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An Open-Label Pharmacokinetic and Pharmacodynamic Assessment of Tenofovir Gel and Oral Emtricitabine/Tenofovir Disoproxil Fumarate

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Abstract

The Microbicide Trials Network-017 study was undertaken to characterize the safety, acceptability, pharmacokinetic (PK), and pharmacodynamic profile of the reduced-glycerin (RG) 1% tenofovir (RG-TFV) gel compared to oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF). The study was a Phase 2, three-period, randomized sequence, open-label, expanded safety and acceptability crossover study. In each 8-week study period, HIV-1-uninfected participants were randomized to RG-TFV rectal gel daily or RG-TFV rectal gel before and after receptive anal intercourse (RAI) (or at least twice weekly in the event of no RAI), or daily oral FTC/TDF. A mucosal substudy was conducted at sites in the United States and Thailand. Samples were collected to evaluate PK and *ex vivo* biopsy challenge with HIV-1. A total of 195 men who have sex with men and transgender women were enrolled in the parent study and 37 in the mucosal substudy. As previously reported, both products were found to be safe and acceptable. Systemic TFV concentrations were significantly higher following oral exposure and daily rectal administration compared to RAI-associated product use ($p < .001$). All three routes of pre-exposure prophylaxis (PrEP) administration resulted in the inhibition of explant infection ($p < .05$), and there was a significant inverse correlation between explant HIV-1 p24 and tissue concentrations of TFV and FTC ($p < .0001$). Despite significant differences in systemic and mucosal drug concentrations, all three PrEP regimens were able to protect rectal explants from *ex vivo* HIV infection. These data suggest that there is a rationale for co-development of oral and topical antiretroviral PrEP for HIV prevention.

Clinical Trial Registration number: NCT01687218.

Keywords: rectal, microbicide, HIV, prevention, tenofovir, emtricitabine

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Introduction

Randomized, placebo-controlled clinical studies of the oral antiretroviral combination emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) tablet taken daily or around the time of sexual intercourse have demonstrated efficacy in reducing incidence of HIV infection in men who have sex with men (MSM).[1–3] Oral FTC/TDF and FTC/tenofovir alafenamide fumarate are now available by prescription for prevention of HIV infection in at-risk individuals in high- and low-income countries.

While the increased availability of FTC/TDF or FTC/TAF pre-exposure prophylaxis (PrEP) is an important step in HIV prevention, it remains to be seen if oral PrEP will be accessible and acceptable for long-term use by at-risk groups, including young women, black MSM, and transgender men.[4–6]

While oral PrEP will fulfill HIV prevention needs for some individuals, options such as a rectal gel, suppository, or enema may be more desirable to others at risk of HIV from receptive anal intercourse (RAI).[7,8] Lubricating gel is frequently used to facilitate anal intercourse[9] and topical HIV prevention candidates formulated as lubricants are likely to be acceptable and easily incorporated into the sexual practices of populations having RAI. Topical PrEP in the form of a rectal microbicide has been in development for over 15 years. Recently, much of this effort has focused on the development of 1% formulation of tenofovir (TFV) gel, initially using the vaginal formulation and later the reduced-glycerin (RG) gel with a lower osmolality.[10] The Microbicide Trials Network (MTN) 007 Phase 1 study demonstrated that this modified formulation was both safe and acceptable to men and women following daily rectal application for up to seven consecutive days.[11] Two subsequent Phase I studies of this RG formulation, CHARM-01 and CHARM-02, confirmed gel safety as well as demonstrating a favorable mucosal pharmacokinetic (PK) profile associated with simulated RAI.[11,12] It is this RG product that was taken into the Phase 2 MTN-017 study.

The objectives of the MTN-017 study were to compare the safety profiles of daily oral FTC/TDF tablet, daily rectal TFV RG 1% gel, and RAI-associated rectal TFV RG 1% gel, and to evaluate and compare their acceptability as potential HIV prevention methods. The overall safety and acceptability findings from the MTN-017 study have previously been published.[8,13] This article describes the PK and pharmacodynamic (PD) data generated in the MTN-017 mucosal substudy.

Materials and Methods

Study design

MTN-017 was a Phase 2 randomized sequence open-label expanded safety and acceptability crossover study of the oral FTC/TDF tablet and rectally applied RG-TFV 1% gel. Participants were randomized to one of six sequences consisting of three 8-week periods with different product use regimens: daily oral FTC (200 mg)/TDF (300 mg), daily rectal RG-TFV 1% gel, or rectal RG-TFV 1% gel used before and after RAI. not exceeding two doses within 24 h, consistent with the method used for vaginal application of 1% TFV gel in the CAPRISA 004 study in South African women[14] (Table 1). If participants did not engage in RAI, they were instructed to use two doses of the RG-TFV 1% gel at least once weekly. Product use was assessed by mixed methods, including unused product return count, text messaging reports, and qualitative plasma TFV PK results.[15] Participants were evaluated at weeks 0, 4 (mid-period), and 8 (end period). There was a 1-week washout between periods.

The primary study objectives were to assess both safety and acceptability of daily oral FTC/TDF, daily rectal RG-TFV 1% gel, and RAI-associated rectal RG-TFV 1% gel. Secondary objectives were to compare systemic and local PK, and to evaluate and compare adherence between the three product use regimens. The MTN-017 study protocol is available at www.mtnstopshiv.org/studies/4495.

Study sites

There were eight study sites: four in the United States (Boston, Pittsburgh, San Francisco, and San Juan), two in Thailand (Bangkok and Chiang Mai), and one each in Peru (Lima) and South Africa (Cape Town). The mucosal substudy described in this article was conducted at the Pittsburgh and Bangkok sites.

Ethical considerations

Before implementation, the study protocol was reviewed and approved by the institutional review boards/ethics committees at each participating site. In addition, the protocol was approved by the Prevention Sciences Review Committee of the National Institute of Allergy and Infectious Diseases of the U.S. National Institutes of Health. All participants provided written informed consent. The trial was registered with ClinicalTrials.gov.

Participants

Healthy HIV-uninfected MSM and TGW ≥18 years of age with a history of RAI (protected or unprotected) at least once

Table 1. Study Regimen

Sequence	*Period 1 (8 weeks)*	*Washout (1 week)*	*Period 2 (8 weeks)*	*Washout (1 week)*	*Period 3 (8 weeks)*
1	Daily oral		Daily rectal		RAI rectal
2	RAI rectal		Daily oral		Daily rectal
3	Daily rectal		RAI rectal		Daily oral
4	Daily rectal		Daily oral		RAI rectal
5	Daily oral		RAI rectal		Daily rectal
6	RAI rectal		Daily rectal		Daily oral

RAI, receptive anal intercourse.

in the previous 3 months were recruited through social and traditional media, online advertising, flyers, community engagement, and word of mouth. Individuals with abnormalities of the colorectal mucosa, significant gastrointestinal symptoms, rectal *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infection or any sexually transmitted infection requiring treatment, chronic hepatitis B infection, hepatitis C exposure, a requirement to use drugs that were likely to increase the risk of bleeding following mucosal biopsy, or symptoms suggestive of HIV seroconversion were excluded from the study.

Study products

CONRAD (Arlington, VA) supplied the RG-TFV 1% gel, which was provided in prefilled applicators (HTI Plastics, Lincoln, NE) containing 4 mL gel. RG-TFV 1% gel (weight/weight) is a transparent gel formulation of tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate), formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, and hydroxyethylcellulose, and pH adjusted to 4–5. The RG-TFV 1% gel has lower glycerin content than the TFV 1% gel (original vaginal formulation) and a significantly reduced osmolality ($\sim$800 vs. $\sim$3,000 mmol/kg, respectively). Oral FTC/TDF was supplied by Gilead Sciences (Foster City, CA). Participants were asked to take either one oral FTC/TDF tablet with water daily or to deliver intrarectally the content of an applicator filled with TFV RG 1% gel using a sachet of lubricant to facilitate insertion (Good Clean Love, Inc., Eugene, OR) either daily or before and after RAI. Study product adherence was monitored through the use of real-time plasma PK and behavioral interviews.[15]

PK analysis

Rectal biopsies for PK and PD (explant infection) studies were collected at the same time. TFV, FTC, and tenofovir diphosphate (TFV-DP) concentrations in plasma, rectal fluid, tissue, and peripheral blood mononuclear cells (PBMCs) were conducted through previously described liquid chromatographic-mass spectrometric methods by the Johns Hopkins University School of Medicine Clinical Pharmacology Analytical Laboratory.[16,17] Assays were validated in accordance with FDA: Guidance for Industry, Bioanalytical Method Validation, recommendations.[18] Briefly, assay lower limits of quantification were as follows: plasma TFV and FTC: 0.31 ng/mL; rectal fluid TFV: 1.25 ng/sponge; rectal fluid FTC: 5 ng/sponge; tissue TFV: 0.05 ng/sample; tissue FTC: 0.25 ng/sample; PBMC; and tissue TFV-DP: 50 fmol/sample. Rectal fluid concentrations were normalized to the weight of rectal fluid collected on the Merocel sponge (Beaver-Visitec International, Inc., Waltham, MA) and reported as ng/mg. Intracellular metabolite concentrations were normalized to cell counts and tissue weights and reported as fmol/10^6 cells (PBMC) and fmol/mg (tissue), respectively.

PD analysis

At the baseline visit and end of dosing period (week 8), rectal biopsies were collected in 20 mL RPMI [with 1.125 μg/mL of Amphotericin Band 0.5 mg/mL of Zosyn (piperacillin and tazobactam)] and transported to the laboratory for *ex vivo* infection within 1–2 h using a common viral stock of HIV-1_{BaL} (10^4 $TCID_{50}$), as previously described.[19] Supernatants for p24 quantification were collected on days 4, 7, 10, and 14 post-HIV challenge, stored, and later assayed for p24 antigen (p24 HIV antigen ELISA; NCI, Bethesda, MD) where the assay's lower limit of quantification (LLOQ) was 10 pg/mL. Nondetectable cumulative p24 measures were converted to 1/2 the LLOQ (5 ng/mL). The sum of all four supernatant p24 values (cumulative p24) was divided by biopsy weight. The median (of up to four biopsies) cumulative p24 with and without biopsy weight-adjusted p24 was the unit of analysis. For PK/PD analysis, drug concentrations below the LLOQ were imputed as LLOQ/2. For analysis and plotting purposes, predose (no drug) concentration values were imputed as LLOQ/20.

Statistical analyses

TFV, TFV-DP, and FTC for all sampled biological matrices were summarized by study visit using median [interquartile range (IQR)] and box plots. Paired comparisons of PK and PD values among and between regimens were made using the nonparametric Friedman test and Wilcoxon signed rank test, respectively. Pairwise correlations between PK and/or PD variables used the Spearman rank order correlation test.

Generalized estimating equation models with a gamma log link, exchangeable correlation structure, and robust errors were used to evaluate the relationship between cumulative p24 antigen (dependent variable) and drug concentration and regimen as independent variables. Explant p24 was evaluated with and without biopsy weight adjustment. All PK variables were explored.

Antiretroviral drug concentration-p24 response modeling explored (1), 2-, 3-, and 4-parameter I_{max} models (E_0 baseline p24 without drug, I_{max} maximum p24 change on drug, IC_{50} molar drug concentration at half-maximal effect, and slope term [Hill coefficient]), (2) weighting schemes for heteroscedasticity, (3) $\pm$ biopsy weight adjustment, and (4) $\pm$ imputation of baseline and/or below the limit of quantification values. Drug concentration explored all matrices assayed. Goodness-of-fit was assessed using the correlation matrix, coefficient of variation, and Schwartz and Akaike information criterion (Phoenix WinNonlin v.8, Certara, Cary, NC).

Results

A total of 195 MSM and transgender women (TW) were enrolled in the parent study and 37 in the mucosal substudy conducted in Pittsburgh, PA, and Bangkok, Thailand. Nineteen participants were enrolled in Pittsburgh and 18 in Bangkok.

PK analysis

TFV and FTC PK data from all biological matrices and across six observation times are summarized in Table 2. Comparing end of treatment period (end period) concentration data, plasma TFV concentrations were highest during the oral administration period ($p < .001$) and tissue and RF TFV were highest in the daily rectal administration period ($p < .001$). TFV concentrations in blood and tissue were lowest during the RAI-associated dosing period (Table 2).

Table 2. Drug Concentration by Analyte and Regimen

Regimen / *Matrix analyte*	*Daily oral*		*Daily rectal*		*RAI rectal*	
	Mid-period	*End period*	*Mid-period*	*End period*	*Mid-period*	*End period*
Plasma TFV (ng/mL)	82.2 (53.7, 133.0); 185	80.5 (46.0, 145.0); 186	2.9 (0.8, 7.9); 184	2.3 (0.5, 8.1);177[a]	0.5 (0.0, 2.7); 185	0.5 (0.0, 3.4); 182[b,c]
Plasma FTC (ng/mL)	240.0 (92.7, 947.0); 185	251.0 (72.1, 1,060.0); 186	all BLQ; 184	all BLQ; 177[a]	all BLQ; 185	all BLQ; 182[b]
PBMC TFV-DP (fmol/106 cells)		58.8 (32.2, 101.8); 185				
Rectal tissue TFV (fmol/mg)		1.5 (0.7, 4.7); 37		9.2 (4.8, 14.6); 36[a]		1.0 (0.3, 4.9);36[c]
Rectal tissue FTC (ng/mg)		0.4 (0.3, 0.7);37		all BLQ; 36[a]		all BLQ; 36[b]
Rectal tissue TFV-DP (fmol/10^6 cells)		32.9 (22.2, 74.8);37		100.0 (68.1, 172.8); 36[a]		36.0 (9.1, 117.2); 36
Rectal fluid TFV (ng/mg)	10.1 (1.2, 39.3); 185	10.0 (0.8, 42.9); 186	17.3 (1.0, 160.1); 182	13.0 (1.6, 89.3); 173[a]	0.9 (0.1, 12.1); 186	1.0 (0.1, 17.4); 182[b,c]
Rectal fluid FTC (ng/mg)	2.2 (0.5, 15.2); 185	2.1 (0.4, 10.7); 186	all BLQ; 182	all BLQ; 173[a]	all BLQ; 186	all BLQ; 182[b]

Data are median (lower quartile and upper quartile); sample number.
$p < .02$, [a]Daily oral vs. Daily rectal, [b]Daily oral vs. RAI rectal, [c]Daily rectal vs. RAI rectal.
BLQ, below the limit of quantification; FTC, emtricitabine; PBMC, peripheral blood mononuclear cell; TFV, tenofovir; TFV-DP, tenofovir diphosphate.

Table 3. Percent of Study Participants Within Specified Adherence Ranges in the Oral Emtricitabine/Tenofovir Disoproxil Fumarate Period Based on Pharmacologic Benchmarks

Drug-period	*7 doses per week*	*4 doses per week*	*<4 doses per week*
TFV mid	88.6%	7.6%	3.8%
TFV end	82.8%	9.7%	7.5%
FTC mid	90.8%	5.4%	3.8%
FTC end	82.8%	10.7%	6.5%

Tissue TFV-DP was highest during the daily rectal dosing period and similar between oral and RAI rectal dosing periods. Comparing plasma concentrations of TFV (oral and rectal administration) and FTC (oral only) did not demonstrate any significant difference for either analyte at the end of the dosing period (week 8) or the mid-period (week 4) (Wilcoxon test, all $p > .57$). Comparing the TFV and FTC plasma concentrations during oral dosing periods against established oral adherence benchmarks (HPTN 066[16]) indicates that 82.8% to 90.8% of participants took 7 doses in the week before sampling (Table 3). This agrees with PBMC TFV-DP data, indicating 87% of participants took seven doses in the prior week, based on HPTN 066 benchmarks. Furthermore, so-called white coat adherence (e.g., dosing only the day before study visits and not on earlier occasions) was rare with only 2% of daily adherent participants (based on plasma TFV) having concomitant PBMC TFV-DP, indicating less than daily dosing

Pharmacodynamics

Ex vivo explant HIV challenge cumulative p24 antigen results with and without biopsy weight adjustment were highly correlated (Spearman, $r = 0.975$, $p < .001$). There was a statistically significant decrease in explant infection compared to predrug baseline in all three regimens with median (IQR) $\log_{10}$ declines as follows: daily oral 0.55 (0.21, 1.00), $p < .001$; daily rectal 0.68 (0.02, 0.97), $p < .001$; and RAI rectal 0.34 (–0.19, 0.78), $p = .025$ (Fig. 1). There was no significant difference in the degree of explant infection between oral and daily rectal dosing or daily rectal dosing and RAI-associated dosing, but inhibition of explant infection was significantly lower in RAI-associated rectal dosing compared to oral dosing ($p = .026$).

PK/PD relationship

Ex vivo infection results in RT were negatively correlated with paired PK drug concentrations in the respective tissue and fluids or plasma across all visits (correlation coefficient ranged from –0.38 to –0.427, all $p < .001$). Figure 2 shows the relative decrease from baseline cumulative p24 antigen with increasing total molar drug concentration.

Generalized estimating equations were used to quantify the impact of drug concentration increase and drug regimen on the cumulative p24 antigen response in the explant assay (Supplementary Table S1). The statistically significant negative slope of the rectal tissue molar sum indicates a 13 ng/mg reduction in p24 antigen for every additional 1 ng/mL increase in colon tissue TFV or FTC concentration. In addition, the daily oral dosing period was independently associated with reduced HIV infectivity, although with a minor p24 effect compared to changes in tissue drug concentration.

The data were also fit to an inhibitory PD concentration-response model (data not shown), which indicated a statistically significant parameter estimate for a 2-parameter inhibitory I_{max} model (E_0 and IC_{50}). More complex models (adding I_{max} and gamma steepness exponent [Hill coefficient] terms) failed to identify statistically significant parameter

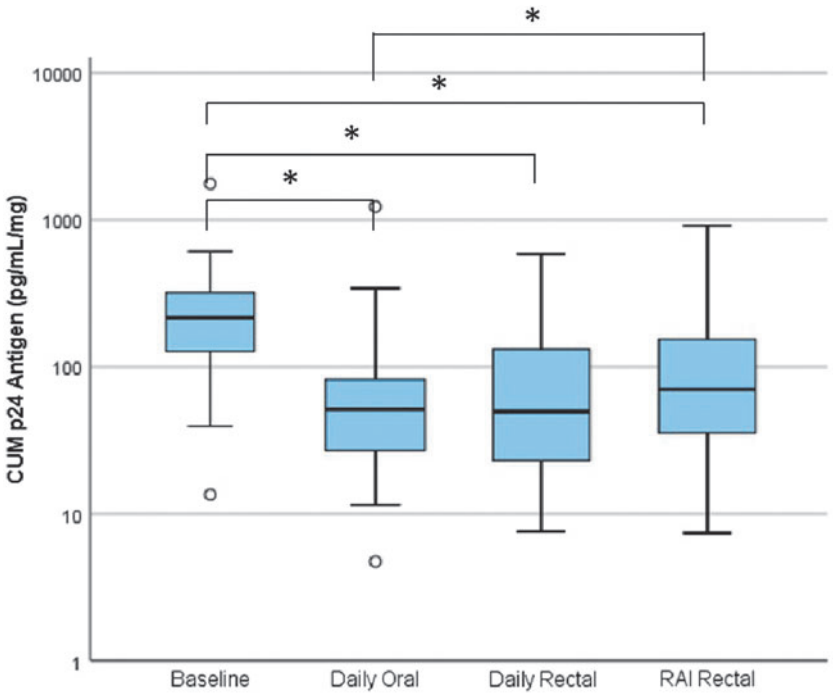

FIG. 1. Side-by-side box plots of cumulative HIV-1 p24 antigen (pg/mL/mg biopsy tissue shown in log scale) for all study conditions. Box indicates IQR, horizontal bar indicates median, *whiskers* indicate 1.5 times the IQR, and *circles* indicate outliers beyond the *whiskers* and less than three times the IQR.*$p < .05$. CUM, cumulative; IQR, interquartile range; RAI, receptive anal intercourse.

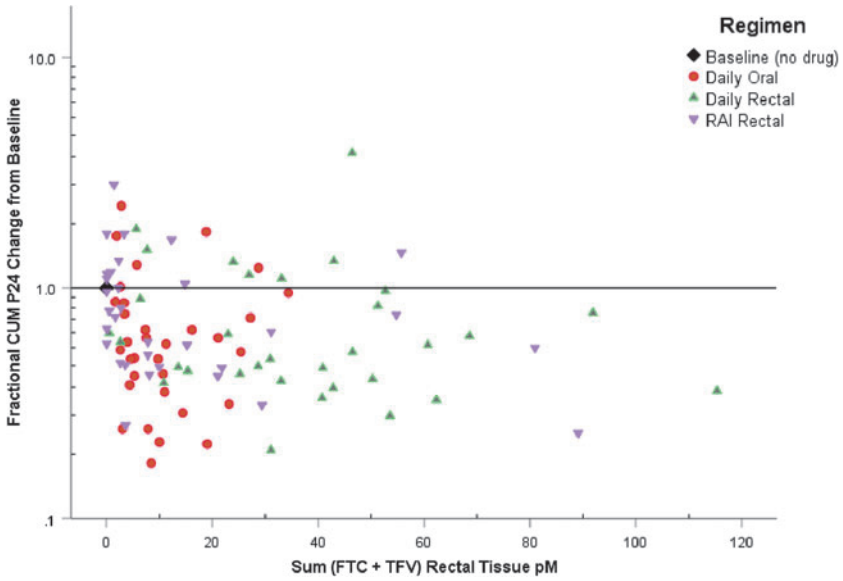

FIG. 2. Fractional change from baseline in median cumulative p24 antigen expressed as ratio of regimen to baseline ratio (y-axis). Molar concentration sum (FTC plus TFV) on x-axis. Reference line (1.0) indicates no change from baseline. FTC, emtricitabine; TFV, tenofovir.

values for all parameters. Even though we estimated statistically significant PD parameter estimates, we rejected the 2-parameter model on grounds of biologic implausibility because (1) the model underestimated E_0 (for which we had empiric baseline [no drug] estimates for comparison), (2) very few observations above the fitted IC_{50} estimate, and (3) the inhibitory p24 asymptote at infinite drug concentration did not approach the minimum cumulative p24 value (LLOQ), which we have observed in other studies using the same explant methods and drugs.

Discussion

In this study, we have demonstrated that both oral and rectal administration of antiretroviral PrEP can prevent *ex vivo* HIV challenge infection of colorectal explants. This provides a rationale for the continued development of topical antiretroviral PrEP for the prevention of RAI-associated HIV infection.

Despite advances in the diagnosis and treatment of HIV infection, new cases are still occurring at an unacceptable level. The 2019 UNAIDS report estimated that ~1.7 million new HIV infections occurred in 2018. Consequently, increased efforts are being made to develop and implement safe and effective HIV prevention strategies. Antiretroviral PrEP is the most advanced HIV prevention intervention and oral PrEP with FTC/TDF is now licensed in several countries. In addition, FTC/TAF (Descovy®) was approved for PrEP use in 2019, although the indication excluded individuals at risk of HIV infection through vaginal sex.[20] Ensuring that the most at-risk populations have access to oral PrEP and support to maximize PrEP adherence during periods of risk for HIV infection remains a challenge.[21] In this setting, other antiretroviral PrEP modalities are being developed, including topical products (microbicides), vaginal rings, and long-acting injectable PrEP.[22] We and others have advocated for the development of topical rectal microbicides for the prevention of HIV infection associated with condomless RAI.[23]

A critical question in the development of topical PrEP is whether a sufficient amount of antiretroviral drug can be delivered to the mucosal tissue at risk of HIV infection. Rectal 1% TFV gel has been shown to protect non-human primates from SIV infection,[24] and has been evaluated in two Phase 1 studies where it was able to significantly inhibit HIV infection in colorectal explants.[11,12] The MTN-017 mucosal PK/PD study was unique as it provided an opportunity to compare the safety, acceptability, and PK/PD profile of both oral and rectal PrEP in a sexually active population of MSM.[13]

The plasma PK concentration of TFV was greater after daily oral FTC/TDF compared to rectal administration and rectal tissue TFV concentrations were greater after daily rectal use of TFV gel in comparison to oral administration of FTC/TDF. These differences in oral dosing and topical dosing were similar to those seen between oral FTC/TDF and vaginal TFV dosing in MTN-001, a clinical trial using similar size, crossover design, and the same drug analytical methods as in MTN-017.[25]

In the HPTN 066 directly observed PK study, participants received oral FTC/TDF in a range of dosing regimens (once weekly to once daily) for 5 weeks.[16] When comparing the HPTN 066 daily FTC/TDF regimen PK data to the MTN-017 oral FTC/TDF data, there were a number of observations: (1) the number of MTN-017 participants with daily adherence was consistently high (>82%); (2) blood concentrations of both FTC and TFV were higher in MTN-017 participants, which may have been due to collection of samples less than 24 h postdosing (the sampling time in HPTN 066); and (3) tissue concentrations of FTC, TFV, and TFV-diphosphate in MTN-017 were largely overlapping those reported in HPTN 066. The data presented herein add substantially to the published rectal tissue data for both oral FTC/TDF and rectal TFV dosing. The duration of dosing in the MTN-017 study (8 weeks) was greater than that seen in the HPTN 066 study (5 weeks) and the MTN-017 participants did not have their product administration directly observed, but they did receive motivational counseling linked to real-time PK data, which may have improved overall product adherence.[15,26]

Ex vivo/in vitro explant models have been used to screen candidate PrEP agents including rectal, vaginal, oral, and injectable forms of PrEP.[11,19,27–30] Because the daily (83%–91%) and four weekly (5%–11%) adherence frequencies were so high during our oral regimen periods, and given the demonstrated efficacy of oral FTC/TDF dose observed with daily, four weekly, and four dose on demand regimens, the rectal tissue concentrations achieved in MTN-017 are associated with a high level of protection.[1,3,31] Consistent with that observation, the magnitude of reduced HIV infectivity as assessed by the *ex vivo* explant HIV challenge may be associated with a high level of clinical HIV protection in this study population of MSM and TW.

It remains uncertain if the mucosal tissue antiretroviral concentration alone—and by extension, the rectal tissue *ex vivo* HIV challenge alone as a biomarker —is sufficient for HIV protection or if a combination of systemic and local mucosal drug concentration is necessary. There has never been a clinical PrEP efficacy trial of a rectal microbicide (low systemic, high rectal drug concentrations) to compare to oral and injectable PrEP trials (high systemic, lower rectal drug concentration), which would be needed to answer this. Topical vaginal dosing of TFV or dapivirine demonstrate reduced HIV infectivity in the *ex vivo* HIV explant challenge model[32–34]; these drugs have also proven effective in randomized clinical trials, although with less magnitude of protection—even with *post hoc* adherence corrections—than oral FTC/TDF combinations and injectable cabotegravir dosing.[35–39]

The MTN-017 explant studies were conducted at two separate clinical sites (Pittsburgh and Bangkok), although the quantification of supernatant HIV-1 p24 antigen from both trial sites was undertaken in Pittsburgh. Two articles have explored the variability of explant infection in studies conducted across multiple sites. In the first study, sites were provided with a common source of virus and experimental compound and were able to demonstrate that multiple investigators could identify when a drug was efficacious when providing standardized reagents and analytical techniques were used.[40] The second study was able to show that using four tissue explants (as used in the MTN-017 study) per experimental time point was adequate for comparative analyses.[41]

Despite differences in plasma and tissue PK exposure related to oral or rectal product administration, significant inhibition of colorectal explant HIV infection was seen with all three dosing regimens. These data are encouraging in terms of generating a rationale for the use of rectal PrEP regimens for HIV prevention. Understanding the PK/PD profile of candidate topical products used on an intermittent basis is important as participants in the MTN-017 study expressed a preference for RAI-associated dosing compared to daily rectal use.[15] While RAI-associated dosing had the lowest PK exposure in plasma and rectal tissue and the smallest reduction in HIV infectivity, this finding is consistent with less frequent dosing, associated reduction in drug accumulation, and more distant sample timing with RAI-associated dosing when compared to daily rectal dosing. Whether intermittent dosing achieves similar drug concentrations at the time of HIV exposure could be estimated using PK models, but the duration for which such HIV suppressive concentrations need to be sustained after an HIV exposure has not been established.

Conclusions

The MTN-017 study demonstrated that both oral and topical antiretroviral PrEP are safe and acceptable to sexually active MSM at risk of HIV infection. This PK/PD substudy confirms that both routes of administration have the potential to inhibit explant infection. These data support further development of topical PrEP for HIV prevention. However, the MTN-017 participants expressed a preference for RAI-associated dosing,[8] and it was this regimen that was associated with the lowest PK exposure in plasma and rectal tissue. It is therefore unclear whether a single dose of TFV gel administered before RAI would be enough to prevent HIV infection. For RAI-associated dosing to move forward, additional studies, such as those conducted for oral FTC/TFV, will be needed to better understand the relationships between drug exposure and mucosal protection from HIV infection. Higher concentrations of TFV, currently being explored as a rectal douche in the DREAM program, may provide a more viable solution for the development of a safe and effective RAI-associated topical PrEP strategy for HIV prevention.[42]

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the other institutions

Authors' Contributions

I.M.M.: designed the study and generated the final draft of the article. R.P.K.N.A.: laboratory support for mucosal studies. M.A.M.: responsible for PK analysis. C.W.H.: study design and PK analysis. S.J.: operational support for the study. J.M.P.: NIH representative for regulatory and safety support. T.H.H.: CDC representative for regulatory and safety support. M.C.: laboratory oversight at the Bangkok site. A.C.: laboratory support at the Bangkok site. B.R.: laboratory support at the Bangkok site. G.D.: study design and provision of tenofovir gel. J.L.S.: safety support for tenofovir gel. J.F.R.: study design and provision of FTC/TDF. R.D.C.: principal investigator of the MTN-017 study.

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Supplementary Material

Supplementary Table S1

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