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## HIV-1 treatment as prevention: the good, the bad, and the challenges

Kumi Smith<sup>a</sup>, Kimberly A. Powers<sup>a,b</sup>, Angela D.M. Kashuba<sup>c</sup>, and Myron S. Cohen<sup>a,b,d</sup>

<sup>a</sup>Department of Epidemiology, University of North Carolina

<sup>b</sup>Department of Medicine, University of North Carolina

<sup>c</sup>Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina, USA

<sup>d</sup>Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, North Carolina, USA

### Abstract

**Purpose of review**—This work focuses on the use of antiretroviral agents to prevent the sexual transmission of HIV-1.

**Recent findings**—Two randomized clinical trials demonstrated that antiretroviral agents provided before exposure to HIV-1 offer substantial protection, ostensibly directly proportional to the concentration of antiretroviral therapy (ART) in the genital secretions. Intense focus on the use of HIV treatment as prevention has led to publication of modeling exercises, ecological studies, and observational studies, most of which support the potential benefits of ART. However, the logistical requirements for successful use of ART for prevention are considerable.

**Summary**—ART will serve as a cornerstone of combination prevention of HIV-1. Continued research will be essential to measure anticipated benefits and to detect implementation barriers and untoward consequences of such a program, especially increases in primary ART resistance.

### Keywords

antiretroviral therapy; pre-exposure prophylaxis; prevention

### Introduction

Literally days after the activity of the first antiretroviral agent, azidothymidine (AZT), was announced, investigators began to explore the idea of treatment as prevention [1]. The promise of this approach is based on the idea that treatment of HIV index cases with antiretroviral therapy (ART) will reduce their viral loads and render them less infectious to their sexual partners. Several obvious challenges to this approach soon surfaced: would the preventive potential of AZT and other drugs be limited by low concentrations in the genital tract or by the development of drug resistance?

This article offers both a historical perspective and a more in-depth, contemporaneous view of the role of HIV-1 treatment as part of secondary HIV prevention. Current evidence suggests that this strategy holds great promise, but considerable research efforts will be

required to employ the right antiretroviral agents at the right times – and perhaps to just the right people – to ensure maximal benefit both for individual ‘couples’ and at the population level.

## The clinical pharmacology of HIV prevention

Two studies published in 2010 demonstrate the ability of ART to prevent HIV acquisition. In the Center for the AIDS Program of Research in South Africa (CAPRISA) 004 study, women at risk of acquiring HIV were randomly assigned to receive either a tenofovir (TFV) containing vaginal gel or a placebo using coitally dependent dosing [2•]. In the Pre-Exposure Prophylaxis Initiative (iPREX) study, at-risk MSM were randomly assigned to receive either a tablet containing tenofovir disoproxil fumarate (TDF) with emtricitabine (TDF + FTC) or placebo dosed daily [3•]. In both trials, rates of HIV acquisition were lower in those receiving the antiretrovirals. In CAPRISA 004, an inverse relationship was noted between drug exposure in the vaginal lumen and risk of infection. As the CAPRISA 004 study measured drug exposure at the site of infection, and as the half-life of topically applied TFV in the genital tract is more than 2 days, these investigators are conducting subsequent analyses to determine whether critical exposures for protection of mucosal tissue in the genital tract can be identified. As iPREX study only measured plasma drug exposure, it is less likely that concentration surrogates can be estimated for rectal mucosal protection from these data. However, both types of concentration measures may be used as surrogates for adherence behavior, which is critical to the success of prevention interventions [4].

For treatment of the index case, the relative ability of different antiviral agents to penetrate mucosal surfaces at the site of transmission is critical for full suppression of HIV replication [5,6]. Drugs both within and between therapeutic classes of antiretrovirals have different potential to concentrate in male and female genital tract secretions and in rectal tissue (Table 1) [5].

### The female genital tract

The female genital tract exposure to 20 antiretrovirals has been studied in cervicovaginal fluid. Although the female genital tract contains upper and lower compartments, analyzing this fluid (a combination of cervical mucus and vaginal fluid) is a noninvasive approach to understanding genital tract pharmacology. As can be seen in Table 1, there is significant variability in drug exposure both within and between antiretroviral classes. To date, no physicochemical properties accurately predict drug penetration into cervicovaginal fluid. Of the nucleoside/ tide analog reverse transcriptase inhibitors (NRTIs), TDF zidovudine (ZDV), FTC, and lamivudine (3TC) achieve concentrations of approximately 100–400% higher than that of blood plasma. Of the non-NRTIs (NNRTIs), only etravirine (ETR) demonstrates concentrations similar to, or higher than, that of blood plasma. For the protease inhibitors, indinavir (IDV) and darunavir (DRV) penetrate cervicovaginal fluid at exposures of approximately 150–200% higher than that of blood plasma. Finally, both drugs in the latest Food and Drug Administration (FDA)-approved therapeutic classes of antiretrovirals (coreceptor antagonists and integrase inhibitors) concentrate in cervicovaginal fluid: raltegravir (RAL) exposure is approximately 200% higher than that of blood plasma, and maraviroc (MVC) exposure is approximately 400% higher than that of blood plasma. Investigators also measured the protein binding of MVC in cervicovaginal fluid and determined that it had 10-fold less protein binding than in plasma (7.5 versus 75%) [7]. As less protein binding results in more amount of drug available for antiviral activity, this phenomenon must be considered in pharmacokinetic-pharmacodynamic analysis of antiretroviral prevention strategies.

Finally, tissue concentrations of TFV, FTC, and MVC have been measured in the vagina and cervix [7,8]. Exposures for all of these drugs fall between those concentrations measured in blood plasma and those in cervicovaginal fluid. This information creates insight into drug distribution in the genital tract and demonstrates that noninvasive sampling of cervicovaginal fluid may be a reasonable surrogate for these concentrations, which can only be measured through invasive sampling methods.

### The male genital tract

Although the male genital tract contains a number of subcompartments (testes, prostate, and seminal vesicles), drug concentrations are typically measured in seminal plasma as an overall marker of drug exposure. Data generated, to date, reveal that drug binding to plasma proteins dictates drug exposure in semen: lower semen concentrations are found with drugs that have higher protein binding [5].

NRTIs, which are generally less than 50% protein bound, achieve exposures in semen ranging from approximately 100 to 600% of those observed in blood plasma [6]. However, these drugs must be phosphorylated intracellularly in order to be active. After oral administration of TDF, intracellular mononuclear tenofovir diphosphate (TFV-DP) concentrations in the semen are at least 800% higher than that in peripheral blood mononuclear cells [9]. This increased extracellular-intracellular relationship in semen does not hold for the two other nucleosides investigated to date: ZDV and 3TC. Despite four-fold to six-fold higher concentrations in seminal plasma, intracellular mononuclear cell concentrations of ZDV triphosphate (ZDV-TP) in semen are 40% of those in peripheral blood mononuclear cells, and mononuclear cell concentrations of 3TC-TP in semen are approximately 100% of those in peripheral blood mononuclear cells [10]. These data illustrate the importance of quantifying intra-cellular drug exposure to develop accurate pharmacokinetic–pharmacodynamic models for HIV prevention. Exposure of the NNRTIs in semen ranges from undetectable to 40% lower than plasma exposure, whereas the majority of protease inhibitor concentrations are more than 80% lower than the blood plasma concentration (the exception is IDV, which is 60% protein bound). RAL concentrations are approximately 150–600% higher in semen than that in blood plasma [11]. MVC semen exposure was recently determined to be 40% lower than that in blood plasma. However, due to low protein binding in the semen, protein-unbound (active) MVC concentrations were still 28-fold higher than the protein-free  $IC_{90}$  for HIV wild-type virus [8].

### Rectal mucosal tissue

The extent of penetration of drugs into rectal tissues also has implications for HIV transmission. Exposures (area under the concentration time curve from 0 to tau, or  $AUC_{0-\tau}$ ) of MVC are approximately 30 times higher in rectal tissues than in plasma [12], whereas exposures of DRV, ritonavir, and ETR are approximately 3, 13, and 7 times higher, respectively, in rectal tissue than in plasma [13]. Some drugs, such as the nucleoside/tide analogs, require cellular uptake and phosphorylation in order to be active. Intracellular and extracellular concentrations of TFV and FTC have been recently measured in plasma and in rectal tissues 1–14 days after a single dose [14]. TFV and FTC exposures ( $AUC_{\text{day 1-14}}$ ) were 34 and four times higher in rectal tissues, respectively, than in blood plasma. Intracellular concentrations of TFV-DP were detected for 14 days in rectal tissue, whereas FTC triphosphate (FTC-TP) was detected for only 2 days after dosing. These data demonstrate that, as with genital tract exposure, antiretroviral rectal tissue exposure varies between and within drug class. Selecting those antiretrovirals with favorable extracellular and intracellular pharmacokinetics may eliminate viral shedding from mucosal surfaces implicated in HIV transmission.

## Viral shedding

However, even when the blood viral burden is suppressed, HIV can be recovered from the male and female genital tract [15–19]. In an unpublished review of 51 identified studies of HIV shedding in the female genital tract, all 31 studies that measured shedding in individuals receiving ART found that suppression in the female genital tract was incomplete [15]. In the most careful study to date, Cu-Uvin *et al.* [20•] found that among women with completely suppressed plasma and genital tract viral loads at baseline, 54% had detectable genital tract viral loads during at least 1 monthly visit over the 1-year follow-up period. In 32% of these women, the genital tract viral loads were detectable at a visit when viremia was suppressed, suggesting that some women with undetectable blood viral loads may maintain a high risk of onward transmission.

Two reviews of viral shedding in the male genital tract collectively identified 22 studies of HIV-RNA persistence in the semen of men receiving ART, despite undetectable blood plasma viral load [15,16]. The most notable among them, by Sheth *et al.* [21], involved longitudinal assessments of paired blood plasma and seminal plasma samples from HIV-infected men starting first-line ART. Among the 13 men who were on prolonged combination ART (cART) with fully sustained viral suppression in blood plasma, four were found to have detectable viral load in seminal plasma. Moreover, the investigators did not find a significant association between isolated semen HIV-RNA shedding and local level of any drug.

In addition to concerns about continued transmission from individuals with suppressed viremia, a substantial number of new (untreated) patients present with HIV resistance to one or more classes of antiretroviral agents [22•,23–25]. Transmitted drug resistance (primary resistance) must reflect transmission from people who are partially treated, people who stopped their treatment, or resistant variants in the genital tract. Patterns of resistance in the genital tract correspond with observed antiretroviral drug exposure in genital excretions. For example, the presence of protease-resistant viral isolates in seminal plasma and vaginal fluid may be related to the poor penetration of protease inhibitors into the genital tract [5]. As antiretrovirals achieving higher exposure in the genital tract are likely to have a greater ability to reduce viral loads in genital compartments, improved understanding of drug penetration into the genital tract could help guide therapy choices.

Translation of these results into public health considerations is more complex. Viral replication in both the female and male genital tract can be independent of the blood [26•], so different variants can be recovered, regardless of the treatment. The transmission potential of these variants, or variants shed in spite of treatment, is unknown. However, virologic comparisons in HIV transmission pairs suggest considerable selection during the HIV transmission event [27]. Careful studies of transmitted drug resistance suggest that some mutations may render viral variants less fit for transmission. For example, multiple resistant variants are less likely to occur than single variants, and among single resistant variants [28•,29–31].

## Antiretroviral therapy, public health, and observational studies

Two kinds of observational studies have been used to support the ability of ART to reduce transmission of HIV: studies of HIV-serodiscordant couples and ecological studies of community populations.

### Serodiscordant couples studies

Observational studies of seroconcordant and discordant couples provide a critical window into the details of HIV-1 transmission. Eyawo *et al.* [32•] have provided an exhaustive

review of discordant couples studies in South Africa, designed to understand whether the male or female partner is more likely to remain uninfected. The complexity of this team's research helps us identify barriers to valid estimations of transmission probabilities. First, not all partners are equally susceptible to HIV; therefore, some partners can remain HIV-negative regardless of the infectivity of their sexual partner. Second, the infectivity of the index case at the time of sexual contact depends primarily on the viral load, which is generally not known and can be highly variable. Third, using the tools of molecular virology, it has become clear that transmission events in 10–30% of couples likely involve a third partner [33,34], with only a minority of new HIV infections taking place within identifiable stable relationships [35•].

These concerns notwithstanding, observational studies offer the most compelling evidence that ART can be expected to prevent HIV-1 transmission. More than a decade ago, a series of reports linked the blood viral load of untreated index cases with the probability of HIV transmission to their partners [36,37]. Obviously, in these studies the blood viral load must serve as a surrogate for the genital tract HIV-1 concentration. In the most widely cited study, from Rakai, Uganda, index case viral load was the chief predictor of heterosexual HIV transmission risk [36]. The authors found that the mean viral load of infected individuals who transmitted the virus to their partners was significantly higher than that of nontransmitters (90 254 versus 38 029 copies/ml) and that no transmissions occurred in couples in whom the infected partner's viral load was under 1500 copies/ml. Observational studies of HIV-discordant couples in Zambia, Spain, Thailand, and the USA uphold these findings [38–40].

Other observational studies have demonstrated reduced HIV transmission when ART in the index case reduced the patient's viral load (at least theoretically); those with information on ART distribution in the index cases are shown in Table 2 [41,42•,43–48,49•]. Bunnell *et al.* [50] estimated that ART was associated with a 98% reduction in the incidence of HIV in heterosexuals, from 43.5 to 0.8 cases per 1000 person-years, and Donnell *et al.* [43] found that only one of 103 genetically linked HIV transmission events in their cohort of 3381 couples occurred in a couple in which the index case was receiving ART, corresponding to a 92% reduction. A similar study of 424 couples in Spain found that none of the partners of treated HIV-infected individuals seroconverted, whereas five of those whose index case was not treated did [42•].

Several other studies, however, suggest that the protective effects of ART on sexual HIV transmission may not be as consistent or absolute. Out of the 26 seroconversions in nonindex partners of 436 HIV-discordant couples in Italy, for example, six took place in couples in whom the HIV-infected partner was receiving AZT at the time [46]. More recently, Sullivan *et al.* [48] found that ART in the index case of cohorts in Rwanda and Zambia was associated with a 94% reduction in HIV transmission, but noted that ART failed to completely eliminate risk, as four seroconversions took place when the index partner was on ART. Finally, investigators in China recently documented 84 transmission events in a cohort of 1927 discordant couples in which over 70% of index cases were receiving ART. Interestingly, the authors found no statistical difference in the seroconversion rates between those whose HIV-positive partner was receiving ART (66 of 1369 or 4.8%) and those whose spouse was not (18 of 558 or 3.2%,  $P = 0.12$ ). Participants in the study reported extremely low rates of extramarital sex and drug use, and those who reported irregular condom use in the past month were 12.64 times as likely to seroconvert (95% confidence interval 8.18–19.75). Findings from the Chinese cohort suggest that heterosexual transmission of HIV may persist even in populations with high treatment coverage [49•].



## Ecological studies of community-level benefit

Studies of HIV incidence and prevalence in populations or communities with ready access to ART have been used to argue that treatment is prevention. Studies from San Francisco ( $n = 3$  studies) [51•,52,53], Taiwan ( $n = 1$ ) [54], and British Columbia ( $n = 3$ ) [55,56,57•] argue that the introduction of ART reduced the expected number of cases of HIV. These studies are all limited in several ways: it is difficult if not impossible to prove that the treated group has actually had contact with the at-risk population; none of these studies report changes in actual incidence of HIV, but rather use HIV prevalence or new cases of HIV detected (San Francisco and British Columbia) as a surrogate for incidence [58]. Indeed, when a more realistic measure of incidence was measured in San Francisco (using an assay of limited sensitivity) no difference could be ascribed to ART [57•]; and these studies are all subject to the ‘ecologic fallacy,’ as falling prevalence of HIV-1 could reflect any number of factors unrelated to the availability of ART [59•].

Furthermore, other studies have come to less optimistic conclusions about the population-level benefits of ART. For example, three analyses of data from MSM in Amsterdam reported evidence of a renewed spread of rectal gonorrhea and early syphilis since the 1990s [60,61,62•], suggesting that sexual risk compensation may outweigh the benefits of treatment. Another found that recent HIV transmission among MSM in Sydney persisted at rates comparable with the pre-highly active ART era in spite of undetectable viral load among a large portion of treated HIV-infected men [63•]. A number of modeling studies have also suggested that wide availability of ART has not had a profound effect on HIV incidence [64,65,66•]. Although it is possible that new infections are attributable to transmissions during acute/ early infection or increased risk due to untreated sexually transmitted infections (STIs), the mixed results of these studies underscore the speculative nature of the treatment as a prevention strategy.

## Mathematical modeling

Perhaps nothing has caused more confusion than the plethora of mathematical models purporting the benefits (and sometimes cost) of treatment as prevention. Substantial uncertainty surrounds many central assumptions: does ART actually reduce HIV transmission at the level of the couple, and by how much; how durable is the suppression of transmission; how many people can be detected and treated, and for how long; and what role does amplified transmission play, especially during acute/ early HIV infection.

We have recently summarized at least some of the mathematical models [67], and an exhaustive review is beyond the scope of this article. In addition, *Current Opinion in HIV and AIDS* devoted an entire recent issue to modeling, which highlighted advances and discussed trade-offs between model complexity and real-world relevance [68,69]. To some extent, the enthusiasm for treatment as prevention is driven by Utopian modeling: if you assume you can find almost all of the HIV-infected people, and you treat them all for life, and acute/early infection is only modestly important, and treatment reliably and durably suppresses HIV transmission, then the epidemic can be modeled away [70]. And if everyone benefits from earlier treatment, elimination of the epidemic can be achieved at a tolerable cost. However, by using more conservative assumptions and accounting for possible behavioral changes due to perceived noninfectiousness, other models have found that ART scale-up might be ineffective or in some cases even worsen the spread of HIV [71,72,73•, 74•]. Additionally, the cost can become exorbitant. In the most recent model, Long *et al.* [75•] argued that even with optimistic assumptions about infectivity reductions, ART coverage, and behavior change (and even without accounting for heightened infectivity during acute HIV), annual test-and-treat programs are unlikely to result in HIV elimination in the USA without additional measures.

## Clinical trials

We are aware of only a single clinical trial designed to demonstrate that HIV treatment prevents secondary HIV transmission. In the ongoing HPTN052 study of more than 1800 HIV-1-discordant couples in whom the infected person has a high baseline CD4 cell count (>350–550 cells/ $\mu$ l), index cases have been randomized to immediate versus deferred (beginning at CD4 >250) treatment arms, with 5 years of active follow-up. The primary end point is the magnitude and durability of the prevention benefit of ART, based on the measurement of virally linked transmission events. In addition, the study will measure the benefit of earlier ART for the health of the index case. The study is approximately 50% complete. During the course of this trial, WHO changed their treatment guidelines to suggest that all patients be treated at CD4 cell counts of more than 350 cells/ $\mu$ l [76], based on a ‘moderate’ level of evidence deduced from two observational trials [77,78]. After careful consideration of all evidence and the trial design, the multinational DSMB that oversees HPTN052 study concluded that the trial should continue unchanged.

It should be emphasized that this trial is designed to measure HIV prevention under idealized conditions and to provide healthcare providers with the most accurate information to pass on to their patients, especially discordant couples. In 2008, the Swiss AIDS commission issued a statement indicating the belief that patients treated – under circumstances in which viral load suppression has been demonstrated – could safely engage in unprotected intercourse [79]. Following the controversial statement, investigators in Switzerland, some of whom were authors of the original Swiss statement, found that unprotected sex among HIV-1-infected patients on ART may have in fact increased in the wake of the announcement [80]. The Swiss cohort reminds us that perceptions of infectiousness among patients are highly impressionable and that the use of ART for prevention must address efficacy at both the individual and population level [81]. The results of HPTN052 study will likely provide more precise information to people with HIV-1 infection and their sexual partners.

## Test and treat

Given that treatment reduces transmission at some level, tremendous interest in a ‘test and treat’ strategy has emerged and has been embraced by at least some professional organizations. This strategy requires widespread, regular HIV testing; linkage to care; and immediate treatment (irrespective of CD4 cell counts). Because none of these strategies have actually been implemented – let alone proven of benefit – a series of feasibility trials have been planned or launched, as summarized in Table 3.

An alternative approach would lead to targeting of HIV-infected patients with the greatest risk of HIV transmission. Investigators in Botswana have modeled the benefit of a strategy designed to find and treat patients with the highest viral load [82]. It has long been known that patients with clade C HIV infection can sustain very high viral loads in blood and genital secretions [83]. In addition, clade C variants retain the R5 phenotype even in advanced HIV disease, perhaps amplifying transmission [84]. In more recent work, Novitsky *et al.* [82] demonstrated the ability to find and follow patients with high plasma HIV-1-RNA levels (> 50 000 copies/ml). Among 4348 drug-naive, HIV-positive individuals participating in clinical studies in Botswana, a greater proportion of those in cART-initiating cohorts had high viral loads than did those in general population cohorts, and the median baseline plasma HIV-1-RNA level was higher in the cART-initiating cohorts by approximately 1 log<sub>10</sub>. Additionally, in a longitudinal analysis of 42 seroconverters, the median duration of high viral loads was 350 days following seroconversion, with 33% of participants maintaining high viral loads for at least 180 days. On the basis of these

observations, and assuming that individuals who maintain high plasma viral loads for extended periods contribute disproportionately to onward transmission, the authors suggested that a modified test-and-treat approach with targeted ART initiation could have the potential to mitigate the HIV epidemic in some settings.

## The problem of acute and early HIV infection

The acquisition of HIV is associated with a complex illness designated as acute HIV-1. During this phase, viral replication is unrestrained by host response, and irreparable immune damage occurs. Several lines of evidence demonstrate that people with early HIV infection are more contagious than those with chronic HIV infection. The contribution of early infection to the spread of HIV has been extensively modeled and reviewed in detail [85]. Results have varied widely, reflecting the differences in assumptions used, data available, and populations studied. For example, an early model of HIV transmission among MSM in the USA that did not confine transmission to steady partnerships estimated that up to 50% of incident infections were due to contact with an index case with early HIV [86]. By contrast, a model of HIV transmission in Uganda that assumed sexual contact occurred only within monogamous heterosexual pairs estimated that 9% of transmission events were attributable to early index cases [87]. In a recent study from Malawi, Powers *et al.* [88] used a model that allowed transmission both within and outside of steady pairs to estimate that 38% of all incident cases of HIV can be ascribed to exposure to a person with early HIV infection. Epidemiologic evidence further supports the importance of early/acute HIV in onward transmission. For example, Hightow *et al.* [89] reported that 12 of 84 patients with newly diagnosed HIV infection in North Carolina had acute HIV infection, suggesting the importance of these individuals to the sexual network the authors described.

Obviously, the benefits of the ‘test and treat’ strategy will be reduced by the extent that early HIV contributes, unless such individuals can be detected and secondary transmission reduced. However, no strategies to prevent transmission of HIV from those with acute/early HIV have been developed. In a recent report, Pettifor *et al.* [90] noted the difficulty of behavior change in such individuals. The use of ART during acute/early HIV infection – either for personal or public health benefit – is controversial [91].

## Conclusion

It has become clear that HIV prevention requires a combined prevention effort, and the use of antiretroviral agents will serve as a cornerstone of this effort. The demonstration that ART can be used as pre-exposure prophylaxis is not surprising and is consistent with the ability of these drugs to block replication of HIV-1. We can also expect treated patients to be less contagious, as long as they remain suppressed. However, the replication of HIV-1 in the genital compartment in spite of viral suppression in blood motivates the ongoing research designed to understand the magnitude and durability of HIV treatment as prevention. Finally, challenges remain in defining the optimum strategy for using treatment as prevention, finding the most contagious people, and providing both personal and public health care. The extent to which we can meet these challenges will determine the success of the ‘test and treat’ strategy.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest



•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 338).

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### Key points

- Antiretroviral therapy (ART) will serve as a cornerstone of combination prevention of HIV-1.
- Critical areas of scientific research must improve our understanding of drug penetration into the genital tract and the risk of transmitted drug resistance.
- Implementation challenges remain in finding the most contagious people and treating them optimally during the early disease stages.
- Observational data, mathematical models, and ecological studies provide seemingly compelling evidence of ART's preventive effects, but are subject to many limitations.

Table 1

Exposures in relevant mucosal fluids and tissues relative to exposure in blood plasma

Drug	Female genital tract		Male genital tract		Rectal tissue
	CVF	Tissue	Seminal plasma	Intracellular Tissue	
NRTIs					
Tenofovir	1.7	4.0 <sup>a,0,6,b,c</sup>	4.4 (5.1) <sup>d</sup>	9.4 (17.5) <sup>d</sup>	339
Abacavir	0.7	0.4	1.5		
Lamivudine	16	4.0	6.0	1.0	
Zidovudine	11	1.9	2.0	0.4	
Didanosine	2.1	1.0			
Emtricitabine	6.2	42 <sup>a,c,7,b,c</sup>	6.0	ND	4.49
Stavudine	0.04	0.04	0.02		
PIs					
Lopinavir	0.04	0.3	0.05		
Atazanavir	0.17	0.3	0.1		
Ritonavir	1.1	0.2	0.03		
Indinavir		1.3 <sup>e</sup>	1		
Darunavir			0.12		
Amprenavir		0.5	0.2		
Nelfinavir			0.05		
Saquinavir		ND	0.05		
NNRTIs					
Efavirenz	0.003	0.006	0.03		
Nevirapine		0.8	0.7		
Delavirdine		0.2	0.16		
Entry inhibitors					
Maraviroc	1.9 (2.7) <sup>d,f</sup>	(1.9) <sup>f</sup>	0.6 <sup>f</sup>		9 (28) <sup>d,f</sup>
Integrase inhibitors					
Raltegravir	1.0 <sup>e</sup>		3.2		

Comparisons are between tissue/BP-paired samples after a single dose unless otherwise noted. AUC represents the area under the concentration-time curve. BP, blood plasma; CVF, cervicovaginal I fluid; ND, no data; NNRTI, nonnucleoside/tide reverse transcriptase inhibitor; NRTI, nucleoside/tide analog reverse transcriptase inhibitor; PI, protease inhibitor. Reproduced with permission from [5].

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<sup>a</sup> Cervical tissue.

<sup>b</sup> Vaginal tissue.

<sup>c</sup> AUC tissues0–14days:AUC BP0–14days.

<sup>d</sup> Dose steady-state ratio.

<sup>e</sup> With boost ritonavir.

<sup>f</sup> AUC tissue:AUC BP.

**Table 2**  
Studies of serodiscordant couples with some antiretroviral therapy coverage and documented HIV transmissions

Author	Study design	Number of couples	Study population	ART coverage (%)	Transmissions without ART (of total untreated index cases)	Transmissions with ART (of total treated index cases)	Conclusion
Castilla <i>et al.</i> [41]	Retrospective cohort	393	HIV clinic patients and their seronegative partners	45.5	27/313	2/80	Combined ART applied according to current guidelines has a great potential for preventing HIV transmission to sexual partners
Del Romero <i>et al.</i> [42]	Prospective cohort	424	Couples recruited through HIV-positive patients at an HIV/STD clinic	23.8	5/341	0/191 <sup>a</sup>	Heterosexual infectivity of HIV-1 in individuals taking effective ART is low
Donnell <i>et al.</i> [43]	Prospective cohort	3381	HIV-positive and HSV-positive individuals and their HIV-negative partners from the Partners in Prevention HSV/HIV Transmission Study	10.3	102/3032 <sup>b</sup>	1/349 <sup>b</sup>	Provision of ART to HIV-1-infected patients could be an effective strategy to achieve population-level reductions in HIV-1 transmission
Hernando <i>et al.</i> [44]	Prospective cohort	339	HIV-positive patients and their partners attending a HIV/STD clinic	33.0	5/227	0/112	Couples-based safe sex counseling and ART can reduce but not eliminate sexual HIV-1 transmission
Melo <i>et al.</i> [45]	Prospective cohort	93	HIV clinic patients and their seronegative partners	44.0	6/52	0/41	Transmitters showed significantly higher median viral loads, suggesting that heterosexual transmission of HIV is more a function of viral load than sex of index case. Antiretroviral use may play a role in the prevention of HIV-1 heterosexual transmission
Musico <i>et al.</i> [46]	Retrospective cohort	436	HIV-positive clinic and HIV surveillance center clients with their seronegative partners	15.0	21/372	6/64 <sup>a</sup>	ART in HIV-1-infected men reduces, but does not eliminate heterosexual transmission of infection
Reynolds <i>et al.</i> [47]	Prospective cohort	250	Serodiscordant couples offered free ART if eligible	17.6	42/218	0/32	HIV-1 transmission may be reduced among HIV-1-discordant couples after initiation of ART due to reductions in viral load and increased consistent condom use
Sullivan <i>et al.</i> [48]	Prospective cohort	2993	Serodiscordant couples initiated on ART if eligible	25% initiated during course of study	264/2125 <sup>b</sup>	4/808 <sup>b</sup>	ART was associated with a 94% reduction in transmission; ART initiation is a critical component of a package of biomedical and behavioral prevention services
Wang <i>et al.</i> [49]	Prospective cohort	1927	Former plasma donors and their seronegative spouses	71.0	66/1303	18/540	Transition events occurred with equal frequency in couples regardless of whether the partner was provided ART

ART, antiretroviral therapy; HSV, herpes simplex virus; STD, sexually transmitted disease.



<sup>a</sup> Mono/dual therapy and combined therapy.

<sup>b</sup> Genetically linked transmissions.

**Table 3**

## Planned and ongoing 'test and treat' feasibility studies

Project title	Principal investigator(s)	Source of funding	Study site (features)	Progress
Population effects of Antiretroviral Therapy (Pop-ART)	Sarah Fidler, Department of Medicine, Imperial College	Medical Research Council, UK	Africa (scale-up of ART for all HIV-positive adults and expansion of VCT and ART access to reduce HIV transmission)	Funding pending
Methods for Prevention Package Program (MP3): 'PreventionRx'	Connie Celum, Department of Global Health, International Clinical Research Center, University of Washington	National Institute of Allergy and Infectious Disease, USA	Uganda (efficacy trial of a multicomponent HIV prevention package in behaviorally at-risk individuals and serodiscordant couples)	Field activities to be initiated in mid-2010
Methods for Prevention Package Program (MP3): 'Enhanced Prevention in Couples' (EPIC)	Wafaa El-Sadr, Center for Infectious Disease Epidemiologic Research at Mailman School of Public Health	National Institute of Allergy and Infectious Disease, USA	Lesotho (feasibility study of a prevention package including early ART initiation, male circumcision, and behavioral counseling)	Study ongoing
Botswana–Harvard Partnership Study Series	Max Essex, Harvard School of Public Health AIDS Initiative		Botswana (targeted treatment program for HIV-infected individuals at greatest risk of transmitting HIV)	Study ongoing
Makerere University–University of California San Francisco Research Collaboration	Diane Havler, HIV/AIDS Division and Positive Health Program at San Francisco General Hospital		East Africa (project to identify sustainable methods to treat HIV earlier to benefit overall health, education, and economics in East Africa)	Conceptual stages
HIV Prevention Trials Network 065: Test and Link to Care-Plus (TLC-Plus)	Wafaa El-Sadr, Center for Infectious Disease Epidemiologic Research at Mailman School of Public Health	National Institute of Allergy and Infectious Disease, USA	USA (a study to evaluate feasibility of an enhanced test and link to care along with treatment approach for HIV prevention)	Protocol pending
Treatment as Prevention (TasP)	Marie-Louise Newell, Africa Centre for Health and Population Studies, University of KwaZulu-Natal; François Dabis, University of Bordeaux, France	French Agency for Research on HIV/AIDS and Viral Hepatitis, France	South Africa (cluster randomized trial of early versus delayed ART initiation for HIV-infected individuals)	Initial phase to begin in 2011

Minutes from a self-organized meeting of all principal investigators (or a knowledgeable colleague) at the 18th Annual Conference on Retroviruses and Opportunistic Infections; 2011; Boston, Massachusetts. Courtesy of Sten Vermund, Vanderbilt University School of Medicine. ART, antiretroviral therapy; VCT, voluntary testing and counseling.