Oral Antiretroviral Drugs as Public Health Tools for HIV Prevention: Global Implications for Adherence, Drug Resistance, and the Success of HIV Treatment Programs

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Recent data from studies on treatment as prevention (TasP) and preexposure prophylaxis (PrEP) show that antiretroviral drugs can be used in prevention, as well as in treatment. The movement from first-generation antiretroviral therapy (ART) coformulations based on thymidine analogues to second-generation ART coformulations based on tenofovir may coincide with future prevention strategies that also use tenofovir/emtricitabine, raising concerns regarding drug resistance. In published studies, failure of prophylaxis was associated with poor adherence and low plasma drug levels. Although rates of drug resistance in cases of failed prevention was low, regular human immunodeficiency virus (HIV) testing was undertaken in these clinical trials. Although legitimate concerns exist about ART adherence and drug resistance associated with PrEP and TasP in real-world settings, efforts to curb the continuing HIV epidemic through use of these novel prevention strategies should move forward because the development and approval of newer drugs reserved for prevention might take many more years. Efforts must be made to monitor ART adherence and to intervene through counseling and other means in order to optimize adherence and retention in care, whenever necessary. Finally, further research involving the generalized epidemic is needed to determine when suboptimal drug use may occur and when regular testing and monitoring of the long-term consequences of ART use may not be routine.

Keywords. antiretroviral drug resistance; adherence; PrEP; TasP.

The continued success of antiretroviral therapy (ART) scale-up in resource-limited settings is tempered by continuing high rates of new infections in developing countries, especially in sub-Saharan Africa [1]. Indeed, rates of new human immunodeficiency virus (HIV) infections continue to increase in multiple countries, which calls for more-aggressive and more-comprehensive HIV prevention programs to prevent new infections and slow the progression of the pandemic [2]. In the absence of an effective vaccine, a number of interventions have been tested in randomized controlled trials. A vaginal microbicide gel containing tenofovir (TDF)/emtricitabine (FTC) was found to afford about 50% protection among individuals with high adherence [3]. Male circumcision also offers around 50% protection [4] and is undergoing scale-up in a number of countries. Data from studies using oral ART interventions such as treatment as prevention (TasP) [5] and oral preexposure prophylaxis (PrEP) [6–8] have been reported and

indicate that antiretroviral drugs (ARVs) can be used in prevention, as well as in treatment.

In addition, prevention of mother-to-child transmission of HIV has arguably been the greatest success in regard to use of ARVs, since, under ideal conditions, provision of ART and replacement feeding and/or continued ART with breast-feeding can, in both developed and developing countries, reduce vertical HIV transmission from an estimated 30%–35% with no intervention to 1%–2% with intervention [9, 10]. This progress notwithstanding, a high prevalence of nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance has been reported following failure of single-dose nevirapine as prophylaxis for mother-to-child transmission of HIV. In addition, recent data have shown that adherence to prevention regimens such as PrEP and TasP is essential if we are to ensure treatment success and that the promotion of adherence is essential to optimize the benefits of such approaches and decrease the likelihood of drug resistance [11, 12]. In light of these and other data on the worrying impact of potential transmitted drug resistance on future ART [13–15], a workshop that included a panel of international experts in HIV drug resistance was convened by the Collaborative HIV and Drug Resistance Network and the World Health Organization in Geneva, Switzerland, on 10 and 11 October 2012 to discuss the implications of oral ART prevention strategies in regard to ART adherence and the selection and transmission of drug-resistant variants in resource-limited settings.

TasP

This approach is being explored as a prevention tool following the HIV Prevention Trials Network (HPTN) 052 study, which showed in an analysis of serodiscordant couples that HIV-infected individuals who adhered to effective ART regimens were 96% less likely to transmit the virus to an uninfected sex partner [5]. Earlier data from Canada had shown that increased ART coverage was associated with declining numbers of new HIV infections [16]. Furthermore, the positive effect of ART coverage has been demonstrated in regard to rates of new HIV infections in an HIV-hyperendemic, rural population in South Africa [17]. Modeling studies suggest that expansion of ART coverage in the context of TasP could also be effective in reducing transmission on a population level [18–20], although the estimated cost-effectiveness of this strategy is controversial [21, 22]. Community-based studies exploring TasP are already underway in the United States (ie, the HPTN 065 study (Test, Link to Care, Plus Treat) in New York City and Washington, DC), as well as in high-incidence settings in developing countries (eg, the ANRS pilot study in South Africa, the combination prevention trials study [a CDC-sponsored Harvard Study] in Botswana, the Pop-ART HPTN 071 study in South Africa and Zambia, and a USAID-sponsored Johns Hopkins

University study in Tanzania). There is substantial momentum behind these strategies. Of note, in the HPTN 052 study, excellent ART adherence (>95%), confirmed by pill count, was documented in 79% of patients in the early therapy group and in 74% of those in the delayed-therapy group, and virologic suppression was high, reflecting the success of approaches such as intensive one-on-one patient counseling to achieve high adherence and minimize the likelihood of acquired drug resistance.

A concern, however, is that adherence to ART under real-world conditions, regardless of setting, may be far below that attained in the HPTN 052 study. A meta-analysis involving 28 689 patients found that only 55% (95% confidence interval [CI], 48%–61%) of HIV-infected patients in North America, compared with 77% (95% CI, 67%–86%) in Africa, had documented optimal ART adherence (>80%) [23]. In addition, recent data show that only 328 000 (28%) of an estimated 1.1 million HIV-infected individuals in the United States have managed to attain treatment success, defined as suppression of their HIV RNA load to <50 copies/mL [24]. The reasons for such poor results include lack of awareness of HIV positivity, and therefore lack of treatment initiation, among a substantial proportion of HIV-infected individuals; loss to follow-up among many individuals who did receive treatment; and nonadherence to therapy. These realities call into question the longer-term public health benefits of large-scale TasP strategies and highlight the urgent need to address multiple gaps in HIV care in order to optimize TasP outcomes [25].

In some countries, programs to prevent mother-to-child transmission are moving toward universal use of life-long triple ART (known as Option B +) that, in addition to more-standard programs, will also have the potential to prevent sexual transmission. Women receiving ART will need, when necessary, assistance with postpartum adherence and retention in care. Indeed, a meta-analysis of 51 studies of ART adherence among pregnant and postpartum women in high-, mid- and low-resource countries showed that only 73.5% (95% CI, 69%–78%) had adequate (ie, ≥80%) adherence to their ART regimen. Furthermore, the point estimate of the proportion of women with >80% ART adherence was 75.7% (95% CI, 72%–80%) during the antepartum period and 50.3% (95% CI, 33%–73%) during the postpartum period (P = .009) [12]. In a South African study, pregnant women were substantially more likely to be lost to follow-up than nonpregnant women during both pre-ART care and after ART initiation [26]. Therefore, there is a need for close monitoring and support of adherence to prevent suboptimal drug use and the potential development of drug resistance for both mother and infant [27, 28].

Finally, changes are occurring in the nucleoside reverse-transcriptase inhibitor (NRTI) composition of first-line regimens in some resource-limited settings, with TDF replacing thymidine analogues (zidovudine [ZDV] and stavudine [d4T]), particularly in southern and eastern Africa. Data suggest that

TDF (as well as d4T), when used with an NNRTI in first-line therapy, is associated with a high prevalence of the K65R mutation in cases of virological failure where subtype C virus infections are prevalent [14, 29–31], leading to potential high-level cross-resistance to all currently approved NRTIs except ZDV. Subtype C viruses seem more likely to develop the K65R mutation, based on sequence polymorphisms [32]. Table 1 summarizes HIV drug resistance data from PrEP studies reporting drug resistance. Of note, TDF is likely to become the most widely used NRTI in first-line therapy, as well as in second-line therapy for patients in whom a first-line thymidine analogue-based regimen has failed. Depending on rates of virological failure associated with TDF-containing regimens, the prevalence of the K65R mutation may increase, with a resulting increased risk of PrEP failure, if TasP programs are widely implemented. Importantly, however, there are no reliable data on the risk of virologic failure of NNRTI-based first-line therapy in areas where the K65R mutation exists. The high level of resistance conferred by K65R and the low genetic barrier of FTC/lamivudine (3TC) would result in functional monotherapy with the NNRTI, likely resulting in high risk of virologic failure.

ORAL ARVs FOR USE AS PrEP

Multiple clinical trials of TDF/FTC or TDF alone as PrEP have been undertaken in resource-limited settings. TDF alone was assessed in 2 studies: VOICE [33] and Partners PrEP [7] (Table 1). The former study was unable to show a statistical difference in efficacy of TDF as compared to placebo, and therefore the TDF-alone arm was halted. In contrast, TDF alone was almost as efficacious as TDF/FTC in the latter study. TDF/FTC was effective in TDF2 [8] and Partners PrEP [7] but not in FEM-PrEP [34] (Table 1). In these studies, failure of prophylaxis was associated with poor adherence and low plasma drug levels. There was a clear dose-response relationship between evidence of PrEP use and efficacy, as documented by blood drug levels. Indeed, when both TDF and FTC were detected in blood, protection was very high in the aforementioned studies. Low adherence levels were observed in the iPrEx and FEM-PrEP trials. However, evidence of benefit was found in the former, while the latter was stopped for futility. In the CAPRISA 004 study that evaluated TDF gel as a vaginal microbicide in at-risk women, high-level protection was also observed in participants who were demonstrated to have been adherent on the basis of high concentrations of the active form of TDF in cells harvested from the vaginal cavity [3].

Importantly, perceptions of risk seem to have played an important role as a potent driver of adherence in the PrEP studies performed to date. The highest levels of adherence (97% of doses taken; 82% with drugs detectable) was achieved in the Partners PrEP study, with higher efficacy (75% for TDF/FTC and 67% for TDF alone) with intensive ART adherence monitoring, followed by intensification of counseling for participants with <80% adherence [35]. Trust and commitment within the stable partnership involving a known HIV-infected partner, ongoing exposure, and a decision to maintain the relationship were all associated with high adherence [36]. In contrast, in FEM-PrEP, which enrolled young women, close to 70% of subjects perceived themselves to be at little or no risk for HIV infection, and low-level adherence overall was documented. In iPrEx, men who practiced unprotected receptive anal intercourse had higher PrEP adherence than other men and benefitted from higher levels of HIV protection (58%) if they took TDF/FTC. Men who were not having sex were least likely to take PrEP. Of note, there was no evidence of risk compensation in these PrEP clinical trials. Therefore, understanding the interface of risk perception and HIV prevention will be key for any PrEP strategy moving forward. It is also critical to consider temporal patterns of adherence and characteristics of sexual exposure. For example, isolated lapses and exposures of variable risk will influence the likelihood of transmission. In contrast, low-level adherence confers little risk in the absence of sexual exposure. Of note, while poor adherence to PrEP had little prevention benefit, there is no evidence in results of published PrEP trials that it led to the development of resistance. Indeed, more likely causes of drug resistance in these studies may have been exposure to drug-resistant HIV variants in sexual partners or the selection of resistant viruses in newly infected individuals who may have had undetectable HIV infection at the time of enrollment into the study. Finally, in addition to nonadherence, variable drug concentrations at the exposure site (eg, vaginal or rectal mucosa), the integrity of the vaginal epithelium, and the amount of virus in any individual exposure may all be factors governing the likelihood of infection and help to explain divergent results obtained in some PrEP trial results to date [37].

In PrEP trials, routine HIV testing was also undertaken. and prophylaxis was promptly stopped when an incident infection could be shown to have occurred. A major concern is that routine testing will not be available in real-world settings and that selection of drug-resistant variants may occur if failure of prophylaxis occurs unnoticed, since HIV infections will have been exposed to suboptimal dual therapy. Another concern, of course, is that some people may become exposed to transmitted drug-resistant variants of HIV that may not be susceptible to the drugs used in PrEP or other prophylaxis strategies. So far, it is encouraging that there have not yet been any reported cases of transmitted drug resistance involving the K65R multi-NRTI resistance mutation. However, this may change as a result of ART scale-up.

CONCLUSIONS AND RECOMMENDATIONS

While real and legitimate concerns exist about ART adherence and drug resistance in the context of PrEP and TasP in real-world settings, efforts aimed at HIV prevention through use of

Table 1. Drug Resistance in Preexposure Prophylaxis (PrEP) Studies to Date That Have Used Regimens Containing Tenofovir (TDF)/Emtricitabine (FTC)

Study, Location	Location(s)	Subjects, No.	Study Population	Overall Reduction in Risk[a]	Infections in TDF/FTC Group[b]	Resistance in Patients Randomized to TDF/FTC Group[b]
Partners PrEP [7]	Kenya, Uganda	4747	Men and women in serodiscordant relationships	75 (55–87)	13/1579	1/8 (17%) with M184V[c]
FEM-PrEP [34]	Tanzania, Kenya, South Africa	2120	High-risk women	No significant difference	33/1024	4/33 (12.1) all M184V/I
CDC TDF2 (unpublished data)	Botswana	1200	Heterosexual men and women	62 (22–83)	9/601	1/9 (11.1) with K65R and M184V[d]
iPrEx [6]	US, Ecuador, Peru, Brazil, Thailand, South Africa	2499	High-risk MSM	44 (15–63)	36/1251	None
VOICE (unpublished data)	Uganda, Zimbabwe, South Africa	5029	Sexually active women	Ongoing	Ongoing	Ongoing
ADAPT-HPTN 067 (unpublished data)	South Africa, Thailand (intermittent PrEP)	360	MSM and high-risk women	Ongoing	Ongoing	Ongoing
HPTN 069 (unpublished data)	US	400	MSM	Ongoing	Ongoing	Ongoing
ANRS IPERGAY	Canada, France (initial phase); other European countries (continuation phase)	1900	MSM	Ongoing[e]	Ongoing	Ongoing

Abbreviations: CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; IPERGAY, Intervention Preventive de l'Exposition aux Risques avec et pour les Gays; MSM, men who have sex with men.

[a] Data are % reduction (95% confidence interval), compared with placebo.

[b] Data are proportion or proportion (%) of subjects.

[c] This individual was found to be HIV infected before receiving TDF/FTC.

[d] This individual had acute HIV infection at the time of enrollment.

[e] Results expected in quarter 3 of 2016.

these novel prevention strategies should go forward. Efforts must be made to monitor ART adherence and to intervene through counseling and other means in order to optimize adherence and retention in care whenever necessary.

The movement from first-generation NRTI treatment combinations, such as ZDV/3TC or d4T/3TC, to second-generation coformulations, such as TDF/FTC, may coincide with future prevention strategies that also use TDF/FTC. The use of the same drug(s) or drug classes for both PrEP and first-line treatment should be avoided because of concerns regarding selection and transmission of drug resistance. Despite these concerns, various mathematical modeling efforts suggest that the benefits of PrEP will far outweigh any disadvantages in regard to new HIV transmissions, and further studies will assist in the prediction of the impact of such interventions on the transmission of drug resistance. It is encouraging that very few cases of emergence of either the M184V mutation or the K65R mutation, associated with resistance against FTC/3TC and TDF/d4T/abacavir, respectively, have been reported until now among individuals becoming newly infected in any of the PrEP trials that have been performed. Moreover, more patients overall possessed virus with M184V than K65R mutations, reflecting the higher barrier to K65R resistance that is associated with TDF [32].

Of note, the ongoing phase III ANRS-funded IPERGAY (Intervention Preventive de l'Exposition aux Risques avec et pour les Gays) clinical trial is evaluating whether TDF/FTC can prevent HIV transmission if received on an intermittent/demand basis (prior to anticipated sexual relations) as PrEP. This strategy allows individual-based risk management according to lifestyle, and it is expected to have better adherence, tolerance, and costs. Finally, it also may limit overall levels of drug exposure and drug resistance (Table 1).

Very little is known about the potential long-term consequences of TasP. Current and future studies should fill this knowledge gap. The urgent need to reduce incident infections means that reservations regarding transmission of drug resistance should not limit the use of TDF/FTC as PrEP or as part of TasP, given the accumulation of clinical data on the efficacy and safety of these drugs. Furthermore, there must be recognition that the requirements for approval of ARVs by regulatory agencies are considerable. The drugs that have already been approved for treatment are now also available for prevention, even though only TDF/FTC is licensed for use and this only in some parts of the world. The development and approval of newer drugs exclusively for prevention might take many more years.

There is a need for high-quality data regarding PrEP and resistance to TDF/FTC. Although clinical trials of PrEP have thus far shown very low rates of resistance in cases of prophylaxis failure, these studies may not be fully relevant to practice in real-world settings because of repeated testing of the individuals studied to date at regular intervals. Therefore, selection of drug resistance is likely to be much higher in real-world settings, and this is a concern. Thus, we recognize that the risks of our recommendations are that K65R and/or M184V/I may be selected at higher frequencies following failure of PrEP, leading to therapy failure when ART is subsequently commenced and the potential for onward transmission of drug-resistant variants of HIV. Further research is needed in regard to the generalized epidemic in circumstances in which uncontrolled drug use may occur and where regular testing and monitoring of long-term consequences of ART use may not be routine [38].

Furthermore, we encourage future trials to assess drugs that are unlikely to be used in first-line therapy in Africa. For example, use of maraviroc is not recommended without tropism testing, and this is a barrier to its use in resource-limited settings. However, a tropism test would not be needed if it is used for PrEP, given that almost all transmitted viruses are R5 tropic. Indeed, the HPTN 069 is an ongoing phase II, double-blind, 4-arm, multisite randomized trial in the United States assessing the safety and tolerability of PrEP regimens to prevent HIV transmission in at-risk men who have sex with men and with 3 active drugs being investigated (maraviroc, FTC, and TDF; Table 1).

Notes

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