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The future of long acting agents for PrEP

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Abstract

Purpose of Review: The main reason for failure of oral pre-exposure prophylaxis (PrEP) regimens for HIV is poor adherence. Intramuscular cabotegravir was recently approved for PrEP, and a number of other long-acting antiretroviral formulations and products are currently in clinical development. This includes subcutaneous and intravenous injections, implants, and microarray (microneedle) patches, as well as extended duration oral drugs. The success and future uptake of these products will depend on a variety of factors.

Recent Findings: Long-acting delivery of antiretroviral agents for PrEP confers significant advantages over short-acting oral delivery. This is exemplified by the superior efficacy of intramuscular cabotegravir given every eight weeks as compared to daily oral co-formulated tenofovir disoproxil fumarate and emtricitabine. There is also evidence for PrEP efficacy for a broadly-neutralizing monoclonal antibody given intravenously every eight weeks. One of the leading candidates for long-acting PrEP, islatravir, was being studied as a monthly oral drug or a non-erodable subcutaneous implant inserted for up to 12 months. However, clinical studies of this agent were put on hold in late 2021 because of unanticipated lymphopenia.

Summary: Long-acting antiretroviral products have substantial promise for PrEP, and have particular advantages over daily oral drugs based mainly on improved adherence. However, there are barriers to further uptake that include the need for more intensive interaction with systems of health care delivery, greater expense and complexity of implementation, and unexpected long-term toxicities.

Keywords

HIV; long-acting antiretrovirals; implants; microarray patches; islatravir; lenacapavir; broadly-neutralizing antibodies

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Conflicts of interest

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Introduction

Why should we pursue long-acting approaches to drug delivery for HIV pre-exposure prophylaxis (PrEP) when co-formulated daily oral antiretrovirals are widely available and work so well? Injectable cabotegravir provides an immediate answer to this question. Recent large randomized prospective controlled clinical trials clearly demonstrate the superior efficacy of this agent, as compared to daily oral PrEP.[1] There are several possible explanations for this outcome, but they include improved adherence to bimonthly injection visits as compared to self-administered oral drugs, improved potency and barrier to resistance of cabotegravir monotherapy as compared to combination oral nucleoside reverse transcriptase inhibitors (NRTIs), and better tolerability and toxicity profile of the injected drug.

Besides benefiting adherence, long-acting formulations have a number of potential advantages over daily oral therapy.[2] This includes use in previously adherent patients complaining of pill fatigue. In much of the world there is still significant HIV-associated stigma, and long-acting formulations often free patients from the need to carry around pills. Patient surveys consistently show a preference for long-acting forualtions over comparable daily pills; this includes recent surveys conducted in adolescents.[3] With the recent approval of injectable cabotegravir for HIV prevention, these formulations are likely to gain even greater appeal to those at risk of acquiring HIV infection.

Long-acting formulations and products do, however, have a number of potential drawbacks. This includes concerns about what happens if a recipient develops adverse effects from a product that is not easily removable. Only topical or implanted drugs can be removed quickly in case the recipient suffers a significant adverse event.[2] As we have learned from the example of islatravir, because these formulations produce detectable concentrations of drug for several months, initial short-term clinical studies may miss important adverse effects that only appear much later during large clinical trials. This represents a significant theoretical drawback for the development process.

Long-acting agents present logistical challenges for HIV care providers. Most PrEP recipients on oral treatments may only need to be seen every 3-6 months, so accommodating monthly or bimonthly visits for injections could cause additional administrative burden. When used for prevention applications like PrEP, there is an expectation that any product should be nearly risk-free because the target population is already essentially healthy and disease-free.

Additional concerns include the possibility of adverse drug-drug interactions from concurrent agents used during administration of the LA drug. The latter concern particularly applies to concurrent inducing agents such as rifamycin antibiotics or St. Johns wort. [4] There is substantial concern about the safety of these formulations and possible pharmacokinetic changes in users who become pregnant. Very little data on the safety and tolerability of long-acting cabotegravir and rilpivirine in pregnant women have been provided to date, and women of child-bearing potential are often excluded from early clinical trials.[5]

Drug resistance occurring during use is another important concern for long-acting formulations used as prevention when incident infections occur. Fortunately, such outcomes appear to be exceedingly rare in studies of injectable cabotegravir for PrEP. But several cases of cabotegravir resistance were noted in participants in the HPTN 083 study, even in a handful of subjects who received their bimonthly injections on time.[1,6] Proper ways to monitor recipients for possible seroconversion and acquisition of drug resistance are ongoing challenges in developing LA formulations for PrEP.

Long-Acting Antiretroviral Approaches in Pre-Clinical and Clinical Development

A number of long-acting drug delivery platforms are under investigation for HIV prevention (*see* Table 1). As a general rule, agents that are most suitable for long-acting formulation and delivery are those with exceptionally high antiviral potency.[2] Since the allowable mass of active pharmaceutical ingredient that can be delivered in a single dose is small, the agents involved must have extraordinary capacity to inhibit viral replication at low concentrations. Transcutaneous drug delivery strategies like microarray patches, and transmucosal strategies like vaginal rings, require the drug to passively cross membrane barriers; this requires special physicochemical properties like low molecular weight (<500 Dalton), melting point <250 °C, and moderate log P.[7]

Route of delivery is a key determinant of the suitability of long-acting agents for prevention applications. As is the case with hormonal contraception, every different product is likely to appeal to different populations. Factors that determine user preference include dosing interval, convenience, protection from stigma, whether or not the product can be self-administered, and out-of-pocket costs.[8] Having access to a menu of several possible choices means the intervention can be tailored to the needs of the individual.

Infrequently Administered Oral Drugs

Oral drug administration has a number of obvious advantages over parenteral or topical administration. Most orally administered drugs lack the pharmacokinetic properties required to allow dosing as infrequently as once weekly. Infrequently administered oral drugs are therefore unusual in the human pharmacopeia. For prevention applications like PrEP, infrequently dosed oral agents would have the advantage of self-administration, convenience, and the possibility of low cost as compared to other routes of drug delivery.

Islatravir (4'-ethynyl-2-fluoro-2'-deoxyadenosine [ISL]) is a very potent nucleoside reverse transcriptase inhibitor with a novel mechanism of action.[9] Unlike other currently approved NRTIs, ISL retains its 3’-hydroxyl group in the ribose ring. This drug has higher affinity for the active site of the HIV reverse transciptase, contributing to its potency. The incorporation of ISL-monophosphate into the reverse transcriptase active site blocks primer translocation and halts HIV replication without immediately causing chain termination, since the drug contains the 3’-hydroxyl. ISL has a favorable resistance profile for HIV treatment and prevention. The major resistance mutation associated with the use of this drug has been M184V, which only modestly reduces drug sensitivity in vitro.[10]

Islatravir also has a halogen substitution at the 2-position of the adenine ring that impairs degradation by adenosine deaminase, resulting in a prolonged intracellular half-life for ISL-TP of greater than 72 hours.[11] The combination of high potency and exceedingly slow clearance of the parent compound and its active metabolite prompted examination of islatravir for infrequent oral administration. Pharmacokinetic studies demonstrated that oral doses of islatravir of 60 or 120 mg could produce intracellular concentrations of ISL-TP that exceeded the target for antiviral effect (0.05 pMol/million cells) for at least 4 weeks.[12] Trials of oral islatravir for PrEP at these doses were underway when unexpected lymphopenia was reported in November, 2021. [13]

After 24 weeks (six doses), mean reductions in total lymphocyte counts of 21% and 36% were reported in the 60 mg and 120 mg arms, respectively, in the monthly oral PrEP trials, as compared to a 4% increase with placebo. The mechanism of this adverse effect, and the timing of onset, are yet to be determined, as there has been limited disclosure of the details of these findings. In HIV seronegative individuals with normal lymphocyte counts at baseline, a modest reduction in lymphocyte count could still maintain counts in the normal range, and this might be acceptable in otherwise healthy recipients. The fact that lymphopenia with ISL does appear to be dose-dependent provides some encouragement that a tolerable dose and regimen can be found for PrEP applications. However, as of February, 2022, clinical trials of islatravir were still on hold, and the future of ISL as monthly oral PrEP, or in implant form (see below) is uncertain.[13]

Other approved antiretroviral agents could also be considered for less frequent oral administration. This is especially true of the NRTI's tenofovir and emtricitabine, already approved for daily oral PrEP. The estimated half-life of the active metabolite of tenofovir, intracellular tenofovir-diphosphate (TFV-DP), is 60-100 hours. Tenofovir prodrugs could therefore be given less frequently than once per day while maintaining antiviral effect.[14] The practicality of this kind of dosing is questionable unless the interval can be extended from once-daily to once-weekly. Since the prodrug tenofovir alafenamide (TAF) is ten times more potent than tenofovir disoproxil fumarate (TDF) in vitro and in vivo, an increased dose might be feasible for once-weekly dosing.[15]

In the prevention setting, it is important to note that TAF and TDF have activity against both hepatitis B virus (HBV) and HIV, and could potentially prevent both infections.[16] Emtricitabine intracellular triphosphate has an estimated half-life in human PBMCs of 39 hours [17], and this drug also has activity against HBV. Could a tenofovir prodrug and emtricitabine be given orally for PrEP once-weekly? The pharmacokinetic properties of both drugs suggest that this could be a possibility, although the initial dose might have to be increased, and no studies have been conducted to confirm this.

Subcutaneous Drug Administration

Lenacapavir is a first-in-class, highly potent inhibitor of assembly of the HIV-1 capsid. Because the mechanism of action of this drug is unique, resistance mutations selected in vitro are distinct from those selected by any other ARV. Lenacapavir's pharmacokinetic properties make it an excellent candidate for LA administration. Single subcutaneous doses of 100, 300, or 450 mg produced mean plasma concentrations at or above the protein-

adjusted EC95 for at least 12 weeks, and a subcutaneous dose of 927 mg produces mean concentrations at that target after six months.[18]

In small numbers of HIV-infected volunteers not currently taking antiretroviral therapy, a single dose of LENACAPAVIR at 50, 150, or 450 mg reduced mean plasma HIV RNA concentrations by 1.5-2.0 logs 10 days after administration, at which point oral therapy was instituted. The very long half-life of the subcutaneous drug requires a loading dose with an oral formulation for the first 14 days of treatment, potentially complicating its PrEP applications. But the high barrier to resistance and very slow clearance make this drug an attractive investigational candidate for PrEP.[18]

Intravenous Drug Administration

HIV broadly neutralizing antibodies (bnAbs) target specific antigens on the HIV external membrane glycoprotein gp120. They were originally isolated from B-cell screening of HIV-infected individuals and thus are entirely human and non-synthetic.[19] In clinical studies, bnAbs are generally well tolerated with an excellent safety and tolerability profile. These agents suppress viral replicationin HIV-infected indicuals, but plasma viral RNA rebounds rapidly with monotherapy, and antibody-resistant viruses emerge.[20]

Two large randomized prospective clinical trials found that infusions of a single bnAb, VRC01, every eight weeks had no overall impact in reducing HIV seroconversion in at-risk women and men. However, in a pre-planned analysis, VRC01 infusions were estimated to reduce HIV acquisition by 75% in regions where study participants were exposed to antibody-sensitive virus.[21] The results of these large trials suggest that bnAb PrEp is going to require a combination of at least two and possibly three bnAbs. Fortunately, the nature of these proteins should allow their co-formulation and simultaneous infusion, thus making the complexity of a combination product invisible to end users.

A key pathway for human antibody clearance is binding to the neonatal Fc receptor, followed by endosomal uptake and either degradation or surface re-cycling. A leucine-serine (LS) substitution in the Fc portion of the antibody increases binding affinity for the neonatal Fc receptor and greatly increases endosomal recycling of intact antibody to the cell surface, thus reducing overall antibody clearance. Two such modified antibodies, VRC01-LS and VRC07-LS, have plasma half-lives in human volunteers that may allow intravenous or possibly subcutaneous dosing every 3-6 months.[22]

The future use of bnAbs for PrEP is likely to focus on their long-acting equivalents to allow infrequent administration. Although the AMP trials involved q8 weekly drug infusions, less frequent administration – every three months to every six months – seems feasible.

Transcutaneous and Transmucosal Drug Administration

Vaginal Ring Technology—The dapivirine vaginal ring has been approved for PrEP use in a small number of countries in sub-Saharan Africa, and has been granted a favorable review by the European Medicines Agency (EMA). Registrational trials of this product showed only 27-35% overall effectiveness in preventing acquisition of new HIV infections, suggesting that this methodology is far less effective than other approved methods.[23] This

seems to reflect the fact that the device can be removed by the user, as sub-analysis of data from Phase 3 studies indicates higher efficacy in women who actually use the devise as directed.

Several approaches are being pursued to improve the effectiveness and durability of vaginal rings for PrEP. This includes creation of a combination device containing both dapivirine and a long-lasting hormonal contraceptive. The current ring must be switched out every 28 days, but novel technologies may be applied to produce a product with a dosing interval closer to three months, which could improve acceptability.[23]

Microarray Patches—Transcutaneous drug delivery using microarrays composed of hundreds of microneedles is an exciting and novel approach with significant implications for HIV treatment and prevention.[24] Two basic technological approaches are being considered. In one, non-erodable needles are loaded with one or more drugs that can elute out in the subdermal space over the duration of placement of the patch, usually a few days to a few weeks. In another, needles are composed of nano-particles that are released from the patch and form a subdermal reservoir that can release drug systemically over a period of weeks or even months after the patch is removed.[24] Both are in pre-clinical development, although feasibility studies have been conducted in healthy human volunteers.

One important limitation of transdermal patch technology is drug loading capacity. Focus therefore needs to be restricted to highly potent active pharmaceutical ingredients. A microarray patch that contains rilipivirine nanocrystals delivered detectable drug in the plasma of rats for seven days after the patch was removed.[25] A cabotegravir nanoparticle patch delivered detectable drug in the same animal model system for 28 days. These approaches hold particular attraction for situations in which injection or infusion is undesirable, for example in infants, children, or adolescents. How transdermal drug delivery compares to other platforms for PrEP will require larger clinical trials.

Subcutaneous Implants

Contraceptive implants are widely used for prevention of pregnancy, and implant technology is an attractive and novel approach to PrEP. [26] A particular attraction of implant technologies is the possibility of delivering drug over a very extended period of time – in the case of implants for hormonal contraception, up to five years for a single device. Other potential advantages of implant technology include the ability to remove the device in the case of side effects or the desire to end therapy. Multiple drgus can be incorporated into a single implant, or multiple implants can be inserted at the same time, as is the case for the five-year levonorgestrel implant.[26]

Subcutaneous implants also have some potential disadvantages in the PrEP setting. This includes the need for insertion and removal by trained personnel using sterile technique. If the implant is non-bioerodable, then the device must be removed at the end of its dosing lifespan, and this requires a minor surgical procedure. Devices can migrate to a point where they are no longer palpable, but radio-opaque material can be incorporated to allow location using standard X-ray. [26]

The only antiretroviral implant tested to date in humans is for delivery of islatravir. Initial clinical studies of a non-erodable ISL polymer implant in HIV seronegative volunteers found that devices containing 54 or 62 mg of drug achieved a near-constant, linear (zero-order) release rate throughout the entire 12 week duration of implantation. Both implants maintained intracellular isaltravir-triphosphate (ISL-TP) concentrations above the antiviral target of 0.05 pmol/10^6 cells for the full 12 week duration of insertion. Overall tolerability of the implants was good, although about half the recipients of the 62 mg implant reported induration and erythema at the insertion site for at least 30 days after placement.[27] Modelling studies based on these data indicate that intracellular ISL-TP concentrations would remain at or above the target for at least 16 months with the 54 mg product, raising the possibility of a once-yearly implant for PrEP. Unfortunately the lymphopenia observed with long-term islatravir dosing place the immediate future of these implants in doubt.

Tenofovir alafenamide (TAF) is another potent antiretroviral suitable for implant technology. Several approaches have been pursued for the creation of a TAF implant, and their pre-clinical development was recently reviewed.[28] Several, but not all, of these approaches have produced significant local toxicity in animals, including necrosis of tissue in the vicinity of the implant. However, other TAF implant technologies have been better tolerated, including a device containing pure TAF powder loaded into platinum cured microperforated silicone tubing coated with polyvinyl alcohol (PVA).[28] This implant produced measurable plasma concentrations of tenofovir for more than 6 weeks and delivered tenofovir at an approximately constant rate up to 40 days after placement.[29] These implants were well-tolerated in dogs, suggesting that local toxicity with TAF implants may depend on how the TAF is delivered locally, and at what rate.[28] Phase one clinical trials of the PVA TAF implant are underway in South Africa (CAPRISA 018) without significant toxicity reported to date.

Some of the problems associated with non-erodable implants could be addressed with other approaches, including bioerodable or biodegradable implants. This is similar to technologies used to deliver leuprolide and related peptide-based hormone receptor agonists.[30] With these products, the formulation is injected to form a solid gel that absorbs water, disperses, and slowly releases drug over a period of several months. This has the advantage that the implant does not require surgical removal. However, this also limits the possibility of removing the implant in case of toxity or the desire to stop treatment.

A bioerodable dolutegravir implant delivered detectable drug concentrations in nonhuman primates for up to 9 months after a single injection.[31] This polymer system is injected and solidifies over the first 48 hours, degrading slowly as it releases drug from the depot. This implant was well tolerated, with no local tissue necrosis. The dolutegravir implant prevented SIV infection after repeated high-dose vaginal challenge in nonhuman primates, suggesting possible utility in the PrEP setting.

Future approaches to long-acting drug administration

There is no shortage of clever ways to administer drugs in a long-acting format. This includes a variety of self-assembling nanostructures that can release drug over a period of months,[32] osmotic pumps, and sophisticated programmable reservoirs.[28] Injectable

lipophilic prodrugs can form nanocrystal depots that deliver TAF in animals for more than two months.[33] A similar system delivers cabotegravir for more than a year after a single injection.[34] Products like these could have a significant impact on future approaches to PrEP, but in most cases remain years away from clinical implementation. Readers interested in staying up-to-date with this field are encouraged to visit the website for the Long-Acting Antiretroviral Research Resource Program (LEAP) at www.longactinghiv.org.

Conclusions

Long-acting drug delivery is likely to have a profound impact on future PrEP. The success of injectable cabotegravir, as compared to daily oral tenofovir disoproxil fumarate and emtricitabine, is likely to encourage the development of a broader array of long-acting choices for those at risk of acquiring HIV. The recent unexpected occurrence of lymphopenia with islatravir emphasizes the need for better long-term safety data with these formulations as compared to their immediate release counterparts. Innovation will expand the number of antiretroviral choices available to those at risk of HIV, creating a menu of products with greater convenience, tolerability, and effectiveness.

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Key points

Long-acting formulations may improve PrEP efficacy by reducing the required dosing interval, resulting in greater convenience and adherence.

A variety of long-acting formulations with possible use in PrEP are in clinical development; this includes intravenous, subcutaneous, implant, transmucosal, and transdermal drug delivery, as well as extended duration oral drugs.

Long-acting antiretrovirals implants are drug delivery devices that do not depend on user compliance/reliability, and have several advantages over other long-acting antiretroviral formulations in current development.

Investigational formulations in clinical and pre-clinical development can deliver effective concentrations of antiretroviral drugs for more than a year after a single administration.

Table 1.

Long-Acting Drugs and Formulations with Potential Application to HIV Prevention

Drug Class	Agent	Formulation	Development Stage
	Islatravir (MK-8591)	Monthly oral; Implant	Phase II/III (on hold)
NRTI	TAF	Implant	Preclinical
	GS-9131	Implant	Preclinical
NNRTI	Elsulfavirine	Injectable	Preclinical (oral drug approved in Russia)
PI	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
	Dolutegravir	Implant	Preclinical
INSTI	Raltegravir	Injectable	Preclinical
	Albuvirtide	Intravenous and injectable	Approved in China
	bNAbs (e.g., VRC01, VRC07)	Intravenous	Phase I/II/III
Entry Inhibitors	Combinectin	Intravenous	Phase I
Capsid Inhibitors	Lenacapavir	Oral and subcutaneous	Phase II/III