Current state and limitations of daily oral therapy for treatment

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Purpose of review
We aim to review the strengths and weaknesses of current antiretroviral therapy (ART), and describe ongoing research to address limitations to current therapy.

Recent findings
Current ART is highly effective and well tolerated. As a result of a decrease in medication side-effects and pill burden, and the known health effects of uncontrolled viremia, ART is now recommended at all CD4 cell counts in the USA. Novel medications are being developed to further decrease side-effects and offer alternative options for patients with multiclass resistance. New combination pills will further decrease pill burden.

Summary
Current treatment for HIV is characterized by highly potent oral antiretroviral medications, which are well tolerated, resulting in outstanding rates of virologic suppression in patients who are adherent to therapy. Despite the marked improvement in therapeutic options, limitations to therapy still exist including reliance on daily adherence, long-term toxicity of medications, drug–drug interactions, long-term effects of HIV even in the setting of viral suppression, high lifetime cost of treatment, and limited options for some patients with multiclass resistance. Emerging alternative treatment strategies include nucleoside reverse transcriptase inhibitor-sparing or limiting regimens and long-acting injectable combination therapy.

Keywords
antiretroviral, HIV, limitations, oral, strengths

INTRODUCTION

Advances in the field of HIV therapeutics have transformed HIV from a progressive illness with high morbidity and mortality to a chronic disease. Virologic suppression is now achievable with combination antiretroviral therapy (ART) in the vast majority of patients living with HIV, leading to improved health outcomes and reduced risk of HIV transmission. With optimal ART, life expectancy now approaches that of uninfected individuals [1].

Despite the remarkable improvement in HIV outcomes over the past two decades, limitations to therapy persist (Table 1). In addition, it is now clear that even prolonged suppressive ART does not significantly reduce the latent viral reservoir, and as a consequence HIV treatment must be taken indefinitely. We will review the current state and limitations of ART, and discuss ongoing work to address these shortcomings.

CURRENT STATE OF HIV THERAPY

The current state of HIV treatment is characterized by highly potent therapy, which is typically well tolerated, with excellent rates of virologic suppression in patients who are adherent to therapy [2,3]. For treatment naive patients, optimal ART consists of two nucleoside reverse transcriptase inhibitors (NRTI; one of them lamivudine or emtricitabine) along with a third active drug from another class of medications: a ritonavir boosted protease inhibitor, or an integrase inhibitor (INSTI) [4]. With an increase in the number of effective medications,

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KEY POINTS

- Current ART is highly potent and well tolerated, resulting in excellent rates of virologic suppression in patients who are adherent to therapy.
- As no HIV cure exists, medications must be taken indefinitely to maintain virologic suppression.
- Treatment is limited by reliance on daily adherence, long-term toxicity of medications, drug–drug interactions, lifetime costs, and lack of treatment options for patients with multiclass resistance.
- More work is needed to develop medications with fewer long-term toxicities, and treatment strategies that do not rely on daily medication adherence.

the 2015 Department of Health and Human Services guidelines offers five recommended regimens for initiating ART. Selection of ART can now be individualized to each specific patient based on baseline HIV viral load and CD4 cell count, comorbid diseases, potential drug–drug interactions, ability to take medications with food, and patient preferences. Even for patients with multiclass resistance, combination therapy is typically effective; as a result, a high proportion of individuals in care are virologically suppressed [5].

In addition to being highly effective, antiretroviral medications have become easier to tolerate, with fewer side-effects than older medications. Early generation NRTIs, associated with severe mitochondrial toxicity have almost entirely been replaced by better tolerated NRTIs. In addition, the high rates of nausea and diarrhea commonly observed with early protease inhibitor-based treatments are rarely seen today. Importantly, the high pill burden of older regimens has been replaced by coformulated single pill regimens appropriate for the majority of patients with HIV, provided they do not have multiclass resistance. Lower pill burden has been shown to improve adherence [6▪], and there are now four single pill combination therapies, all of which are effective as first-line or switch regimens.

Table 1. Strengths and limitations of current ART

Current ART strengths	Current ART limitations
Highly potent	Dependence on daily adherence
Few side-effects, well tolerated	Long-term toxicity of ART
Low pill burden	Drug–drug interactions
	Long-term effects of HIV even in setting of viral suppression
	Cost
	Limited treatment options in patients with multiclass resistance
	Treatment is noncurative

ART, antiretroviral therapy

The evolution of highly potent, well-tolerated ART has influenced the United States' guidelines for initiating therapy. There is good evidence to show that short-term risk for death or AIDS-defining illness is low in patients with high CD4 cell counts [7,8], and hence for many years, the risks of ART outweighed the benefits in patients with intact immune function. However, we now know that untreated HIV leads to complications aside from impaired immunity including, but not limited to, non-AIDS-defining malignancies, cardiovascular disease (CVD), kidney disease, neurological disease, and advanced aging. Although no randomized study of early versus deferred therapy has proven that early ART reduces the risk of these unfavorable clinical conditions, observational data strongly suggest that treatment before significant immunosuppression improves outcomes [9,10,11]. Furthermore, it has been well established in observational and controlled studies that antiretroviral therapy reduces the risk of HIV transmission [12,13]. On the basis of these data, and the availability of well-tolerated medications, the USA now recommends initiating antiretroviral therapy in all HIV-infected individuals regardless of CD4 cell count [4].

LIMITATIONS TO CURRENT THERAPY

Treatment depends on daily adherence

The CDC estimates that for every 100 patients with HIV infection in the USA, only 28 are virologically suppressed. Most patients with uncontrolled viral replication are either unaware of their diagnosis or have been diagnosed but are not consistently in care, illustrating the importance of upstream interventions to link and retain patients to healthcare providers [14].

However, treatment failure is still present in approximately 20% of patients prescribed therapy, almost exclusively because of incomplete adherence. Not surprisingly, the rates of adherence are lowest in youth and adolescent populations [15,16].

In contrast to the risks of nonadherence to other chronic medications, a specific concern in patients who are intermittently adherent to ART is the development of antiviral resistance. Regimens differ in the risk of resistance when virologic breakthrough occurs, a phenomenon commonly called 'barrier to resistance'. Resistance to regimens containing boosted

protease inhibitors, for example, rarely develops even in patients who take their medications inconsistently [17]. As a result, boosted protease inhibitors are preferentially prescribed for those at high risk for intermittent adherence. Unfortunately compared with other regimens, protease inhibitors are associated with the most side-effects [18] and a higher pill burden of three pills once daily. This leads to the paradox that our preferred treatment regimen for patients with intermittent adherence is relatively poorly tolerated and has the highest pill burden, potentially leading to a cycle of worsened adherence. It is hoped that the newly approved coformulations of atazanavir and darunavir with cobicistat, and the anticipated approval of single-tablet regimen of darunavir, cobicistat, emtricitabine, and tenofovir alafenamide (TAF), will help make these protease inhibitor-based regimens easier to take.

One strategy to improve adherence is to adopt the model of directly observed therapy (DOT), widely used for treatment of tuberculosis. In addition to being highly resource intensive for a treatment requiring lifelong therapy, research of DOT programs for ART has shown mixed results. One study showed that DOT was effective in a population of IV drug users [19], but a similar study of DOT in a standard clinic population did not show overall improvement in adherence [20].

Long-acting injectable medications are an effective approach to circumvent the need for daily medication adherence for birth control (depo-provera) and antipsychotics (haloperidol, fluphenazine, risperidone, olanzapine, paliperidone, and aripiprazole) [21,22], and there is strong interest in adopting this strategy for HIV treatment. In the LATTE-1 trial, the combination of oral rilpivirine (an NNRTI) and cabotegravir (a novel INSTI) was shown to be noninferior to two NRTIs and cabotegravir for maintenance therapy [23▪▪], and both medications are being developed as long-acting injectable formulations that achieve therapeutic serum drug levels [24]. The ongoing LATTE-2 trial is a phase IIb study comparing the efficacy of this regimen via daily oral administration versus intramuscular administration at 4 and 8 week intervals. As we continue to identify and address structural barriers to adherence, the LATTE-1 trial provides proof of concept that long-acting injectable therapy is a feasible and promising treatment strategy for patients who are unable to achieve daily adherence or who would prefer monthly injections over daily pills.

Toxicity of antiretroviral therapy

As patients with HIV live longer, they are at greater risk for diseases of aging, some of which overlap with known adverse effects of current ART. As a result, there is a growing burden of long-term toxicity from chronic HIV therapy. Although each medication is associated with its own distinct set of side-effects, it is worth noting the specific risks of several of the most commonly used medications (Table 2). Early NRTIs including zidovudine, stavudine, and didanosine generated several debilitating or even life-threatening adverse effects related to mitochondrial toxicity including peripheral neuropathy, lipoatrophy, pancreatitis, and lactic acidosis. Although these medications are rarely used, newer NRTIs are still associated with several notable long-term toxicities.

Tenofovir disoproxil fumarate (TDF) is a nephrotoxin, and can induce proximal tubule dysfunction; the risk is higher among those with preexisting renal disease and in individuals taking boosted protease inhibitor-based regimens [25]. Tenofovir-based renal toxicity should be suspected in any patient on this medication who develops new-onset creatinine elevation, proteinuria, or glycosuria. In addition, through unclear mechanisms, tenofovir-based treatments induce greater loss in bone mineral density than nontenofovir-containing regimens

Table 2. Common side effects of specific antiretrovirals

Drug	Toxicity
Tenofovir	Renal impairment
	Decrease in bone mineral density
Abacavir	Potential hypersensitivity reaction in patients with HLA-B∗5701
	Potential increase in cardiovascular events shown in some observational cohort studies especially in patients with cardiovascular risk factors
Efavirenz	Neuropsychiatric side-effects
	Dyslipidemia
	Teratogenic in nonhuman primate studies
Atazanavir	Indirect hyperbilirubinemia
	P-R interval prolongation on electrocardiogram
	Nephrolithiasis, cholelithiasis
	Dyslipidemia
Darunavir	GI side-effects
	Rash
Raltegravir	Increase in creatine kinase, myopathy, and rhabdomyolysis have been reported (rare)
Elvitegravir/cobicistat	Nausea
Dolutegravir	Insomnia
	Headache

GI, gastrointestinal.

[26]. One observational study demonstrated an increase in fractures among those receiving tenofovir [27]. As a result of these limitations of tenofovir, its prodrug TAF is in the late stages of development. Although the active component of TAF is the same as TDF, TAF achieves five times higher intracellular concentrations with 90% lower plasma levels than TDF. As a result, the renal and bone effects of TAF are significantly lower than TDF [28▪▪,29]. In addition, the smaller milligram dose of TAF compared to TDF will allow novel coformulations, such as the above-mentioned single-tablet pill of TAF, emtricitabine, darunavir, and cobicistat. Approval of the first TAF-based treatments is expected in 2015.

Abacavir, a tenofovir-sparing NRTI, may be associated with increased CVD. Although a biologic mechanism for this effect has not been definitively determined, some in-vitro and in-vivo studies have demonstrated that abacavir treatment may induce higher levels of inflammation, leukocyte adhesion, and platelet aggregation, all of which could increase cardiovascular risk. As a result, abacavir should be used with caution (if at all) in patients with preexisting CVD [30]. In addition, abacavir can induce a life-threatening hypersensitivity reaction in individuals positive for the HLA-B∗5701 allele. Negative testing for HLA-B∗5701 is mandatory prior to starting abacavir-containing regimens.

To limit exposure to NRTIs, multiple trials have assessed the viability of two drug regimens. Several early studies in this class failed to show efficacy of this strategy [31,32]. The first successful study of two-drug therapy was the Global AntiRetroviral Design Encompassing Lopinavir/r and Lamivudine versus LPV/r based standard therapy (GARDEL) trial, which showed that a two drug regimen of lamivudine plus ritonavir boosted lopinavir twice daily was noninferior to a three drug regimen with two NRTIs plus ritonavir boosted lopinavir, even in patients with a high viral load [33▪]. Although there are elements to the study design, such as twice daily dosing, that are barriers to its overall generalizability, this study is a proof of concept that two drug regimens may be sufficient to achieve virologic suppression in treatment naive patients. Two subsequent trials have shown the efficacy of lamivudine and protease inhibitors for maintenance therapy, and the LATTE-1 trial described above showed the efficacy of a fully NRTI sparing regimen [23▪▪,34,35].

Finally, efavirenz predictably induces central nervous system side-effects. The most commonly reported complaints are dizziness, sleep disturbance, abnormal dreams, and morning grogginess. Although the severity of these side-effects abates over the first several weeks of treatment, a subset of patients has long-term side-effects of depression. An analysis of four randomized controlled trials demonstrated an excess in suicidality among those receiving efavirenz-based treatments compared with strategies that did not include efavirenz [36]. Although the absolute risk was low, this adverse effect is serious enough to warrant generally avoiding efavirenz in patients with psychiatric illness, in particular depression. Despite these limitations, efavirenz-based treatments (especially with tenofovir and lamivudine or emtricitabine) have potent and durable antiviral activity, widespread availability globally, and relatively low cost. As a result, this remains the WHO recommended first-line regimen, and is the most commonly used initial treatment worldwide.

Drug–drug interactions

Drug–drug interactions can be a barrier to therapy in patients with multiple comorbidities requiring other medications. The most common interactions are those related to ritonavir and cobicistat containing regimens, as both of these drugs are powerful inhibitors of cytochrome p450-mediated metabolism, in particular the enzyme cyp3a4. Such inhibition can markedly increase serum levels of medications metabolized by this pathway. One particularly common complication is iatrogenic Cushing's syndrome resulting from the concomitant use of ritonavir or cobicistat containing regimens and corticosteroids, even in the setting of inhaled, topical, or intraarticular steroid administration [37]. Statins (excluding the rarely used pitavastatin), benzodiazepines, phosphodiesterase inhibitors, and amlodipine, also reach elevated serum concentrations in the setting of ritonavir or cobicistat, and should be generally used at reduced doses.

In addition, administration of proton-pump inhibitors can interfere with the absorption of rilpivirine and atazanavir, limiting treatment options for patients with gastroesophageal reflux disease (GERD). Finally, rifampin, a cytochrome p450 inducer, increases the metabolism of hepatically cleared antiretroviral medications, and is of particular importance globally for the treatment of tuberculosis in areas with high endemic prevalence.

Long-term effects of HIV even in setting of viral suppression

As successful antiretroviral therapy has been available for less than two decades, the long-term consequences of treated HIV infection are not known. Although virologic suppression is almost always achievable with combination ART, it appears that successful treatment does not fully restore health, especially for those with a history of severe HIV-related immune suppression before ART.

A strong body of literature supports the association between HIV and CVD including coronary heart disease, ischemic stroke, heart failure, and arrhythmias [38–40]. To what extent the excess burden of traditional cardiovascular risk factors (especially smoking) in patients with HIV accounts for this increased risk remains unclear [41]. For example, one epidemiologic study showed that the rate of myocardial infarction is 1.5 times higher in individuals with HIV than individuals without HIV even after adjusting for traditional risk factors [38]. By contrast, a recent analysis done in the Kaiser healthcare system showed that, among a predominantly healthy population with high rates of virologic suppression and low rates of smoking, an excess risk of myocardial infarction among those with HIV is no longer observed [42].

If people with treated HIV continue to be at excess risk for CVD, both treatment with certain antiretrovirals and HIV itself may be responsible. Among currently used HIV medications, some (but not all) observational cohort studies implicate abacavir and lopinavir/ritonavir, as reviewed in a comprehensive editorial [43]. Nonmedication factors may include elevated levels of systemic inflammation and immune activation, even in the setting of virologic suppression [44,45]. In addition, markers of hypercoagulation including D dimer and fibrinogen have been shown to be elevated, and these proteins have been associated with an increase in clinically relevant CVD [44–46].

Furthermore, despite improvement in immune function, the rate of non-AIDS-defining malignancies, such as lung adenocarcinoma, Hodgkin's lymphoma, anal cancer, and head and neck cancer, is increased in patients with HIV as compared to the general population [47] and the risk of dying from non-AIDS-defining cancer remains high even when the virus is suppressed [48]. A proposed mechanism for this increased risk is the heightened degrees of immune activation and inflammation that is present with uncontrolled viremia, even with relatively preserved CD4 cell counts [49▪]. Thus, it is likely that the risk is incurred before initiation of ART and not necessarily a limitation to current available therapy; nonetheless, it is not fully reversed by effective treatment.

Cost

Although HIV treatment is widely considered cost-effective based on a measure of life-years gained from therapy, costs of care for patients with HIV are substantial and most of the cost attributed to ART [50]. With increased survival of patients, the lifetime cost of care is increasing [51]. Although generic prices for HIV drugs could drive down costs, in the USA none of the commonly used coformulations is available generically. For example, abacavir and lamivudine are both available as generics, but the coformulated single pill of the two drugs is brand name only. Long-acting ART may be a good value for patients with poor daily adherence by decreasing the rate of virologic failure, but in order to be cost-saving or even cost-effective as first-line therapy, it must be priced on a par with currently available regimens [52].

Resistance still can limit treatment options

There still remain occasional patients with multiclass resistance for whom current therapeutic options are not sufficient. This is perhaps best illustrated by the following patient seen recently in consultation: a 67-year-old man diagnosed with HIV in 1989 and treated with sequential monotherapy through the 1990s. As a result, he developed high-level resistance to NRTIs, NNRTIs, protease inhibitors, early resistance to INSTIs; his tropism test shows non-CCR5 virus. Despite combination ART with all available classes of medications, he has not been able to achieve virologic suppression. Without the development of new drugs, there are no therapeutic options to achieve virologic control in patients such as him with high-level multiclass resistance.

After rapid development of new HIV medications in the late 1990s, HIV drug development has slowed down significantly. Between the years 1996 and 2007, 20 new HIV medications were approved by the FDA along with eight different combination pills. Since 2007 only two new medications and three new combination pills have been approved, but there are several important drugs in the pipeline. In addition to the new drugs discussed earlier (TAF, cabotegravir, injectable rilpivirine, and coformulated protease inhibitor-based regimens), BMS-663068 is a novel attachment inhibitor with promising initial results in antiretroviral (ARV) experienced patients with multiclass resistance [53].

CONCLUSION

Advances in ART have transformed HIV care. Long-term virologic suppression requires lifelong exposure to ART, and highlights some limitations of ART despite the ability to control viremia. With no cure in sight, the two important cornerstones of improving therapy are production of new medications with fewer long-term toxicities, and a development a treatment strategy that does not rely on daily medication adherence.

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