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Pre-exposure prophylaxis for HIV prevention: how to predict success

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Use of antiretroviral drugs to prevent sexual transmission of HIV-1 has been a critical priority since their development. In the past 2 years results from seven important prevention trials have been reported (table). One of the trials, HPTN 052,[1] showed nearly complete prevention of HIV transmission when viraemia was suppressed. The other studies focused on antiretroviral agents for pre-exposure prophylaxis: two used 1% tenofovir gel (CAPRISA 004[2] and VOICE[3]), four used oral tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in combination (iPrEX,[4] TDF2,[5] Partners in Prevention [PIP],[6] and Fem-PrEP[7]), and two used oral TDF alone (VOICE[3] and PIP[6]). Somewhat confusingly, the findings of these studies have led to reports both of successful prevention of HIV infection (CAPRISA 004,[2] iPrEx,[4] TDF2,[5] and PIP[6]) and of futility (VOICE[3] and Fem-PrEP[7]).

Clearly, results on pre-exposure prophylaxis will be used to inform policy and to plan future research, and so the trials' findings need to be considered carefully. There were key differences in the pre-exposure prophylaxis trials (table): each included different populations with distinct routes of HIV transmission. For example, iPrEx[4] was the first success for oral pre-exposure prophylaxis and focused on men who have sex with men. It is reasonable to assume that anal intercourse was the key route of transmission in the iPrEx trial,[4] and was less frequently the source of HIV infection in the heterosexual women and men in the Fem-PrEP,[7] VOICE,[3] TDF2,[5] and PIP[6] studies. HIV acquisition is more efficient after anal intercourse,[8] and more HIV variants are acquired during anal intercourse than cervicovaginal exposure.[9]

We have reported substantial differences in anti-retroviral drug concentrations in mucosal tissues.[10–12] After oral administration of co-formulated TDF and FTC, there were 100-fold higher concentrations of tenofovir in rectal tissue compared with cervicovaginal tissue.[12] Intracellularly phosphorylated tenofovir (TFV-DP) and emtricitabine (FTC-TP) are required to inhibit HIV replication.[12] 100-fold higher concentrations of TFV-DP were detected in the rectum as compared with cervix and vagina.[12] Conversely, FTC-TP concentrations were 10–15 fold higher in vaginal and cervical tissue than in rectal tissue. Although we do not know the concentrations of TFV-DP and FTC-TP required to prevent HIV infection, the differences in tissue concentrations are substantial and suggest implications for HIV prevention. In the VOICE trial,[3] the lack of protection with oral TDF could reflect low tissue concentrations of the drug. How, then, can we explain the protection provided by TDF in PIP[6]? It seems possible that HIV transmission in a discordant couple relationship might be

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prevented differently, or more readily. It is also possible, indeed likely, that adherence in a discordant relationship is better, resulting in a critical (currently unknown) tissue concentration being achieved. The protection from HIV observed with the TDF and FTC combination in TDF2[5] and PIP[6] suggests an important role for higher FTC concentrations, perhaps in combination with the lower concentrations of tenofovir, in the female genital tract. The differences in benefit of 1% tenofovir gel in CAPRISA 004[2] and VOICE[3] demand further exploration; the studies used different dosage schedules, and women at different sites might differ in ways that affect study outcomes (table).

Adherence, however, will still determine the value of antiretroviral agents both in clinical trials and in clinical practice. In HPTN 052[1] HIV viraemia was prospectively monitored in infected trial participants to ensure adherence, which allowed determination of the antiretrovirals' ability to suppress transmission under ideal conditions. To date, the only prospective measurement of adherence in pre-exposure prophylaxis trials has been by self-report or pill counts, which might overestimate adherence.[13] These values have then been compared to potential efficacy with post-hoc measurement of blood concentrations in a limited number of samples using a case-control design. In the iPrEx trial,[4] the investigators used combined data to argue that pre-exposure prophylaxis was perhaps more than 90% protective in participants who took the treatment reliably. In CAPRISA 004,[2] the effectiveness of protection was 52% with more than 80% adherence as measured retrospectively by evaluation of used gel applicators. But such retrospective analyses cannot be used to confirm the intervention's success or failure. Less adherence to daily use of 1% tenofovir gel in VOICE[3] could have compromised benefit relative to the coitally-driven use of the gel in CAPRISA 004.[2] Paradoxically, daily use may confer a degree of difficulty that reduces adherence.

We believe that, before future pre-exposure prophylaxis studies are undertaken, knowledge of biological plausibility must be secure. Evidence of strong and durable tissue concentrations of active agents should be a condition of such studies taking place. Powerful antiviral agents limited in their tissue penetration, intracellular metabolism, or tissue half-life are not appropriate for pre-exposure prophylaxis. Moreover, adherence must be measured prospectively in future trials.[14,15] Under these conditions trial participants who do not adhere to treatment can be counselled or the study analysis designed to incorporate these most rigorous measures of adherence. To predict success in clinical practice reliably, both the drug concentrations needed for protective efficacy and the best way to assess adherence in clinical trials must first be defined. Effectiveness trials that depend on adherence and many other factors—the real world—should await proof that antiretroviral agents work as anticipated.

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Table

Antiretroviral-based HIV prevention studies

	Study population	Location	Route of HIV transmission	Intervention	Outcome	Comments
CAPRISA 004[2]	889 heterosexual women at high risk of infection, aged 18–40 years	South Africa	Vaginal	Coitally-dependent TFV 1% gel (two doses up to 12 h precoitus and postcoitus)	39% protection; 54% protection calculated in participants using >80% of doses	High TFV-DP concentration in vaginal and cervical tissue critical for efficacy
iPrEX[4]	2499 MSM at high risk of infection; approximately 70% of mixed ethnicity; mean age in TDF/FTC group 27·5 years	North and South America, Thailand, South Africa	Rectal/penile	Daily oral TDF/FTC	44% protection; 92% protection calculated for subjects with detectable drug concentrations	High TFV-DP concentrations in rectal tissue might be critical for efficacy
TDF2[5]	1200 sexually active adults; 55% male, 45% female; 94% unmarried; approximately 90% age 21–29 years	Botswana	Vaginal/penile	Daily oral TDF/FTC	63% protection	>30% did not complete study; cannot draw definitive conclusions for women and men separately
PIP[6]	4747 heterosexual serodiscordant couples; 38% negative-female, 68% negative-male partner; 98% married; median age 33 years	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Vaginal	Daily oral TDF or TDF/FTC	62% protection with TDF alone; 73% protection with TDF/FTC	Discordant couples may be a distinct, unique population
FEM-PrEP[7]	1951 heterosexual women at high risk of infection aged 18–35 years	Kenya, South Africa, Tanzania	Vaginal	Daily oral TDF/FTC	Trial discontinued for futility in April, 2011	Adherence assessment with monthly clinical samples to measure drug concentration is pending
VOICE (MTN-003)[3]	5029 heterosexual women aged 18–45 years in high-prevalence areas	Uganda, South Africa, Zimbabwe	Vaginal	Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel	Oral TDF group discontinued for futility in September, 2011; TFV 1% gel and placebo gel groups discontinued for futility in November, 2011; oral TDF/FTC group continues	For TDF, the tissue concentration may be critical; for TFV 1% gel, adherence analysis is pending
HPTN 052[1]	1763 heterosexual serodiscordant couples; 50% negative-female, 50% negative-male partner; 94% married; 61% aged 26–40 years	Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand	Vaginal/penile	Immediate or delayed ART in HIV-infected partner	96% protection	Suppression of viraemia on therapy assured by routine monitoring

MSM=men who have sex with men. TDF=tenofovir disoproxil fumarate. TFV=tenofovir. TFV-DP=tenofovir diphosphate. FTC=emtricitabine. ART=antiretroviral therapy.