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Antiretrovirals to Prevent HIV Infection: Pre- and Postexposure Prophylaxis

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Abstract

More than 3 million people are now receiving antiretroviral therapy (ART) worldwide. Currently, the indications for ART depend primarily on CD4 count, blood viral burden, and clinical signs and symptoms suggesting advanced HIV disease. However, interest is increasing in ART's preventive potential. Postexposure prophylaxis following both occupational and nonoccupational exposure to HIV is the standard-of-care in many settings. Observational and ecologic studies suggest that ART administered to HIV-infected people reduces transmission within serodiscordant couples. Pre-exposure prophylaxis to prevent HIV infection is a potentially safe and intermittent intervention for very high-risk people, and clinical trials to evaluate this preventive strategy are underway. The prevention benefits of ART may begin to affect the decision of when to start therapy and add a much-needed strategy to current HIV prevention efforts.

Introduction

The public health impact of using antiretroviral therapy (ART) has been largely ignored as a strategy for HIV prevention. ART can be used to prevent HIV transmission through three mechanisms: 1) reduction of HIV viral load in individuals aware of their status; 2) postexposure prophylaxis following risk exposures; and 3) as pre-exposure prophylaxis with oral and/or topical microbicides. The concept of using ART to decrease infectiousness in an HIV-infected individual stems from the strong association between risk of HIV transmission by all exposure routes and HIV viral levels in the blood [1–3]. The use of postexposure prophylaxis following occupational exposures is now the standard of care in many settings, and accumulating evidence from large registries will further inform this practice. Postexposure prophylaxis following nonoccupational exposure and studies on its feasibility and acceptability are expanding, as is the development of guidelines for its use based on exposure risk. To date, ART as pre-exposure prophylaxis to prevent HIV infection has primarily been studied in animals, but human studies of its safety and efficacy are ongoing.

Sexual Transmission of HIV

To date, a Ugandan study of serodiscordant couples provides the strongest evidence for a direct correlation between the probability of HIV sexual transmission and increasing blood viral load [1]. This association was confirmed in subsequent studies of serodiscordant couples in Zambia and Thailand [4, 5]. In the Ugandan and Thailand studies, no transmission events occurred when HIV RNA was less than 1500 copies/mL [1] and 1094 copies/mL [5], respectively. The association between peripheral HIV viral load and sexual

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transmission likely reflects the correlation between HIV concentrations in blood and in genital [6] and rectal [7] secretions. However, importantly, the correlation between HIV concentrations in blood and genital secretions is inconsistent, as demonstrated by significantly increased HIV shedding in the genital tract in the setting of sexually transmitted diseases (STDs) [8, 9].

The wider implementation of methods to detect acute HIV infection (AHI) has led to several insights into viral and transmission dynamics following HIV acquisition. In a prospective study in Malawi, HIV shedding was significantly increased in semen during AHI, when very high levels of virus are detected in blood [10]. HIV concentrations in semen peaked 4 weeks after infection and were contained in most subjects at 10 weeks after infection [10]. Increased viral shedding in genital secretions during AHI supports recent data, which suggest that a significant proportion of sexual HIV transmission is driven by AHI [11•, 12••]. In the Rakai study, nearly half of HIV transmission events among discordant couples occurred during early HIV infection [11•]. Similarly, a retrospective study using cluster analysis of viral variants in HIV-infected patients in Montreal suggested early infections accounted for approximately half of transmissions over a 5-year period [12••].

Effects of ART on Infectiousness

The greatest potential public health benefit of ART lies in preventing transmission in serodiscordant couples, reflected in the substantial number of undiagnosed individuals in serodiscordant relationships detected through massive household screening in Uganda [13•]. Evidence of ART's prevention benefits can be found in retrospective analysis, prospective observational studies, and ecologic data. A retrospective study of 436 serodiscordant couples found that the relative risk of HIV transmission from a man to his female partner was lower in the 15% of men who received zidovudine monotherapy for more advanced disease (OR, 0.5; 95% CI, 0.1–0.9) [14]. Another retrospective study comparing HIV transmission events among 393 discordant couples in the pre-highly active ART (HAART), early HAART, and post-HAART periods reported an 80% reduction in HIV transmission events following the introduction of triple drug therapy in the infected partner (OR, 0.14; CI, 0.03–0.66) [15].

In an observational study in Zambia and Rwanda, index partners in 248 of 1034 discordant couples initiated ART if their CD4 cell count was less than 200 cells/μL [16•]. For susceptible partners, the risk of acquiring HIV decreased if their HIV-infected partner received ART (OR, 0.19; 95% CI, 0.05–0.8), even after adjustment for self-reported condom usage (adjusted OR, 0.21; 95% CI, 0.05–0.8). Similarly, a study in Uganda reported a 98% reduction in the estimated risk of HIV transmission following ART initiation: a decrease from 45.7 to 0.9 transmissions per 1000 person-years in 454 of 926 participants with 2 years of follow-up [17••]. Findings from this study are somewhat limited due to loss to follow-up and exclusion from analysis of almost 50% of subjects. Importantly, only individuals with low CD4 counts or advanced HIV disease were started on ART in these studies, whereas earlier initiation of ART at higher CD4 counts, especially in people at risk for transmitting HIV, could be implemented as a prevention strategy. Notably, such observational studies are susceptible to the effects of unexpected modifiers and the inability to determine long-term benefit.

The variable findings from ecologic analyses on the preventive benefit of ART likely reflect the inability of such studies to relate HIV-infected individuals on ART to HIV incidence or prevalence and to correlate HIV transmission with prevalence, because many HIV-infected individuals remain undiagnosed, and those with high viremia may account for a disproportionate number of incident cases. In San Francisco, a 60% reduction in expected HIV cases among men who have sex with men (MSM) was attributed to increased ART

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availability [18]. Following the introduction of free ART in Taiwan, a 53% reduction in anticipated HIV cases was accredited to increased access to ART [19]. In contrast, another study among MSM in San Francisco found no decline in incident HIV infections despite increased availability of ART [20], and increased incident HIV was reported among MSM in STD clinics in Amsterdam following increased ART availability [21].

To better define the ability of ART to prevent HIV transmission, a randomized trial comparing two treatment strategies to prevent sexual HIV transmission among 1750 serodiscordant couples over a 5-year period is underway (www.hptn.org). HIV-infected partners with CD4 counts between 350 and 550 cells/mm^3 are randomized to immediate ART versus delayed ART until their CD4 counts fall below 250 cells/mm^3 or they develop an AIDS-defining illness. In addition to the impact of ART on HIV transmission, the study will assess the safety, adherence, and development of ART resistance in the study population.

ART for Postexposure Prophylaxis

Most data on the biologic plausibility of ART to prevent HIV infection following exposure derive from the rhesus macaque model using simian immunodeficiency virus (SIV) infection or SIV/HIV chimeric viruses (SHIV). Although some SIV and SHIV macaque studies have suggested that ART could prevent transmission, subsequent studies using different inoculum doses, ART agents, and delay to ART administration after exposure have been less promising [22]. In efforts to more closely simulate high-risk human sexual exposures, the macaques model has recently used repeated rectal inoculations with lower virus titers (3.8×10^5 viral particle equivalents) [23•, 24]. The most recent advance in HIV animal models is the ability to infect bone marrow/liver/thymus humanized mice with HIV following one intrarectal exposure [25•], with subsequent CD4 depletion in gut-associated lymphoid tissue and the development of AIDS-associated pathology. This new murine model shows great potential for advancing the study of HIV prevention strategies, including pre-exposure prophylaxis [26•].

Postexposure prophylaxis following occupational and nonoccupational exposure

The use of postexposure prophylaxis following occupational exposure to HIV, now considered standard of care in many countries, is based on findings from a single, small, retrospective case-control study of ART prophylaxis following needlestick exposure among US healthcare workers [27]. Findings led to the widely adapted postexposure guidelines by the US Centers for Diseases Control and Prevention (CDC), which were updated in 2005 [28].

A randomized, controlled trial of ART prophylaxis following nonoccupational HIV exposure is not feasible due to the prohibitive cost of enrolling the large sample size required to establish preventive benefit, related to the inefficiency of sexual transmission per exposure. Regardless, the use of ART prophylaxis following nonoccupational exposure is expanding worldwide, as reflected by the creation of the European Project on Non-Occupational Post-Exposure Prophylaxis for HIV (EURO-NONPEP). In 2001, the group convened representatives from 14 countries to establish unified guidelines for postexposure prophylaxis and a registry of potential nonoccupational exposures [29]. The registry will permit the large-scale evaluation of the uptake, safety, efficacy, and sustainability of nonoccupational postexposure prophylaxis. The first US guidelines for nonoccupational postexposure prophylaxis were published in 2005 [30]; they recommend a three-drug regimen for 28 days following high-risk sexual exposure to a known or suspected HIV-infected partner.

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Clinical studies of nonoccupational postexposure prophylaxis

Several feasibility studies of nonoccupational postexposure prophylaxis were reviewed recently [22]. The studies suggest that nonoccupational postexposure ART is acceptable given 64% to 100% completion rates for a 28-day ART course; however, nonoccupational postexposure prophylaxis failures have been described [22]. Seven seroconversions were reported among 702 individuals who received two or three drugs for 28 days with 12 weeks of follow-up [31]. Four of the seven seroconverters were considered postexposure failures given self-reported 100% adherence to their ART course, and failure was associated with anal intercourse exposure and delayed initiation of ART. Three seroconverters started treatment more than 55.5 hours after exposure, albeit still within the window for which postexposure ART is recommended. Failures associated with delay to treatment are particularly concerning, because even individuals who perceive themselves at risk for HIV infection do not start ART promptly [32]. Interestingly, none of the seroconverters received three drug postexposure ART, and although the study was not designed to compare the efficacy of dual versus triple-drug postexposure ART, the finding lends some support to CDC recommendations for triple ART for high-risk exposures.

Antiretroviral selection for nonoccupational postexposure prophylaxis

With or without data from a randomized clinical trial, nonoccupational postexposure prophylaxis is increasingly implemented to prevent HIV infection [33], and the selection of ART agents must incorporate expanding data on the pharmacology of specific agents, the cost of treatment, the presence or likelihood of resistance in source partners, and tolerability. For example, ART for nonoccupational postexposure prophylaxis has been associated with a sixfold higher rate of ART toxicity and an eightfold higher rate of drug discontinuation, compared with ART prescribed for treatment of HIV-infected individuals [34]. Mathematical modeling analysis suggested that two-drug postexposure ART may be more efficacious than a triple-drug regimen due to equivalent efficacy and higher completion rates [35]. However, despite higher rates of side effects during nonoccupational postexposure prophylaxis, associated symptoms are usually mild and reversible, and do not necessitate treatment discontinuation. Reports of postexposure prophylaxis discontinuation due to ART toxicities have been published for occupational [36, 37] and nonoccupational [38, 39] exposures; however, a study of nonoccupational ART prophylaxis found no difference in discontinuation rates when comparing a triple drug regimen including a protease inhibitor to a dual nucleoside/tide reverse transcriptase inhibitor regimen [38].

More recently, two case-controlled studies evaluated the use of tenofovir in dual nonoccupational postexposure regimens following high-risk sexual exposures. Forty-four subjects received tenofovir disoproxil fumarate and lamivudine in one study, and 68 additional subjects received the combination of tenofovir disoproxil fumarate and emtricitabine in a second study. Both tenofovir-based dual regimens were associated with higher completion rates of a 28-day postexposure course compared with historical controls taking two- or three-drug regimens containing zidovudine ($P < 0.0001$) [40]. High dropout rates during nonoccupational postexposure prophylaxis treatment have been reported [41, 42], particularly for postexposure prophylaxis following sexual assaults [43].

ART Pharmacology in the Genital Tract

Because the risk of sexual HIV transmission correlates with peripheral viral load, it seems logical that ART—which predictably decreases HIV RNA in blood to undetectable levels and decreases HIV concentrations in seminal plasma [44], female genital tract secretions [45], and rectal secretions [46]—would decrease infectiousness in those taking effective ART. Indeed, HIV-1 RNA levels in plasma and genital secretions declined rapidly and in

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parallel following ART initiation with a nonnucleoside reverse transcriptase inhibitor in a recent study among Kenyan female sex workers [47••]. Notably, in half the subjects, HIV RNA remained detectable in cervical and vaginal secretions after 28 days of treatment, suggesting persistent infectiousness.

The pharmacology of ART in the genital tract suggests that certain antiretroviral agents may be preferable for the prevention of HIV following sexual exposure (Fig. 1) [48, 49••, 50]. Previous data found that the genital tract concentrations of most protease inhibitors are less than 10% of plasma levels, and the genital tract concentrations of most nucleoside/tide analogue reverse transcriptase inhibitors are two- to sixfold higher than in blood [22]. Two recent studies found that genital tract concentrations of lamivudine, emtricitabine, zidovudine, tenofovir, and maraviroc were higher than in blood plasma; lopinavir and atazanavir achieved low to moderate concentrations in the genital tract, and efavirenz concentrations were less than 1% of levels in blood [49••, 51•].

First-dose genital tract drug-exposure data are particularly relevant to pre- and postexposure ART, and they are available for tenofovir in men [52] and for 12 antiretroviral agents in women [49••, 52]. Many antiretrovirals are detected in genital secretions within 1 to 2 hours of the initial ART dose; abacavir, tenofovir, and didanosine achieve higher genital tract concentrations after a single dose than during steady-state conditions [49••]. Most recently, maraviroc demonstrated the highest concentration in cervicovaginal secretions relative to blood plasma compared with all currently available ART agents within 8 hours of a single dose [51•], and shows promise as an effective pre- or postexposure oral agent.

In sum, the available pharmacologic data suggest that the prompt initiation of ART with some combination of lamivudine or emtricitabine, zidovudine, tenofovir, maraviroc, and possibly lopinavir or atazanavir, would result in their rapid accumulation in tissues exposed to HIV. Efavirenz is a less attractive candidate for pre- or postexposure prophylaxis given poor penetration into the genital compartment. Additional pharmacology data on other new antiretrovirals including integrase inhibitors are expected.

Pre-Exposure ART Prophylaxis to Prevent HIV Transmission

Animal models of pre-exposure prophylaxis

The strategy of preemptive ART as oral therapy or a topical microbicide to prevent HIV infection derives from rhesus macaques studies [53, 54]. In a series of studies using the rectal mucosal challenge model, oral tenofovir delayed but did not prevent $SHIV_{SF162P3}$ in three of four macaques after repeated exposures [55]. In a follow-up study using a single high-dose intrarectal inoculum, two of five tenofovir- treated macaques were protected [24]. High doses of tenofovir combined with emtricitabine, both given once daily subcutaneously, protected six of six macaques from SHIV despite repeated rectal exposures [56]; however, it should be noted that such findings cannot be translated to protection in humans given the supratherapeutic doses of tenofovir. Furthermore, because ART was given daily, it is unclear if ART given before exposure to SHIV actually prevented infection or if ART given after exposure eliminated early infection and halted seroconversion. Finally, in the absence of autopsy evaluation, there is no proof that the animals remained uninfected.

More applicable results were reported in a study using intermittent dosing of ART before and after intrarectal exposure. Subcutaneous emtricitabine, 20 mg/kg, given with a supratherapeutic dose of tenofovir, 22 mg/kg, 2 hours before and 24 hours following intrarectal exposure prevented infection in all six exposed macaques [23•]. This approach more closely simulates true pre-exposure prophylaxis than other models; however, it also

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incorporated supratherapeutic doses of tenofovir with twofold higher concentrations in the macaques compared with humans.

Pre-exposure clinical trials

The first clinical trials of pre-exposure prophylaxis in HIV uninfected individuals were abandoned following community protests regarding trial design, the perceived lack of community input, and the risk versus benefit for the study populations. In particular, objections arose regarding the risk of resistance with the use of a single ART agent, based on data from animal studies [55, 57]. Mathematical modeling analysis of the Botswana tenofovir trial determined that less than 1% of the anticipated 45 seroconverters among 600 participants would acquire or develop a tenofovir resistance [58]. However, the preventive advantages of combination tenofovir–emtricitabine in the rhesus macaques model [56] resulted in a switch to combination tenofovir and emtricitabine in some studies.

Clinical trials of either tenofovir or combination tenofovir–emtricitabine as oral pre-exposure prophylaxis in HIV uninfected high-risk individuals are under way in Botswana, Thailand, Peru, Ecuador, and the United States [59–61]. The only available data in humans come from a safety trial of pre-exposure tenofovir in 936 high-risk women in Ghana, Cameroon, and Nigeria. The study reported no difference in adverse events or grade 3 or 4 laboratory abnormalities in subjects receiving tenofovir versus those receiving placebo [62]. Fewer seroconversions occurred in the tenofovir arm versus those receiving placebo (2 vs 6); however, neither sample size nor study duration were sufficient to determine efficacy. In addition, no tenofovir resistance was detected in seroconverters.

Newspaper reports on the black market sale of antiretrovirals at clubs for self-administered use prior to high-risk sex [63, 64] indicate that individuals are using ART as intermittent pre-exposure prophylaxis, even without proof of efficacy. In addition, in 2004, 7% of attendees at minority gay pride events in four cities reported prior use of ART as pre-exposure prophylaxis [65].

Topical ART as pre-exposure prophylaxis

Trials of topical microbicides for the prevention of HIV infection in women have been disappointing; however, topical antiretroviral agents still hold promise for HIV prevention. Tenofovir vaginal gel was well tolerated in HIV-infected and uninfected women with twice daily application [66•]. Although systemic low levels of tenofovir were detected in some subjects, no mutations conferring tenofovir resistance were detected in the HIV-infected women with detectible plasma or cervicovaginal HIV RNA [66•]. A recent study measured tenofovir concentrations in cervicovaginal fluid, vaginal tissue, and blood plasma obtained over 24 hours following a single 4-mL dose of 1% tenofovir gel in 21 healthy female volunteers, with an assay sensitivity of 1 ng/mL [67]. Tenofovir was detected in the blood plasma of all subjects; concentrations in most were less than 5 ng/mL, although concentrations up to 19.5 ng/mL were measured in 20% of subjects. After 24 hours, tenofovir levels in vaginal fluid and tissue measured up to 4.5 to 47.1×10^4 ng/mL and 15×10^3 ng/mL, respectively, which is similar to concentrations protective in prior macaques studies using subcutaneous dosing of tenofovir.

ART as a Public Health Measure for Prevention

The public health benefit of ART for prevention will depend on several factors: 1) the proportion of HIV-infected individuals treated; 2) targeting ART to those most likely to transmit HIV; 3) ART efficacy in reducing viral load in the genital tract; 4) persistent infectiousness of treated participants and the emergence and transmission of drug-resistant strains; and 5) behavioral disinhibition. Several mathematical modeling studies suggest that

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ART could substantially reduce HIV-associated mortality and transmission with widespread implementation. However, the preventive benefit could be undermined if ART leads to behavioral disinhibition [68–70]. A recent modeling analysis concluded that pre-exposure prophylaxis could prevent 2.7 to 3.2 million new cases of HIV in sub-Saharan Africa over 10 years if it is targeted to the highest risk groups, and disinhibition could be prevented [71]. Notably, the model assumed a 90% efficacy of ART to prevent HIV transmission, and ART efficacy was the most important determinant of preventive benefit.

ART and Sexual Behaviors

Nonoccupational postexposure prophylaxis

Previous studies on the impact of nonoccupational postexposure ART on sexual behavior have found low rates of repeat postexposure requests and decreases in self-reported high-risk sexual exposures. Almost half of participants receiving nonoccupational postexposure prophylaxis from a community-based program and remaining on study at week 26 reported a decrease in the number of sexual partners [72]. Despite widespread availability of postexposure prophylaxis in all hospital emergency departments and the Municipal Health Service in Amsterdam, requests for postexposure following sexual exposure increased very minimally between 2000 and 2004 [39].

In contrast, MSM in Australia who received nonoccupational postexposure prophylaxis reported more unprotected anal intercourse 1 year later than MSM who had not received postexposure prophylaxis (50% vs 36%; $P = 0.009$), and they were at increased risk for acquiring HIV (incidence, 2.37 cases per 100 person-years; RR, 2.3; 95% CI, 1.05–5.06) [73]. Even more concerning, 21% of 89 subjects in another study reported unprotected sex during their course of ART postexposure prophylaxis [74]. A postexposure program in San Francisco found that the addition of five risk-reduction counseling sessions decreased self-reporting of unprotected intercourse [75]. In another study evaluating attitudes toward postexposure ART among MSM [76], subjects expressing future intent to use postexposure prophylaxis were more likely to state that ART could prevent HIV infection and that advances in ART decreased their concern regarding unprotected sex and acquiring HIV infection. Those intending to use ART prophylaxis were also more likely to report high-risk sexual behaviors and substance abuse.

In summary, most data from several prospective studies of postexposure prophylaxis after sexual exposure fail to demonstrate an association between postexposure prophylaxis and sexual disinhibition. Furthermore, reports of repeat requests for nonoccupational postexposure prophylaxis and subsequent high-risk behavior in studies of postexposure prophylaxis cannot be interpreted as an increase or change in behavior, but may simply reflect ongoing pre-existing high-risk behaviors.

The only available data on the impact of pre-exposure ART on sexual behavior comes from the pre-exposure study of tenofovir in West Africa, in which the average condom use increased from 52% at last coital act prior to screening to 95% at 12 months (for coitus in the previous 7 days) [62]. However, reports of self-administered black market ART in uninfected individuals prior to high-risk sex necessitate dialogue on whether pre-exposure prophylaxis could propagate or lead to high-risk sexual behavior [63–65].

Future Strategies for ART as Prevention

Given expanding data supporting the association between incident HIV and sexual transmission from acutely infected index partners [11•, 12••] and strong evidence that ART decreases infectiousness [11•], targeted ART for acutely infected individuals could prevent a

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substantial number of new infections in high-incident areas. No established guidelines exist for ART initiation for treatment during AHI due to an inability to demonstrate clinical benefit; however, the ability of ART to prevent ongoing transmission from acutely infected individuals has not been studied. The preventive benefit of providing ART to individuals acutely infected with HIV clearly depends on the ability to diagnose AHI, which currently depends on detecting HIV RNA in seronegative individuals. Although this technology is costly and currently unavailable in most resource-poor settings, screening of HIV antibody–negative specimens via HIV RNA pooling is feasible, less expensive than individual HIV RNA testing, and effective in detecting AHI [77, 78]. Nevertheless, targeted testing for AHI in high-risk settings, such as STD clinics in sub-Saharan Africa, could decrease missed opportunities to diagnose HIV and prevent ongoing transmission in those with high viremia.

The ongoing pre-exposure prophylaxis trials include daily dosing of tenofovir or combination tenofovir–emtricitabine; however, intermittent ART prior to unprotected or high-risk sex represents a more practical and cost-effective strategy, particularly in resource-poor settings. Accordingly, the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial is investigating the topical administration of tenofovir gel 12 hours before and 12 hours following coitus. Additional studies using exposure-associated and/or scheduled tenofovir–emtricitabine in macaques and the new HIV-infected bone marrow/liver/thymus humanized murine model are anticipated to further elucidate pre-exposure dosing strategies. To date, studies of pre- and postexposure prophylaxis in humans have focused on only one strategy, whereas strategies combining oral and vaginal ART in high-risk individuals may provide the greatest efficacy of ART for prevention.

Conclusions

ART represents the most powerful available biologic intervention for HIV prevention. As indicated in this review, postexposure prophylaxis is widely accepted and topical and systemic ART pre-exposure prophylaxis will almost certainly be developed. Belief in the benefits of ART for discordant couples is so strong that the Swiss Federation has already released a supportive policy statement, although this has been controversial [79]. We believe ART represents the very best marriage of treatment and prevention, and that this realization will continue to grow rapidly. Perhaps most important, with increased attention, the public health benefits of ART can reach their full potential.

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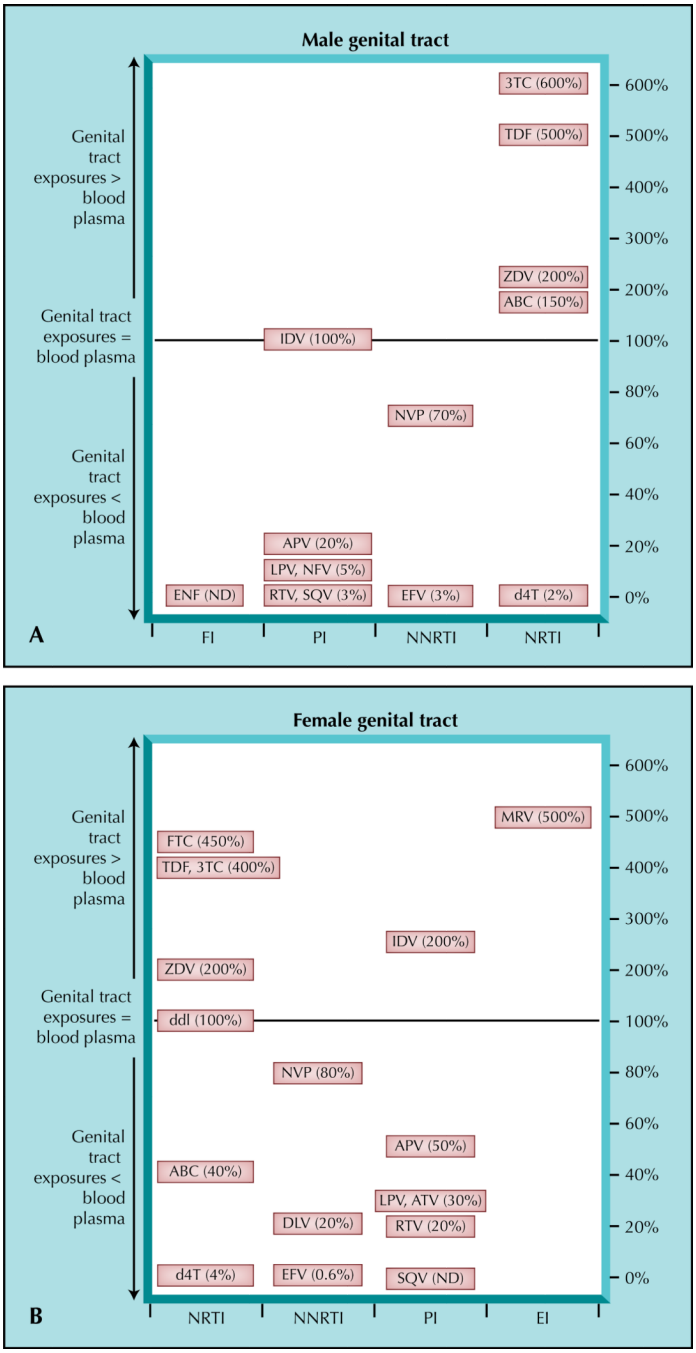

Figure 1.

Antiretroviral drug levels in the male (**A**) and female (**B**) genital tracts relative to blood plasma levels (ratio of genital to blood plasma levels). 3TC—lamivudine; ABC—abacavir; APV—amprenavir; ATV—atazanavir; d4T—stavudine; ddI—didanosine; DLV—delavirdine; EFV—efavirenz; EI—entry inhibitor; ENF—enfuvirtide; FI—fusion inhibitor; FTC—emtricitabine; IDV—indinavir; LPV—lopinavir, MRV—maraviroc, NFV—nelfinavir; NNRTI—nonnucleoside reverse transcriptase inhibitor; NRTI—nucleoside reverse transcriptase inhibitor; NVP—nevirapine; PI—protease inhibitor; RTV—ritonavir;

SQV—saquinavir; TDF—tenofovir; ZDV—zidovudine. (*Adapted from* Cohen et al. [22] and Dumond et al. [51•].)

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