses, yet bictegravir concentrations remained low in mucosal tissues and secretions throughout the dosing and follow-up period. These findings confirm previous findings of low bictegravir concentrations in mucosal secretions and tissues compared with plasma in people living

with HIV receiving daily bictegravir.[23] Although the mechanisms behind poor bictegravir penetration into the rectal mucosa are unclear, low vaginal bictegravir concentrations in a previous study suggest similar mechanisms across mucosal sites.[23] Our results suggest that high systemic bictegravir concentrations may help limit virus dissemination following mucosal infection. However, low mucosal bictegravir concentrations may not be able to prevent the initial infection of HIV target cells or limit early rounds of virus replication in mucosal tissues following a single dose. Notably, a study in non-human primates increased bictegravir dosing to an estimated twice that of a clinical dosing formulation to achieve protection.[15] Therefore, it may be possible that existing clinical formulations of 50 mg bictegravir used for HIV therapy do not provide sufficient mucosal concentrations to prevent infection of mucosal cell targets in an event-driven dosing strategy, and higher doses of bictegravir may be necessary to increase mucosal concentrations and overall efficacy.

In contrast to emtricitabine, elvitegravir and bictegravir were largely undetectable on penile swabs examined here and concentrations were also low in urine. Limited detection of elvitegravir on penile samples is consistent with a previous analysis of urethral and glans surface swabs, but may also reflect lower elvitegravir concentrations previously observed in seminal plasma.[24,25] Lack of bictegravir detection on penile swabs could be an indicator of low mucosal bictegravir penetration at multiple mucosal sites as also observed in rectal sampling. It is unclear if low concentrations of elvitegravir and bictegravir in urethral and glans secretions are associated with limited biological protection from penile exposure to HIV. Low urine concentrations of elvitegravir and bictegravir likely result from limited renal clearance of both INSTIs, and it is unclear to what extent urine INSTI concentrations contribute to penile drug concentrations. It will be important to assess the efficacy of elvitegravir- and bictegravir-containing regimens in non-human primate models to determine if the lower penile drug exposures are associated with reduced biological efficacy.[26–28]

This study is limited in that we only examined current treatment fixed-dose combinations containing boosted elvitegravir and unboosted bictegravir given 24 h apart. Higher or alternative dosing formulations and strategies may provide additional advantages to event-driven prevention development that were not explored in this study. It is unclear if these findings can be extended to other INSTIs for event-driven dosing strategies, such as cabotegravir, which has been shown to have a low tissue-to-plasma ratio similar to bictegravir.[29] This study was also conducted in only a small number of self-selected MSM participants particularly as an event-driven prevention strategy for unanticipated rectal exposure to HIV as previously explored in non-human primate studies. Thus, these results may not be representative of all MSM or women, and additional studies may be able to expand upon these findings to develop and implement event-driven dosing strategies for men and women. The participants receiving bictegravir in this study were significantly older than those receiving elvitegravir; however, we are unaware of reported age-related differences in drug metabolism for antiretroviral drugs.[17] The small number of mucosal specimens examined at each time point contributes to highly variable measurements, which may limit identifying additional meaningful differences between elvitegravir and bictegravir pharmacokinetics. We examined total drug concentrations in all specimens, and both elvitegravir and bictegravir are known to be highly protein bound in plasma. It is unclear how protein binding in the rectal mucosa may affect the ability of either drug to prevent

HIV infection. However, previous studies report that protein binding for ARVs, including bictegravir, in mucosal secretions is lower than that in plasma, which may indicate greater ability to prevent infection of mucosal target cells.[23]

Current formulations of elvitegravir and bictegravir are designed to suppress viral loads following HIV infection. The results presented here combined with results of efficacy studies in non-human primates suggest that combinations of NRTIs along with boosted elvitegravir or unboosted bictegravir provide potential event-driven options to prevent HIV infection. Differential distribution of elvitegravir and bictegravir support optimization of bictegravir dosing to maximize efficacy of event-driven HIV prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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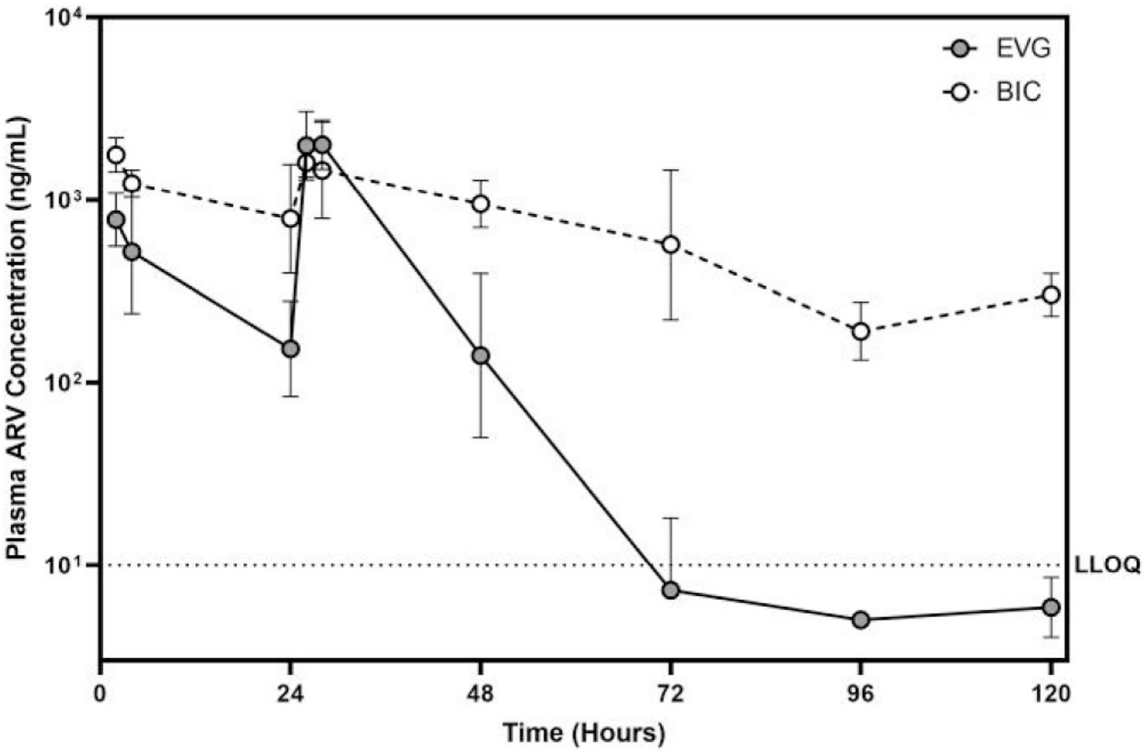

Figure 1.

Mean boosted elvitegravir (EVG) and unboosted bictegravir (BIC) concentrations in plasma specimens collected from MSM following two oral doses of integrase strand transfer inhibitor-containing regimens given 24 h apart. Geometric mean concentrations and 95% CIs for plasma are presented from 2 to 120 h following the first dose. The dotted line indicates the lower limit of quantification (LLOQ) for EVG and BIC measurements in plasma (10 ng/mL).

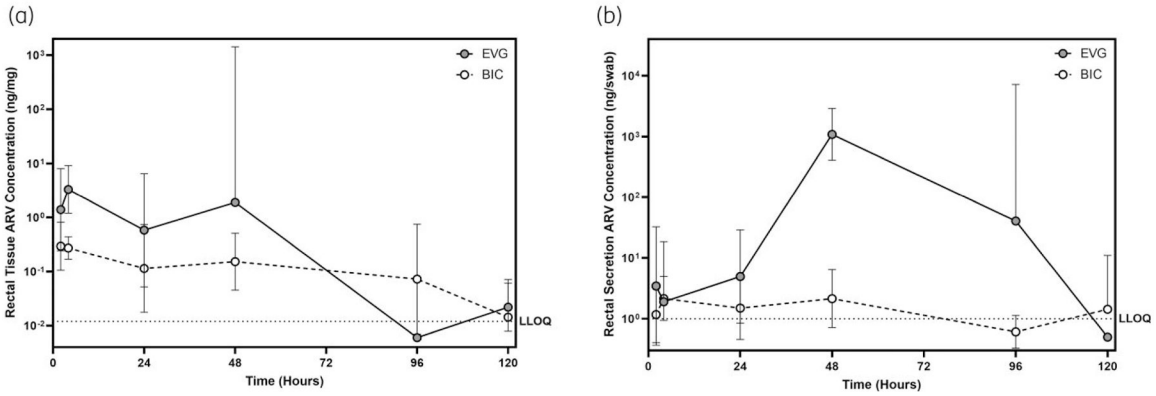

Figure 2.

Mean boosted elvitegravir (EVG) and unboosted bictegravir (BIC) concentrations in rectal tissue and rectal swab specimens collected from MSM following 2 oral doses of integrase strand transfer inhibitor-containing regimens given 24 h apart. Geometric mean concentrations and 95% CIs for rectal tissue (a) and rectal secretion (b) are presented from 2 to 120 h following the first dose. The dotted line indicates the lower limit of quantification (LLOQ) for EVG and BIC measurements in tissue (1 ng/sample) and swabs (1 ng/swab).

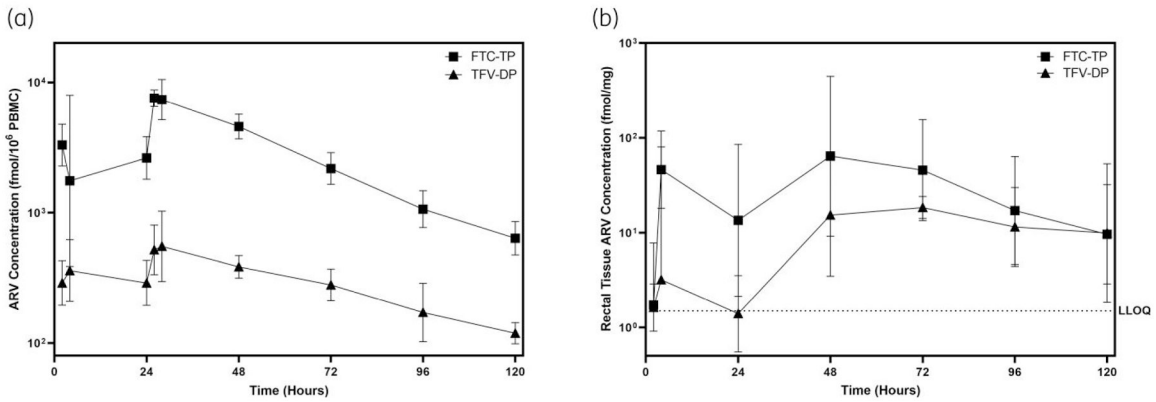

Figure 3.

Mean tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) concentrations in PBMCs and rectal tissues collected from MSM following two oral doses of integrase strand transfer inhibitor-containing regimens given 24 h apart. Geometric mean concentrations and 95% CIs for PBMCs (a) and rectal tissues (b) are presented from 2 to 120 h following the first dose. The dotted line indicates the lower limit of quantification (LLOQ) for antiretroviral drug measurements: 100 fmol/sample for TFV-DP and 500 fmol/sample for FTC-TP.

Table 1.

Demographics of MSM receiving two oral doses of integrase strand transfer inhibitor-containing regimens containing boosted elvitegravir (EVG) or bictegravir (BIC) given 24 h apart

	EVG (*n* = 39)	BIC (*n* = 24)	Total (*n* = 63)
Age, years			
Median	25	32[a]	26
18–29	29 (74%)	9 (38%)	38 (60%)
30–39	8 (23%)	13 (54%)	21 (33%)
40–49	2 (3%)	2 (8%)	4 (6%)
Race/ethnicity			
Black	25 (64%)	17 (71%)	42 (67%)
White	8 (21%)	5 (21%)	13 (21%)
Asian	1 (3%)	1 (4%)	2 (3%)
Hispanic	2 (5%)	0 (0%)	2 (3%)
Other/mixed race	3 (8%)	1 (4%)	4 (6%)

[a] $P = 0.013$.

Table 2.

Pharmacokinetic parameters of elvitegravir and bictegravir in plasma

	C_{max} (ng/mL)[a]	T_{max} (h)	$AUC_{0–120h}$ (ng × h/mL)[b]
Elvitegravir	2012 (1473–2193)	28	44 472 (4341)
Bictegravir	1769 (1427–2193)	2	94 437 (8748)

[a] Values presented as geometric mean (95% CI).

[b] Values presented as calculated $AUC_{0–120h}$ (standard error).

Table 3.

Pharmacokinetic parameters of elvitegravir and bictegravir in rectal tissue

	C_{max} (ng/mg)[a]	T_{max} (h)	$AUC_{0–120h}$ (ng × h/mg)[b]	$AUC_{0–120h}$ tissue:plasma ratio
Elvitegravir	3.31 (1.20–9.13)	4	469.78 (321.92)	10.6
Bictegravir	0.29 (0.11–0.82)	2	20.53 (5.14)	0.2

[a] Values presented as geometric mean (95% CI).

[b] Values presented as calculated $AUC_{0–120h}$(standard error).

Table 4.

Antiretroviral drug detection

Specimen	EVG	BIC
Urethral swab	14/68 (21%)	3/71 (4%)
Glans swab	9/80 (11%)	2/71 (3%)
Urine	4/73 (5%)	32/70 (46%)

Table 5.

Pharmacokinetic parameters of emtricitabine triphosphate and tenofovir diphosphate in PBMCs

	C_{max} (fmol/10^6 PBMC)[a]	T_{max} (h)	$AUC_{0–120h}$ (fmol × h/10^6 PBMC)[b]
Emtricitabine triphosphate	7549 (6528–8729)	26	367 192 (24 152)
Tenofovir diphosphate	552 (297–1026)	28	39 333 (3278)

[a] Values presented as geometric mean (95% CI).

[b] Values presented as calculated $AUC_{0–120h}$ (standard error).