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Authors
Havlir, Diane
Gandhi, Monica

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Implementation challenges for long-acting antivirals as treatment

Diane Havlir and **Monica Gandhi**

Department of Medicine, HIV/AIDS Division, University of California, San Francisco, San Francisco, California, USA

Abstract

Purpose of review—Long-acting injectable antiretroviral therapy (ART) formulations hold great promise in helping to close the significant gap between efficacy and effectiveness in HIV treatment by eliminating the requirement for lifelong daily pills. However, significant systems-level and individual challenges to implementation of long-acting ART in HIV treatment are anticipated.

Recent findings—Studies of long-acting ART formulations are burgeoning, but the drugs are still in early phases of investigation and key knowledge gaps in pharmacokinetics and pharmacodynamics, as well as their effectiveness in settings with the largest burden of HIV disease and in key populations, remain. Extrapolating from the literature on implementation barriers to using long-acting contraception on a global scale, we explore the implementation barriers to rolling-out long-acting ART, including country approval and endorsements; prioritization of patient populations for preferred use, clinic infrastructure requirements, steady supply chains, decentralization of care, provider and patient training programs, and laboratory monitoring; and the need to examine patient preferences and conduct rigorous implementation science research to effectively scale-up this intervention.

Summary—Long-acting ART for HIV treatment harbors exciting potential to shift treatment paradigms. Current knowledge gaps in the use of these agents remain, leading to multiple anticipated systems-level and individual-level barriers to implementation. Addressing these gaps and barriers will help fulfill the promise of these agents against the pandemic.

Keywords

antiretroviral; implementation; long-acting

INTRODUCTION

The management of HIV infection mandates lifelong and daily consumption of multiple antiretroviral medications. With the development and advancement of these highly potent

Correspondence to Diane Havlir, MD, UCSF HIV/AIDS Division at SFGH 995 Potrero Avenue, Building 80, Ward 84, San Francisco, CA 94110, USA. Tel: +1 415 476 4082 Ext. 401; diane.havlir@-ucsf.edu.

Conflicts of interest

The authors have no conflicts of interest.

combination antiretroviral therapies (ART), life expectancies with chronic HIV infection have risen around the world [1,2] and the prospect of the 'end of AIDS' through treatment-as-prevention is now an active debate [3▪▪,4,5]. However, as HIV has transformed from a life-threatening illness to a chronic controllable condition, difficulties in patients linking to or staying in care, maintaining adherence to daily medications, and pill fatigue have plagued the field [6,7]. Moreover, cost constraints, lack of political will, and uneven access to ART across the globe limit the benefits of current ART formulations.

Long-acting injectable ART formulations hold great promise in helping to close the gap between efficacy and effectiveness in HIV treatment by eliminating the requirement for lifelong daily pills in the modern management of HIV. In this review, we will discuss the potential benefits of long-acting ART in addressing treatment gaps, the analogy of long-acting ART to long-acting contraceptive formulations, and both systems-level and individual challenges to implementing long-acting ART agents in a range of settings, including sub-Saharan Africa. We will then discuss the knowledge gaps that still require further investigation in multiple settings before the benefits of long-acting ART can be realized.

BACKGROUND

The treatment gap with current antiretroviral therapy formulations

The most recent report from the US-based Medical Monitoring Project estimates that only 37% of HIV-infected individuals are being prescribed ART nationwide [8], with 30% achieving virologic suppression. The latest data from Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that only 12.9 million people out of 35 million living with HIV had access to ART in 2013 [9]. Although the barriers to accessing ART differ significantly for resource-rich and resource-limited settings, the limitations of current regimen formulations in terms of cost, acceptability, dosing requirements, and delivery methods have contributed to treatment gaps in both settings. This gap has sparked emerging interest in long-acting formulations of HIV treatment, which can be administered less frequently and potentially delivered more cost effectively [10,11▪].

Potential impact of long-acting agents on treatment gaps

The requirement of currently available formulations of ART to be dosed orally once (or twice) daily has a substantial and negative impact on long-term adherence [12]. The benefits of ART are obviously dampened in those with inadequate adherence to treatment [13,14], and failure of HIV-positive individuals to take antiretrovirals as prescribed can lead to increased transmission within a community. Multiple factors are associated with reduced adherence in the developed and developing setting, including stigma [15,16], race/ethnicity [17–20], depression [18,21,22], cognitive impairment [23], substance use [16,24], younger age [19,24,25], and adverse effects to medications [26]. Furthermore, rates of adherence to ART often decline over time [19,21,27,28], even when antiretrovirals are provided at no cost. There is therefore a compelling need for interventions that can improve treatment adherence to chronic HIV therapy, including the development of nanoparticle-based long-acting ART formulations, which can be provider (or self)-administered on a weekly, monthly, or quarterly basis [29–33,34▪▪]. The current state of the science has accumulated

the most evidence for two specific long-acting ART agents in HIV treatment and/or prevention [29–33,34▪▪,35,36] – the long-acting integrase inhibitor, cabotegravir, and the long-acting nonnucleoside reverse transcriptase inhibitor, rilpivirine – with others envisioned in the future.

The analogy to long-acting contraception

In 2008, more than 50% of pregnancies in the USA were unplanned [37]. The promised revolution of the daily oral contraceptive pill (OCP) on reproductive planning for women worldwide has been thwarted by multiple systems-level and individual challenges [38,39]. The wide gap between the theoretical efficacy and actual effectiveness of daily OCPs has some similarities with current HIV treatments, with issues of nonadherence, cost, and accessibility all contributing [40]. As with HIV-related outcomes in the USA, disparities in the use and effectiveness of daily hormonal contraceptives are influenced by poverty, race, and insurance status [40]. Long-acting hormonal contraceptives, such as the hormone-based intrauterine systems, subdermal delivery systems (i.e., implants) and quarterly hormonal injections are less subject to individual adherence barriers because all are provider-administered, and more effective than daily OCPs for contraception in real-world settings. For instance, in the FEM-PrEP trial, wherein preexposure prophylaxis (PrEP) was studied in at-risk HIV-noninfected African women, pregnancy rates were much higher among OCP users (35.1%) than those on long-acting injectable contraceptive (1.6%) [41]. However, a number of implementation challenges to the global use of long-acting contraceptives remains that should be examined as an analogy when considering the eventual implementation of long-acting ART.

IMPLEMENTATION CHALLENGES

Health systems challenges

Once efficacy data are in place to support moving forward with long-acting agents, a Food and Drug Administration-equivalent approval process for use of these agents in countries outside of the USA will be required. There is a roadmap to achieving approval of new antiretroviral agents in resource-limited settings that is feasible, but requires the collective effort and willpower of the pharmaceutical industry, manufacturers, and global agencies [42]. Uptake may also depend on endorsement by the World Health Organization Consolidated Antiretroviral Guideline Committee, which exerts considerable influence over country guidelines in many regions of the world. We can safely speculate that development of these long-acting agents with consideration of populations in regions of the world with the greatest HIV burden will catalyze approval, uptake, and access.

Identification of populations eligible for long-acting agents

With the anticipated arrival of long-acting agents, one of the first decisions that health systems will need to make is the determination of patient eligibility for these new agents (Table 1). The easiest and most equitable approach, on face value, would be to offer long-acting treatments for those whose virus can be suppressed by the regimen and for whom there are no contraindications. There is a strong argument for this approach, as we have no data to prove which populations would benefit most. However, practical constraints, such as

logistical requirements and funding, may force the prioritization of patient populations who are best able to access and afford long acting regimens. A recent costing model suggests that over a range of anticipated costs for long-acting agents, limiting access to patients with difficulties maintaining adequate adherence with subsequent virologic failure may be the most cost-effective approach [11▪]. The various assumptions to generate this model may not be applicable to many settings. Current cost projections for these long-acting ART agents are speculative at best since the more expensive manufacturing process for nanoparticle-based ART compounds may be balanced by the ability to administer them infrequently, so further cost–effectiveness modeling once the development and marketing of long-acting ART agents is more advanced will be helpful.

On a health systems level, how then might we identify populations most apt to benefit from these new and exciting ART formulations? We may not have the data for some time on the relative benefit of long-acting versus daily regimens for specific populations. Prioritizing those who have the lowest viral suppression rates on daily regimens is one approach. The inherent assumption in this approach is that it is the daily requirement for pills (and not the requirement to routinely attend clinic appointments), which serves as the main driver for low viral suppression rates. Examples of populations who could benefit from this prioritization scheme include adolescents [19], sex workers, or those suffering from mental illness [18,21–23,25], substance abuse [16,24,43], and housing instability [44]. However, there are other characteristics of these populations that may make them less likely to benefit from long-acting agents, such as mobility and transience. Unless there is universal, readily accessible, record-keeping systems to clearly document dosing, these populations may suffer ‘adherence lapses’ with long-acting ART. We have not achieved universal medical record-keeping in the USA, let alone in most international settings. Moreover, many well done studies on social determinants of health demonstrate that unless the underlying survival, mental health treatment, and rehabilitation needs of patients are met, the nature of the antiretroviral regimen is unlikely to make a large difference on adherence rates and outcomes [45].

Logistical requirements

The first generation of long-acting agents will require clinic and hospital infrastructure readily available in the USA, but not yet available in many high HIV burden regions in the world. Steady supply chains for both the oral and injectable forms of cabotegravir and rilpivirine will be necessary because, as could be currently envisioned, patients should receive this combination of medications first in oral form to ensure tolerance before transitioning to an injectable form. Long-acting ART agents are likely to require refrigeration, especially when prolonged storage is necessary, requiring the incorporation of a cold chain for transport and administration. Required laboratory studies for all ART agents, including long-acting ART, will include hepatic and renal monitoring for safety and plasma HIV RNA levels to ensure viral suppression has been achieved on the oral regimen first, and subsequently maintained on the long-acting ART. HIV drug resistance testing is standard in the USA and may be needed in resource-limited settings for long-acting ART implementation, depending on the target patient populations and local prevalence of drug resistance.

Clean needle access and trained staff to administer and document injections will be additional logistical requirements for long-acting ART. Capacity for well-tolerated injectable practices exist across a variety of health sectors in resource-limited settings, as has been demonstrated in reproductive health (e.g. long-acting contraception) and tuberculosis treatment settings with expertise in multi-drug-resistant tuberculosis (e.g. aminoglycosides). One of the key requirements for equitable access to long-acting ART is that the administering health center is readily accessible to the client and does not require travel to a centralized high-level health center. We know that geographic and transportation-related barriers are associated with poor treatment outcomes across the continuum of HIV care [46]. For the potential of long-acting agents to be maximized, injection services in the context of HIV care need to be de-centralized. Healthcare systems that suffer from routine ART stockouts are not good candidates for eventually delivering long-acting ART. One consideration for the implementation of long-acting agents in rural resource-limited areas is to consider mobile health approaches wherein the treatment is provided by a traveling health group with the capacity to meet the client in or proximal to their residence [47–50].

Patient management challenges

In many regards, long-acting agents can simplify patient management. In the ideal setting, a client completes a 6-month induction period with orally administered ART and transitions to intermittent therapy with long-acting ART to maintain viral suppression for decades without a requirement of daily pills. In the real world, there are innumerable clinical developments that can pose patient management challenges (Table 1). What happens when a patient becomes pregnant? What happens when a drug that interacts with the injectable is required? What should be done when a patient misses a visit outside of the window that is considered safe from the standpoint of development of resistance? What if a patient is moving to a place where there is no capacity for administering injectables?

Clearly, even with daily oral antiretroviral therapy, anticipated and unanticipated patient management issues commonly arise. Two optimal ways to address these issues are to include potential pitfalls and barriers to long-acting ART when training providers and patients on their use and to ensure that providers have access to information/advice lines in real time.

Provider and staff training

Effective provider and staff training is essential to the success of the roll-out of long-acting agents. Providers need to understand the characteristics of the drugs in the injectable regimen, as well as the features of the oral dosing regimen that will comprise the induction strategy. Patient management issues as described above need to be anticipated and a venue for posing questions in real-time needs to be made available. Providers should be given tools and learning aids to discuss this new approach to the management of HIV disease with their patients and staff. Continuing medical education in its many formats around the world is a key resource in the rapidly evolving field of HIV medicine.

Successful roll-out with provider oversight will depend not only on education programs, but also on systems that enable responsible prescribing and monitoring. These systems include facilities for well tolerated injections and proper laboratory monitoring as described above.

Proactive efforts that promote and track retention are essential. These tracking measures will depend on the setting, the volume of patients and resources. Regardless of the setting, there needs to be a rapid response system set up for missed visits. Patient populations with traditionally poor adherence may need proactive reminder calls or texts. In the case of missed visits, understanding the reason for the missed visit, and addressing the underlying determinants will be essential to ensuring retention to the regimen and care.

Consumer challenges

Many of the challenges consumers of long acting agents will face are not specific to HIV treatment. The clients must understand the purpose of their medications and the side-effects. They must understand the importance of adhering to visits and monitoring for both side effects and efficacy. They must understand the risks of stopping therapy. Clients may like the idea of a treatment requiring an injection every few months, but the injections may be painful and associated with inflammation, a side-effect that can diminish enthusiasm for the new formulation.

Stigma remains an unfortunate and ongoing challenge for persons with HIV around the world. On the one hand, not having to take medications daily could reduce the impact of stigma for a particular individual. However, receiving an injection at a treatment hub associated with HIV care could potentially and unintentionally reveal HIV status, resulting in even greater stigma-related effects. For this reason, delivery systems must be patient-centric and be designed to minimize stigma. For example, co-locating and integrating services, such as HIV treatment with antenatal care centers, or HIV treatment with injection drug user services, may facilitate adaptation to long-acting ART.

Patient preference is also likely to play a significant role in the use of long-acting ART in a variety of settings. The literature on preferences for long-acting contraception will be helpful to inform our field and studies have shown that patient resistance to new medical technologies (perceiving long-acting contraception as ‘alien’) [51], increased cost, and a perception of ‘loss of control’ when contraception is provider-administered, rather than self-administered, all can reduce interest in long-acting contraception. Given that distrust of the medical system and the benefits of ART have been key factors to racial/ethnic disparities in HIV treatment outcomes in the USA [52▪], and that historically-grounded distrust of Western medicine has contributed to ART nonadherence in Africa [53], studies on the acceptability of long-acting ART in various patient populations and educational interventions to enhance acceptability will be key to address this particular consumer challenge.

Finally, fragmented health systems in the USA that place a burden on a patient to enroll in a new system with every new job or family status change are a threat to continuity of care for any type of chronic disease. Patients need support at a community or systems level to ensure that they do not disrupt their chronic treatment in the face of a changing framework of healthcare.

KNOWLEDGE GAPS

Although long-acting ART formulations harbor great promise for the field of HIV treatment, the field is still nascent and multiple knowledge gaps remain (Table 2), contributing to the long list of implementation challenges above. As these gaps close with further study, some of the health systems and individual challenges to implementation will be clarified, although others will be raised.

Pharmacokinetic and pharmacodynamics

Although some data on the pharmacokinetics and pharmacodynamics of long-acting rilpivirine and cabotegravir have been presented [29,30,31,32,33, 34▪▪,35,36], further pharmacokinetic study of these agents will be required to understand the optimal dosing interval for these agents to optimize efficacy and minimize adverse effects and drug resistance.The dosing interval must be selected based on the anticipated trough of the ART agent at the end of the quarterly, monthly, weekly, or other injection interval to ensure that this trough is still well above the concentration required to inhibit viral activity without exerting selective pressure for the development of viral resistance. Further pharmacodynamic analysis of the relationship between drug level and desired treatment outcome, including both virologic suppression and side-effects, will be required before dosing intervals can be fully established; a key factor to implementation.

Drug–drug interactions

Little information is currently known about key drug–drug interactions between the long-acting ART agents in development and other drugs in prevalent use among HIV-infected populations. Interactions between hormonal contraceptives –both long-acting formulations and daily OCPs –and oral ART formulations are complex and still not fully understood. The co-administration or co-formulation of long-acting ART and long-acting contraception is an exciting possibility for HIV-infected women of childbearing age [54]. However, drug–drug interactions between long-acting ART and hormonal contraception will be key to examine, both in small intensive pharmacokinetics studies and in large-scale efficacy trials, before the implementation of this strategy can be considered. Other drugs that will require drug–drug interaction studies with long-acting ART formulations include those required for the treatment of hepatitis C infection, including the new orally available agents, and some substances of abuse and antidepressants prior to the implementation of long-acting ART among hepatitis C-coinfected patients, substance users, or those with concomitant depression.

Studies in key populations

As is common in many phase I and II studies of new drug formulations [55], the studies of long-acting rilpivirine and cabotegravir conducted to date have been performed in relatively homogeneous populations. During the phase III trials and in postmarketing surveillance and studies, the pharmacokinetics and treatment responses of long-acting ART must be studied in adequate numbers of women for sex-stratified results to be presented [56–58]. Studies in children and in pregnant and breastfeeding women will be important to extend the benefits of these agents to these key populations. Moreover, studies in genetically diverse

populations, both in the USA among racially/ethnically diverse patients, and in African patients, will be necessary before widespread implementation of these agents across the planet and inregions hardest hitbyHIV canbeenvisioned. Given the expected individual-level challenge of patient preference for long-acting ART to contribute to implementation challenges in key populations, further study on the perceived barriers to uptake of long-acting ART in different settings will be warranted.

Implementation science investigations

The approval process for new treatments provides evidence for how well a drug works in a randomized trial setting, but may leave unanswered questions on how to optimize effectiveness in real world settings. As outlined by Glasgow *et al.* [59], bringing interventions to scale and integrating research with practice will require improved strategies to implement optimal HIV treatment and prevention modalities in vulnerable populations. The implementation of long-acting ART in underserved populations will require research investment to address implementation questions via alternate study design such as pragmatic trials, interrupted time series, and adaptive design [59,60]. These studies require integration of the social and biologic sciences with systems-level and costing analyses. For instance, we understand much more about individual decisions about maintaining daily adherence to pills than we do about missed clinic visits [61]. The success of long-acting agents hinges heavily on the latter. Understanding patient attitudes and behavior, systems' issues, and the cost of alternative models represents a significant knowledge gap for successful deployment of long-acting ART.

CONCLUSION

Long-acting ART agents hold great potential to close the treatment gap for HIV. They may offer an alternative for large numbers of patients who struggle with adherence to a daily pill-based regimen. Exploiting the strength of long-acting regimens requires filling significant knowledge gaps about their pharmacodynamics, pharmacokinetics, and drug–drug interactions. The field will require research into optimal implementation strategies that take in consideration patient attitudes and behaviors, health systems, and financing, including vulnerable and key affected populations.

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KEY POINTS

- Long-acting agents have the potential to shift treatment paradigms.
- Exploiting the strength of long-acting regimens requires filling significant knowledge gaps about their pharmacodynamics, pharmacokinetics, and drug–drug interactions.
- Addressing these gaps and barriers will help fulfill the promise of these agents against the pandemic.

Table 1

Health systems and patient challenges to the implementation of long-acting ART

Systems-level challenges to implementing long-acting ART
FDA-equivalent approval process in countries outside the USA and endorsement by global recommendation guidelines
Determination of which patient populations to prioritize, both in resource-rich and constrained settings, for long-acting ART based on patient characteristics, adherence level, inadequate virologic suppression rates, cost constraints and accurate cost projections, cold chain requirements, etc.
Requirement for clinic or hospital infrastructure (clean needles, trained staff) for provider administration
Need for steady supply chains for the injectable forms of ART
Likely requirement for cold chain for transport of nanoparticle long-acting ART and refrigeration at site
Possible requirement for HIV drug resistance testing prior to use, laboratory monitoring (including for safety and HIV viral load) during use
Decentralization of care (including mobile health units) to minimize prolonged travel to clinic sites with capability to administer long-acting ART
Requirement for education programs to inform providers/clinics of the evidence behind long-acting ART, as well as bolstering systems as above to prescribe long-acting ART and monitor its outcomes
Current knowledge gaps in use of long-acting ART in children, pregnant and breastfeeding women, those on prevalent-use concomitant medications such as contraceptives, hepatitis C drugs
Individual-level challenges to implementing long-acting ART
Possible injection site reactions or other possible side effects
Possible increase in stigma from receiving injections at HIV-associated site
Patient preference and acceptability of injection-based therapy; loss of perceived “control” associated with not taking oral medications
Insurance status and cost
As with all chronic diseases, patient understanding of the need for the medication and commitment to adherence

ART, antiretroviral therapy; FDA, Food and Drug Administration.

Table 2

Knowledge gaps in implementing long-acting ART for treatment

Yet undefined dosing intervals for each drug to maximize benefit while minimizing potential for development of drug resistance
Lack of comprehensive pharmacokinetic and pharmacodynamic data to date, including full profile of possible side effects
Drug-drug interactions between long-acting ART and both oral and long-acting hormonal contraception
Drug interactions between long-acting ART and other prevalent-use medications such as oral therapies for hepatitis C infection, substances of illicit use, antidepressants
Lack of pharmacokinetic and outcome data in large enough samples of women to perform sex-stratified analyses
Lack of pharmacokinetic and outcome data in children, pregnant and breastfeeding women, populations of racial/ethnic diversity
Lack of qualitative data on patient preference for long-acting ART and barriers to acceptability
Actual cost projections of long-acting ART, balancing manufacturing costs with need to administer less frequently
Knowledge of optimal storage and shipment conditions for long-acting ART formulations to ensure steady supply and ascertain cold chain requirements

ART, antiretroviral therapy.