# Long-acting implants to treat and prevent HIV infection

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**Purpose of review**
Subcutaneous implants are a promising technology to enable long-acting parenteral delivery of antiretroviral drugs (ARV) because they may be able to provide protective drugs concentrations for a year or longer following a single implant. The present review covers the current status of preclinical and clinical development of antiretroviral implants.

**Recent findings**
Over the past three decades, subcutaneous implants have been widely used for long-acting hormonal contraception and the treatment of hormonally-driven malignancies. They are economical and scalable to manufacture, but require special procedures for insertion and removal. They are generally well tolerated, and can remain in place for up to five years. As long-acting delivery of ARV would confer significant advantages, a few investigational implants are under development for the delivery of ARV; most remain at preclinical stages of development. Islatravir, a potent nucleoside analog reverse transcriptase translocation inhibitor that shows particular promise, has entered clinical testing in implant form. Investigational implants containing tenofovir alafenamide and nevirapine, and entecavir (for hepatitis B virus) have been developed and tested in animal models, with varying degrees of success. There is also burgeoning interest in bioerodable implant formulations of established ARVs.

**Summary**
LARV implants are a promising new technology, but are in early stages of clinical development. Their potential advantages include more consistent and predictable drug release than that provided by intramuscular injections, the possibility of combining several partner drugs into one implant, and the fact that implants can be removed in the case of a desire to stop treatment or the development of adverse events.

**Keywords**
bioerodable implants, HIV, inert polymer implants, long-acting antiretroviral implants, nonbioerodible implants

## INTRODUCTION

Great advances over the past three decades have led to the development and optimization of antiretrovirals that are highly potent, safe, and well tolerated. There is, however, no currently available ARV drug or formulation with a dosing frequency less than once daily. Nonadherence to daily oral medication remains the most significant barrier to long-term suppression of HIV replication and prevention of the emergence of drug-resistant virus [1]. People who experience even short periods of nonadherence are in danger of losing the health benefits of antiretroviral therapy and narrowing their choices for future treatment or prevention.

ARV dosing strategies that are less frequent than daily, enabled by the development of long-acting products and formulations, have emerged in recent years as a promising approach to adherence support [3▪]. Injections of ARVs at infrequent intervals, for example every few months, would dramatically lessen the adherence concerns for those having difficulty taking once-daily pills [4]. Both injectable and implantable parenteral strategies have the advantage of avoiding hepatic first-pass metabolism and degradation in the digestive tract, while also lessening the extreme peaks and valleys which can

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## KEY POINTS

- 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.
- An important advantage of implant technology is that sustained-release inert polymer implants can be removed in the case of adverse drug reactions or the desire to discontinue treatment.
- Another notable advantage of implant technology is avoidance of a prolonged pharmacokinetic 'tail' at subtherapeutic concentrations of ARV, which is seen after intramuscular injections, thus lessening the selection pressure for drug resistance.
- Implants may provide more consistent, predictable drug release than intramuscular formulations.
- Bioerodable implants offer key advantages over nonbiodegradable implants, chief among them that they do not require removal, but can be removed soon after injection in case of adverse effects.

be associated with oral administration. In general, implant formulations avoid the high peaks and 'dose dumping' that has occasionally been associated with intramuscular injections. An additional potential benefit of long-acting parenteral formulations would be their use in the many clinical situations where oral medications cannot be used temporarily or permanently, for example because of gastrointestinal surgery, malabsorption, swallowing dysfunction, pill aversion, or neurologic disease [5▪]. In areas of the world where visible antiretroviral use is heavily stigmatized, these formulations have the potential to remove such stigma, as the use of these agents is not outwardly visible and does not involve or require pill bottles.

Long-acting injectable nanoformulations of cabotegravir and rilpivirine are already in phase III clinical trials for HIV treatment, and cabotegravir is in advanced clinical development for HIV preexposure prophylaxis; these formulations are extensively reviewed elsewhere in this volume of *COHA*. A critical drawback of the injectable long-acting ARVs is that they are nondialyzable and cannot be removed from the body after injection. They can maintain detectable concentrations of drug in the bloodstream for longer than a year in some cases [2]. If such formulations were to provoke an adverse effect, that adverse effect must be endured for an extended period of time; as drug concentrations decay and become subtherapeutic, drug resistance can occur.

Implants and similar sustained release technologies have been developed to deliver drugs used in the treatment and prevention of a variety of medical conditions other than HIV (see Table 1). Implant indications include hormonal contraception, prostate cancer, coronary artery disease, and cytomegalovirus retinitis, among others. Since 2013, over 53 million contraceptive implants have been distributed in the developing world, and major global gains in rates of modern contraception are attributable to increased uptake of contraceptive implants, particularly in sub-Saharan Africa [3▪,4]. In some parts of the word, implants now represent half of all contraceptive methods used among women [3▪]. Broadly, there are two categories of implants: matrix-style and reservoir-style. Matrix-style implants involve drug dispersed in a polymer which slowly biodegrades, controlling the rate at which the drug is released systemically. Reservoir-based implants involve a core of specially formulated drug which is encased in a polymer barrier, the properties of which control the rate of drug release. Implants have several important advantages over injectable drug delivery strategies, broadly and in the setting of HIV (see Table 2).

This review will address the state of the field of implant technology for the delivery of antiretroviral drugs (ARVs), with an emphasis on the ability of these drug delivery systems to provide effective concentrations of medications for a period of years, based on extrapolation from implant systems in current use for conditions other than HIV infection.

## LONG-ACTING ANTIRETROVIRAL IMPLANTS IN PRECLINICAL AND CLINICAL DEVELOPMENT

ARV agents that are most suitable for implant formulation and delivery are those with exceptionally high antiviral potency. Because the allowable mass dose of active pharmaceutical ingredient that can loaded into a single implant rod is small, the agent or agents involved must have extraordinary capacity to inhibit viral replication at low concentrations, otherwise drug delivery by implant becomes infeasible even if one considers inserting multiple rods at the same time. Transdermal strategies (such as drug delivery via matrix-based adhesive patch or reservoir-based patches) generally depend on the drug having adequate properties for passively permeating through skin—these include low molecular weight of less than 500 Da, melting point less than 250°C, and moderate log *P* [1,2,3▪,5▪].

In contrast to most ARVs, hormones used in contraception are exceedingly potent. For perspective, a single 3-year etonogestrel (Nexplanon)

**Table 1.** Properties of selected implants for non-HIV indications[a]

| Drug and indication | Materials | Dose (mg/day) | Duration | Size |
|---|---|---|---|---|
| Etonorgestrel (Implanon; Nexplanon) *Hormonal contraception* | Ethylene vinyl acetate (EVA) copolymer, barium sulfate, magnesium stearate | 65 mg (0.06 mg/day) | 3 years | 2 × 40 mm (1 rod) |
| Levonorgestrel (Norplant; Jadelle) *Hormonal contraception* | Dimethylsiloxane/ methylvinylsiloxane core in thin-walled silicone (provided w. disposable trocar) | 150 mg (0.03–0.04 mg/day (p 12 months) | 5 years | 2.5 × 43 mm (2 rods) |
| Leuprolide acetate (Viadur) *Hormone-responsive prostate cancer* | Dimethyl sulfoxide, osmotic tablets | 65 mg (0.17 mg/day) | 1 year | 4 × 45 mm (wt. 1.1 g) |
| Risperidone subcutaneous implant [32–34] *Schizophrenia* | Risperidone | 375, 48, 720, or 960 mg (2, 2.7, 4, and 5.3 mg/day, respectively) | 6 months | *Not mentioned in primary publication* |
| Buprenorphine (Probuphine) (subcutaneous) *Matrix-style implant for maintenance treatment of opioid addiction* | Drug released through four individual poly(ethylene-vinyl acetate) (EVA) rods | 80 mg buprenorphine hydrochloride (0.44 mg/day) | 6 months | 2.5 x 26 mm |
| Ganciclovir (Vitrasert) (intravitreal) *Cytomegalovirus retinitis* | Ganciclovir, magnesium stearate, PVA and EVA polymer coating | 4.5 mg (1.40 μg/h, range from 0.5 to 2.88 μg/h) | 5–8 months | 2.5 × 1 mm |
| Dexamethasone (Ozurdex) (intravitreal) *Macular edema* | Dexamethasone, NOVADUR solid polymer (PLGA matrix, degrades to water and $CO_2$) | 0.7 mg (3.9 mcg/ day) | 6 months | 1 × 0.5 mm |
| Fluocinolone acetonide (Retisert) (intravitreal) *Posterior uveitis not due to infection* | Fluocinolone Acetonide + magnesium stearate, microcrystalline cellulose, encased in silicone elastomer cup w polyvinyl alcohol membrane and orifice | 0.59 mg (initial rate 0.6 mcg/day ×30 days, then 0.3–0.4 mcg/ day thereafter) -linear release characteristics; no bolus release initially | 30 months | 3 × 2 × 5 mm |

Note: Intravitreal implants are surgically placed into the posterior segment of the eye via a pars plana incision.
EFdA, 4′-ethynyl-2-fluoro-2′-deoxyadenosine; EVA, ethylene vinyl acetate; NMP, N-methyl-2-pyrrolidone; PCL, poly (ε-caprolactone); PLGA, biodegradable polylactic co-glycolic acid; PVA, polyvinyl alcohol.
[a]Refs: Package Inserts: Viadur, Probuphine, Vitrasert, Ozurdex, Retisert, Nexplanon, Jadelle, Implanon, Norplant.

**Table 2.** Potential advantages and disadvantages of antiretroviral implants as compared to injectables

| Advantages | Disadvantages |
|---|---|
| Swift/easy removal at the end of treatment or in setting of adverse effects | Specialized device w need for training/sterility/ equipment/ procedure for insertion & removal |
| No oral lead-in required | Minor surgical procedure required to remove |
| No oral TDF/FTC needed to protect during subtherapeutic PK 'tail' | Must be removed at the end of product lifespan |
| Lower dose/day | Impossible to discern from palpation how long the device has been in place |
| Can remain in place for years (require less interaction with healthcare system) | Can migrate from original insertion site to a place where palpation is difficult (esp. in beagles) |
| More consistent and predictable drug release kinetics | Regulated as both a drug and a device |
| PK properties may not depend on injection site | More complex uptake into generic marketplaces |
| Palpable under skin indicating its presence | Visibility (arm) & possible stigma |
| Radio-opaque for visualization in case of unintended subcutaneous migration | |
| Biodegradable versions also possible | |
| Avoid high injection volumes | |

implant delivers an average daily dose of etonogestrel of only 62 μg (0.06 mg) per day [6], and a single levonorgestrel (Jadelle) 75 mg implant delivers an expected daily dose of 82 μg (0.08 mg) over the 5-year insertion period [7]. In the case of the levonorgestrel implant, the release rate is known to slow over the first 2 years after insertion, dropping from approximately 100 μg/day during the first month to 40 μg/day at 12 months and 30 μg/day after month 24 [7] (see Table 1 for more details). Few marketed drugs have a daily dose of active pharmaceutical ingredient this low. The most potent approved antiretroviral drugs, tenofovir alafenamide and rilpivirine, have daily oral doses of 25 mg/day.

Several antiretroviral compounds have now been identified whose *in vitro* potency approaches that seen with drugs used in implants marketed for other indications. These are reviewed below, and a summary of candidate ARV implants is provided in Table 3.

## Tenofovir prodrugs

Tenofovir is the world's most widely used antiretroviral, and is currently marketed as two different oral prodrugs. Since its intracellular active metabolite, tenofovir-diphosphate (TFV-diphosphate), has an estimated half-life of 60–100 h, tenofovir prodrugs could easily be given less frequently than once per day while maintaining antiviral effects [8]. The prodrug tenofovir alafenamide (TAF) is 10 times more potent than tenofovir disoproxil fumarate (TDF), and has the added advantage that it is taken up into cells from the plasma as the prodrug, which is converted to the parent drug and then to the active intracellular diphosphate inside the cell [9]. In addition, from the perspective of prevention, TAF has activity against both hepatitis B virus (HBV) and HIV, and could potentially prevent both infections, in addition to treating them in those who have already acquired coinfection [10].

Several approaches have been pursued for the creation of a TAF implant. In the first, investigators loaded pure TAF powder into platinum cured microperforated silicone tubing that was coated with polyvinyl alcohol (PVA). The 1.9 × 40 mm implants were inserted subcutaneously into beagle dogs. This implant produced measurable plasma concentrations of tenofovir for more than 6 weeks and delivered tenofovir at an approximately constant rate for 5 to 40 days after implantation [11]. The zero-order, linear kinetics were observed over the first 30 days, after which there was a steeper decline with first-order kinetics because of drug depletion. The implants were well tolerated in the beagles, without significant AEs. Strikingly, intracellular tenofovir-diphosphate concentrations were 11–32 times higher than those associated with effective preexposure prophylaxis in humans in the iPrEX study of 16–48 fmol/$10^6$ cells after using TDF [11,12]. One advantage of this implant technology is that its physical characteristics (tube diameter, number, and size of perforations) can be easily modified to alter the release rate of drug. This device has now entered Phase I testing in humans, although no data are yet publically available.

Another approach for innovative delivery of TAF is a silicone-based transdermal matrix-based (drug-in-adhesive) patch with polyisobutylene adhesives, which has been tested on dermatomed human cadaver skin and has been established to yield a permeation flux of 7 μg/$cm^2$/h over 1 week, which extrapolates to a release rate of 8.4 mg of TAF per day. This noninvasive approach offers convenience, simplicity, has no procedural requirements and thus stands to be more user friendly [5▪].

**Table 3.** Properties of selected ARV implants

| Implant type | Model | Drug name | Size | Dose (mg/day) | Duration of levels/activity |
|---|---|---|---|---|---|
| *Nonbioerodable* | | | | | |
| 1. Granulated drug core, PVA coating, permeable silicone tubes [35] | Rats | Nevirapine (NVP) | | | 90 days |
| 2. Pure drug powder core, platinum microperforated silicone tubing, PVA coating [11] | Beagle dogs | Tenofovir alafenamide (TAF) | 1.9 x 4.0 mm | *In vivo* release rate: 1.07 mg/ day (Human doses down to 0.15 mg/day) | 40 days |
| 3. Refillable nonpolymer nanochannel delivery implant (NDI)[15▪] - Titanium drug reservoir - Silicone nanochannel membrane - Twoi sealable refillable silicone drug loading ports | Rhesus macaques | Tenofovir alafenamide (TAF) and Emtricitabine (FTC) | FTC: 43 mm x 28.5 mm x 8.7 mm; 250 nm nanochannel TAF: 5 mm x 20 mm x 12.3 mm; 20 nm nano-channel | *In vitro:* TAF: 0.21 ± 0.03 mg/ day FTC: 2.67 ± 0.35 mg/day | 83 days (TFV-DP); 28 days (FTC-DP) |
| 4. Silicone-based transdermal matrix-based (drug-in-adhesive) patch w polyisobutylene adhesives [5▪] | Dermatomed human cadaver skin | Tenofovir alafenamide (TAF) | 7 × 7 cm | Permeation flux of 7 μg/cm$^2$/h (extrapolates to 8.4 mg TAF/ day) | 1 week (in vitro) |
| 5. Biocompatible polymer blended with entecavir via hot melt extrudates and polymer coated tablets (both administered subcutaneously) [16] | Rats (Wistar han) | Entecavir (ETV) | Dose 350 mg/kg | | 87 days |
| 6. Titanium osmotic mini-pump system (Medici DDS$^{TM}$) [36] | | TDF-FTC | 'match-stick sized' | | 6 months to 12 months |
| 7. Biodegradable and nonbiodegradable matrix-based polymer with islatravir [37▪▪] - HME process: barrel temp above melting point for polymer but below melting temp for drug→ solid crystalline drug in polymer matrix | Rats, NHP | Islatravir (ISL) aka EFdA (MK-8591) | 2 mm × 40 mm | > 10 μg/day for entire study | > 6 months (for 40 wt% and 60 wt% MK-8591 in PCL, and 50 wt% MK-8591 in EVA) >12 months (for 60 wt% MK-8591 in PCL implants) |
| 8. Biodegradable and nonbiodegradable matrix-based polymer [23▪▪,37▪▪] (same polymer and applicator as Nexplanon) | Humans (healthy volunteers) (N=16; 12 drug and 4 placebo) | Islatravir (ISL) aka EFdA (MK-8591) | 2 mm × 40 mm | 54 and 62 mg (0.17 mg/day) | 12 months+ |
| *Bioerodable* | | | | | |
| 9. Ultra-long-acting removable DTG/ PLGA/NMP in 0.3 : 1:2 ratio [25▪▪] (formulation optimized for *mice*, not macaques) | Rhesus macaque (treatment) | Dolutegravir (DTG) | | 100 mg | |
| 10. Ultra-long-acting removable DTG/ PLGA/NMP in 0.3:1:2 ratio [25▪▪] (formulation optimized for mice) | Humanized BLT mouse (prevention) | Dolutegravir (DTG) | 1 cm | 250 mg/kg (5.5–7.0 mg DTG in 50–80 μl) | > 5 months (flat shape of concentration: time curve at 140 days) |
| 11. Reservoir-style implant [26▪] (extruded tube of a biodegradable polymer, PCL, filled w TAF and castor oil excipient in 2 : 1 ratio) | *In vitro* | Tenofovir alafenamide (TAF) | 1, 4, and 7 cm (length) Wall thickness 100 μm | Release rates: 0.28 ± 0.06 mg/day (100 μm thickness) Range from 0.15 mg/day (for 200 μm thickness) to 0.91 mg/day (for 45 μm thickness) | 180 days (in vitro) |

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The combination of TAF and FTC (shown to be efficacious as PrEP in the DISCOVER trial) [13,14] has been investigated in rhesus macaques, using a refillable nonpolymer nanofluidic implant (nanochannel delivery implant, NDI) consisting of a titanium drug reservoir, silicone nanochannel membrane, and two sealable refillable silicone drug loading ports [15▪]. The advantage of this approach is that when drug is exhausted, more drug can be administered transcutaneously into the ports, without the need to remove and reimplant a new device. The NDI achieved concentrations of TFV-diphosphate in PBMCs that reached target 3 days after implantation, and continued to increase from a mean of $71.7 \pm 29.7$ to $533.3 \pm 198.4$ fmol/$10^6$ PBMCs over 70 days (equivalent to 12 times the iPrEX $EC_{90}$) [12,15▪]. Concentrations of FTC-TP in PBMCs were detected and sustained from day 3 to day 28 ($1223.7 \pm 416.8$ to $1656.7 \pm 290.8$ fmol/$10^6$ PBMCs), but unlike TAF did not attain target protective concentrations (equivalent to an $EC_{90}$ extrapolated from the iPrEX study of 5000–6000 fmol/$10^6$ freshly lysed PBMCs). The NDI was fairly well tolerated, but 1 in 3 animals had swelling/seroma around the device, which resolved in 7 days, one animal had dehiscence over the NDI at 60 days, and 2 animals developed skin ulceration over the implant at day 70.

## Entecavir

Developed as a possible way to prevent acquisition of hepatitis B virus infection, entecavir has been given subcutaneously in two different forms. In both cases, subcutaneous delivery in rats was not tolerated. Tested technologies included both a biocompatible polymer blended with entecavir via hot melt extrusion, and polymer coated tablets, both administered subcutaneously. When a dose of 350 mg/kg was implanted, it did achieve concentrations in the range of those associated with efficacy in rats (44–109 nM). However, in almost all cases, there was skin ulceration with surface tissue adhesion to the implant, and erosion through skin. On histological examination, there was local necrosis overlying the implant, which was attributed to entecavir itself, given that it was also observed in people who received uncoated tablets of entecavir [16].

## 4′-Ethynyl-2-fluoro-2′-deoxyadenosine (MK8591; islatravir)

4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EFdA; MK8591; islatravir [ISV]) is a highly potent nucleoside reverse transcriptase inhibitor with a novel mechanism of action [17]. ISV is a 4′-substituted NRTI that retains its 3′-hydroxyl group, unlike any other currently approved NRTI. As a consequence, this drug has higher affinity for the active site of the HIV reverse transciptase, contributing to its potency. The incorporation of ISV-monophosphate into the RT active site blocks primer translocation and halts HIV replication without causing chain termination, since the drug contains a 3′-hydroxyl. ISV also has a halogen substitution at the 2-position of the adenine ring that impairs degradation by adenosine deaminase and contributes to the prolonged intracellular half-life of active phosphorylated metabolite ISV-TP, estimated at greater than 72 h [18]. ISV has substantial efficacy in treatment and prevention of HIV in animal models with doses as low as 0.1 mg/kg/day. In animals, the drug is safe and well tolerated across a range of doses [19].

ISV 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* [20]. These suggest the possibility of using ISV in patients already harboring M184V-containing HIV, and of using this drug in combination with other existing antiretroviral NRTIs and other drug classes. ISV is approximately 10-fold more potent against HIV-2 isolates than against HIV-1 *in vitro*, indicating broad-spectrum activity and possible global utility for this agent [21]. Possible uses for ISV implants, like those for TAF, include preexposure prophylaxis as a single agent, or eventual combination with other long-acting antiretroviral drugs for HIV treatment.

In studies comparing two nondegradable polymer implants in rats, the apparent ISV plasma half-life was nearly 100 days, suggesting the possibility for developing human implants with a dosing interval of 1 year or longer [22]. Phase I clinical studies of ISV are currently underway in human subjects, and preliminary findings in healthy human volunteers showed that a 62 mg implant can achieve a constant, linear (zero-order) release of drug that results in levels of triphosphorylated active metabolite [ISV-TP] in PBMCs of 0.076 pmol/$10^6$ over 12 months, which is approximately 7 times the $IC_{50}$ *in vitro* for wild-type virus, maintaining intracellular concentrations above the target of 0.05 pmol/$10^6$ cells [23▪▪]. The $t_{1/2}$ observed in humans of parent ISV was 50–60 h and of active metabolite ISV-TP was 120–177 h. The implants were generally well tolerated, though with local erythema, itching, and induration that was mild and to some extent dose-dependent. Importantly, based on modeling, the projected time at which concentrations fall below the target is not until 16 months after implant was placed. This raises the possibility of implant

placement frequency less often than yearly for HIV treatment and prevention [17].

### Bioerodable implants

Some problems associated with medical implants could be addressed with newer technologies. For example, bioerodable/biodegradable implants, for instance using polylactic acid or polylactide, have been deployed in drug-eluting stents [24]. In the case of a bioerodadable antiretroviral 'implant,' the formulation would be injected, forming a solid gel that would disperse over several months' time. This has the advantage that the implant system does not require eventual removal. However, if there is the desire to remove the implant for adverse drug effects, surgical removal becomes more difficult, and potentially impossible, several months after injection, because the implant has dispersed.

One example of a bioerodable implant currently in preclinical testing is ultra-long-acting dolutegravir (DTG). Ultra-long-acting DTG delivered via a removable implant system has been tested in a macaque model for HIV treatment and a humanized bone marrow-liver-thymus (BLT) mouse for HIV prevention [25▪▪]. The technology involves subcutaneous injection of an admixture of DTG, PLGA, and NMP in a ratio of 0.3:1:2. Liquid drug is injected and then solidifies over the first 48 h *in vivo* into an implant once it reaches the aqueous environment of the body, and then biodegrades slowly, resulting in sustained drug release. This delivers drug at effective concentrations for up to 9 months and can be safely removed should an adverse event or pregnancy occur. Implants were well tolerated in both animal models, with no local necrosis. The sustained drug concentrations resulted in both suppression of viremia in the macaques and prevention from acquiring HIV via a high-dose repeat vaginal challenge.

Another bioerodable approach that has been tested *in vitro* involves the creation of an extruded tube made of a biodegradable polymer, PCL of various thicknesses, filled with TAF and castor oil excipient in a 2 : 1 ratio [26▪,27]. The implant achieved over 180 days daily TAF release rates of $0.28 \pm 0.06$ mg/day (100 μm thickness), with a range from 0.15 mg/day (for 200 μm thickness) to 0.91 mg/day (for 45 μm thickness). This is above the concentration of 0.15 mg/day that is estimated to be sufficient to achieve target TFV-diphosphate intracellular concentrations for anti-HIV efficacy and protection. Daily release rates can be modified by changing the implant surface area, PCL tube wall thickness (the thinner the more drug release), or PCL crystallinity.

## ANTIRETROVIRAL IMPLANTS: CHALLENGES AND OPPORTUNITIES

Theoretical advantages of implant technology for HIV treatment and prevention include the ability to remove the device in the case of side effects or the desire to end therapy, less frequent dosing because of the slow release of drug and longer apparent half-life, a lower drug dose per day because of potency and formulation properties, protection from poor adherence as compared to daily oral drugs, and the possibility of directly observed therapy. In the case of formulations with a prolonged low-level pharmacokinetic 'tail,' the device can simply be removed, allowing drug concentrations to decline rapidly. Medical implants are placed where they cannot generally be detected by partners, family members, or colleagues, affording better protection of health privacy. The widespread use of contraceptive implants in low income countries proves that these devices can be implemented cheaply and safely in remote areas.

Although implants have some clear advantages over injectable formulations, they also have some drawbacks (see Table 2). This includes the need for insertion and removal by well trained personnel using sterile technique. Because these devices are removable, it is likely that a novel antiretroviral developed for implant technology would not require a partnered oral formulation or oral lead-in to rule out toxicity or hypersensitivity, as is the case for injectable cabotegravir and rilpivirine [28,29]. Nonetheless, different dose formulations would still need to be developed to allow for dose escalation in clinical dose-finding and safety studies.

In HIV prevention applications, an antiretroviral implant could be developed as a stand-alone. However, partner formulations would need to be identified for HIV treatment. Ideally, a single implant could contain two or more antiretrovirals with similar pharmacokinetic properties, or two separate implants could be inserted simultaneously. As an intermediate approach, a long-lasting implant could be paired with periodic injections of an intramuscular formulation like LA-cabotegravir or LA-rilpivirine, or one or more long-acting, broadly neutralizing monoclonal antibodies [30,31].

## CONCLUSION

Implants show great promise for HIV treatment and prevention. Potential advantages over intramuscular injections include the fact that implants are removable in cases of toxicity, produce more consistent and predictable drug release, have pharmacokinetic properties that may not be dependent on the injection site, and likely will not require an oral lead-in phase. In addition, implants can sustain

therapeutic drug concentrations and remain in place for years, based on experience with hormonal contraception. However, implants require specialized training for insertion and removal, a minor surgical procedure if they need to be removed, and are more expensive and complex to manufacture than injectables, making transition to a generic marketplace more difficult as compared to injectable formulations. Many of these problems can and will be solved with future innovation, adding to the number of antiretroviral choices available to people living with or at risk of HIV.


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## Conflicts of interest

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