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The Clinical Pharmacology of Antiretrovirals for HIV Prevention

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Structured Abstract:

Purpose of review: Pre-exposure prophylaxis (PrEP) clinical trial results using antiretrovirals can seem confusing, if not conflicting. We review recent antiretroviral pharmacokinetic studies to help explain PrEP trial results.

Recent findings: Pharmacokinetic studies indicate that topical dosing, compared to oral dosing, achieves far higher colon and vaginal tissue drug concentrations, and far lower drug concentrations in blood. After oral dosing, higher tenofovir diphosphate concentrations are found in colon tissue than cervicovaginal tissue, but the reverse is the case for emtricitabine triphosphate though it doesn't persist as long. Vaginal dosing achieves measurable tenofovir concentration in the rectum and vice versa. Within and among oral PrEP trials, increased drug concentration is associated with increased HIV protection, with drug concentration differences best explained by adherence, rather than pharmacokinetics. The poor level of protection in topical studies is not consistent with concentration-response in oral studies indicating unknown variables in need of further investigation.

Summary: Sparse pharmacokinetic sampling in large trials combined with more intensive sampling in smaller pharmacokinetic-focused studies help explain trial outcome differences due largely to differences in adherence, tissue pharmacokinetics, and type of HIV exposure. Pharmacokinetic analysis can identify protective drug concentration targets, guide dose optimization, and inform future trials.

Keywords

Pre-exposure prophylaxis; tenofovir; emtricitabine; pharmacokinetics; microbicide

Introduction:

We review key, recent clinical pharmacology studies to aid interpretation of completed pre-exposure prophylaxis (PrEP) randomized clinical trials (RCTs) using antiretroviral (ARV) drugs. The goal is to establish concentration-response between and within studies to identify effective target drug concentrations and other influential variables, like adherence, that affect PrEP efficacy. Target concentrations, once established, guide dose optimization and development of ARVs in the PrEP pipeline.

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None

Text of Review:

Selection of ARVs for PrEP

Since 2002, numerous vaginal microbicides for PrEP contained luminally active agents – detergent, polyanionic, or pH buffering mechanisms of action – which did not contain ARVs. These were selected for study, in part, to avoid resistance to treatment ARVs, limit systemic toxicity possible with oral drugs, and achieve high local concentrations at the putative mucosal site of action. As these non-ARV formulations failed to prevent HIV infection, treatment proven tenofovir (TFV) was studied in a vaginal gel formulation and in its licensed oral formulations, tenofovir disoproxil fumarate (TDF) alone (Viread™) and coformulated with emtricitabine (Truvada™) [1-6]. Extensive pharmacokinetic, safety, and antiviral data established for treatment accelerated development of tenofovir-containing oral and topical formulations for PrEP. Applying these drugs to sexual HIV prevention, however, required additional data to guide rational dosing and formulation development, especially for topical application, to understand the complex interactions of many influential drug and HIV-related variables (Figure 1), including: vaginal and rectal tissue pharmacokinetics (PK), mucosal tissue toxicity (which might reduce adherence if symptomatic or increase HIV susceptibility), luminal distribution of HIV within the female genital tract and colon to assure adequate distribution of ARVs in development [7].

TFV and FTC remain the only ARVs proven efficacious in clinical PrEP trials. Tenofovir, an adenine nucleoside analog reverse transcriptase inhibitor, is a component of first line highly active ARV therapy (HAART). TFV is a phosphonate, which requires only two phosphorylation steps by human nucleoside kinases to form the active moiety, tenofovir diphosphate (TFV-DP), which remains in the cell with an extended 150 to 180 hour half-life in peripheral blood mononuclear cells (PBMCs) of HIV patients, far longer than the 17 hour plasma half-life of the parent drug [8-11]. The oral formulation, TDF, is an esterified prodrug with increased bioavailability compared to TFV. FTC is a cytidine nucleoside analog reverse transcriptase inhibitor which, compared to TFV, has a shorter half-life of both parent drug in plasma and the active intracellular anabolite, emtricitabine triphosphate, 8–10 hours and 39 (range 29–56) hours, respectively [12, 13].

Pharmacology of oral and topical PrEP

PK-focused studies describe the concentration-time course of TFV and FTC in diverse anatomic sites relevant to HIV protection.

HIV distribution after intercourse.—Identification of the viral target in space and time enables optimization of PrEP ARV formulation and dosing to assure that the ARV outdistances and outlasts the virus at the site of infection. Over a decade ago, murine and primate models of retrovirus infection indicated that virus passes from vaginal lumen to mucosal tissue rapidly within one hour and infects T cells in genital mucosa and regional lymph nodes, both directly and indirectly via dendritic cells, within 24 hours [14-16]. Recently, Louissaint, *et al*, described the distribution of cell-free and cell-associated HIV surrogates (virus sized particles and autologous white blood cells) in the colon and vagina following simulated sex. Rectally dosed HIV surrogates distributed to the recto-sigmoid

colon, were associated with rectal biopsies taken 5 hours after simulated sex, and were usually cleared within 24 hours[17]. Vaginally dosed HIV surrogates were concentrated in the peri-cervical area, with no evidence of uterine distribution, through 8 hours at which time surrogates were found in vaginal tissue biopsies, but little remained at 24 hours[18]. In both colon and vagina, the cell-free and cell-associated surrogates shared a largely coincident luminal distribution. Taken together, these animal and human studies indicate that optimal PrEP drugs, whether oral or topical, deliver HIV inhibiting ARV concentrations to the peri-cervical region or into the recto-sigmoid prior to and for at least 24 hours following sex.

Luminal drug distribution.—Methods developed by Cao and Goldsmith enable description of the luminal distribution and clearance of rectal microbicide formulations using non-invasive single photon emission computed tomography (SPECT) [19, 20]. In feasibility studies, a rectal gel achieved the greatest accumulation in the recto-sigmoid colon, similar to the HIV surrogate studies above, with the maximal extent of distribution into the sigmoid and even the descending colon in a small subset of individuals. Gel migrated retrograde with time and was visible within the colon throughout 24 hours. These methods are being used to optimize development of rectal microbicides.

Mucosal tissue distribution and clearance of ARVs.—Schwartz, *et al.*, studied the 24-hour blood and genital tract pharmacokinetics of single and multiple doses (14 days) of 1% TFV (40-mg) vaginal gel in 49 women [21]. Multiple days of vaginal dosing with one or two doses daily resulted in little or no accumulation of TFV in plasma, compared to a single dose. The systemic multiple dose concentrations are 7.5 and 40-times lower than trough and peak TFV concentrations, respectively, after a daily oral 300 mg TDF dose in a comparable cohort of healthy women [22]. In the multiple dose group, TFV and TFV-DP were detected in 100% and 27% of vaginal biopsies, respectively. Tissue TFV peaked 4 hours after dosing at 2.7×10^4 ng/mL; TFV-DP peaked at 8 hours at 3.1×10^3 ng/mL (among the 27% of detectable samples). There was no difference in vaginal tissue TFV between the proximal and distal biopsy locations.

MTN-001 employed a cross-over design in which 144 African and US participants received daily doses of 300 mg oral TDF, 1% (40-mg) TFV vaginal gel, or both, each for 6 weeks in randomized sequence. Findings included one hour peak TFV in both blood and tissue, 60-fold greater serum concentrations after oral dosing compared to vaginal, and >130-fold higher vaginal tissue TFV-DP concentrations with vaginal compared to oral dosing [23]. TFV-DP was detected in greater than 90% of women in the vaginal dose phase. Rectal fluid TFV concentrations were greater after vaginal dosing than after oral dosing, consistent with a previous report in macaques by Nuttall, et al.[24], suggesting vaginal dosing may provide some level of rectal protection.

MTN-001 also documented high 94% adherence using self-reported, but serum TFV concentrations indicated inconsistent TFV use in 64% of participants. Further, compared to African women, US women showed a 2- to 5-fold greater pre-dose serum TFV concentration (greatly influenced by timing of the prior unobserved dose), despite having a

similar peak and half-life after an observed clinic dose[23]. This indicated similar PK, but large adherence differences.

In RMP-02/MTN-006, Anton, *et al.*, compared a single 300 mg oral TDF dose to a rectal 1% (40 mg) TFV gel dose (single and 7 daily doses)[25]. Similar to vaginal dosing, plasma TFV concentrations were 20-fold greater after oral compared to rectal dosing, tissue TFV-DP concentrations were 100-fold greater after rectal compared to oral dosing, and rectal dosing achieved measurable TFV concentrations in cervicovaginal fluid. Unique among the small PK studies, Anton challenged rectal biopsies with HIV *ex vivo* and saw a increasing TFV-DP concentrations associated with decreasing HIV replication.

In a 12 subject, single dose oral TDF/FTC (Truvada™) study with 2 weeks of post-dose sampling, Patterson, *et al.*, identified a tri-phasic concentration-time course with a 49 hour terminal (gamma) half-life[26]. Twenty-four hours after dosing, rectal biopsy homogenates in 6 men demonstrated TFV-DP concentrations >100-times greater than TFV-DP in vaginal biopsy homogenates in 6 women. While TFV-DP was still detectable 2 weeks later, the rectal-vaginal difference had disappeared. Cervical TFV-DP was erratically detected, though at similar concentrations to vaginal tissue. In contrast, FTC-TP was 10-fold greater in vaginal tissue compared to rectal tissue, but was not detectible in either beyond 2 days[26].

In another single dose oral TDF study, collecting paired rectal and vaginal biopsies in 6 women, Louissaint, *et al.*, confirmed several of the key Patterson findings: 49 hour terminal TFV plasma half-life and greater than 100-fold rectal:vaginal concentration ratio at 24 hours that did not persist at 2 weeks [27]. Because these were paired biopsies in the same women, the colon:vaginal ratio cannot be attributed to gender differences. However, when the investigators looked at TFV-DP concentrations in the highly relevant CD4+ T cells extracted from tissue, the rectal:vaginal TFV-DP ratio was only 20-fold. In addition, they demonstrated a complex biphasic PBMC TFV-DP peak - first peak at 8–16 hours, second peak at 96 hours - before beginning terminal elimination with a 48 hour PBMC half-life, similar to the plasma TFV gamma decay estimate, and a longer 112 hour half-life in CD4+ T cells. This complex early biphasic peak and delayed time to terminal decay may partly explain the shorter PBMC TFV-DP half-life estimates compared to the 150 to 180 hour estimates in studies of HIV patients [9-11]. The half-lives in homogenates and unselected cells extracted from vaginal and rectal tissue was similar to PBMCs with CD4+ cell half-lives typically longer. A second 6 woman, single oral TDF dose study by Chen, *et al.*, replicated this complex biphasic TFV-DP pattern between day 1 and 3 before a terminal elimination half-life of 64 hours and 100 hours in PBMC and CD4+ cells, respectively[28].

Other ARVs with potential benefits over TDF/FTC are in earlier phases of PrEP development. CCR5 inhibitor, maraviroc, does not have other in-class drugs to raise resistance concerns, demonstrates greater vaginal (2-fold) and rectal (26-fold) tissue homogenate concentrations when compared to blood plasma after oral dosing, and cervicovaginal fluid concentrations exceeded plasma concentrations 3 days post-dosing [29, 30]. However, given poor adherence in some PrEP RCTs, a 16 hour plasma maraviroc half-life, far shorter than TFV-DP, may be a liability if similarly brief in tissue. The 50 hour plasma half-life of rilpivirine, a licensed oral non-nucleoside reverse transcriptase inhibitor,

is far longer than maraviroc and lacks the initial phosphorylation delay seen with TFV-DP and FTC-TP – characteristics which may have advantages if its tissue distribution and clearance are favorable[31]. Directly attacking the adherence issue, an injectable rilpivirine formulation sustains blood, vaginal tissue, and rectal tissue concentrations in men and women for 28 days [32]. Also addressing adherence, a monthly vaginal ring containing dapivirine, an experimental non-nucleoside reverse transcriptase inhibitor, is being studied in two RCTs scheduled for completion in 2015. Importantly, rilpivirine and dapivirine have potential for within class cross-resistance.

PK data informs RCTs.

Sparse PK data embedded in PrEP RCTs, especially when linked to smaller bridging PK studies, enhances understanding of concentration-response and modifying factors essential for dose selection and future trial design.

Within study concentration-response.—Several PrEP RCTs included PK data which provide evidence of concentration-response (Table). CAPRISA 004 showed a decrease in HIV incidence with cervicovaginal fluid TFV concentrations higher than 1,000 ng/mL [33]. Presence of TFV and FTC moieties in blood plasma and in PBMCs was associated with 92% relative risk reduction compared to only 42% in participants randomized to drug [34]. Partners PrEP reported a smaller bump in relative risk reduction in both TDF and TDF/FTC arms rising to 86% and 90%, respectively, when TFV was detected (using a more sensitive assay than in iPrEX)[35]. In CDC TDF2, TFV and FTC were more commonly detected in non-seroconverters, 80% and 81%, respectively, compared to seroconverters, 50% for both drugs [36]. In FEM-PrEP, concentrations at the beginning and end of the seroconversion window appeared to be less frequently detectable in seroconverters, 15%, compared to non-seroconverting participants at similar time intervals, 26%, but these were not statistically significant [37].

Among study concentration-response in oral studies.—The TFV plasma concentrations reported in completed oral PrEP RCTs indicates a concentration-response among these studies (Figure 2), with the exception of iPrEX which has a unique risk population[34-38]. TFV concentration data contains substantial heterogeneity due, most likely, to variability between individuals and in time of unobserved prior doses. Similarly, confidence intervals of relative risk reduction are also large in some studies due to few seroconversion or small sample size.

iPrEX is the outlier among oral studies with median detectable ARV concentrations around 10 ng/mL, not much different from FEM-PrEP; yet, iPrEX had a 42% relative risk reduction compared to none[34, 37]. Since receptive anal intercourse is the primary HIV risk for the men who have sex with men (MSM) in iPrEX, two adjustments are warranted. First, several oral dose PK studies indicate active drug TFV-DP concentrations are 20 to >100 times greater in rectal tissue, most relevant in iPrEX, when compared to vaginal tissue[26, 27]. Since plasma TFV, not rectal tissue, is measured in RCTs, this colon:vaginal ratio effectively shifts the “effective” iPrEX plasma concentration rightward along the concentration axis. There is a second countering leftward shift in “effective” TFV concentration due to

increased risk of HIV infection via receptive anal intercourse in iPrEX compared to vaginal or penile exposures, the dominant risks in the other oral studies. The magnitude of site of infection and anatomic variation in active drug tissue concentration effects are too imprecise to make specific adjustments, but these factors may combine to bring iPrEX more closely in line with the concentration-response seen among the other studies.

Adherence influential in oral studies.—The variation in concentration among RCTs far exceeds variability attributable to either inter-individual variability in prior PK studies or prescribed daily dosing time in the day prior to clinic blood sampling. Comparison of geographic sub-populations in MTN-001 found 5-fold differences in pre-dose serum TFV concentration. Since pre-dose concentration is influenced by timing of the prior unobserved dose and individual PK variation, which was not seen following observed doses, we attribute most of these concentration differences to adherence.

Factors mitigating beneficial ARV effect in topical studies.—Since tissue concentrations with topical dosing exceed those after oral dosing by more than 100-fold, one would anticipate topical dose studies to have the best HIV protection. Even assuming the low level of adherence seen in FEM-PrEP, expected tissue concentrations in CAPRISA 004 and VOICE gel arm would exceed Partner's PrEP vaginal tissue concentrations by 10-fold. Results to the contrary – only 39% relative risk reduction in CAPRISA 004 and none in VOICE TFV gel arm – we postulate an unexplained dose-related variable at work that reduces the efficacy of topical dose regimens. Excessively high local concentrations of drug or the gel delivery vehicle are potential candidates worthy of additional exploration. If these are at fault, a simple formulation change (dose reduction and/or gel modification) could transform topical TFV dosing into a highly effective PrEP method.

Conclusion:

Small clinical pharmacology studies richly inform our interpretations of concentration-response in oral PrEP RCTs and indicate that differences in adherence and anatomic site of HIV risk are both powerful explanatory variables which can guide selection of alternative regimens to achieve target concentrations. The underperformance of topical PrEP studies cannot be explained by low adherence and may be due, in part, to some product related factor mitigating the high level of protection expected based on the concentration-response seen in oral studies. Beyond simply informing interpretation of their trial outcomes, earlier completion of these clinical pharmacology studies should improve the drug development process for the next generation of PrEP agents.

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Key Points:

- Small, intensive clinical pharmacology studies improve our ability to interpret outcomes in PrEP trials.
- Increasing tenofovir concentration is associated with increasing HIV protection both within and among oral PrEP trials.
- Adherence is responsible for most of the concentration variation in oral PrEP studies.
- High rectal-to-vaginal ratios of active tenofovir diphosphate after oral dosing make it risky to generalize MSM PrEP concentration targets to other at risk populations.
- Because tenofovir dosing in the vagina and rectum achieves local active drug tissue concentrations greater than 100-times concentrations achieved with oral dosing, far greater than could be explained by adherence differences, other influential variables must be imputed to explain poor outcomes in topical studies.

Modified from Hendrix, *et al. Ann Rev Pharm Tox* 2009; 49: 349-375. Figure 5.

Figure 1.

Variables affecting pre-exposure prophylaxis (PrEP) trial outcomes. A variety of drug (white boxes) and viral (gray boxes) variables interact in complex ways to influence seroconversion outcomes. Primary drug and viral processes generally follow a temporal sequence (left to right, solid lines, heavy arrows), however, they also interact at many locations and are heavily influenced themselves by numerous other human, viral, and environmental variables (dotted lines, light arrows).

Figure 2.

Conceptual concentration-response among pre-exposure prophylaxis (PrEP) trials. Antiviral effect (solid line) is based on $E_{\max}$ model fitting of oral studies, excluding iPrEX. A second hypothetical dose-rate dependent effect (dashed line) is postulated for topical studies which suppresses the concentration-dependent antiviral effect clearly seen in oral studies. The net protective effect (dotted line) is a bell-shaped curve. Notes on imputed values: VOICE gel arm confidence intervals are based on protocol design to confidently exclude a 35% effect. Since FEM-PrEP concentration data is below LLOQ, it is estimated using the seroconversion window upper quartile (10 ng/mL). “Effective” tenofovir concentration (open circle) for VOICE is adjusted to account for the 130-fold greater vaginal tissue concentration with vaginal dosing compared to oral dosing; FEM-PrEP served as conservative, low adherence reference. CAPRISA 004 is estimated at one-third the daily VOICE gel prescription (10 v. 30 prescribed monthly doses) based on BAT24 (two doses with sex) and reported sexual frequency (5/month). Interquartile proportions are from MTN-001.

Within study concentration-response comparisons: relative risk reduction increases with drug concentration at varying thresholds.

Table.

Study	Regimen	Relative Risk Reduction (95% CI)	
		All Subjects	Drug Detectible Adherence
FEM-PEP	TDF/FTC po qd	0.0 (−0.73 – 0.42)	SC 15%, NSC 26%, ns ^a ; LLOQ 10
VOICE	TDF po qd	0.0 ^b	<i>In Analysis</i>
iPrEX	TDF/FTC po qd	0.42 (0.15 – 0.63)	0.92 (0.40 – 0.99) ^c ; LLOQ 10
CDC TDF2	TDF/FTC po qd	0.63 (0.22 – 0.83)	SC 50%, NSC 80% ^a ; LLOQ 0.3
Partners	TDF po qd	0.67 (0.44 – 0.81)	0.86 (0.57–0.95) ^c ; LLOQ 0.3
	TDF/FTC po qd	0.75 (0.55 – 0.87)	0.90 (0.56–0.98) ^c ; LLOQ 0.3
CAPRISA 004	TFV gel BAT24	0.39 (0.04 – 0.60)	>1,000 CVF ^e
VOICE	TFV gel qd	0.0 ^b	<i>In Analysis</i> 0.54 (0.20 – 0.96) ^f

SC, seroconverter; NSC, non-seroconverter

ns, not statistically significant

LLOQ, lower limit of assay quantitation, ng/mL, varies among studies biasing percent detectible across studies TDF, tenofovir disoproxil fumarate; TFV tenofovir, FTC, emtricitabine

^aPercent of subjects in seroconversion category (SC or NSC) with drug detectible drug in plasma

^bVOICE confidence intervals not reported

^cIncreased relative risk reduction with detectible drug in plasma

^dIncreased relative risk reduction in subset with accessibility to study drug

^eIncreased relative risk reduction if CVF (cervicovaginal fluid) >1,000 ng/mL

^fIncreased relative risk reduction if >80% adherence by self-report