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# Antiretroviral Pharmacology in Mucosal Tissues

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## Abstract

Strategies to prevent HIV infection using pre-exposure prophylaxis (PrEP) are required to curtail the HIV pandemic. The mucosal tissues of the genital and rectal tracts play a critical role in HIV acquisition, but antiretroviral (ARV) disposition and correlates of efficacy within these tissues are not well understood. Pre-clinical and clinical strategies to describe ARV pharmacokinetic-pharmacodynamic relationships (PK/PD) within mucosal tissues are currently being investigated. In this review, we summarize the physiochemical and biologic factors influencing ARV tissue exposure. Further, we discuss the necessary steps to generate relevant PK/PD data and the challenges associated with this process. Finally, we suggest how pre-clinical and clinical data might be practically translated into optimal PrEP dosing strategies for clinical trials testing using mathematical modeling and simulation.

### Keywords

pre-exposure prophylaxis; antiretrovirals; pharmacokinetics; mucosal tissues

Antiretroviral therapy (ART) has saved millions of lives and greatly increased the life expectancy of individuals living with HIV.[1] The Joint United Nations Programme on HIV/AIDS (UNAIDS) set a goal of having 15 million individuals living with HIV on ART by 2015, reaffirming that widespread ART implementation is a global priority.[2] It is well recognized that these drugs penetrate into the genital tract and decrease viral shedding.[3-5] Antiretroviral therapy, therefore, was postulated to and could potentially prevent transmission and acquisition of HIV. Indeed, pharmacologic interventions aimed at preventing the spread of HIV utilizing currently approved antiretroviral (ARV) medications have shown success in various settings.[6-8]

Most recently, the successful use of ART for prevention of transmission has focused on the use of these agents to prevent HIV acquisition.[9-12] If ART stops replication in an HIV-positive individual and prevents transmission, it is reasonable to think that ART can also prevent transmission in an HIV-negative individual when confronted with a replication-competent founder virus. Accordingly, pre-exposure prophylaxis (PrEP) using topical or systemic (oral or injectable) ARVs to prevent HIV infection around the time of exposure makes the issue of drug penetration into genital and rectal mucosal tissues critically important. Many factors can affect drug concentrations and the concentration-response

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relationship in these tissues, and not all are fully understood. This review will summarize these factors, and propose how they may contribute to achieving protective concentrations and effective dosing strategies for PrEP. We will also address the limitations of the methods currently used to generate these data and suggest ways to improve the applicability of the results.

## Evolution of Drug Concentration Data in Mucosal Tissues

Evaluation of drug exposure in female genital and in colorectal tissues began in the 1970s. Early publications examined the distribution kinetics of antibiotics in these tissues with the goal of identifying ideal candidates for surgical prophylaxis in gynecologic and colorectal surgery.[13] These pharmacokinetic studies of antibiotic distribution in the surgical setting continued throughout the 1980s.[14,15] Additional investigations identified antibiotics that were wellsuited for the outpatient treatment of gynecologic infections.[16-18] Measures of drug exposure in these early studies typically consisted of single concurrent tissue and serum samples obtained after a single dose of antibiotic and were reported as a tissue: plasma ratio. Later studies conducted more rigorous examinations, utilizing single and multiple dose kinetic data to report tissue: plasma ratios.[19-21] Due to different distribution characteristics in tissues compared to plasma, single time point concentration ratios could over- or under-estimate true tissue exposure.[19] Therefore, a more comprehensive measure of drug exposure in these tissues, the area under the concentration-time curve (AUC), was utilized to calculate tissue:plasma AUC ratios. These early studies made it clear that drug concentrations at sites of action cannot be assumed to be the same as plasma concentration, and that the ability of drugs to penetrate into tissue can vary greatly even among members of the same drug class, which may prove quite important in clinical trial and clinical results.[22]

Mucosal tissues of the vagina, cervix, and colorectum are a primary target for early HIV infection and replication.[23] Simian immunodeficiency virus (SIV) pathogenesis research in macaques has demonstrated rapid viral penetration into genital and rectal tissues after local inoculation. Viral DNA has been detected in the vaginal epithelium within hours after inoculation, and founder populations of virus can be detected in cervicovaginal tissues as early as 24 hours post-inoculation.[24-26] Clinical studies have confirmed cervical, vaginal, and colorectal transmissibility of HIV.[27-29]

While initial viral populations are small, rapid local and systemic dissemination occurs during the first 4 days of infection, making this time period a critical target for pharmacologic interventions.[24] Therefore, an important determinant in successful PrEP must be the ability of ARVs to achieve and sustain adequate concentrations in the mucosal tissue, whether through topical or systemic administration. In order to prevent the index infection in the new host, sufficient concentrations of ARVs must be present at the time of exposure and for some yet-to-be-defined length of time afterwards. Penetration of ARVs into the colorectum, semen, and tissues of the female genital tract (FGT) has been extensively researched.[19,20,30-33] The resulting data have revealed a high degree of variability in penetration, both between and within drug classes.

The penetration profiles for the ARVs are summarized in Figure 1.[19-21,30,31,33-42] Oral ARV formulations comprise the majority of penetration data. Generally, the nucleoside/tide reverse transcriptase inhibitors (NRTIs) achieve high concentrations in the female genital tract. Zidovudine (ZDV), emtricitabine (FTC), and lamivudine (3TC) all have steady-state and non-steady state tissue:plasma AUC ratios greater than 1.00. Ratios of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are more variable, with most PIs having poor penetration (<0.20) into the FGT and NNRTIs having highly drug-specific penetration. The CCR5 antagonist maraviroc (MVC) penetrates well

into the FGT (AUC ratio 1.9-2.7), while the integrase strand transfer inhibitor raltegravir (RAL) shows moderate penetrative ability (AUC ratio 1.00 in HIV negative women and 4.00 in HIV positive women, driven primarily by differential blood plasma exposure).[35]

There are some inconsistent trends in penetration between single and multiple doses. In the case of efavirenz (EFV), stavudine (d4T), and atazanavir (ATV), the extent of penetration is constant regardless of the number of doses given, reflecting a constant relationship between systemic and local exposure. However, for tenofovir (TFV), abacavir (ABC), and lopinavir (LPV), drug exposure declines in the genital tract with repeated dosing. The tissue:plasma AUC ratio declines from 1.1 after a single dose to 0.75 after multiple dosing for TFV, from 0.21 to 0.08 for ABC, and from 0.17 to 0.08 for LPV. This suggests that, with repeated dosing, entry mechanisms for some ARVs either become saturated, up-regulated (e.g. efflux transporters) or down-regulated (e.g. uptake transporters), decreasing the ability of these drugs to reach the FGT.

The pharmacokinetic profiles of alternative ARV formulations have also been studied. Topical tenofovir (TFV) gel has been successful in preventing HIV infections in clinical trials, and achieves favorable tissue concentrations when applied vaginally or rectally as either a gel or a ring.[43,44] This formulation has also been shown to rapidly distribute between vaginal and rectal tissue after application to either site, although the exposure in the non-dosed site reaches only approximately 5% of the exposure seen at the site of dosing.[43] A study in 24 HIV-negative women showed that a vaginal ring formulation of dapivirine achieved cervicovaginal fluid (CVF) concentrations that were 3 log units higher than plasma concentrations and 4 log units higher than the reported in vitro $EC_{50}$ of HIV-1 (LAI).[45] Further, a novel NNRTI rilpivirine (RPV) has shown penetration AUC ratios of 1.2-1.95 in CVF and 0.48-1.0 in vaginal tissue when administered as a long acting injectable formulation.[41]

## Factors Influencing Drug Entry into Tissues

The data described above highlight the need to identify the variables affecting mucosal penetration of small molecules. Once these variables are understood, they can be considered in the ARV development process and help identify ideal drug candidates for PrEP.

There are several physiochemical factors that influence tissue penetration: blood perfusion, protein binding, molecular size, lipophilicity, ionization state, and membrane transporter affinity. Adequate tissue blood flow is a necessary requirement for drug efficacy, particularly for drugs that are efficiently metabolized by target organs, also called “high extraction compounds”. For highly-extracted drugs, there is a direct relationship between tissue perfusion and drug entry into tissues, and lack of perfusion is a likely contributor to the difficulty of treating infections at certain anatomic sites (e.g. CNS, bone, etc). One of the primary determinants of pharmacodynamic efficacy is the fraction of unbound drug available to cross cellular membranes and enter tissues and cells.[46,47] Differential protein binding between two similar drugs can have large pharmacodynamic implications. For example, it has been shown that ARVs which are highly protein-bound (e.g. EFV, LPV) have much lower exposure in tissues than those which have less protein binding (e.g. FTC, TFV).[19] Chemical characteristics can also affect drug entry into tissues and cells, mostly by affecting the ability of a compound to diffuse across cellular membranes. Perhaps the most well-established characteristic is the inverse relationship between the molecular size of a drug and its penetrative capability.[46] An additional factor is the lipophilicity of a drug. Highly lipophilic compounds (e.g. propranolol) are able to cross cellular membranes much more easily (and have better intestinal absorption) compared to hydrophilic drugs (e.g. hydrochlorothiazide). This is an important consideration in drug development, where

formulation changes can occur as a result of poor intestinal absorption. Finally, the ionization state of a compound, which is determined by its pKa, is another element that can aid or hinder diffusion across membranes. Drugs that are mostly ionized at physiologic pH (e.g. ZDV) are much less likely to enter tissues and cells compared to drugs that are neutral at an identical pH (e.g. FTC). It should be noted that while a drug's pKa is unchanging; its ionization state can differ among tissues due to local pH changes. For example, an acidic environment (e.g. prostatic fluid; pH 6.6) can cause a drug with a pKa >6.6 (e.g. ZDV; pKa 9.68) to be ionized and trapped.[48,49]

In addition to physiochemical properties, the effect of transporter expression and differences in transporter affinity among ARVs may play a critical role in determining mucosal penetration. The effect of transporters on ARV uptake and elimination from tissues has been thoroughly evaluated. A review by Kis and colleagues summarizes the inhibitory and induction effects of ARVs on the ATP-binding cassette (ABC) and solute carrier (SLC) transporter families, which are known to contribute to ARV penetration into various tissues and compartments.[50] Briefly, the efflux transporters of the SLC family, especially p-glycoprotein (P-gp), are the primary method of cellular efflux for almost all ARVs with the exception of the NNRTIs. Transporters responsible for ARV uptake are more varied, but are generally comprised of the organic anion transporters (OATPs). Importantly, all ARVs with the exception of RAL inhibit and/or induce one or more of these transporters to some degree, irrespective of whether they are substrates for the transporters. This has implications not just for drug disposition in tissues, but also for drug-drug interactions. Notably, the authors mention a lack of data on the expression of these transporter groups in the FGT despite adequate expression data in other compartments. One study examined P-glycoprotein (P-gp) localization by immunohistochemistry staining in the upper genital tract of 14 women and found P-gp expression in the ovaries, fallopian tubes, corpus luteum, ectocervix and endocervix, though the degree of expression was highly variable between patients and tissues.[51] Additional publications on transporter expression in the FGT are severely lacking. A recent study examined the expression of uptake (OAT1, OAT3, OATP1B1) and efflux (MDR1, MRP2, and MRP4) transporters in vaginal, cervical, and rectal tissue.[52] Gene expression of the efflux transporters was variable between subjects but consistently expressed, whereas uptake transporters were rarely expressed in these tissues. Similar trends were observed in protein levels, and are supported by drug disposition data.

The inability to visualize the distribution of ARVs within mucosal tissues hinders the progress of PrEP research. Even for ARVs that are known to permeate well into FGT and colorectal tissue, there are few data evaluating drug exposure in specific areas or cellular subsets vulnerable to HIV infection (i.e. mucosa vs. submucosa vs. lymphoid aggregates; mononuclear versus epithelial cells). Techniques that would allow visualization and quantification of ARVs in tissues would be invaluable not only for prevention, but also for treatment and eradication strategies. One such approach is matrix-assisted laser desorption/ionization (MALDI): a mass spectrometry technique that has been used since the 1980s for peptide identification.[53] Through the use of multiple laser ionizations, MALDI is able to generate information about relative concentrations of tissue constituents which, when coupled with imaging software, allow for the visualization of target analytes within a tissue. Recently, this technique has been modified to identify small molecules within specific tissue areas and even within individual cells.[54,55] MALDI has been used previously to quantify ARVs in plasma and represents a promising approach to understanding drug disposition in tissues.[56]

Another possible avenue for future research could include the use of a quantitative structure activity relationship (QSAR) model to isolate the chemical moieties and pharmacokinetic parameters (e.g. protein binding) that improve or hinder penetration. These models have

been successfully used to identify structural characteristics that enhance HIV inhibition, but to date, no validated QSAR model has been developed for ARV penetration into the mucosal compartment.[57] This model was used to determine penetration of drugs across the blood-brain barrier (BBB) and achieved a positive predictive value of 100% and negative predictive value of 83%.[58] The authors were also able to identify factors, such as binding affinity to efflux transporters, which affect BBB penetration. We recently used a similar approach to develop a QSAR model for drug entry into female genital tissues, utilizing a newly validated QSAR model for transporter affinity.[59] Our model was modestly predictive, and identified MRP4 as a novel contributor to FGT penetration.[60] Validation of this model and/or the addition of other models of drug penetration into vaginal/cervical and rectal tissues would greatly inform the drug development process and identify PrEP candidates from an early stage.

Finally, biological factors can affect both ARV penetration into tissues and infection susceptibility. For example, the N(t)RTIs require intra-cellular phosphorylation to their active forms through cellular kinase activity. It has been determined that kinase activity in quiescent or activated cells changes the rate and extent of phosphorylation of ARVs. Specifically, zalcitabine, lamivudine, stavudine, and didanosine are preferentially phosphorylated in activated cells.[61,62] No noted differences in phosphorylation have been found between activated and quiescent cells for tenofovir.[63] Importantly, these differences in active metabolite concentrations may not correlate with anti-viral activity, as zalcitabine, lamivudine, and didanosine are more active against HIV in quiescent cells despite lower metabolite concentrations than in active cells.[62] It may be that increased numbers of endogenous nucleotides in activated cells decrease their effectiveness.

Altered mucosal integrity may also result in large inter-individual variability in ARV penetration, particularly for topical dosage forms. Compromised mucosal integrity has been associated with increased viral penetration.[64] It is not known whether this relationship holds true for topical ARV penetration, but inflammation and physical breaks in skin are known to increase plasma exposure to topical products. Further, while the integrity of the upper genital tract tissues (e.g. endometrium) is heavily influenced by the menstrual cycle, hormonal influence on the vaginal and rectal mucosa is less understood. There are numerous studies examining the role of estrogen on HIV susceptibility, however studies exploring the hormonal influence on drug exposure are lacking.[65,66]

## Drug Persistence and Functional Half-Life

Given that the index infection likely takes place within the mucosa or submucosa of mucosal tissues, the presence of adequate concentrations of ARVs at the time of exposure is critical in PrEP. Also critical is the length of time compounds reside in the tissue. Compounds with long tissue half-lives (or delivery systems with continuous drug exposure) would be favored for both virologic and adherence factors.[9,4,11] For any ARV used in PrEP, the time spent above target concentration must at least be as long as the length of time that viable virus remains in the mucosal cavity after coital exposure. The life span of the HIV virion in plasma has been reported as 6 hours, while HIV-infected CD4+ T cells have a lifespan of approximately 2 days in plasma.[67] The life span of both infected cells and virion in the mucosal cavity remains unknown and demands exploration. One study examined virion persistence after vaginal inoculation of SIV in macaques and found that low levels (hundreds to $10^4$ copies/μg tissue) were present 1 day after inoculation.[25] If we assume the life span in the mucosal cavities are identical to those in plasma, then protective ARV concentrations would need to be continually present for up to 3 days after each exposure. Recently, the iPrEX, FemPreP, and VOICE studies have demonstrated that study volunteers have difficulty adhering to a once-daily dosing regimen, which compromises PrEP

efficacy.[9,11,12] These studies demonstrated that daily prophylaxis against HIV infection (whether oral or topical) will be minimally effective if the functional half-life is too short, or the mucosal tissue penetration too low, to permit any reasonable degree of tissue protection.

TFV and FTC have reported plasma half-lives of 17 and 10 hours, respectively. However the half-lives of their active intracellular metabolites (TFV-dp and FTC-tp) in PBMCs are much longer at approximately 144 and 38 hours, respectively.[68,69] In mucosal tissues, we have documented that TFV-dp and FTC-tp have half-lives of 2-6 days.[30] We have also noted that the high TFV and TFV-dp exposures achieved in colorectal tissue (100X higher than vaginal or cervical tissue) after a single dose were advantageous to the iPrEX cohort of men who have sex with men who did not take daily tenofovir/emtricitabine (Truvada) as instructed but rather intermittently and yet were still protected from HIV infection.[9,70]

Despite potential advantages in PrEP, a number of concerns are inherent with a long half-life compound: in particular, the development of resistance. Due to an increase in elimination time, there may be extended periods where drug concentrations are sub-therapeutic in mucosal tissues. If HIV transmission occurs during this time, prolonged exposure to sub-therapeutic drug concentrations has the potential to select for viral resistance.[71] This is especially true for long-acting injectables, where subtherapeutic concentrations may persist for weeks, rather than hours.[41] Obviously, allergic reactions might also be exacerbated with unremitting exposure to an allergen as was observed with penicillin and serum sickness.[72]

## Generating Effective Drug Target Concentrations and Dosing Strategies

In order to ensure adequate ARV drug concentrations within mucosal tissue, therapeutic tissue concentration targets must be defined. To date, target ARV tissue concentrations for HIV prevention have not been established, but if determined would represent an important advance in PrEP research. Once the appropriate models for defining these are identified, dosing strategies can be designed to achieve concentrations above this target while preventing long periods of subtherapeutic drug exposure and minimizing the risk of drug resistance.

The variable efficacy of topical and systemic PrEP observed in clinical trials is highly dependent on adherence, but is also due to limited mucosal tissue penetration for the ARVs studied thus far. Numerous methods are currently under investigation to identify those drugs and concentrations that successfully prevent HIV infection upon exposure to the virus. These include cellular studies, humanized mice and nonhuman primate models, the human mucosal tissue explant model, and retrospective analysis of clinical trial data.[73-75] The generation of “threshold” ARV concentrations above which HIV transmission is unlikely would provide a target around which dosing strategies could be generated for clinical studies.

Pharmacodynamic measures of efficacy, such as time above MIC, have been successfully implemented as targets to guide antibiotic dosing. Similar measures of efficacy need to be developed for HIV chemoprophylaxis. The process is complex, requiring dose fractionation to determine the best efficacy target.[76] Unfortunately, establishing target concentrations in mucosal tissues is a complex process. For example, while bacterial infections are extracellular, and the concentration of antimicrobials in the interstitial fluid is pharmacodynamically active (and can be measured with dialysis techniques or in blister fluid), the intracellular nature of HIV requires an understanding of active intracellular concentrations.[76,77] Based on the physicochemical and biological factors listed above, it is therefore more important to understand protein-unbound drug concentrations in tissues or cells, rather than plasma. Further, due to differences in rates of tissue distribution, single time-point estimates of drug concentration may be inadequate to fully describe these

pharmacokinetic-pharmacodynamic relationships, and multiple sampling to quantify area under the concentration time curve (AUC) is necessary. With newer technologies such as MALDI imaging, simultaneously exploring the pharmacokinetics and pharmacodynamics of drug distribution and effect tissues may be possible.

Pharmacokinetic modeling and simulation approaches can identify optimal (preferably coitally-independent) dosing strategies for clinical trial investigation which surpass the target mucosal tissue concentrations for a predefined critical length of time. [78-80] Indeed, it would be unreasonable to identify a target concentration that was only achievable by dosing multiple times per day, as even once daily dosing has been challenging for some clinical study subjects to adhere to. Adherence has been shown to correlate with efficacy in multiple studies and has been thoroughly reviewed by Koenig and colleagues.[10,81,82] The factors affecting drug adherence are complex, but the frequency and complexity of the dosing regimen in a healthy population is certainly a contributing factor.[83] Several novel formulations are currently in development and may be useful to overcome the adherence barrier.[84] For example, a long-acting parenteral ARV formulation or a slow-release vaginal ring formulation should increase the probability of achieving consistent target concentrations. It has yet to be determined if these drug delivery modalities will be acceptable to study volunteers and utilized more consistently than daily dosed products.

## Future Directions in Prevention Pharmacology

The necessity of an effective prophylactic regimen is highlighted by the inability of treatment regimens to completely prevent viral shedding in genital and rectal tissues. HIV RNA is easily detectable in the genital tissues and fluids of HIV-infected women and in the seminal fluid and rectal tissue of HIV-infected men and is highly correlated with plasma RNA levels.[85-87] Importantly, viral shedding is reduced by ART by as much as 2 log units; demonstrating that therapy likely reduces the infectivity of HIV-infected individuals.[5,88] Reduced viral shedding can have profound clinical implications. The HPTN 052 study demonstrated that among serodiscordant couples, early initiation of ART in the infected partner was associated with a 96% reduction in HIV transmission compared to deferred initiation.[6] The large decrease in transmission observed in this study would not have been possible without decreased viral shedding. Unfortunately, both genital and rectal shedding have been shown to persist even in the setting of undetectable plasma viral RNA.[89-91] While it is unknown whether the viral RNA found in these tissues represents viable and infectious HIV, it is a concerning finding nonetheless. The apparent inability of treatment regimens to eradicate HIV in the genital tract suggests that effective PrEP will require novel dosing strategies or dosage forms to prevent infection at these sites. What remains unclear is whether a disparity exists between effective ARV concentrations for prevention of acquisition via PrEP versus prevention of transmission via treatment. Concentration-response relationships are well characterized for ARVs in plasma, but have not been studied at the tissue level. It is possible that differences in immune cell populations between plasma and tissue have an effect on drug efficacy. For instance, higher levels of HIV targets in rectal tissue compared to plasma may require higher concentrations of drug at this site to prevent infection.[28]

The *in vitro* and pre-clinical methods developed to understand ARV pharmacokinetics and efficacy in mucosal tissue compartments have greatly improved our understanding of ARV pharmacology. However, these are not without limitations. Nonhuman primate models of prevention are limited by the numbers available for study, and have some clinically relevant pharmacologic and virologic distinctions. The humanized mouse model can use clinically relevant viruses but challenges remain in characterizing pharmacologic differences with smaller sampling capacity.[73] The human tissue explant model can use relevant tissue and

viruses, but data on ARV disposition and PK-PD relationships are lacking, as are standardized methods and approaches.[74] Target effective ARV concentrations can be generated from all these models, but a lack of robust and consistent data across all models currently limit our ability to determine how they should be utilized for informing drug development go/no go decisions and clinical trial design. As previously indicated, PK modeling is critical for generating dose-concentration relationships even in early drug development and should be used for PrEP.[92-94] Simulations run on a successful PK model will identify which dosing regimen best achieves target concentrations, once identified. This information will streamline trial development and increase the likelihood of success. The use of modeling and simulation for dosing regimen selection and clinical trial design is an important cost-effective technique, particularly in chemoprophylaxis studies whereby clinical dose-finding studies are unattainable due to patient risk and sample size requirements. Models can be generated which take into account what is already known about a drug and factor in various assumptions, such as intra- and inter-patient variability, adherence, and dropout rates.[95,96] These strategies have been used in the past for faster market approval.[97] An additional benefit of modeling is that once generated, a model can be used not only to evaluate the drug for which it was developed, but for other drugs within that class as well.[95] This will be extremely beneficial for PrEP, with multiple candidates being available in similar therapeutic drug classes.

## Conclusion

Successful HIV prevention strategies have been demonstrated in clinical trials, but implementation in the real world is a challenge. Use of ARV treatment as prevention has already become policy in the setting of discordant couples, and may be expected to inform when ART is started and continued and which drugs are selected.[98,99] Curing HIV infection will require that ART stop replication in every compartment, a feat which has already proven a challenge. The mixed results of both topical and systemic PrEP trials demand preclinical and early phase strategies to improve the knowledge of efficacy targets and develop maximally effective dosing strategies that will be accepted by study participants and eventually the target market. The mucosal compartment plays an important role in transmission as the site of first exposure to HIV. Therefore, research aimed at understanding drug targets to prevent infection at this location, or even distal to this location (e.g. regional lymph nodes) is essential for developing successful next generation PrEP strategies. Determining the optimal time that drug should reside in mucosal tissues will also help define dosing strategies. Factors influencing tissue disposition are poorly understood, but should be identified so that chemicals and formulations can be optimally designed for this purpose. Validating animal and ex vivo models against clinical outcomes in humans will determine their utility in making go/no go decisions and informing clinical trial design. Finally, pharmacokinetic/pharmacodynamic and clinical trial modeling and simulation have an important role to play in potentially informing the drug development process and increasing the probability of PrEP success in large clinical trials.

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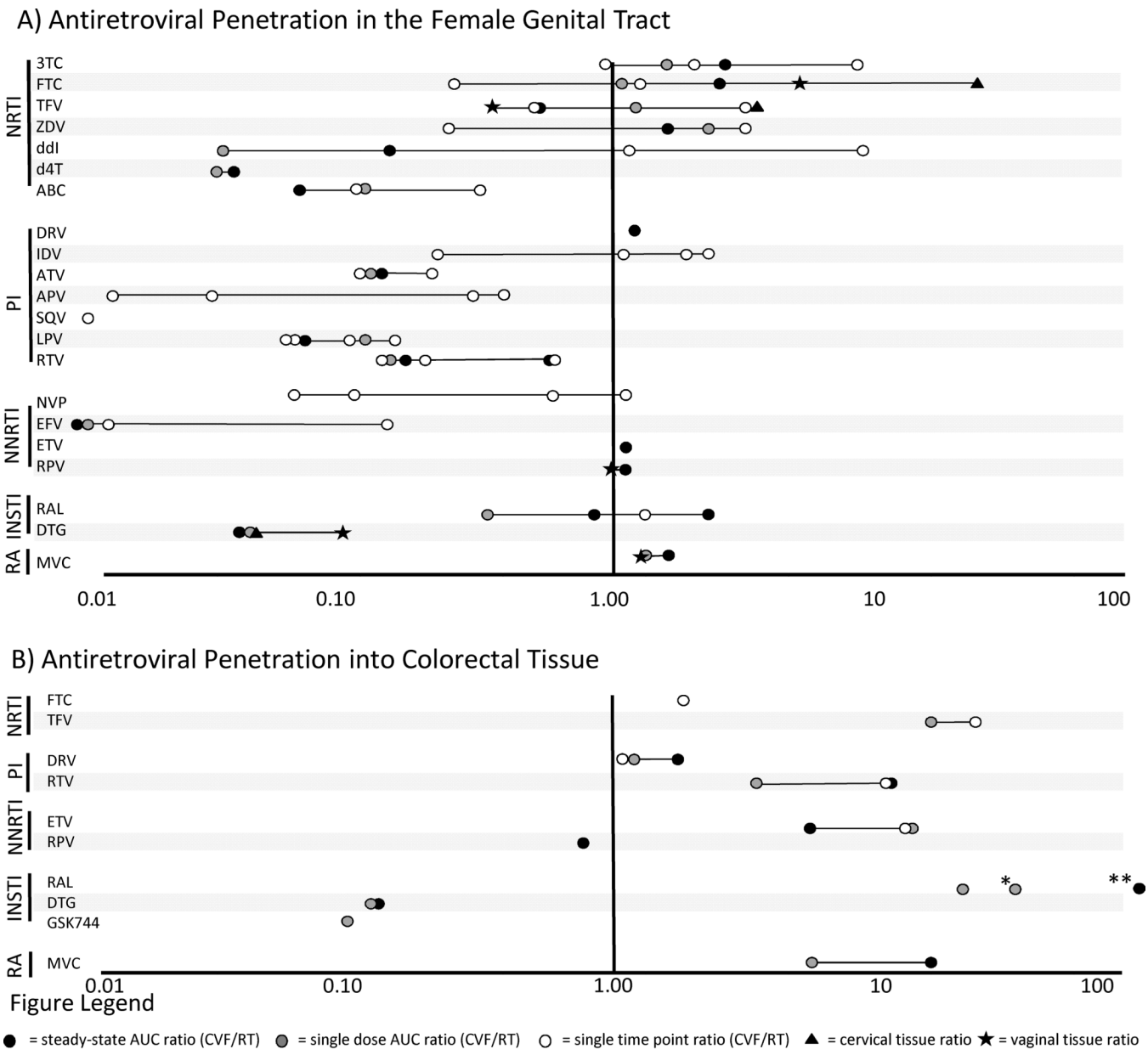


**Figure 1. A&B: ARV Penetration into Mucosal Tissues**

Data are from references 19-21, 30, 31, 33-42. 3TC=lamivudine, FTC=emtricitabine, TFV=tenofovir, ZDV=zidovudine, ddI=didanosine, d4T=stavudine, ABC=abacavir, DRV=darunavir, IDV=indinavir, ATV=atazanavir, APV=amprenavir, SQV=saquinavir, LPV=lopinavir, RTV=ritonavir, NVP=nevirapine, EFV=efavirenz, ETV=etravirine, RPV=rilpivirine, RAL=raltegravir, DTG=dolutegravir, MVC=maraviroc, NRTI=nucleoside reverse transcriptase inhibitor, PI=protease inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, INSTI=integrase strand transfer inhibitor, RA=receptor anatagonist