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Pharmacokinetics of Antiretrovirals In Genital Secretions and Anatomic Sites of HIV Transmission: Implications for HIV Prevention

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Abstract

The incidence of HIV remains alarmingly high in many parts of the world. Prophylactic use of antiretrovirals, capable of concentrating in the anatomical sites of transmission, may reduce the risk of infection after an unprotected sexual exposure. To date, orally and topically administered antiretrovirals have exhibited variable success in preventing HIV transmission in large-scale clinical trials. Antiretroviral mucosal pharmacokinetics may help explain the outcomes of these investigations. Penetration and accumulation of antiretrovirals into sites of transmission can influence dosing strategies and pre-exposure prophylaxis clinical trial design. Antiretroviral tissue distribution varies widely within and between drug classes, attributed in part to their physicochemical properties and tissue-specific drug transporter expression. Nucleoside (-tide) reverse transcriptase inhibitors, the CCR5 antagonist maraviroc, and the integrase inhibitor raltegravir demonstrate the highest penetration into the male and female reproductive tracts and colorectal tissue relative to blood. This review will describe antiretroviral exposure in anatomic sites of transmission, and place these findings in context with the prevention of HIV and the efficacy of pre-exposure prophylactic strategies.

1. Introduction

Antiretrovirals improved the length and quality of life for HIV-infected patients, making it a manageable chronic disease [1–3]. Despite these advances, the incidence of HIV remains high, with approximately 2.3 million new cases reported globally in 2012 [4]. Viral shedding in both the male and female genital tract is responsible for the sexual transmission of HIV during unprotected intercourse, which remains the most common route of HIV transmission [4]. Strict adherence to antiretrovirals to potently suppress genital tract shedding, and thus interrupt HIV transmission, was recently proven in the HPTN 052 trial [5]. In the serodiscordant couples enrolled in this trial, antiretroviral therapy used in the HIV-infected partner (with sustained suppression of plasma HIV RNA to < 400copies/mL) was shown to reduce the risk of HIV transmission to the HIV-negative partner by 96%.

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Antiretrovirals administered both orally and topically have also been explored for pre-exposure prophylaxis (PrEP) in HIV-negative individuals at risk for HIV acquisition [6–9]. Since antiretroviral therapy was already established to reduce the risk of infection to occupationally exposed health care workers [10], and to newborns of infected mothers [11, 12], it was considered biologically plausible for antiretrovirals to protect mucosal tissues from sexual exposure to HIV. Multiple clinical studies have assessed the ability of antiretrovirals, particularly tenofovir (TFV) and emtricitabine (FTC), to reduce the risk of transmission.

The male and female genital tracts are complex and dynamic compartments. Drug distribution to these sites is influenced by multiple factors: hormonal changes, inflammation, and concomitant sexually transmitted infections may modulate the amount of drug that reaches these anatomical sites, or the amount of drug required to protect against altered permissiveness to infection. Specific characteristics of the antiretrovirals such as protein binding, lipophilicity, and pK_a, may also dictate the drug's ability to penetrate, or distribute to the male and female genital tract or colorectal tissue [13, 14]. The aim of this review is to highlight the pharmacokinetic data available for antiretroviral penetration into the anatomical sites of transmission, including the female reproductive tract, male reproductive tract, and colorectal tissue, and to place these data in the context of antiretroviral PrEP efficacy.

Rapid penetration, high accumulation, and a long half-life within the sites of initial HIV transmission are important features for PrEP interventions. Less favorable features include frequent dosing requirements and extensive adverse effect profiles. Protease inhibitors (PIs) and non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) have not been extensively explored as PrEP strategies, in part due to their adverse effect profile and limited tissue distribution. In addition, the improper use of NNRTIs as PrEP may more easily lead to resistance for individuals who fail prophylaxis. Also, it is unclear whether utilizing post-transcriptional agents such as PIs are a suitable strategy for PrEP. In contrast, nucleoside(tide) reverse transcriptase inhibitors (NRTIs), integrase strand transfer inhibitors (INSTI), and the CCR5 antagonist maraviroc exert their antiviral activity prior to integration and have more favorable adverse effect profiles. Many of these agents have been the focus of PrEP development. The pharmacokinetic profiles of these agents within each of these compartments is reviewed in detail below, and where applicable, correlated to outcomes from PrEP clinical trials.

2. Literature Search

A literature search was performed in PubMed using the following terms: antiretroviral (as well as individual drug names), pharmacokinetic, cervicovaginal fluid, semen, seminal plasma, vagina, vaginal tissue, cervix, cervical tissue, rectum, and rectal tissue. All original research articles, related review articles, and abstracts from prominent conferences that addressed antiretroviral pharmacokinetics in human mucosal sites of transmission prior to March, 2014 were included in this review. Reference lists of select articles were also reviewed. A detailed table recapitulating pertinent research articles and abstracts is provided by Else and colleagues [15].

3. Female Genital Tract

The female genital tract (FGT) is a dynamic compartment of multiple tissue types under direct hormonal control. The effects of hormonal changes on genital tract antiretroviral disposition have not been fully quantified. Since fluctuating hormone levels can influence drug disposition factors such as protein binding and drug transporter activity [16] the potential to influence antiretroviral distribution to the FGT exists. Additionally, data generated in macaques suggest that females are more susceptible to HIV during the late luteal phase of their menstrual cycle, when progesterone concentrations are elevated and host immunity compromised [17]. If drug distribution is not concomitantly elevated, the pharmacokinetic-pharmacodynamic relationship could be detrimentally altered. Despite these complexities, useful antiretroviral pharmacokinetic data have been generated for NRTIs, NNRTIs, PIs, INSTIs, and entry inhibitors that aid in the design of PrEP strategies.

The relative exposure within the anatomical sites responsible for, or susceptible to, HIV transmission (i.e. vaginal tissue (VT), colorectal tissue, cervicovaginal fluid (CVF), and seminal plasma (SP)) are summarized in Figure 1 as relative penetration ratios. These ratios are predominantly generated from area under the concentration-time curves (AUC) of the matrix of interest relative to plasma, where 1 represents similar total drug exposure in the matrix of interest relative to blood. Most of the data generated within the FGT are from sampling CVF. Although vaginal and cervical tissue biopsies provide the best representation of drug penetration into the site and cells of interest, collection is limited by the frequency and quantity of tissue that can be collected. Yet, drug concentrations within CVF provide estimates for relative drug penetration to the vagina and cervix [18–20]. Since these samples can be self-collected by research participants multiple times over a dosing interval, this is a non-invasive approach to providing insight into FGT pharmacokinetics. It is important to note that cervical, vaginal, and rectal tissue biopsies are generally homogenized prior to analysis. One limitation of this process is that it does not provide structural differentiation of heterogeneous drug distribution. Novel approaches such as matrix-assisted laser desorption/ionization (MALDI) may provide further insight regarding the specific localization of antiretrovirals within tissue [21].

NRTIs are phosphorylated intracellularly to their active form and compete with endogenous nucleotides to terminate the formation of HIV DNA [22]. Most NRTIs extensively penetrate the FGT [23, 24]. This may be due, in part, to their low plasma protein binding (<0.7–49%), which allows protein-unbound drug to distribute to peripheral sites [25]. The relative exposure of NRTIs in CVF under steady-state dosing conditions (calculated as the $AUC_{CVF} \div AUC_{BP} \times 100\%$ over a dosing interval), from highest to lowest, have been reported as follows (median [interquartile range (IQR)]): lamivudine 411% (230,594), FTC 395% (187,671), zidovudine 235% (121,2115), TFV 75% (37,645), didanosine 21% (1,40), abacavir 8% (8,13), and stavudine 5% (0,12) [23]. However, since NRTIs exert antiviral activity only when phosphorylated intracellularly, and extracellular parent drug concentrations may not accurately predict intracellular phosphorylated metabolite concentrations, the two should be considered independently. Intracellular drug concentrations measured in cells from endocervical cytobrush sampling and tissue biopsies can be useful measures of phosphorylated NRTI concentrations within the FGT, although

the methods of measurement are more complex and consequently, the data available are sparse.

A majority of NRTI mucosal pharmacokinetic research has been focused specifically on TFV and FTC, as these agents comprise the backbone of many antiretroviral regimens and have been the most widely studied as PrEP strategies. They demonstrate different distribution into the FGT. Following a single oral dose of Truvada®(a fixed-dose combination tablet consisting of tenofovir disoproxil fumarate (TDF) and FTC) in healthy volunteers, detectable concentrations of TFV and its active tenofovir-diphosphate (TFV-dp) metabolite were present in VT for up to 10 and 14 days respectively, with maximum TFV-dp concentrations of ~10 fmol/mg achieved within 48 hours [19]. The 14-day TFV exposure in the CVF was 251 (151–1,257) days·ng/mL, which was approximately 2.6 times greater than that measured in the BP, and a terminal elimination half-life of 70h was noted. Louissaint and colleagues, utilizing a novel accelerator mass spectrometry approach, confirmed the results of this study [26]. Following a single oral slurry dose containing 300mg TDF and 4.3mg of carbon-14 labeled TDF, the TFV-dp median (IQR) C_{max} reported in the VT was 1 (0.6–1.7) fmol/mg 24 hours after the dose. TFV and TFV-dp median (IQR) terminal half-lives in VT were 47 (38–53) and 53 (45–68) hours respectively, suggesting that residual TFV detected in the late phase of drug elimination is likely from cleaved TFV-dp.

FTC penetration into the FGT is greater than that of TFV, with a median (IQR) $AUC_{1\text{-}14d}$ of 2,445 (2,309–3,631) days·ng/mL in the CVF, which is nearly 27-fold higher than BP exposure [19]. FTC is both a substrate and inhibitor of the multidrug resistance protein (MRP) efflux pump MRP-1 [27]. Immunofluorescent labeling of MRP1 in vaginal tissue [28] and the expression of ABCC1 (the gene that codes for MRP-1), found to be as extensive in human ectocervix/vaginal tissue as human liver tissue [29], suggests this transporter may have significant effects in vaginal tissue drug disposition. The fact that FTC is capable of inhibiting the transporter responsible for its removal from the cell may contribute to the greater initial tissue penetration observed. However, FTC residence within the FGT is significantly shorter than TFV, with a terminal CVF elimination half-life of 40 hours. Similarly, active FTC-tp has been detected within VT only up to 48 hours following a single oral dose. The mechanism(s) responsible for this observation has yet to be elucidated.

PrEP strategies have also utilized the topical administration of TFV formulated as a 1% intravaginal gel. A Phase I study of TFV 1% gel in 45 healthy volunteers demonstrated rapid absorption of TFV from the vaginal lumen into tissue with maximal VT concentrations of 2.2×10^5 ng/mL achieved 2 hours post-dose with concomitant VT TFV-dp concentration of approximately 8500 fmol/mg [30]. Systemic exposure to TFV was limited with a median (IQR) estimate for C_{max} of 3.4 (2.4–6.1) ng/mL after 2 weeks of repeated topical applications. Similarly, the MTN-001 trial compared the pharmacokinetics in blood, VT, and vaginal and rectal fluid following oral TDF versus topical administration of 1% TFV gel [31]. Oral dosing of TDF achieved the lowest TFV and TFV-dp concentrations in VT with >50% of the biopsies with no quantifiable TFV or TFV-dp concentrations. After topical dosing with 4mL of TFV 1% gel, TFV-dp concentrations were 100-fold greater (1807 fmol/mg) than after oral dosing. This calculated difference is likely a conservative estimate

as the TFV-dp concentrations associated with oral dosing were censored at the lower limit of quantification (25 fmol/mg). Median TFV concentrations in VT and cervicovaginal lavage samples with topical dosing were 113 ng/mg and 3.1×10^6 ng/mL respectively. Concomitant oral dosing provided no additional drug exposure benefit in VT.

PIs, which prevent the maturation of viral proteins essential for infectivity, demonstrate low penetration into the FGT [32]. Despite the ability of PIs to rapidly suppress viral replication in the BP and their widespread use in highly active antiretroviral therapy (HAART), their ability to penetrate and accumulate within the FGT is limited and drug specific. To date, there have been no studies evaluating the tissue concentrations of PIs within the FGT, limiting our understanding to concentrations measured in CVF. Indinavir and darunavir demonstrate relatively enhanced penetration into the FGT with indinavir concentrations found in cervical lavages 1.32 to 3.8-fold greater than matched BP concentrations and median darunavir exposure in the CVF, expressed as AUC_{12h}, nearly 1.5 times that reported in the BP [33, 34]. In contrast, ritonavir, atazanavir, nelfinavir, amprenavir, and lopinavir exhibit limited penetration into the CVF with mean CVF:BP trough concentration ratios ranging from 0.03–0.8 [24]. Similarly the median exposure achieved in CVF following a single dose of ritonavir, lopinavir, and atazanavir were all below 20% of the exposure in blood plasma [23].

PIs, with the exception of indinavir, are more than 90% protein-bound to albumin and α-1 acid glycoprotein, which may, in part, limit their access to the FGT [25, 35]. Yet albumin and α-1 acid glycoprotein concentrations in CVF are only ~1% of what is reported in BP [36]. It is possible therefore, that although *total* PI concentrations within CVF are low, a high proportion of the drug detected is not bound to proteins and is available to exert antiviral activity [37]. However, no studies have investigated free drug concentrations of PIs in the CVF. Drug transporters may also contribute to the relatively reduced penetration of PIs into the FGT. Atazanavir, ritonavir, lopinavir, saquinavir, and indinavir are all substrates for P-glycoprotein, MRP1 and MRP2, efflux transporters expressed within vaginal tissue [27–29, 38]. The combined effect of these 3 transporters may minimize the ability of PIs to concentrate within cells of the FGT.

NNRTIs exhibit limited penetration into the FGT. Median etravirine exposure in the CVF is similar to that of the BP with a CVF:BP etravirine AUC_{12h} ratio of approximately 1.3 [33, 39]. Nevirapine trough concentration in the CVF is ~80% of BP [40]. Efavirenz CVF concentrations are 0.4–0.8% of reported values in the BP [23, 24, 40]. The limited entry into the FGT by NNRTIs may be influenced by their affinity to plasma proteins. The NNRTIs are approximately 60–99.9% protein-bound [41–43], which can limit the amount of protein-unbound drug that can cross cellular membranes and distribute into peripheral compartments. Although total NNRTI concentrations appear to be lower in the FGT, free drug concentrations may in fact be higher due to decreased protein concentrations in the CVF as discussed previously. However, the exact numbers remain to be quantified.

Dapivirine, a potent NNRTI initially abandoned from clinical development due to low oral bioavailability, is now being considered for HIV prevention with new intravaginal gel and drug-eluting ring formulations [44]. The ability of dapivirine intravaginal ring to prevent the

transmission of HIV is currently being investigated in Phase 3 trials. The intravaginal ring, which is inserted monthly, achieves and maintains (up to 24-hours after ring removal) CVF dapivirine concentrations nearly 500-times higher than the *in vitro* concentration needed for 99% viral inhibition (3.3ng/mL)[45]. Dapivirine has been shown to provide protection from HIV infection in *ex-vivo* cervical biopsy challenge experiments from the MTN-013/IPM026 clinical trial [46]. A significant (p=0.0157) inverse linear relationship between decreased HIV replication in *ex vivo* assays and increased dapivirine cervical tissue concentrations has been demonstrated.

Maraviroc, a CCR5 receptor antagonist, suppresses viral replication by inhibiting the entry of CCR5-tropic HIV into the host cell [47]. Preventing the initial entry of HIV into the cell with maraviroc may be critical for preventing the transmission of HIV, as nearly 97% of viruses utilize CCR5 in the early stages of mucosal transmission [48–50]. A single and multiple dose investigation of maraviroc determined that CVF concentrations met or exceeded BP concentrations within 4 hours after a single dose, and CVF AUCs were 2–3 fold higher than BP exposures [18]. At the end of the 12-hour dosing interval, CVF concentrations were nearly 10 times higher than BP and decayed linearly for 72 hours after the last dose. Maraviroc protein binding in CVF was found to be 10 times lower than in the BP (7.6% vs ~76%), suggesting there is relatively more protein-free drug available to exert antiviral activity in the FGT compared to BP. VT exposure was ~200% higher than observed in BP. The favorable pharmacokinetic profile and extensive FGT penetration of oral maraviroc has prompted further exploration of this agent as PrEP in both oral and topical formulations [51, 52]. The Phase 1 pharmacokinetic study of dapivirine, maraviroc, and combination intravaginal rings (MTN-013/IPM026) demonstrated maraviroc, unlike dapivirine, achieves very low cervical tissue concentrations (only 4 of 24 cervical biopsies had concentrations above the limit of quantification) after 28 days of topical ring use [46]. Additionally, *ex vivo* challenge assays showed maraviroc conferred no protection in cervical tissue biopsies, likely due to limited release from the rings.

INSTIs exert their antiviral activity within the cell by prohibiting the integration of viral cDNA into the host's genome [53–55]. Raltegravir and the newly approved dolutegravir, are two highly active agents with well-characterized FGT pharmacokinetics [20, 56, 57]. Raltegravir penetrates extensively into the FGT whereas dolutegravir has shown limited vaginal and cervical exposure. Patterson and colleagues first characterized raltegravir exposure in the CVF of both HIV-infected and uninfected women receiving raltegravir 400mg twice daily [56]. CVF AUC_{12h} exceeded that of the BP by nearly 4-fold in the HIV-infected cohort. Clavel et al. confirmed these results by employing a 1-minute soak of blotting paper in the posterior fornix of the vagina as an alternative to direct CVF aspiration. They report a median raltegravir CVF:BP ratio of approximately 2.3 in HIV-infected women in the DIVA 01 study [57]. Patterson et al. noted similar raltegravir exposure in the CVF of uninfected women.

Dolutegravir exposure in the CVF is ~7% of BP, with no accumulation observed after repeated doses [20]. Sparse pooled sampling of vaginal and cervical tissue also revealed low penetration, with approximately 10% of BP AUC_{24} observed in these tissue compartments. This may be attributable to dolutegravir's relatively high protein binding (>99% protein

bound in BP), which may limit the entry of free drug into the tissue [55]. Given dolutegravir's limited aqueous solubility and high permeability, which would appear to favor its passage through cellular membranes, it is also likely that efflux transporters (specifically P-glycoprotein and breast cancer resistance protein (BCRP)), may be limiting the drug's accumulation in this compartment [58].

3.1 Correlation to Prevention

Multiple factors influence the potential efficacy of a prevention agent including drug exposure at the site of action, residence time within the site of transmission, and patient adherence to the PrEP regimen [59]. Tenofovir, in both oral and topical formulations, is the most widely studied antiretroviral for the prevention of HIV transmission, although efficacy has varied. In CAPRISA 004, HIV transmission was 54% lower in subjects with greater than 80% adherence to coitally-dependent dosing of TFV 1% vaginal gel when compared to placebo gel [8]. Daily oral TDF/FTC was 62.2% effective in preventing HIV transmission in heterosexual adults in Botswana in the TDF2 study, and was 75% effective in heterosexual, serodiscordant couples in the Partners PrEP trial [6, 9]. Conversely, the FEM-PrEP and VOICE trials conducted in high-risk heterosexual women were terminated early due to the futility of both daily oral and topical TFV formulations in preventing HIV seroconversion [7, 60].

Although poor medication adherence in these trials has been identified as contributing to inconsistent and variable efficacy, antiretroviral mucosal tissue pharmacokinetics may also explain the relative success and failures. A post-hoc analysis of CVF samples collected during the CAPRISA 004 trial revealed that CVF TFV concentrations greater than 1000 ng/mL was associated with significantly ($p=0.01$) lower HIV incidence rate relative to subjects using placebo gel [61]. As indicated from the pharmacokinetic data, achieving CVF concentrations in excess of 1000 ng/mL, is not likely following inconsistent oral administration of TDF [19]. Even after daily dosing of an oral TFV-containing PrEP regimen it is unlikely to achieve CVF concentrations in excess of 1000ng/ml [23]. Therefore multiple factors, in addition to local tissue concentrations, may influence the efficacy of a PrEP strategy. Currently, it is not fully understood how or where PrEP agents exert their antiviral activity and confer protection. Data from the nonhuman primate model suggests that virus crosses the FGT epithelial barrier and establishes a small founder population of infected cells within hours of exposure [62]. Without any intervention, this small population of cells is capable of generating enough virus to disseminate and establish systemic infection in secondary lymphoid organs. It is possible that topically applied PrEP agents, which achieve high concentrations locally, are capable of preventing the establishment, or thwarting the spread of, the local founder population of infected cells early after exposure. Oral agents, which achieve higher systemic concentrations, may prevent later stages of infection by halting dissemination and established infection in lymphoid tissue. The threshold concentrations required for protection both in mucosal and lymphoid tissue are currently unknown. Additionally, it has not yet been determined if the threshold concentration of TFV needed for protection is the same when coadministered with FTC. These target concentrations may differ depending on whether additive or synergistic protective activity exists

The ≥100-fold TFV-dp concentrations in VT associated with topical versus oral dosing, may suggest that topical administration may be more amenable to intermittent dosing schemes. The CAPRISA 004 trial demonstrated that 80% adherence to coitally administered TNF 1% gel (1 application up to 12 hours before and 1 application up to 12 hours after intercourse) reduced HIV acquisition by 54% relative to women adherent to placebo gel [8]. This success was not demonstrated in the topical arm of the VOICE trial [63], where women were instructed to administer a dose of gel daily, regardless of coital exposure. The study investigators reported <30% adherence in all study arms and were forced to terminate the study due to futility. This is consistent with the low-adherers of CAPRISA 004, whereby investigators noted 28% effectiveness (95% CI -40–64; p=0.3) in study subjects with <50% adherence [8]. Therefore, it appears that coitally-dependent dosing, rather than daily, may facilitate adherence, minimize prophylaxis-fatigue, and increase the probability of achieving protective concentrations at the time of exposure.

Since medication adherence is a significant barrier to efficacious PrEP regimens and successful clinical trials [64], other formulations that require single doses or administrations to achieve sustained antiretroviral concentrations are being investigated. Drug-eluting intravaginal rings containing TFV, maraviroc, or dapivirine, as well as new long-acting injectable formulations of rilpivirine (TMC278LA) and the INSTI GSK1265744, are promising alternatives [65–67].

4. Colorectal Tissue

Receptive anal intercourse is an efficient mode of HIV transmission not only for men who have sex with men (MSM), but also for heterosexuals, where its prevalence is increasing yet may be underreported [68, 69]. Achieving inhibitory concentrations of antiretrovirals within the colorectal tissue is essential in both protecting uninfected partners engaging in unprotected receptive anal intercourse and minimizing viral shedding in infected individuals on HAART [70]. Antiretroviral pharmacokinetic data within colorectal tissue has been described for TFV (both oral and topical formulations), FTC, darunavir, ritonavir, etravirine, raltegravir, dolutegravir, and maraviroc. The colorectal penetration ratios of these compounds, relative to BP exposure, are depicted in Figure 1b.

Both TFV and FTC demonstrate extensive penetration into colorectal tissue, but to different degrees [19]. Following a single oral dose of TDF/FTC, both TFV and TFV-dp were detectable within colorectal tissue biopsies for up to 14 days. TFV AUC was approximately 34-fold greater than that of BP over the 14 days studied, and TFV-dp concentrations were 2–3 logs higher than vaginal and cervical tissue. Differential expression of drug transporters may help explain the strikingly different TFV concentrations observed in colorectal verses vaginal tissue [38]. Nicol et al. recently found increased expression of the efflux transporters MRP2 and MRP4 within vaginal epithelial tissue and increased expression of the influx transporter OAT-1 within rectal epithelial tissue. Both *in vitro* and clinical data suggests that TFV is a substrate for the efflux transporter MRP4 and the uptake transporter OAT1 [71–74]. Although the role MRP2 plays in TFV disposition is less clear due to conflicting *in vitro* data [71, 72, 75], the combined effects of MRP4, MRP2, and OAT1 may help to explain the differential distribution of TFV to vaginal versus rectal tissue. TFV may be

preferentially fluxed from the vasculature into cells of the rectal tissue via OAT-1 and removed from vaginal tissue by MRP2 and MRP4. Although MRP4 was also found within colorectal tissue, immunohistochemical staining indicates that this efflux transporter is concentrated to submucosal lymphocytes rather than epithelial cells, as it resides in vaginal tissue. Reduced expression of this efflux transporter on epithelial cells may result in less TFV efflux from colorectal tissue. It is also plausible that TFV present within the colorectal lumen is actively transported into the tissue via OAT-1 present on the apical membrane of rectal epithelium.

FTC exposure in colorectal tissue exceeded BP exposure by 3-fold following a single oral dose [19]. Although parent FTC was detected within the colorectal tissue for 14 days, the active FTC-tp decayed much more rapidly, and was detectable only for 48 hours after a single dose. Further investigation into differential phosphatase and kinase activities that are responsible for the intracellular metabolism of TFV and FTC are warranted, as this may help to explain the different residence times reported for TFV-dp and FTC-tp in colorectal and vaginal tissue.

A phase 1 trial to assess the acceptability, as well as the pharmacokinetics and pharmacodynamics, of vaginally formulated 1% TFV gel administered intrarectally confirmed TFV's ability to penetrate into the colorectal tissue compartment when administered as both oral and topical formulations [76]. The study compared TFV colorectal exposure following a single oral dose of TDF 300mg, a single topical 4mL 1% TFV gel application, and repeated daily topical TFV applications. Topical gel administration resulted in rapid absorption and phosphorylation of TFV, with a median TFV-dp rectal tissue concentration of 176 fmol/mg (range 0–1229) 30 minutes following a single topical dose. As expected, TFV-dp was not detected in any (n=18) rectal tissue biopsies at this early time point following an oral dose. Twenty-four hours after topical and oral dosing, median colorectal TFV-dp concentrations were 285 (range 0–490) fmol/mg and 29 (range 0–992) fmol/mg, respectively. Overall, topical administration resulted in colorectal exposures 6–10-fold higher than oral administration, which is significantly lower than the ≥100 fold-difference in vaginal vs oral administration of tenofovir in women. Although 7 days of daily rectal administration of 1% TFV gel did not result in TFV accumulation in colorectal tissues, TFV-dp accumulated ~6 fold.

Darunavir, ritonavir, and etravirine colorectal tissue pharmacokinetics have also been measured in healthy volunteers after both single and multiple doses [77]. After 7 days of repeat dosing, ritonavir, darunavir, and etravirine colorectal exposure was ~13-fold, ~ 3-fold, ~ 7-fold higher than blood plasma respectively. Since ritonavir, darunavir, and etravirine all have high affinity for plasma proteins (>95% bound to protein), and yet their exposure in colorectal tissue is 2 to12-fold greater than their exposure in the FGT, additional factors must contribute to the differential tissue bioavailability of these antiretrovirals. Higher expression of the efflux transporter P-glycoprotein in vaginal versus colorectal tissue may explain why darunavir and ritonavir, both substrates for this transporter, accumulate within colorectal tissue relative to vaginal tissue [38]. The rectal mucosa is also highly vascularized, which may lead to increased perfusion and drug delivery to this site relative to

the FGT. Additionally, fecal elimination and mucus trapping may contribute to the higher concentrations noted in the rectal tissue [78].

Similar to the exposure differences noted in the FGT, raltegravir and dolutegravir demonstrate significant differences in colorectal tissue penetration. Raltegravir rapidly distributes into colorectal tissue, exceeding exposure in the plasma by 39-fold following a single 400mg dose in healthy volunteers [79]. After repeated twice daily dosing for 7 days, raltegravir exposure in rectal tissue was more than 200-fold higher than blood plasma exposure throughout the 12-hour sampling period. Raltegravir also concentrates in gut associated lymphoid tissue: exposure at the terminal ileum and splenic flexure exceeded that of the blood plasma by ~160 and ~650-fold respectively. Conversely, dolutegravir exhibits limited penetration into the colorectal tissue. Although dolutegravir can be detected in colorectal biopsies within 1 hour of dosing, concentrations achieved are only ~20% of the exposure reported in the BP following single and multiple dosing [80]. Despite low tissue penetration relative to blood plasma exposure, dolutegravir concentrations reported in the colorectal tissue remain above the protein-adjusted concentration for 90% viral inhibition (64 ng/mL) throughout the dosing interval [81]. The mechanisms responsible for these differences in colorectal distribution are currently unknown.

Maraviroc exhibits extensive rectal tissue penetration in healthy volunteers following single and multiple dosing [82]. Maraviroc colorectal tissue concentrations exceeded BP concentrations at all time points, and were ~7 and 26 times greater than exposure in blood plasma after single and multiple dosing, respectively. At steady state, the maximal maraviroc concentration achieved within rectal tissue is nearly 10-fold greater than in vaginal tissue (7119 ng/g vs. 848 ng/g) [18]. The enhanced accumulation of maraviroc within the colorectal tissue relative to the vaginal tissue may also be attributed to greater expression of P-glycoprotein within the vaginal tissue [38]. Maraviroc, a substrate for the efflux transporter P-glycoprotein, may be more readily removed from vaginal tissue, whereas it can more easily accumulate within the cells of colorectal tissue [83]. The fact that maraviroc is predominantly eliminated in the feces may also contribute to the higher relative exposure ratios achieved in the rectal tissue with multiple dosing (ratio =26) compared to a single dose (ratio=7).

4.1 Correlation to Prevention

Viral suppression in blood plasma has been correlated with reduced rectal viral shedding in the MSM population adherent to HAART [84], including those with sexually transmitted infections. This is likely attributable to the relatively extensive penetration and distribution of antiretrovirals in colorectal tissue, as previously described. Therefore, antiretrovirals with favorable rectal tissue disposition may provide protection for uninfected men or women engaging in unprotected receptive anal intercourse. The favorable pharmacokinetic profile of TFV and FTC within rectal tissue is reinforced by the success of iPrEx, a large international PrEP trial demonstrating TDF/FTC combination tablet administered once daily is effective in reducing HIV transmission in MSM by 44% [85]. At the visit where HIV was confirmed, stored samples from this study revealed detectable drug in plasma or peripheral blood mononuclear cells (PBMCs) of 8% of those who became infected, compared to 44% of

those who remained uninfected. A post-hoc analysis of cryopreserved PBMCs from iPrEx [86] was compared to similarly collected samples from a study of healthy volunteers (also called the STRAND study) maintained on various dosing strategies (2 vs. 4 vs. 7 doses/week) of TDF 300mg [87]. By extrapolating TFV-dp concentrations achieved in iPrEx, Anderson and colleagues proposed that low adherence to Truvada® resulted in high HIV protection, such that 2 doses/week (28% adherence) would still be 76% protective. The rapid and high exposure of TFV and TFV-dp noted by Patterson et al. [19] would explain these findings. Comparing 76% efficacy with 28% adherence in modeled iPrEx data to 0% efficacy seen with 30% adherence in FEM-PrEP, suggests that differential local drug exposure in rectal versus vaginal tissue may have impacted HIV prevention efficacy in these trials. Drug penetration to mucosal sites of HIV transmission may be a critical facet in selecting optimal PrEP strategies. As was stated earlier, the site of PrEP activity is currently unknown. Further investigation into the relative importance of systemic versus local drug concentrations will assist in the optimization of PrEP strategies.

5. Male Genital Tract

Viral shedding is detected in semen within days following primary HIV infection [88, 89]. Both cell-associated and cell-free virus in seminal fluid has been implicated in HIV transmission [90]. Genetic variants of HIV found in semen that differ from BP [91–93] suggest that compartmentalization can occur, and high concentrations of antiretrovirals may be necessary in the male genital tract (MGT) to limit transmission of HIV [94, 95].

The penetration of antiretrovirals into the MGT is often assessed by the concentration of drug present in semen, or seminal plasma. Semen, however, is a complex matrix consisting of sequential secretions from the seminal vesicles (50–70% of human ejaculate), prostate (20–30%), testes (10%), urethral and bulbourethral glands, epididymis, and ampullae (10%) [13, 15]. Due to the sequential nature of human ejaculation, drug concentrations within composite SP may not precisely reflect drug penetration to the various tissues and glands that generate semen. Split ejaculation sampling has been used to separate a single ejaculate into multiple fractions according to the time course of its release [96]. The early fraction of the ejaculate is comprised predominately from fluid generated by the prostate and testes, whereas the late fraction is comprised mostly of seminal vesicular fluid. Analyzing drug concentrations in seminal fractions acquired in early and late ejaculation separately, attempts to distinguish drug concentrations in testes/prostate and seminal vesicles respectively. However, split ejaculation sampling is challenging and has not yet yielded data suggesting differential penetration of antiretrovirals that are of clinical consequence [97]. As such, composite semen samples have typically been used as a relatively practical surrogate marker for MGT drug exposure [98].

The entry of xenobiotics into the MGT is limited by the blood-testes barrier. The blood-testes barrier is comprised of tight-junction complexes between Sertoli cells, which limit the passage of certain large molecules present in the circulation from entering the lumen of the seminiferous tubules [99, 100]. Such a barrier helps to create a protected compartment for the maturation of germ cells. This anatomical barrier is supplemented by active transporters, including P-glycoprotein, BCRP, and MRP1, which regulate the efflux and entry of

antiretrovirals into this sanctuary site [27, 101, 102]. Therefore, drugs with small molecular weights, low affinity for plasma proteins, and which are not substrates for multiple efflux transporters, will likely penetrate the MGT more readily.

NRTIs penetrate well into the MGT when compared to other antiretrovirals and often exhibit SP exposures that exceed those reported in the BP [19, 103–111]. Lamivudine exhibits the greatest SP exposure relative to BP with a median (IQR) SP AUC_{12h}: BP AUC_{12h} ratio of 6.67 (4.10–9.14) [110]. FTC also exhibits superior penetration into semen with SP $AUC_{1\text{-}14d}$: BP $AUC_{1\text{-}14d}$ ratio (IQR) of 4.5 (3.3–6.1) [19]. TFV achieves 24-hour post-dose concentrations within SP that exceed BP concentrations by 5-fold [111]. Stavudine, zidovudine, and abacavir have also demonstrated favorable distribution into the MGT with SP concentrations approximately 1.5–4-fold greater than BP concentrations [19, 105, 106, 110]. These NRTI penetration patterns are attributed to their relatively small molecular weight and low plasma protein binding [13].

Although intracellular NRTI concentrations are of greatest importance for antiviral efficacy, less information is available regarding the concentrations of active phosphorylated NRTI metabolites within seminal mononuclear cells. Dumond and colleagues report that elevated exposures of parent lamivudine and zidovudine in the SP did not result in increased intracellular concentrations in seminal mononuclear cells relative to the concentrations seen in PBMCs [110]. Despite nearly 7-fold greater lamivudine exposure in the SP, lamivudine-triphosphate concentrations within seminal mononuclear cells were found to be comparable to concentrations found within PBMCs, with a median AUC SP:BP ratio of 1.0 (IQR 0.62–1.3). Active zidovudine-triphosphate concentrations reported within seminal mononuclear cells achieve only 36% of the exposure found in PBMCs. Tenofovir is the exception: it is the only NRTI investigated that has increased exposure in both seminal plasma and seminal mononuclear cells [111]. Under steady state conditions, extracellular TFV trough concentrations in the SP are approximately 7-fold higher than BP, and TFV-dp concentrations in seminal mononuclear cells are approximately 18-fold higher than in PBMCs. The authors attribute the differing intracellular concentrations of tenofovir, lamivudine, and zidovudine to the different kinase activities and cellular activation states present within the MGT and blood.

Raltegravir also exhibits substantial penetration into the MGT [112–114]. Median raltegravir exposure (AUC_{12h}) is nearly 2–3 times greater in the SP compared to the BP [112, 115]. Investigations utilizing single paired samples early in the dosing interval (2–5hrs post dose), have found SP:BP ratios ranging from 1.4 to 1.6. This suggests a lag time in drug distribution to semen and suggests that paired samples obtained near the end of the dosing interval will be more reflective of exposure across the full dosing interval. Similar to the FGT and rectal tissue, dolutegravir exhibits limited penetration into the MGT, with SP exposure only ~7% of that achieved in the BP after both single and repeat doses [80].

Maraviroc demonstrates limited penetration into the MGT [82, 116], with a SP:BP exposure ratio of 0.56 (IQR 0.44–0.70) [82]. Earlier discussions regarding protein binding in CVF also apply to semen. Semen contains a considerably smaller concentration of albumin relative to blood plasma (approximately 1 g/L vs. 40 g/L) [98]. This difference may lead to

reduced protein binding within SP and result in higher concentrations of active free drug. Maraviroc was the first compound for which protein binding was determined in semen. Median protein binding was 9%, approximately 10-fold lower than 76% protein binding reported in BP [82, 83]. Therefore, although total maraviroc exposure in SP is ~50% less than BP, unbound exposure in SP is ~200% more than protein-free exposure observed in BP. This is an important clinical finding, as it has been implicated that only protein-free drug is able to exert antiviral activity [37]. Additionally, the differential unbound concentrations of maraviroc in the FGT, MGT, and BP supports that drug transporters, and other influences likely compromise the free-drug equilibrium suggested by the first tenet of the free-drug hypothesis. Without the influence of active drug transport, one would expect the free-drug exposure to be similar in these different tissues, which has not been demonstrated for maraviroc.

With the exception of indinavir, PI concentrations achieved in the MGT are only a fraction of BP exposure [97, 107, 108, 112, 117–124]. Atazanavir, darunavir, and amprenavir achieve exposures in the SP that are 10–20% of those in BP [112, 121, 122, 124] while, lopinavir, saquinavir, and ritonavir exposures are all below10% of BP [117–120, 123]. NNRTIs also display poor penetration into the MGT as concentrations achieved within SP for nevirapine, etravirine, and efavirenz, are approximately 60%, 16%, and 3–10% of BP respectively [105, 108, 112, 125, 126]. The reduced penetration of these compounds into the MGT is likely influenced by their high affinity for plasma proteins. Despite low *total* concentrations of darunavir, ritonavir, etravirine, and efavirenz in the seminal plasma, these drugs demonstrate free drug exposures similar to or greater than those reported in the blood plasma [77, 127]. For example, the protein-free AUC_{12h} for etravirine was nearly 5-fold higher in the SP than in BP. Due to the complexities of measuring protein binding in both the blood plasma and genital tract secretions, most pharmacokinetic studies to date report total drug concentrations. For highly protein-bound drugs like efavirenz, etravirine and the PIs, this may underestimate the relative penetration of active drug in these sites.

5.1 Correlation to Prevention

The pharmacodynamic response of suppressing HIV in the MGT with antiretroviral therapy has been explored in many studies [105, 110, 111, 117, 118, 123, 128]. HAART-induced reductions in BP HIV RNA, are generally associated with parallel reductions in seminal plasma [128, 129]. It has been estimated that the likelihood of having a detectable (> 400 copies/mL) HIV viral load in semen is <4% in subjects with BP HIV RNA <400copies/mL. However, it is difficult to discern the relative contribution of one antiretroviral over another in suppressing viral replication in the MGT when patients are taking combination therapy. Eliminating the potential for confounding by concomitant antiretroviral therapy, data generated by Vourvahis and colleagues demonstrated that seminal HIV-1 RNA decreased on average by 1 log after 14 days of TFV monotherapy [111]. In another study, Dumond et al. demonstrated that 13/14 men taking zidovudine and lamivudine twice daily with a PI or NNRTI had undetectable HIV RNA in the SP [110]. The one subject with detectable HIV RNA in SP was also found to have the lowest intracellular exposure to active phosphorylated zidovudine-triphosphate and lamivudine-triphosphate, underscoring the importance of achieving high intracellular concentrations of NRTIs in the MGT.

Achieving viral suppression within the MGT is a critical prerequisite in reducing the risk of HIV transmission. A mathematical model created by Chakraborty et al. utilized male to female transmission rate estimates from 7 epidemiologic studies and the semen specimens of over 300 infected males, to predict that the risk of HIV transmission is reduced from 1 in 100 heterosexual episodes of intercourse to 3 in 10,000 episodes when the seminal viral burden is reduced from 100,000 copies to 1,000 copies [130]. The HPTN 052 study confirmed these calculations [5].

6. Summary

In the absence of a vaccine, using antiretrovirals to minimize the infectiousness of HIV-positive individuals, and protect HIV-negative individuals from becoming infected, is an important interventional approach. An antiretroviral's ability to penetrate and accumulate within the male and female genital tract and colorectal tissue has been shown to suppress viral replication in these compartments and, if administered prophylactically, may protect uninfected individuals from the transmission of HIV. Here we have provided a summary of the pharmacokinetic data available in the FGT, colorectal tissue, and MGT. In general, NRTIs exhibit favorable penetration into all of these biological sites, and have been most widely studied for the prevention of HIV. The CCR5 antagonist maraviroc, as well as the integrase inhibitor raltegravir, also penetrate well into the anatomical sites of transmission, which makes these drugs potential candidates for future PrEP regimens. PIs and NNRTIs generally demonstrate low penetration into these compartments. This, along with a more extensive adverse effect profile, has precluded them from being investigated as early PrEP strategies (with the exception of dapivirine). PI and NNRTI total drug concentrations in these compartments are less than that of blood plasma. Although protein-unbound drug may be similar to, or higher than, blood plasma exposure for some of these compounds, their ability to effectively prevent sexual HIV transmission remains unexplored.

Encouraging evidence from the Partners PrEP, iPrEx, TDF2, and CAPRISA 004 trials suggest antiretrovirals, specifically TFV and FTC, provide protection against the sexual transmission of HIV. The ability to correlate pharmacokinetic data at the anatomical sites of transmission with efficacy in these trials may help to establish threshold concentrations necessary for protection against HIV. This information will facilitate a tissue-targeted approach for the future development of optimal prophylactic regimens.

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Key Points

- The ability to distribute into the anatomic tissues associated with HIV transmission is both drug and tissue specific; although most NRTIs have similar or higher exposure, relative to blood, in the genital tract and colorectal tissue.
- Antiretroviral target mucosal tissue concentrations that protect against HIV infection are currently unknown.

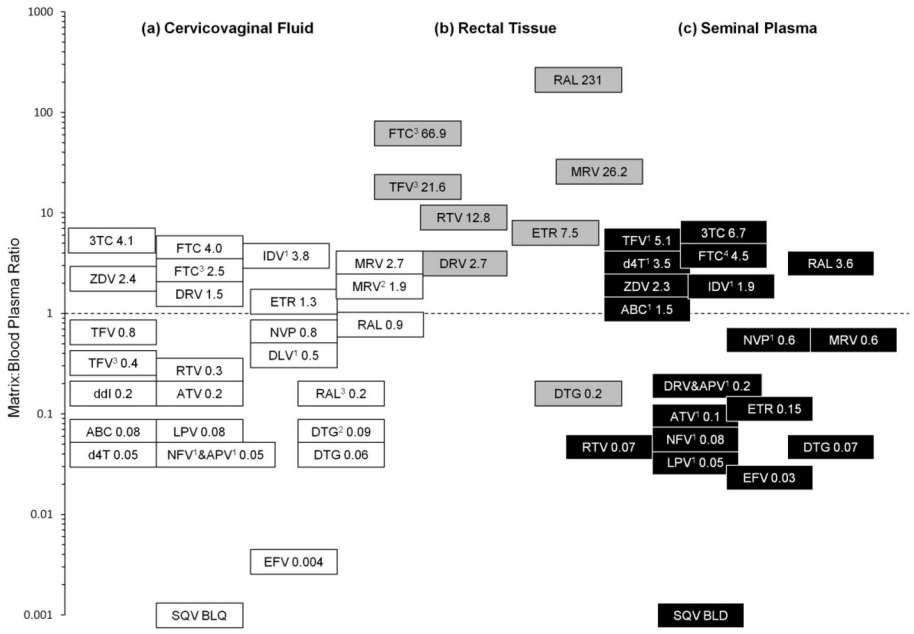

Fig. 1.

Relative antiretroviral exposure at mucosal sites of HIV-1 transmission

Adapted from The Lancet, Vol. 382, Cohen et al., “Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here?”, pg. 1517, 2013, with permission from Elsevier. Cervicovaginal fluid (a), rectal tissue (b), and seminal plasma (c) exposure plotted as a fraction of blood plasma exposure (Matrix $AUC_{(0-\tau)}$ ÷ Blood Plasma $AUC_{(0-\tau)}$, where τ=time at the end of the dosing interval). A ratio of 1 indicates the exposure in the specific matrix is the same as the exposure in the blood plasma. Ratios greater than 1 indicate the drug penetrates well into the matrix of interest whereas ratios less than 1 indicate concentrations in the matrix are lower than that observed in the blood plasma. For antiretrovirals where an AUC in the matrix of interest was unavailable, a ratio reported at a single concentration (preferably the trough concentration) is represented (ie Matrix C_τ ÷ Blood Plasma C_τ). If more than one penetration ratio was available in the literature for a single antiretroviral, an algorithm developed by Thompson et al. [131] was utilized to report the most robust value. 3TC, lamivudine; ABC, abacavir; APV, amprenavir; ATV, atazanavir; BLD, below the limit of detection; BLQ, below the limit of quantification; ddI, didanosine; DLV, delavirdine; DRV, darunavir; DTG, dolutegravir; d4T, stavudine; EFV, efavirenz; ETV, etravirine; FTC, emtricitabine; IDV, indinavir; LPV, lopinavir; MRV, maraviroc; ND; NFV, nelfinavir; NVP, nevirapine; RAL, raltegravir; RTV, ritonavir; SQV, saquinavir; TFV, tenofovir; ZDV, zidovudine.

[1] AUC in matrix unavailable; ratio at trough concentration reported

[2] Relative vaginal tissue exposure at steady state (vaginal tissue $AUC_{(0-\tau)}$ ÷ blood plasma $AUC_{(0-\tau)}$)

[3] Relative vaginal/rectal tissue exposure following a single standard dose (tissue $AUC_{(0-48h)}$ ÷ blood plasma $AUC_{(0-48h)}$) (unpublished data)

[4] Ratio represents total exposure over 14 days following a single dose (ie FTC Seminal Plasma $AUC_{(0\text{-}14d)}$ ÷ Blood Plasma $AUC_{(0\text{-}14d)}$)