CURRENT OPINION

Next-generation oral preexposure prophylaxis: beyond tenofovir

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Purpose of review
Clinical trials of oral preexposure prophylaxis (PrEP) have focused on regimens of tenofovir (TDF) with or without emtricitabine (FTC). However, TDF may be associated with toxicities (renal, bone), and FTC may select for drug resistance. Both are also first-line drugs for HIV treatment. In this review, we discuss agents that might serve as alternatives to TDF/FTC for HIV PrEP.

Recent findings
Several drug characteristics are important to consider when selecting agents for PrEP with the most critical being safety, tolerability, adequate penetration into target tissues for prevention of HIV infection, and long-lasting activity with convenient dosing. With these factors in mind, we review five potentially useful agents for PrEP. The first group includes drugs that are already Food and Drug Administration approved (maraviroc, raltegravir) with attributes that make them attractive for PrEP. The second group includes investigational agents with long-lasting activity that are being developed in parenteral form (rilpivirine-long acting, S/GSK1265744, ibalizumab).

Summary
Future PrEP drugs may give clinicians the flexibility to select agents on the basis of individual patient needs and preferences.

Keywords
HIV preexposure prophylaxis, ibalizumab, maraviroc, raltegravir, rilpivirine, S/GSK1265744

INTRODUCTION

Preexposure prophylaxis (PrEP) for HIV infection is a strategy in which antiretroviral agents are administered to at-risk, HIV-negative individuals to decrease the risk of establishment of HIV infection. Optimal PrEP agent(s) should be safe and tolerable, penetrate and protect against HIV infection in target tissues, long-lasting with convenient dosing, they should have a unique resistance profile or a high barrier to resistance, few or no drug–drug interactions, and be affordable, easy to use, and implement. In addition, antiretrovirals that are not used commonly for HIV treatment should be more attractive for use as PrEP drugs.

On the basis of these desirable properties, initial oral PrEP studies were designed testing regimens of tenofovir (TDF) with or without emtricitabine (FTC). More than 20 000 individuals enrolled in these clinical trials with the goal of assessing safety and efficacy, and some results are now available [1,2▪▪,3▪▪]. However, the potential for side effects and toxicities with TDF/FTC including gastrointestinal, renal, and bone [4], the fact that TDF/FTC is the preferred nucleoside analogue combination in current treatment guidelines [5], and a need for flexibility and individualization of approach makes consideration of other PrEP agents appropriate and necessary. In this article, we review the rationale for choosing among antiretroviral agents for oral PrEP as well as the currently available data on newer antiretroviral agents that offer promise for future PrEP regimens.

FAVORABLE CHARACTERISTICS OF PREEXPOSURE PROPHYLAXIS AGENTS

The US Centers for Disease Control and Prevention (CDC) lists recommendations for characteristics of

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- Most clinical trials of oral PrEP to date have tested tenofovir with or without emtricitabine.

- Oral agents that are already FDA approved for treatment, such as maraviroc and raltegravir, may serve as alternatives for PrEP regimens.

- New and promising long-acting investigational agents, some in the earliest phases of development (rilpivirine-long acting, S/GSK1265744, ibalizumab), might provide a novel approach to PrEP.

prophylactic agents and regimens [6] (Table 1a). These are the CDC recommendations for malaria prophylaxis and they go on to list five preventive drug(s) choices: atovaquone/proguanil, chloroquine, doxycycline, mefloquine, and primaquine. The optimal choice for malaria prophylaxis is individualized with consideration of characteristics of the at-risk individual, properties of the drug(s), and other factors (geography, use of other protective measures, etc.) The same approach can be applied to HIV PrEP regimens.

The Division of AIDS (DAIDS) of the National Institutes of Allergy and Infectious Diseases of the National Institutes of Health formed a working group that considered and defined the optimal properties of an antiretroviral agent(s) for PrEP [7] (Table 1b). Of these properties, the working group emphasized that the first four properties were more important and that safety ultimately was the most important quality of a PrEP agent, due to the fact that these preventive drugs are being targeted for use by HIV-uninfected individuals.

Assessing the current 26 Food and Drug Administration (FDA)-approved antiretroviral drug formulations for safety, tolerability, and convenience quickly removes a number of them from consideration for HIV PrEP regimens, including most of the nucleoside analogues, probably all of the nonnucleosides and protease inhibitors, and the parenterally administered fusion inhibitor, enfuvirtide. In addition to TDF and FTC, the drugs remaining on the list would be the nucleoside analogue lamivudine, the CCR5 antagonist maraviroc (MVC), and the integrase inhibitor raltegravir (RAL). Newer investigational formulations of approved drugs (e.g., rilpivirine) and other investigational antiretroviral agents also could be considered, but by definition have fewer safety data available. Of these, several antiretroviral compounds, both in existing mechanistic classes (nonnucleosides and integrase inhibitors) as well as in newer mechanistic classes (CD4 attachment inhibitors) are under evaluation for PrEP (Table 2, Fig. 1).

MARAVIROC

Maraviroc is an antiretroviral drug that prevents HIV entry into the $CD4^+$ T lymphocyte by binding the CCR5 receptor on the surface of the cell (Fig. 1). Maraviroc was approved by the FDA in 2007 for treatment of HIV infection on the basis of demonstrated safety and efficacy in large phase 3 studies in treatment-experienced [8,9] and treatment-naive [10] HIV-infected patients. Additional data demonstrates the extended safety profile of maraviroc [11–13]. Available safety data for maraviroc in HIV-uninfected individuals is limited to 3 months from a study of rheumatoid arthritis [14]. Despite theoretical concerns about a CCR5 antagonist targeting a host immune cell receptor [15], no evidence of complications or toxicities has been seen for at least 5 years [13].

The pharmacokinetics and prolonged half-life of maraviroc support once-daily dosing [16].

Table 1. Criteria for preventive drug regimens

A. Centers for Disease Control and Prevention recommendations for malaria prophylaxis [6]	B. Division of AIDS of the National Institutes of Allergy and Infectious Diseases Recommendations for Selection of PrEP Drugs [7]
Use the most effective drugs	Safe
No drug is 100% protective; it must combine with personal protective measures	Penetrates target tissues
Choose well tolerated drug(s); minimize side effects	Protects against HIV in tissues
Consider concomitant conditions (e.g., pregnancy, renal disease)	Demonstrates long-lasting activity with convenient dosing
Consider drug–drug interactions	Unique drug resistance profile and/or a high barrier to drug resistance
Daily medicine is often preferred	No significant drug–drug interactions
Choose the least expensive medicine	Not a part of current HIV treatment regimens
	Affordable and easy to use and implement

PrEP, preexposure prophylaxis.

Table 2. New antiretroviral agents for preexposure prophylaxis

Antiretroviral agent	Mechanism	Dosing route	Dosing frequency	PrEP clinical stage of development
maraviroc	CCR5 antagonist	Oral	once daily	Phase 2
raltegravir	Integrase inhibitor	Oral	twice daily	None planned
rilpivirine long acting	NNRTI	Injectable, subcutaneous	once monthly	Phase 1 pilot
S/GSK1265744	Integrase inhibitor	Injectable, subcutaneous	once monthly (or less)	Phase 1 pilot
Ibalizumab	CD4 attachment inhibitor	Injectable, subcutaneous	once every 1–4 weeks	Phase 1 pilot

NNRTI, nonnucleoside reverse transcriptase inhibitor.

Also, because of its mechanism of action, the serum half-life is less important than the length of time maraviroc remains bound to the CCR5 receptor, which appears to be on the order of days [17]. In addition, clinical studies reveal that maraviroc is concentrated in vaginal secretions (three-fold to eight-fold higher) [18] and rectal tissue (eight-fold to 26-fold higher) [19▪] compared with blood levels. Maraviroc is metabolized by the cytochrome P450 enzyme system and drug–drug interactions may be expected [20]. Viral drug resistance to maraviroc is uncommon [21]; virologic breakthrough on a maraviroc-containing regimen is most commonly accompanied by the emergence of dual-tropic virus, rather than drug-resistant viral strains [9].

Maraviroc was studied as a PrEP agent in a humanized mouse model [22]. The investigators administered maraviroc orally once daily (or no treatment) for a week to 14 RAG-humanized mice; mice were challenged with HIV-1 vaginally on the 4th day and followed for development of infection. By 6 weeks, all eight nontreated mice were infected compared with none of the six maraviroc-treated mice.

In summary, maraviroc is generally safe and well tolerated, with favorable pharmacokinetic properties allowing once-daily dosing, concentration in target tissues, and uncommon development of drug resistance. In addition, maraviroc is used infrequently in HIV treatment regimens, with
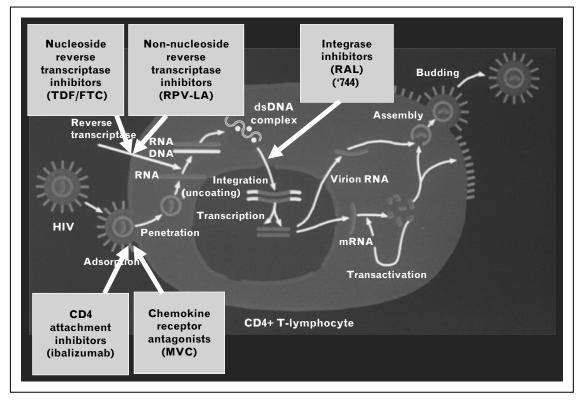

FIGURE 1. HIV life cycle and mechanisms of HIV preexposure prophylaxis agents. '744, S/GSK1265744; FTC, emtricitabine; MVC, maraviroc; RAL, raltegravir; RPV-LA, rilpivirine long-acting; TDF, tenofovir.

current guidelines listing it as 'acceptable' for initial treatment [5]. Recognizing the limited safety data in HIV-uninfected individuals, an NIH-sponsored phase 2 study of maraviroc recently opened to accrual (HIV Prevention Trials Network Study 069/AIDS Clinical Trials Group study 5305 [23]).

RALTEGRAVIR

Raltegravir is an HIV integrase inhibitor (Fig. 1) that was FDA approved in 2007 for the treatment of HIV infection on the basis of several large phase III studies that demonstrated safety and efficacy in HIV-infected individuals [24,25]. In the treatment-naive studies, raltegravir combined with TDF/FTC was well tolerated and demonstrated fewer drug-related clinical adverse events than an efavirenz-based regimen, although serious events were similar between the two groups. Four-year follow-up data demonstrated durable virologic suppression and few, if any, additional side effects [26]. Current guidelines recommend a RAL-based regimen among preferred initial treatment regimens [5]. RAL also demonstrated safety and tolerability in 100 HIV-uninfected individuals, when used as part of a postexposure prophylaxis regimen to prevent HIV infection [27•] and is used commonly in HIV-uninfected individuals for this purpose.

Raltegravir requires twice-daily dosing for HIV treatment. Although early pharmacokinetic studies suggested once-daily dosing might be possible [28], a large randomized, phase 3 noninferiority trial showed that HIV-infected patients who were randomized to a standard regimen that included twice-daily RAL dosing had significantly better virologic suppression rates than the investigational regimen using once-daily RAL dosing [29]. A pharmacokinetic study in seven HIV-negative female volunteers demonstrated that concentrations of raltegravir in cervicovaginal fluid (CVF) approximated those in blood, whereas the median half-life in CVF of 17 h was about twice as long that seen in blood [30]. Another pharmacokinetic study of 15 HIV-negative men demonstrated raltegravir levels 1.5–7-fold higher in gut-associated lymphoid tissue (GALT) compared with blood levels [31]. Raltegravir is metabolized primarily by glucuronidation, and thus has few drug-drug interactions [32].

Raltegravir has a low genetic barrier to resistance; single substitutions in the integrase gene have been associated with drug resistance to raltegravir and dual substitutions occur commonly following virologic failure on a raltegravir-containing regimen [33]. In addition, cross-resistance to other integrase inhibitors such as elvitegravir has been shown in vitro and clinically [34,35]. However, as a newer HIV drug, resistance to raltegravir currently is thought to be uncommon in the community [36].

Raltegravir was assessed as PrEP in the same animal model that was used to assess maraviroc, as discussed above [22]. In this study, six mice received daily dosing of raltegravir for a week and were compared with eight control mice after a vaginal challenge of HIV-1 on day 4. During the follow-up period, all of the control mice were HIV infected, whereas none of the raltegravir-treated mice had evidence of HIV infection.

In summary, raltegravir is generally safe and well tolerated, concentrates in vaginal secretions and GALT, and demonstrates efficacy as PrEP in an animal model, but may require twice-daily dosing, has a low genetic barrier to resistance, and is used commonly in HIV-treatment regimens. Due to these limitations, no current clinical studies of raltegravir PrEP are planned.

RILPIVIRINE LONG ACTING

Rilpivirine, a nonnucleoside reverse transcriptase inhibitor (NNRTI) (Fig. 1), was approved in oral form by the FDA in August 2011. The safety and efficacy of an oral rilpivirine-based regimen in treatment-naive, HIV-infected individuals was comparable to an efavirenz-based regimen in two large phase 3 multinational, randomized, clinical trials, known as ECHO (Efficacy comparison in treatment-naive, HIV-infected subjects of TMC 278 and efavirenz) and THRIVE (MC 278 against HIV in a once-daily regimen versus efavirenz) [37]. Rilpivirine (vs. efavirenz) was associated with fewer adverse events leading to discontinuation, including fewer treatment-related grade 2–4 adverse events such as rash, dizziness, abnormal dreams, and nightmares, and fewer grade 2–4 lipid abnormalities. Over 4 years in a phase 2 study comparing rilpivirine-based and efavirenz-based regimens, there were no new safety issues, and rilpivirine was associated with a lower overall incidence of grade 2–4 adverse events at least possibly related to study treatment [38].

A parenteral, long-acting form of rilpivirine (RPV-LA) was developed with the goal of improving treatment adherence and testing as a potential agent for PrEP [39]. Using nanotechnology to produce this parenteral form of rilpivirine, a proof-of-concept study was conducted in mice and dogs showing sustained concentrations of the drug for over 3 weeks and 3 months, respectively [39]. These encouraging results led to a clinical pharmacokinetic study in which 27 female volunteers were given intramuscular injections of RPV-LA at three doses, 300, 600, or 1200 mg with six male volunteers given a single injection of 600 mg [40]. In this study,

RPV-LA was generally well tolerated and achieved concentrations in genital tract tissue, suggesting efficacy for its use in PrEP. Compared with plasma, RPV-LA concentrations were 1.2–1.95-fold higher in female genital tract fluid and 0.48–1.0-fold in vaginal tissue, and in men, similar (0.89–0.92-fold) in rectal tissue. Else *et al.* [41] updated these data in 10 women and six men who received a single 600 mg intra-muscular injection of RPV-LA and found that cervi-covaginal fluid and rectal tissue concentrations were equivalent to plasma, but vaginal tissue concen-trations were lower and rectal fluid concentrations were much lower. Rilpivirine is metabolized by the hepatic CYP3A isoenzyme system, and drug–drug interactions may be expected [42].

Like other NNRTI, rilpivirine has a lower genetic barrier to resistance [43]. Following failure on a rilpivirine-containing regimen, a substitution at reverse transcriptase E138K occurs most commonly as can other NNRTI-associated mutations. Cross-resistance between rilpivirine and other NNRTIs also occurs frequently [43].

RPV-LA appears to be a promising drug for PrEP on the basis of its infrequent dosing that results in prolonged plasma and tissue levels. However, the parenteral formulation is investigational and early in clinical development. Further studies are necessary to assess its safety and tolerability and efficacy as PrEP. Additional areas of concern are the lower genetic barrier to resistance with resultant cross-resistance in the NNRTI class, and the fact that rilpivirine (and the other NNRTIs) are used commonly for HIV treatment.

S/GSK1265744

S/GSK1265744 is an investigational HIV integrase inhibitor in early clinical development. A complex phase I/IIa study assessed oral S/GSK1265744 (vs. placebo) in 18 HIV-negative individuals with single escalating doses (5, 10, 25, and 50 mg), in 30 HIV-negative individuals at daily doses (5, 10, or 25 mg) for 14 days, and in 11 HIV-infected men not on other antiretrovirals who received 30 mg once daily for 10 days, 3 days of no treatment, and then 14 days of combination antiretroviral therapy [44]. Overall, S/GSK1265744 was generally well tolerated with similar rates of adverse events compared with the placebo arms. In the 11 HIV-infected participants, S/GSK1265744 was associated with a median HIV RNA decrease of 2.6 log copies per ml, suppression of HIV RNA less than 50 copies/ml in all but one participant by day 14, and no emergence of drug resistance mutations.

Pharmacokinetic assessment of S/GSK1265744 demonstrated a long half-life of 30 h, suggesting the need for infrequent dosing [44]. S/GSK1265744 also is available in a long-acting parenteral form [45]. S/GSK1265744 has a similar drug resistance profile to dolutegravir, an investigational integrase inhibitor in phase 3 development [44]. Further studies are ongoing to assess safety and efficacy in HIV-negative volunteers [46], including in a pilot study in combination with RPV-LA [47]. Despite current limited safety and tissue penetration data, the long-acting parenteral formulation of S/GSK1265744 appears to be a promising agent for PrEP, although integrase inhibitors are used commonly in HIV treatment.

CD4 ATTACHMENT ANTAGONIST: IBALIZUMAB

Ibalizumab (previously known as TNX-355 and Hu5A8) is an investigational monoclonal antibody that binds to an area of the CD4 receptor that results in a distortion of the CD4–gp120 complex that prevents binding to the chemokine receptor, thereby inhibiting viral entry [48,49] (Fig. 1). Notably, although related monoclonal antibodies also exert an immunosuppressive effect, no effect has been reported with ibalizumab due to its indirect actions on the CD4 receptor that do not interfere with normal major histocompatibility complex class II binding [50].

Ibalizumab is a parenteral drug that has been given via weekly or biweekly injections in phase I and II clinical trials of HIV-infected individuals [51–53]. These studies showed ibalizumab was generally well tolerated with minimal adverse events. In a single-dose study, ibalizumab was associated with reductions in HIV RNA levels of 0.5–1.7 log copies per ml [52]. However, in one study, viral load levels returned to baseline by the end of the study period, suggesting that ibalizumab monotherapy resulted in the development of resistance [52]. As a monoclonal antibody, ibalizumab is not expected to have drug–drug interactions.

A randomized, double-blinded, placebo-con-trolled, phase I pilot study is ongoing to assess the safety, tolerability, and pharmacokinetics of ibalizumab with three dosing schedules among at-risk, HIV-negative volunteers [54].

Favoring ibalizumab for PrEP is its novel mech-anism of action, initial favorable safety/tolerability profile, and pharmacokinetics supporting infre-quent dosing of as few as every 4 weeks. Issues with its role for PrEP are the limited safety/tolerability data, theoretical safety risks as a CD4 attachment antagonist, the lack of data on tissue distribution including the genital tract and rectum, the obser-vation of drug resistance when used as monotherapy

in HIV-infected individuals, and the possible need for weekly or biweekly parenteral dosing.

CONCLUSION

The next generation of candidate oral PrEP agents appears promising and several alternatives to TDF/FTC are on the horizon. Although immediate consideration is being given to oral agents that already are FDA approved for HIV treatment (MVC, RAL), there are also investigational long-acting parenteral drugs that are being further explored for PrEP (RLV-LA, S/GSK1265744, ibalizumab). The future of PrEP will likely entail a patient-centered approach in which one regimen does not fit all and selection of the best agent(s) will depend on consideration of a number of characteristics related to the patient, the PrEP regimen, and their community.

Acknowledgements

Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 612).

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