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The Promise of Improved Adherence With Long-Acting Antiretroviral Therapy: What Are the Data?

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Abstract

As with other chronic conditions, adherence to daily medications remains a challenge for many individuals living with HIV due to structural, behavioral, and social barriers. Unfortunately, high levels of adherence to antiretroviral therapy are required to maintain virologic suppression. Alternative approaches are being explored to decrease the burden of daily pill administration, including long-acting injectable, oral, and implantable products. Phase 3 data support the efficacy of nanoformulated injectable cabotegravir and rilpivirine for HIV treatment in patients with undetectable viremia, but we have yet to learn how this strategy may benefit those with medication adherence challenges. Despite this, the affected community and HIV providers are very interested in exploring the role of long-acting therapies to address some types of barriers to medication adherence. This review summarizes available information about the potential for long-acting therapy to improve adherence for some patients and outlines associated opportunities and challenges with the implementation of long-acting therapy for the treatment and prevention of HIV.

Keywords

adherence, antiretroviral therapy, HIV, long-acting, cabotegravir, rilpivirine

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For many chronic conditions, long-acting (LA) medication therapies have improved medication adherence compared to daily oral therapy, leading to improved clinical outcomes. The term LA has been used in drug delivery to describe applications for multiple routes of administration, including oral, topical and parenteral, which includes intravenous, intramuscular, subcutaneous injections, and implantable devices. Generally, it is proposed that to be considered a LA therapy, an oral drug should achieve at least once weekly dosing, an injection at least monthly, and an implant at least 6-monthly dosing.¹ Existing LA drugs have specific pharmacokinetic and pharmacodynamic properties that make them compatible with this approach. In addition to the need for a favorable safety profile, formulation of LA drugs requires low aqueous solubility (water-soluble drugs dissolve rapidly and release drug), high potency (to minimize the requirement for high plasma concentrations), and a long pharmacokinetic half-life (to minimize rapid clearance).¹

Contraception is one example of improving therapy effectiveness with LA delivery. Options for contraceptive hormone delivery include daily oral pills, weekly topical patch, monthly

vaginal rings, quarterly injection, and implants or intrauterine devices (IUD) approved for use years after placement. In one study of nearly 7500 women, individuals using LA reversible contraception (injection, implant or IUD) had a 20-fold lower risk of pregnancy (hazard ratio 20.1, 95% CI 13.7-34.9).² This improvement in effectiveness is related to both adherence to, and continuation of, the contraceptive.³ In addition to highlighting that less-frequent administration can improve medication adherence, contraception is an example of how patient choice related to medication delivery can improve therapeutic outcomes through shared decision making.

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Bisphosphonate therapy for osteoporosis also offer LA oral and injectable therapy to overcome challenges to daily oral adherence.⁴ Related to both adherence and persistence on therapy, weekly oral therapy and less frequent injectable therapy perform better than daily oral therapy.⁵⁻⁸ Adherence to once yearly intravenous zoledronic acid, measured as proportion of days covered (PDC), was higher compared to quarterly intravenous ibandronate (82% vs 60%, $p < 0.0001$).⁹ In a 24-month clinical trial of annual infusions vs. weekly oral therapy, 74.2% of individuals preferred yearly therapy compared to 15.3% who preferred weekly dosing, illustrating that patients often desire as infrequent of administration as possible.¹⁰

For patients with structural, behavioral, or cognitive barriers to medication adherence, LA therapy is a useful strategy to overcome some of these barriers. For patients with schizophrenia, it is reported that up to two-thirds of individuals are partially non-adherent to oral therapies, resulting in increased risk of hospitalization for relapse.¹¹ Compared to oral agents, LA injectable antipsychotics are associated with lower risk of relapse, fewer hospitalizations, and greater retention on therapy.¹¹⁻¹³ In addition, one study found that individuals who were nonadherent to oral antipsychotics were less likely to discontinue LA therapy ($p = 0.033$) compared with patients on oral therapy.¹⁴

Building upon success in these disease states, LA antiretrovirals are currently being developed for the treatment and prevention of HIV infection. Although access to and linkage to care for the treatment of HIV is critical, it is less likely to be influenced by the choice of prescribed medications. Therefore, herein we address treatment adherence defined as retention in care (i.e. attending clinic visits as scheduled) or medication adherence (i.e. taking the dose and frequency of medication as prescribed). In this review, we summarize these emerging therapies, with an emphasis on the role of LA therapy to address some barriers to medication adherence and to inform the implementation of LA therapy for HIV into clinical practice.

Ethical Approval and Informed Consent

Ethical approval and informed consent were not required as this manuscript is a review of previously published data.

LA Antiretroviral Therapy for HIV Infection

Modern antiretroviral therapy (ART), featuring 2 to 3 antiretroviral agents from at least 2 different antiretroviral classes, has transformed HIV infection into a long-term, chronic medical condition.¹⁵ ART reduces HIV-associated morbidity and mortality, leading to a similar life expectancy to their peers for patients with HIV.¹⁶ Contemporary oral ART is extremely effective at suppressing HIV viremia, often with once daily single tablet dosing and minimal toxicity.¹⁵ So why do we need LA formulations as an alternative? Adherence to lifelong daily therapy is challenging for many patients.¹⁵ A small proportion of patients with HIV have trouble swallowing pills or absorbing

them, but very many express fatigue at the relentless demands of daily pill taking, without an end in sight.^{17,18} Other barriers to adherence include internal and external stigma, low health literacy, financial barriers, mental health/substance use disorders, or competing priorities related to life events, caregiving, or unstable housing.¹⁵ Many of these barriers cannot be overcome through choice of medication, but multiple investigational or reformulated LA antiretroviral agents are in development for the treatment and prevention of HIV to provide potential alternatives related to pill taking barriers and importantly, offer patient choice in their preferred route of medication administration (Table 1).¹⁹ An alternative LA delivery system may offer several advantages, including relief from the “pill fatigue” endorsed by many patients²⁰ (Figure 1) and better protection of health privacy, which is particularly relevant for people with HIV who may experience stigma.²¹

The first long-acting, complete ART regimen includes injectable formulations of cabotegravir, an integrase strand transfer inhibitor, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor. This 2-drug combination has completed phase 3 trials,^{22,23} and is approved in Canada,²⁴ by the European Medicines Agency,^{25,26} and the US Food and Drug Administration.²⁷ However, whether or not this strategy will improve adherence to antiretroviral therapy in patients with specific barriers to adherence has yet to be established.

LA Cabotegravir with Rilpivirine for the Treatment of HIV

The phase 3 randomized trials of cabotegravir and rilpivirine included patients with HIV naïve to ART (FLAIR) and those with antiretroviral treatment experience, but virally suppressed on an oral ART regimen (ATLAS).^{22,23} The FLAIR study required a 6-month oral induction phase to achieve virologic suppression prior to receipt of the LA injection,²² and ATLAS had a 4-week lead-in to ensure tolerability of oral cabotegravir and rilpivirine prior to injection.²³ The drugs require a loading dose of 600 mg and 900 mg, cabotegravir and rilpivirine respectively, by two 3 mL injections (one into each gluteus medius muscle), followed by maintenance doses of 400 mg and 600 mg given as 2, 2 mL injections every 4 weeks. Both studies demonstrated that monthly injections of cabotegravir and rilpivirine were noninferior to continued oral ART, based on detectable viral load at Week 48 (plasma HIV-1 RNA ≥ 50 copies/mL pooled results: 1.9 vs 1.7%).^{22,23} Collectively, both studies had 591 participants in each arm (injectable therapy versus continuing oral therapy). Of note, 6 of 7 participants with confirmed virologic failure in the Phase 3 trials who received injectable cabotegravir and rilpivirine, had resistance mutations detected at the time of failure, in contrast to 3 of the 7 participants with virologic failure on oral therapy.²⁸ The participants with virologic failure on injectable therapy also had non-clade B subtype HIV (A6, A1, and AG); an area requiring further study.

Serious adverse events were rare in both trials (4%), but injection site reactions were common in the injectable arms (80%).^{22,23} As the injection site reactions were generally mild

Table 1. Long-Acting Antiretrovirals Currently in Development.

Antiretroviral Class	Agent	Formulation	Stage of Development
Attachment Inhibitors	UB-421	Intravenous	Phase II/III
Capsid Inhibitors	GS-CA1 (GS-6207)	Injectable	Phase I
Entry Inhibitors	Ibalizumab	Intravenous	FDA Approved
	Leronlimab, PRO 140	Intravenous and Injectable	Phase III
	Albuvirtide	Intravenous and injectable	Approved in China
	bNAbS (e.g., VRC01)	Intravenous	Phase II/III
	Combinaectin	Intravenous	Phase I
Integrase Strand Transfer Inhibitor	Cabotegravir	Injectable	Phase III/NDA, Phase II/III (Prevention)
	Raltegravir	Implant Injectable	Preclinical Preclinical
Non-nucleoside reverse transcriptase Inhibitor	Rilpivirine	Injectable	Phase III/NDA
	Elsulfavirine	Injectable	Preclinical
	Islatravir (MK-8591)	Oral	Phase I Phase IIa (Prevention) Phase I (Px)
Nucleoside reverse transcriptase Inhibitor	MK-8504, MK-8583 (tenofovir prodrugs)	Implant	Phase I
	TAF	Oral	Phase I/II (Prevention)
	GS-9131	Implant	Preclinical
Protease inhibitor	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical

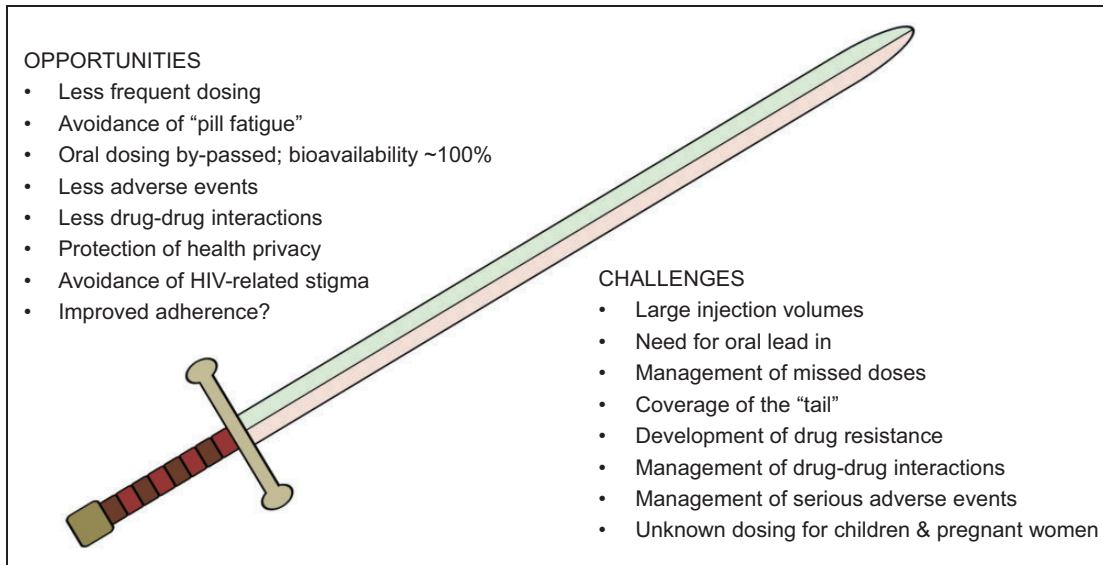


Figure 1. Long-acting antiretroviral therapy: potential opportunities and challenges.

and short-lived (median duration 3 days), these rarely led to treatment discontinuation. Firsthand observations from our own patients is that they anticipate some mild discomfort after the injections and may make adjustments to their schedules or planned activities, but generally find the injections very manageable. The ongoing ATLAS-2M trial is evaluating injections every 2 months compared to monthly, which will halve the number of injections, and potential injection site reactions.²⁹ The European Medicines Agency approved LA cabotegravir and rilpivirine for administration either monthly or every 2 months based on preliminary ATLAS-2M results,^{25,26} and approval of the every 2 month option is anticipated in both the US and Canada in the future.

So, who may benefit from this strategy if it becomes available? Phase 3 trial participants were non-pregnant adults with well controlled HIV disease, generally normal renal and hepatic function, and limited comorbidities. Only one prior regimen switch was permitted prior to entry into the ATLAS trial.²⁹ Hepatitis B coinfection was exclusionary for both studies, as cabotegravir and rilpivirine are not effective treatment options for hepatitis B chronic infection like some other antiretrovirals. Particular efforts were made to enroll women into the trials, resulting in 27.5% all participants being women.^{22,23} However, overall, only 29% of all participants were non-white. Consequently, data are lacking for children and adolescents, pregnant people, those with impaired organ function, and most importantly perhaps, those with poorly controlled HIV disease. An ongoing trial for this key population with barriers to adherence is described in more detail below. Until results from this study is available, we can only conclude that LA antiretroviral therapy may provide a very welcome alternative to daily oral therapy for the many people with HIV who fit the entry criteria for the phase 3 trials.

Additional Lessons Learned from HIV Pre-exposure Prophylaxis (PrEP) Studies

In 2010, oral emtricitabine with tenofovir disoproxil fumarate (FTC/TDF) was shown to provide protection against the acquisition of HIV infection in a seminal study of 2499 HIV-seronegative men who have sex with men or transgender women.³⁰ When compared to placebo, FTC/TDF reduced HIV incidence by 44% (95% confidence interval, 15 to 63; $P = 0.005$). Protection would have been closer to 90% though, if the analysis were restricted to participants with drug detected at any concentration in blood.³¹ Only 55% of participants tested at week 8 had drug detected, and detectable drug in blood plasma or peripheral blood mononuclear cells was less frequent in the incident HIV cases compared to uninfected controls (8% vs 44%, $P < 0.001$), highlighting the importance of medication adherence.

More recently, the HPTN083 study evaluated LA cabotegravir given by intramuscular injection every 8 weeks compared to daily oral FTC/TDF in a phase 2b/3 randomized, double-blind, double-dummy trial.³² 4750 adult men who have sex with men and transgender women were enrolled at 43 sites. The Data Safety Monitoring Board (DSMB) stopped the study early after a total of 52 HIV infections had occurred: 13 infections in the cabotegravir arm (incidence rate 0.41%) and 39 infections in the FTC/TDF arm (incidence rate 1.22%). The hazard ratio in the cabotegravir versus FTC/TDF arms was 0.34 (95% CI 0.18-0.62), corresponding to a 66% reduction in incident HIV infections in study participants given cabotegravir compared to FTC/TDF. While the study had a non-inferiority design, these results met the statistical criteria for superiority of the regimen containing cabotegravir compared to FTC/TDF. HPTN 084 has a similar design but enrolled cisgender women. This trial was also recently halted early by the

DSMB.³³ A total of 40 HIV infections occurred during follow-up, with 4 infections in the cabotegravir LA arm (incidence rate 0.2%) and 36 infections in the FTC/TDF arm (incidence rate 1.86%). The hazard ratio in the cabotegravir LA versus FTC/TDF arm was 0.11 (95% CI 0.01-0.31), meaning 89% reduction. Although pharmacokinetic analysis of stored samples are currently underway to assess medication adherence, it is a reasonable hypothesis that this improvement in effectiveness is related to the difference in adherence between oral and injectable therapy. Overall, these results provide a clear demonstration of the benefits of an LA formulation as compared to standard oral daily dosing for HIV pre-exposure prophylaxis. Further, the availability of multiple, highly effective HIV prevention products is expected to increase patient uptake and persistence due to patient preference for the delivery method, similar to the role of choice in hormonal contraception.²

Challenges with Long-Acting Therapy

The logistical challenges associated with rolling out LA strategies for ART in healthcare systems throughout the world will require planning and preparation due to the change in medication provision and tracking compared to oral therapies. Other potential challenges include the need for an oral lead-in, the management of missed doses, and the long pharmacokinetic tail.

Implementation in HIV clinics. At present, the injection requires two 3 mL injections for the loading dose^{24,27} and for every 8 week maintenance injections as investigated in ATLAS-2M,^{25,26} or two 2 mL injections for every 4 week maintenance injections,^{24,27} which must be injected into the gluteus medius muscles. The co-packaged product requires refrigeration and must be brought to room temperature prior to injection and then used within 2 hours of being drawn into the syringe for injection.²⁷ Given this process, initial steps for administering LA cabotegravir and rilpivirine include clinic staff training, planning for clinic workflow and patient scheduling, cold chain management, and drug product acquisition, storage and inventory.

Ongoing monthly or bimonthly visits to the clinic will be a new procedure for both patients and providers. From the clinic perspective, this will increase staffing requirements as well as introduce adherence monitoring requirements to ensure patients are returning on schedule for the injection visit. From the patient perspective, this may increase time away from work or personal responsibilities to attend injection appointments.

Preliminary data from a study involving healthcare workers (“staff participants”) involved in clinical trials at 8 clinics in the US reported that at baseline, staff participants most frequently had concerns about the ability of patients to adhere to monthly visits, patient transportation, and the clinic’s ability to flag missed visits. All of the concerns decreased by month 4 after implementation, highlighting that many of the challenges can be addressed through planning and training.³⁴ In addition, for clinics that are not able to accommodate additional visits for injections, the manufacturer is offering alternative options

for medication administration, including an “Alternate Site for Administration” locator in the US via the manufacturer’s website (<https://www.viivconnect.com/injectable/>). Additional implementation strategies are under investigation, including pharmacy-based administration, which may offer the advantage of injection appointment times outside of traditional clinic hours.

Need for oral lead in. All the clinical trials of LA cabotegravir and rilpivirine thus far, both for treatment and prevention of HIV, have included a 4-week oral lead-in (OLI) phase to ensure that the drugs are well tolerated. Emerging data suggest that this may not be necessary, as no safety signals were observed in any of the studies.^{22,23,29} In an extension to the FLAIR study, participants originally randomized to oral therapy who wanted to start injections were given the option of starting immediately without an oral lead-in.³⁵ 111 participants opted to start injections directly (referred to as “Direct To Injection” or DTI) and 121 chose the OLI. The 2 groups had similar demographics except that more White participants opted for DTI (78% DTI vs 69% OLI) and more Black participants chose the OLI (17% DTI vs 21% OLI). 24 weeks after the switch, 99.1% of participants in the DTI group had undetectable viremia compared to 93.4% in the OLI group. Incidence of drug-related adverse events was the same in both groups, approximately 20%, with only one serious event (Hodgkin lymphoma, not related to the intervention). Taken together, these data support the DTI approach in individuals with virologic suppression, which would remove one of the barriers to starting LA injectable therapy, but is not yet approved by regulatory agencies.

Management of missed doses. A major concern for both providers and patients about implementation of a LA injectable strategy for HIV treatment is the consequences of missed doses. In the Phase 3 trials, a window of +/- 7 days was permitted for receipt of the injections, and 98% of participants were able to meet this timeline.³⁶ The alternate approach for those who could not attend the injection visit was to provide them with oral versions of the study drugs to tide them over to the next injection, referred to as oral “bridging”, and informed by pharmacokinetic modeling studies.^{37,38} The recommendations in package inserts are consistent with these modeling results: within 7 days of a scheduled visit, the injections can be administered as planned, while a planned absence more than 7 days beyond the scheduled injection requires oral bridging, and a clinical assessment upon return for any patient who has an unplanned absence without oral bridging.^{24,27} Based on the modeling data, when injections are resumed, if ≤ 2 months elapsed since the last injection, injectable maintenance doses can be reinstated.^{37,38} If more than 2 months have elapsed, loading doses should be given, followed by resumption of maintenance dosing.

While this is a useful guide to managing missed or delayed doses, uncertainties remain related to the practicality of this approach outside of a clinical trial setting. For example, in the United States, oral cabotegravir is not available in retail

pharmacies. Therefore, patients and providers must plan ahead for any disruption in the dose administration schedule to access oral cabotegravir from the manufacturer and oral rilpivirine from a retail pharmacy.¹³ Delayed or missed doses are often unplanned in real-world settings, which may not allow sufficient time to access oral cabotegravir. One practical strategy may be to provide oral bridging with another commercially available antiretroviral combination that is accessible at a local pharmacy, or that the patient may already have on hand at home, such as co-formulated dolutegravir and rilpivirine.

Implications of the pharmacokinetic “Tail”. As discussed above, one of the key characteristics of drugs suitable for LA formulation is a long half-life. How long the drug persists after final administration is often referred to as the pharmacokinetic “tail”. The reported half-life of LA cabotegravir is 20–65 days, and the half-life of LA rilpivirine is 30–90 days, and concentrations of both have been detected in some patients up to 1 year after the last injection.^{39–43} HPTN 077 was a placebo-controlled phase IIa trial to evaluate the safety and pharmacokinetics of LA cabotegravir for prevention of HIV.⁴³ A prespecified analysis focused on the pharmacokinetic tail phase after the last IM dose.⁴⁴ At 52–60 weeks after the last injection, 23% of men versus 63% of women still had detectable cabotegravir concentrations; at 76 weeks, these rates were 13% of men versus 42% of women. The mean time from last dose to undetectability was much longer for women than for men (67.3 vs. 43.7 weeks). Higher body-mass index was also associated with a significantly longer terminal phase half-life. However, less than 10% of the variability in the tail was explained by sex and BMI, emphasizing the need for more investigation into this issue.

This long half-life support the ATLAS-2M dosing every 2 months and may be a significant advantage for individuals with adherence challenges. However, this may also pose a potential problem in that, after discontinuation of the drug, patients are exposed to decreasing concentrations over time, which will eventually fall below the effective threshold for either HIV prevention or virologic suppression during HIV treatment. In the setting of HIV infection, this may be a setup for the development of virologic resistance, as we have observed with other long half-life antiretroviral medications,^{45–47} and in the prevention setting, represents a period of risk for HIV acquisition for patients at risk for HIV infection. For patients who remain engaged in clinical care, a solution to cover the tail is to transition to alternative oral ART or PrEP therapy, but this represents a substantial challenge for patients who are lost to follow-up.

Patient Preferences and Concerns

Several surveys have demonstrated patient interest in LA formulations for the treatment of HIV. Participants in the phase 3 trials of LA cabotegravir and rilpivirine expressed high levels of treatment satisfaction, even after the experience of 2, 2 mL gluteal injections every month.⁴⁸ In qualitative studies, some

expressed a sense of “freedom” from the logistical and psychosocial demands of daily oral therapy and its attendant stigma.^{49,50} In qualitative interviews, trial participants from the US and Spain reported that the LA therapy was convenient, increased confidentiality and privacy, and had fewer opportunities for stigma, discrimination, or disclosure of HIV status because of daily pill taking.^{21,49}

In addition to clinical trial participants, several studies have found a high level of interest in LA therapies in adults and adolescents living with HIV who have not participated in LA clinical trials. Two studies of 374 and 400 adults with HIV, found 61% and 73%, respectively, of adults would be likely or very likely try LA ART.^{51,52} In 303 youth aged 13 to 24 years, 88.1% reported that they would probably or definitely try a LA injectable ART option.⁵³ This interest persists outside of the US, one study of 409 female sex workers found that 92% of participants in Tanzania and 85% of participants in Dominican Republic would be very likely or likely to use a LA ART.⁵⁴ In qualitative interviews and surveys, participants cited discretion, convenience, confidentiality, reducing pill burden, removing fear of missed dosing, and avoiding daily reminders of living with HIV which led to a feeling of normalcy.^{51,55,56}

However, some concerns about a switch from oral therapy to LA ART were also reported, including comfort with their current oral regimen, known effectiveness of oral options, potential differences in adverse effects between LA and oral formulations, and personal control over daily oral dosing.^{52,55,57} When considering injectable therapy, some concerns were identified in survey respondents specifically related to the injection (Figure 2).⁵¹ Some participants also raised concern that additional visits to the clinic required for LA ART administration may be a source of potential stigma/discrimination due to time away from work or if they have not disclosed their HIV status to friends or family members.^{21,49}

Some studies provide insight into patient characteristics which may predict those individuals who could have the most adherence benefit from LA therapy. Participants who require other daily oral medications did not view replacing oral ART with an injectable option as beneficial compared to those who did not have other routine oral medications. One survey found that patients who did not report any missed oral doses were most concerned with disrupting their established medication administration routine with a switch to LA therapies.⁵² Finally, it remains uncertain if patients who have difficulty attending clinic visits are good candidates for LA ART. One study identified participants who struggle to attend clinic actually preferred LA therapies over oral pills,⁵¹ yet there are obvious concerns surrounding missed LA doses if patients cannot attend clinic visits related to the prolonged pharmacokinetic tail, as discussed above.

In total, the positive qualities of LA ART identified in both phase 3 clinical trial and in other studies suggest that LA ART offers an important option for patients to choose, which may overcome some barriers associated with medication adherence. Certainly LA therapies cannot overcome all barriers to

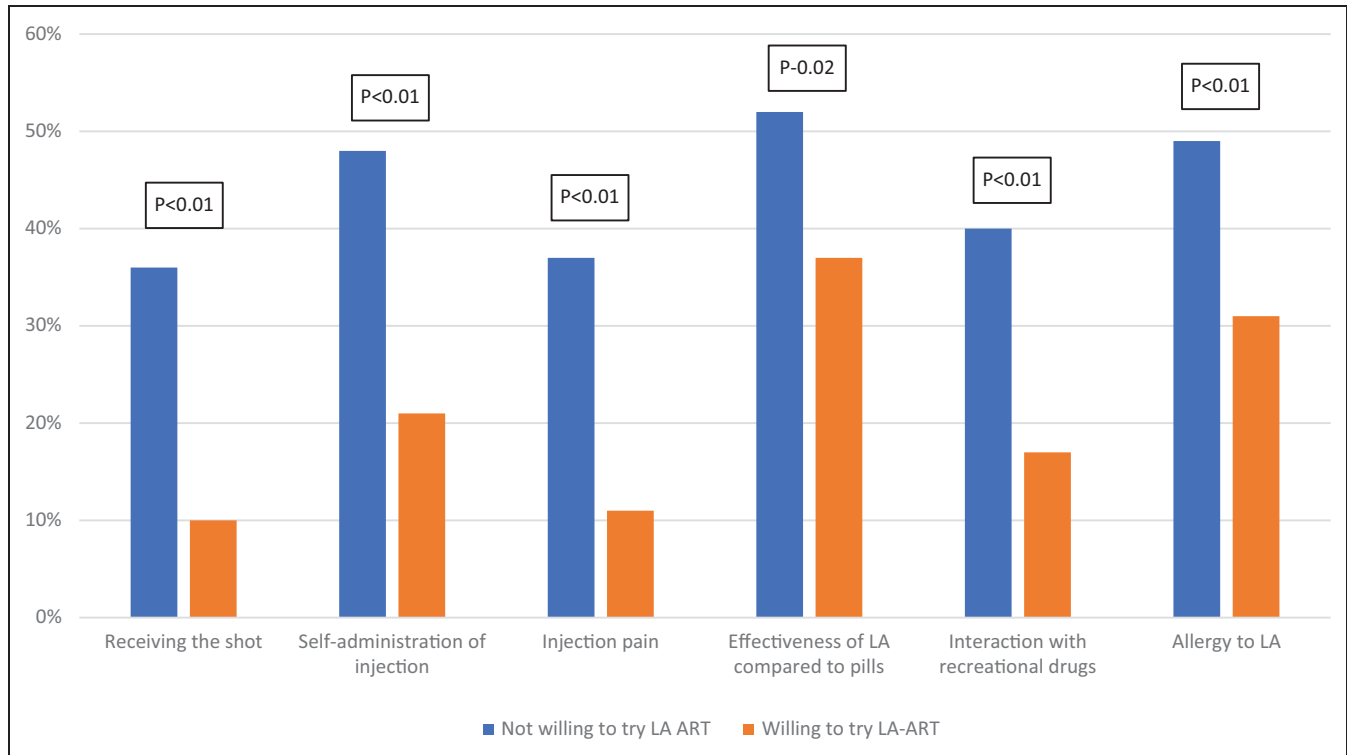


Figure 2. Concerns regarding long-acting injectable antiretroviral therapy. Among 371 participants who indicated if they were willing to try LA ART, differences were found in the frequency of concerns identified between those willing and unwilling to receive LA ART. Adapted from Dandachi et al. *AIDS Care* 2020.⁵¹

adherence and some patients may find additional challenges associated with LA therapies.

Long-Acting Therapy in the Setting of Adherence Barriers

Long-acting therapies are one tool which may improve adherence to ART for some individuals, particularly those with adherence barriers related to pill-fatigue or pill-aversion. Modeling suggests that LA ART may be most cost-effective in those individuals with barriers to adherence to daily oral therapy.⁵⁸ However, given the high adherence to injectable therapy observed in Phase 3 trials of LA cabotegravir and rilpivirine, practical questions exist surrounding the effectiveness of LA therapies beyond clinical trials.

Initial data from the LA cabotegravir and rilpivirine compassionate use program describe 35 individuals who qualified for the program.⁵⁹ Of the participants, most were enrolled due to barriers to oral medication adherence, including difficulty with pill swallowing, pill fatigue, and stigma, the remaining were eligible based on physical, psychological, and cognitive challenges. Of the 28 who entered the program with detectable viremia, 16 (57%) achieved virologic suppression (HIV-1 RNA < 50 copies/mL). Six of 7 participants who enrolled with a suppressed HIV RNA maintained virologic suppression on LA cabotegravir and rilpivirine. Five (14%) patients had incomplete virologic responses and stopped the injectable treatment. Four of these patients had NNRTI resistance-

associated mutations at failure and 2 had integrase inhibitor resistance-associated mutations. These early data demonstrate LA therapy will be a viable option for many patients who struggle with daily oral ART adherence, but the 14% of participants with virologic failure demonstrate the ongoing importance of addressing barriers to adherence.

The AIDS Clinical Trials Group (ACTG) study A5359, the LATITUDE study, is a Phase 3, randomized clinical trial in 350 patients with a history of non-adherence. The LATITUDE study will compare the efficacy, safety, and durability of standard of care oral ART to LA cabotegravir/rilpivirine given IM every 4 weeks (NCT03635788). The trial will include participants with non-adherence to oral therapy which resulted in virologic failure, as well as those who were lost to clinical follow-up. To support patients through the oral lead-in period (6 months to achieve virologic suppression), the trial will utilize conditional economic incentives, a strategy that improved adherence, retention in care, and virologic suppression in other studies of oral ART,⁶⁰⁻⁶² in addition to other adherence interventions supported by clinical guidelines.^{15,63} Other implementation trials of LA cabotegravir and rilpivirine are limited to patients without prior virologic failure, irrespective of resistance (NCT04001803, NCT04399551). Therefore, results from the LATITUDE trial will improve our understanding of how to support adherence to the oral lead-in therapy, as well as the long-term role of LA injectable therapy, compared to standard of care in an important group of patients with barriers to adherence.

Other Long-Acting Antiretroviral Strategies

Although intramuscular injectable LA therapy is now available for HIV treatment and on the horizon for HIV prevention, other methods for LA drug delivery are at various stages of development (Table 1). Ibalizumab, a monoclonal antibody that is a CD4 cell directed post-attachment entry inhibitor, was the first LA therapy approved by the US FDA for highly treatment experienced patients.⁶⁴ Ibalizumab is administered twice weekly as an infusion over 15-30 minutes, but must be used in combination with other oral antiretrovirals. Encouragingly, the LA medications in development span all of the classes of antiretrovirals, which raises hope for a future of multiple fully-suppressive LA therapies for both prevention and treatment of HIV, including for those individuals who are highly treatment experienced.

Other routes of LA drug administration may address some of the challenges with IM LA therapy. For example, an oral or subcutaneous injection product given once weekly would allow for self-administration, which some patients may prefer to either avoid inconvenience or stigma related to frequent visits to the provider, or to offer individual control over their dose administration. Implantable products hold the potential for a removable LA product in case of an adverse effect and also may address patient concerns related to prolonged exposure to therapy after discontinuation. These different routes of administration, and certainly products with a longer duration of action, may also ease the burden of frequent clinic visits for dose administration for both providers and patients. Consistently, less frequent administration of LA therapies was associated with greater interest by patients across disease states.^{21,49,53,57}

Conclusion

Long-acting antiretroviral therapy is an exciting area of investigation and may provide a welcome alternative for patients to both prevent and treat HIV infection. Current data support the efficacy and safety of the first complete LA ART regimen, cabotegravir and rilpivirine, in nonpregnant adults with demonstrated HIV virologic suppression, absence of hepatitis B coinfection, and normal renal and liver function. Many providers and patients are interested to learn how this approach might help those with adherence challenges, but more data from clinical trials including this at-risk population and from real-world clinical experience are needed before any conclusions can be drawn. In addition to this key population, application to pediatric populations and pregnant women should be explored. LA therapies offer a key difference to currently available ART regimens: patient choice related to their preferred way to administer medications. Based on other disease states with multiple routes of administration of available therapies, this may lead to improved adherence and retention in care for some patients. However, caregivers must consider all of the social, structural, and behavioral barriers which may impact patient adherence to both medication and clinical care which may not

be addressed by a change from oral to LA therapies. Overall, provider-patient partnership and communication prior to any change in ART to assure patient comfort with efficacy, adverse effects, and administration requirements, as well as innovative strategies to administer LA therapy at convenient times and locations, will add to the benefits associated with removing adherence barriers through LA ART.

Declaration of Conflicting Interests

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References

- Owen A, Rannard S. Strengths, weaknesses, opportunities and challenges for long acting injectable therapies: Insights for applications in HIV therapy. *Adv Drug Deliv Rev.* 2016;103:144–156.
- Winner B, Peipert JF, Zhao Q, et al. Effectiveness of long-acting reversible contraception. *N Engl J Med.* 2012;366(21):1998–2007.
- Peipert JF, Zhao Q, Allsworth JE, et al. Continuation and satisfaction of reversible contraception. *Obstet Gynecol.* 2011;117(5):1105–1113.
- Fobelo Lozano MJ, Sanchez-Fidalgo S. Adherence and preference of intravenous zoledronic acid for osteoporosis versus other bisphosphonates. *Eur J Hosp Pharm.* 2019;26(1):4–9.
- Cramer JA, Lynch NO, Gaudin AF, Walker M, Cowell W. The effect of dosing frequency on compliance and persistence with bisphosphonate therapy in postmenopausal women: a comparison of studies in the United States, the United Kingdom, and France. *Clin Ther.* 2006;28(10):1686–1694.
- McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone.* 2007;41(1):122–128.
- Rietbrock S, Olson M, van Staa TP. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. *QJM.* 2009;102(1):35–42.
- Ziller V, Kostev K, Kyvernitakis I, Boeckhoff J, Hadji P. Persistence and compliance of medications used in the treatment of osteoporosis—analysis using a large scale, representative, longitudinal German database. *Int J Clin Pharmacol Ther.* 2012;50(5):315–322.

9. Curtis JR, Yun H, Matthews R, Saag KG, Delzell E. Adherence with intravenous zoledronate and intravenous ibandronate in the United States Medicare population. *Arthritis Care Res (Hoboken)*. 2012;64(7):1054–1060.
10. Orwoll ES, Miller PD, Adachi JD, et al. Efficacy and safety of a once-yearly i.v. Infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. *J Bone Miner Res*. 2010;25(10):2239–2250.
11. Kaplan G, Casoy J, Zummo J. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. *Patient Prefer Adherence*. 2013;7:1171–1180.
12. Park SC, Choi MY, Choi J, et al. Comparative efficacy and safety of long-acting injectable and oral second-generation antipsychotics for the treatment of schizophrenia: A systematic review and meta-analysis. *Clin Psychopharmacol Neurosci*. 2018;16(4):361–375.
13. Peters L, Krogmann A, von Hardenberg L, Bodeker K, Nohles VB, Correll CU. Long-acting injections in schizophrenia: a 3-year update on randomized controlled trials published January 2016–March 2019. *Curr Psychiatry Rep*. 2019;21(12):124.
14. Brnabic AJ, Kelin K, Ascher-Svanum H, Montgomery W, Kadziola Z, Karagianis J. Medication discontinuation with depot and oral antipsychotics in outpatients with schizophrenia: comparison of matched cohorts from a 12-month observational study. *Int J Clin Pract*. 2011;65(9):945–953.
15. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV*. Department of Health and Human Services. Accessed March 31, 2021. <https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf>
16. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One*. 2013;8(12):e81355.
17. Dorman RM, Sutton SH, Yee LM. Understanding HIV-related pill aversion as a distinct barrier to medication adherence. *Behav Med*. 2019;45(4):294–303.
18. Flexner C, Thomas DL, Swindells S. Creating demand for long-acting formulations for the treatment and prevention of HIV, tuberculosis, and viral hepatitis. *Curr Opin HIV AIDS*. 2019;14(1):13–20.
19. Flexner C, Owen A, Siccardi M, Swindells S. Long-acting drugs and formulations for the treatment and prevention of HIV. *Int J Antimicrob Agents*. 2020;57(1):106220.
20. Claborn KR, Meier E, Miller MB, Leffingwell TR. A systematic review of treatment fatigue among HIV-infected patients prescribed antiretroviral therapy. *Psychol Health Med*. 2015;20(3):255–265.
21. Kerrigan D, Mantsios A, Gorgolas M, et al. Experiences with long acting injectable ART: a qualitative study among PLHIV participating in a Phase II study of cabotegravir + rilpivirine (LATTE-2) in the United States and Spain. *PLoS One*. 2018;13(1):e0190487.
22. Orkin C, Arasteh K, Gorgolas Hernandez-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med*. 2020;382(12):1124–1135.
23. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med*. 2020;382(12):111201123.
24. Cabenuva[®] and Vocabria[®] [Product Monograph]. Laval, Quebec. Viiv Healthcare ULC. March 2020.
25. Rekambys[®] European Medicines Agency prescribing information. Updated December 17, 2020. Accessed March 31, 2021. <https://www.ema.europa.eu/en/medicines/human/EPAR/rekambys>
26. Vocabria[®] European Medicines Agency prescribing information. Updated February 19, 2021. Accessed March 31, 2021. <https://www.ema.europa.eu/en/medicines/human/EPAR/vocabria>
27. Cabenuva[®] prescribing information. *Viiv Healthcare*. Research Triangle Park; January 2021.
28. Rizzardini G, Overton ET, Orkin C, et al. Long-acting injectable cabotegravir + rilpivirine for HIV maintenance therapy: week 48 pooled analysis of phase 3 atlas and flair trials. *J Acquir Immune Defic Syndr*. 2020;85(4):498–506.
29. Overton ET, Richmond GJ, Rizzardini G, et al. *Cabotegravir + rilpivirine every 2 months is noninferior to monthly: ATLAS-2 M study*. *CROI 2020 Virtual*. March 8–11, 2020, Abstract 34.
30. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363(27):2587–2599.
31. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med*. 2012;4(151):151ra25.
32. Landovitz RJ, Donnell D, Clement M, et al. HPTN083 interim results: Pre-exposure prophylaxis (PrEP) containing long-acting injectable cabotegravir (CAB-LA) is safe and highly effective for cisgender men and transgender women who have sex with men (MSM, TGW). In: *23 rd International HIV Conference; Virtual*. July 6–10, 2020. Abstract OAXLB0101.
33. Delany-Moretlwe S, Hughes JP, Bock P, et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: results from HPTN 084. In: *HIV R4P 2021 virtual conference*. January 27, 2021. Abstract LB1479.
34. Czarnogorski M, Garris C, Wannamaker P, et al. Perceived implementation barriers decrease during initial stages of an implementation science Hybrid III Study (CUSTOMIZE) of Cabotegravir and Rilpivirine Long-Acting (CAB + RPV LA) in US Healthcare Settings: Healthcare Team Perspective. In: *23 rd International AIDS Conference; Virtual*. July 6–10, 2020. Abstract LBPEE42.
35. D’Amico R, Orkin C, Morell EB, et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: ATLAS week 48 results. *HIV Glasgow 2020 Virtual*. October 5–8, 2020. Abstract O414.
36. Teichner P, Cutrell A, D’Amico R, et al. Patient adherence to long-acting injectable cabotegravir + rilpivirine through 48 weeks of maintenance therapy in the phase 3 ATLAS and FLAIR studies. *ID Week* October 2–6, 2019, Abstract 884.
37. Rossenu S, Neyens M, Van Solingen-Ristea R, et al. Population pharmacokinetic (PopPK) modeling and simulation of monthly intramuscular (IM) long-acting rilpivirine (RPV LA) to inform strategies following dosing interruptions in HIV-1 infected subjects. *AIDS 2020 Virtual*. July 6–10, 2020, Abstract PEB0264.

38. Han K, Baker M, Patel P, et al. Population pharmacokinetic (PPK) modeling and simulation of long-acting (LA) cabotegravir (CAB) to inform strategies following dosing interruptions in HIV-1-infected subjects. *ID Week*. October 2–6, 2019, Abstract 1532.
39. McGowan I, Dezzutti CS, Siegel A, et al. Long-acting rilpivirine as potential pre-exposure prophylaxis for HIV-1 prevention (the MWRI-01 study): an open-label, phase 1, compartmental, pharmacokinetic and pharmacodynamic assessment. *Lancet HIV*. 2016;3(12):e569–e78.
40. Spreen W, Ford SL, Chen S, et al. GSK1265744 pharmacokinetics in plasma and tissue after single-dose long-acting injectable administration in healthy subjects. *J Acquir Immune Defic Syndr*. 2014;67(5):481–486.
41. Spreen W, Min S, Ford SL, et al. Pharmacokinetics, safety, and monotherapy antiviral activity of GSK1265744, an HIV integrase strand transfer inhibitor. *HIV Clin Trials*. 2013;14(5):192–203.
42. Verloes R, Deleu S, Niemeijer N, Crauwels H, Meyvisch P, Williams P. Safety, tolerability and pharmacokinetics of rilpivirine following administration of a long-acting formulation in healthy volunteers. *HIV Med*. 2015;16(8):477–484.
43. Landovitz RJ, Li S, Grinsztejn B, et al. Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial. *PLoS Med*. 2018;15(11):e1002690.
44. Landovitz RJ, Li S, Eron JJ, Jr., et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. *Lancet HIV*. 2020;7(7):e472–e481.
45. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS*. 2008;22(17):2279–2289.
46. Geretti AM, Fox Z, Johnson JA, et al. Sensitive assessment of the virologic outcomes of stopping and restarting non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *PLoS One*. 2013;8(7):e69266.
47. Palmer S, Boltz V, Martinson N, et al. Persistence of nevirapine-resistant HIV-1 in women after single-dose nevirapine therapy for prevention of maternal-to-fetal HIV-1 transmission. *Proc Natl Acad Sci U S A*. 2006;103(18):7094–7099.
48. Murray M, Antela A, Mills A, et al. Patient-reported outcomes in ATLAS and FLAIR participants on long-acting regimens of cabotegravir and rilpivirine over 48 weeks. *AIDS Behav*. 2020;24(12):3533–3544.
49. Mantsios A, Murray M, Karver TS, et al. Efficacy and freedom: patient experiences with the transition from daily oral to long-acting injectable antiretroviral therapy to treat HIV in the context of phase 3 trials. *AIDS Behav*. 2020;24(12):3473–3481.
50. Mantsios A, Murray M, Karver TS, et al. “I feel empowered”: women’s perspectives on and experiences with long-acting injectable antiretroviral therapy in the USA and Spain. *Cult Health Sex*. 2020:1–13.
51. Dandachi D, Dang BN, Lucari B, Swindells S, Giordano TP. Acceptability and preferences for long-acting antiretroviral formulations among people with HIV infection. *AIDS Care*. 2020:1–9.
52. Williams J, Sayles HR, Meza JL, et al. Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients. *Nanomedicine (Lond)*. 2013;8(11):1807–1813.
53. Weld ED, Rana MS, Dallas RH, et al. Interest of youth living with HIV in long-acting antiretrovirals. *J Acquir Immune Defic Syndr*. 2019;80(2):190–197.
54. Kerrigan D, Sanchez Karver T, Muraleetharan O, et al. “A dream come true”: Perspectives on long-acting injectable antiretroviral therapy among female sex workers living with HIV from the Dominican Republic and Tanzania. *PLoS One*. 2020;15(6):e0234666.
55. Philbin MM, Parish CL, Kinnard EN, et al. Multisite study of women living with HIV’s perceived barriers to, and interest in, long-acting injectable antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2020;84(3):263–270.
56. Dube K, Campbell DM, Perry KE, et al. Reasons people living with HIV might prefer oral daily antiretroviral therapy, Long-acting formulations, or Future HIV remission options. *AIDS Res Hum Retroviruses*. 2020;36(12):1054–1058.
57. Dube K, Eskaf S, Evans D, et al. The dose response: Perceptions of people living with HIV in the United States on alternatives to oral daily antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2020;36(4):324–348.
58. Ross EL, Weinstein MC, Schackman BR, et al. The clinical role and cost-effectiveness of long-acting antiretroviral therapy. *Clin Infect Dis*. 2015;60(7):1102–1110.
59. D’Amico R, Moodley R, van Landuyt, et al. Compassionate use of long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) for patients in need of parenteral antiretroviral therapy. In: *23rd International AIDS Conference*; July 6–10, 2020, Virtual. Abstract PEB0263.
60. El-Sadr WM, Donnell D, Beauchamp G, et al. Financial incentives for linkage to care and Viral suppression among HIV-positive patients: A randomized clinical trial (HPTN 065). *JAMA Intern Med*. 2017;177(8):1083–1092.
61. Galarraga O, Genberg BL, Martin RA, Barton Laws M, Wilson IB. Conditional economic incentives to improve HIV treatment adherence: literature review and theoretical considerations. *AIDS Behav*. 2013;17(7):2283–2292.
62. Javanbakht M, Prosser P, Grimes T, Weinstein M, Farthing C. Efficacy of an individualized adherence support program with contingent reinforcement among nonadherent HIV-positive patients: results from a randomized trial. *J Int Assoc Physicians AIDS Care (Chic)*. 2006;5(4):143–150.
63. HIV/AIDS Prevention Research Synthesis Project. Compendium of evidence-based interventions and best practices for HIV prevention. centers for disease control and prevention. Updated February 12, 2021. Accessed March 31, 2021. <https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html>
64. *Trogarzo® Prescribing Information*. Theratechnologies Inc; April 2020.