Annual Review of Medicine

Long-Acting HIV Drugs for Treatment and Prevention

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Annu. Rev. Med. 2019. 70:9.1–9.14

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-041217-013717

Keywords

HIV, antiretroviral drugs, long-acting, extended-release, implants, monoclonal antibodies

Abstract

Antiretroviral drugs have revolutionized the treatment and prevention of HIV infection; however, adherence is critical for sustained efficacy. Current HIV treatment consists of three-drug regimens, and current HIV preexposure prophylaxis (PrEP) consists of a two-drug regimen; both generally require adherence to once-daily dosing. Long-acting formulations are useful in the treatment and prevention of other conditions (e.g., contraceptives, antipsychotics) and help promote adherence. Newer long-acting formulations of approved and investigational antiretroviral drugs in existing and newer mechanistic classes are under study for HIV treatment and prevention, including some phase III trials. Although long-acting antiretroviral drugs hold promise, some clinical challenges exist, including managing side effects, drug-drug interactions, pregnancy, and long-lasting drug concentrations that could lead to the development of drug resistance. This review aims to summarize currently available information on long-acting antiretroviral drugs for HIV treatment and prevention.

INTRODUCTION

Current antiretroviral therapy (ART) suppresses HIV replication, preserves or restores CD4 cell counts and immune function, reduces morbidity and mortality, and now prolongs survival to essentially that of the general population (1–3). Current treatment guidelines around the world recommend starting ART in anyone who is HIV infected, regardless of prior illness, symptoms, signs, HIV RNA level, or CD4 cell count (4–7). Current first-line ART regimens consist of three antiretroviral drugs, often coformulated, allowing a one-pill, once-daily oral treatment regimen; these regimens result in virologic suppression in more than 80% of HIV-infected patients in both clinical trials and in clinical cohorts (4–7). HIV pre-exposure prophylaxis (PrEP) is a prevention strategy of giving antiretroviral drugs to an uninfected individual at risk for HIV infection, which reduces the risk of acquiring infection by over 85% in some clinical trials (8, 9).

A major factor preventing more widespread success of oral treatment is suboptimal adherence. Long-acting antiretroviral formulations, especially parenteral ones, could improve success rates while also helping to prevent transmission of HIV (**Table 1**). Low rates of adherence have also reduced the effectiveness of orally administered PrEP, and long-acting formulations could ameliorate this problem as well (10). Finally, in situations where self-administration of oral medication may be difficult because of gastrointestinal, neurologic, or psychiatric disease, parenteral therapy would be of clinical value, even if used only temporarily (11).

No long-acting strategy for treatment or prevention works unless patients are accepting of these forms of drug delivery. Several recently published patient surveys found broad and enthusiastic support for coformulated long-acting and extended-release (LA/ER) antiretroviral delivery technologies. Of 400 adult survey respondents in two US clinics, more than 80% indicated

Table 1 Long-acting antiretroviral agents

Mechanistic drug class	Agents	Formulation	Stage of development
Nucleoside reverse transcriptase inhibitors	EFdA	Implant	Preclinical
	MK-8591	Implant	Preclinical
	Tenofovir alafenamide	Implant	Preclinical
	GS-9131	Implant	Preclinical
Nonnucleoside reverse transcriptase inhibitors	Rilpivirine	Injectable	Phase III
	Elsulfavirine	Injectable	Preclinical
Protease inhibitors	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
Integrase inhibitors	Cabotegravir	Injectable	Phase III
	Raltegravir	Injectable	Preclinical
Entry inhibitors	Ibalizumab	intravenous	US FDA approved
	PRO 140	Intravenous	Phase II
	Albuvirtide	Intravenous and subcutaneous	Phase III
	Broadly neutralizing antibodies	Intravenous	Phase II
	Combinectin	Intravenous	Preclinical
Capsid inhibitors	GS-CA1	Injectable	Preclinical

Abbreviation: EFdA, 4′-ethynyl-2-fluoro-2′-deoxyadenosine.

they would definitely or probably consider switching from oral to parenteral antiretrovirals if the injection frequency were once per month; interest was lower with more frequent injections (12). In 303 adolescent patients ages 13 through 24 years, 86–90% stated they would definitely or probably switch to parenteral antiretrovirals if the injection frequency were once every one to three months (13). Attractions of LA/ER formulations for patients at risk of HIV or already taking oral treatment include the convenience of less frequent dosing, avoidance of pill fatigue, better protection of health privacy, and avoidance of treatment-related HIV stigma (14).

Participants in the 96-week phase IIb LATTE (long-acting antiretroviral treatment enabling)-2 trial also showed exceedingly high levels of satisfaction with intramuscular long-acting cabotegravir (CAB LA) and long-acting rilpivirine (RPV LA) administered every 4 or 8 weeks (15); it should be noted that participants in this study were self-selected on the basis of wanting access to such formulations and may have higher opinions of these products than the general population.

THE USE OF LONG-ACTING/EXTENDED RELEASE FORMULATIONS FOR THE TREATMENT AND PREVENTION OF OTHER DISEASES

Long-acting parenteral agents have proven useful in the treatment and prevention of other important and common human health-related conditions. The greatest experience involves parenteral delivery of hormonal contraceptives to prevent pregnancy, the so-called long-acting reversible contraceptives (16). This includes intramuscular and implantable progesterone analogs, as well as hormone-imbedded intrauterine devices. Contraceptive implants allow continuous release of drug products over several years from a single implant. Etonogestrel implants deliver effective systemic concentrations of hormones for up to three years, and levonorgestrel implants for up to five years, after a single implant (17).

Implantable and injectable hormones are now the most popular form of birth control in many parts of the world and are being used by millions of women. In some sub-Saharan African countries, injections and implants now account for 60–80% of contraceptive use in women, whereas daily oral contraceptives are used by 10% or fewer of women (18). In fact, because HIV infection is so prevalent in this part of the world, many HIV-infected women are already receiving regular injections or implants for contraception (19), resulting in unwanted adverse drug interactions involving concurrent antiretroviral drugs. The nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz—a known cytochrome P450 enzyme inducer—decreased levonorgestrel concentrations by up to 57% and resulted in three unwanted pregnancies in 20 Ugandan women using levonorgestrel implants (20).

A long-acting injectable nanoformulated version of the antipsychotic paliperidone palmitate is widely used for the treatment of chronic schizophrenia, especially in patients unable to adhere to daily oral medications (21). This formulation technology is very similar to that used to create the injectable versions of CAB and RPV for HIV and can be given at a dosing interval of once every one to three months.

Similar technology has been applied to develop sustained release formulations for other drugs in noninfectious diseases settings. A subcutaneous implant for the systemic delivery of leuprolide (Viadur®), a gonadotropin-releasing hormone agonist, was widely used for the treatment of advanced prostate cancer, breast cancer, endometriosis, uterine fibroids, and precocious puberty but is no longer marketed because of increased manufacturing costs (22). Drug-eluting cardiac stents treat and prevent recurrent coronary artery disease (23). Biodegradable polymer systems like drug-eluting cardiac stents are designed to dissolve completely within nine months after stent implantation, and development of biodegradable implants for HIV should also be possible.

LONG-ACTING ANTIRETROVIRALS (FOR TREATMENT AND PREVENTION) IN CLINICAL DEVELOPMENT

Cabotegravir

Cabotegravir (CAB, GSK1265744) is an investigational HIV integrase inhibitor structurally similar to dolutegravir. It demonstrates potent activity against HIV in vitro, across HIV clades (24), including against some strains resistant to other integrase inhibitors (25). The compound is being developed both in oral and long-acting injectable preparations for both treatment and prevention of HIV (26). Phase I and IIa studies tested both single and daily oral doses over 10 days in HIV-uninfected and -infected participants and demonstrated dose-proportional increases in drug concentrations, a prolonged mean plasma half-life of 31.5 h, and in HIV-infected subjects, a significant 2.2–2.3 log10 copies/mL decrease in HIV RNA levels over 11 days (27). A phase I open-label study tested a 200 mg/mL nanosuspension of CAB LA administered at single increasing doses given either intramuscularly or subcutaneously in HIV-uninfected individuals and found prolonged plasma concentration-time profiles with measurable concentrations of CAB up to 52 weeks after dosing (28). CAB LA was generally well tolerated, although a majority of subjects reported mild injection site reactions (pain, erythema, and/or nodule formation). Two phase II prevention studies, ECLAIR and HIV Prevention Trials Network (HPTN) study 077, demonstrated injectable CAB was generally safe and well tolerated in HIV-uninfected individuals, although injection-site reactions were common (29, 30). HPTN study 083, NCT02720094, is an ongoing phase III noninferiority study in HIV-uninfected high-risk men who have sex with men and transgender women; the study compares daily oral tenofovir/emtricitabine with intramuscular CAB given every 8 weeks for HIV PrEP.

Rilpivirine

Rilpivirine (RPV, TMC278) is an NNRTI that demonstrated efficacy and safety as part of an oral combination ART regimen in phase III randomized studies (31, 32) and was approved for the treatment of HIV infection. The drug's physiochemical and pharmacological properties enable formulation as a long-acting injectable nanosuspension, which can be dosed every 4–8 weeks (33, 34). A phase I study of long-acting rilpivirine (RPV LA, 300 mg/mL) demonstrated plasma drug concentrations comparable to those seen with the oral drug (35). Another study explored single doses of RPV LA for PrEP and found RPV concentrations peaked at 6–8 days and were detected in plasma, cervicovaginal fluid, and vaginal and rectal tissue through 12 weeks (36). One participant was found newly HIV-infected at 12 weeks with resistance to RPV (37). A third study found RPV LA suppressed viral replication significantly in ex vivo rectal tissue but not in vaginal or cervical tissue (38). HPTN 076, a phase II prevention study, demonstrated that the RPV concentrations achieved were consistently greater than the protein-adjusted 90% inhibitory concentration for the 8 weeks postinjection (39).

Combination Therapy with Cabotegravir and Rilpivirine

The LATTE study enrolled 243 treatment-naive, HIV-infected participants who received dual nucleoside analogs and either oral CAB (10, 30, or 60 mg daily) or efavirenz (control) for 24 weeks and then, if virologically suppressed, continued CAB and substituted oral RPV 25 mg daily for their nucleoside analogs or continued nucleoside analogs and efavirenz (control) (40). At 96 weeks, 68–84% of participants had HIV RNA levels <50 copies/mL across the study regimens. With

virologic activity similar to efavirenz, CAB 30 mg was selected as the optimal dose for subsequent studies. In the first study of the combination of two long-acting injectable antiretroviral agents, 40 HIV-uninfected individuals received oral CAB 30 mg daily for a 14-day lead-in period and then were randomized to receive parenteral regimens (41). All parenteral dosing cohorts achieved target therapeutic drug plasma concentrations within 3 days of dosing with prolonged exposure, and the injections were generally well tolerated. The investigators concluded that a dual regimen of CAB LA and RPV LA should be further explored for an all-injectable regimen of HIV treatment.

LATTE-2 was a randomized, open-label phase IIb study in 286 treatment-naive HIV-infected adults who originally received oral abacavir/lamivudine plus oral CAB 30 mg daily for 20 weeks and then were randomized 2:2:1 to all-injectable maintenance antiretroviral regimens with CAB 400 mg and RPV 600 mg every 4 weeks, or CAB 600 mg and RPV 900 mg every 8 weeks, or to continue the oral regimen (15). At week 96, HIV RNA was suppressed to <50 copies/mL in 84–94% across the regimens. Injection site reactions occurred commonly, but only two (<1%) participants discontinued the study for that reason. The investigators concluded that this two-drug, all-injectable maintenance antiretroviral regimen was comparable to the oral regimen. This was a landmark study and supported further clinical development.

Several larger phase III studies of a maintenance regimen with injectable CAB and RPV are ongoing:

The First Long-Acting Injectable Regimen study, FLAIR (NCT02938520), a noninferiority study that enrolled individuals suppressed on abacavir/lamivudine/dolutegravir and randomized them to continue that regimen or change to the all-injectable regimen given every 4 weeks

- The Antiviral Therapy as Long-Acting Suppression study, ATLAS (NCT02951052), a non-inferiority study that randomized individuals on ART with suppressed viremia to continue their current ART regimen or receive the all-injectable regimen every 4 weeks
- ATLAS-2M (NCT03299049), which is randomizing individuals with suppressed viremia to the all-injectable ART dosed every 4 weeks versus every 8 weeks.

Ibalizumab

Ibalizumab is a humanized IgG4 antibody that inhibits HIV-1 entry by binding to the extracellular domain of CD4, preventing subsequent entry into $CD4^+$ T cells through allosteric inhibition (42). The ibalizumab binding site is distinct from the major histocompatibility complex sites of CD4, thus reducing the likelihood of immunosuppression. This drug was recently approved by the US Food and Drug Administration (FDA) for use in heavily treatment-experienced adults with a multidrug-resistant HIV-1 infection who are failing current therapy. Ibalizumab is given intravenously as a single loading dose of 2,000 mg, followed by maintenance dosing of 800 mg every two weeks. In clinical trials in antiretroviral-experienced patients, ibalizumab demonstrated antiviral activity, but treatment was frequently associated with early rebound of viremia and resistance (43, 44). In a phase III clinical trial, 43–50% of participants reached viral loads <50 copies/mL by week 25 when ibalizumab was combined with an optimized background regimen (45). Compared to other long-acting antiretrovirals being used clinically, ibalizumab has the disadvantage of intravenous administration and a biweekly dosing interval. Subcutaneous administration of this drug has been investigated.

PRO 140

PRO 140 is a humanized monoclonal IgG4 antibody that binds to the HIV-1 binding domain of the CCR5 receptor and inhibits binding and entry of CCR5-tropic viruses (46). Its binding site is

distinct from that of the CCR5 antagonist maraviroc, and PRO 140 is active against maraviroc-resistant viruses (47). PRO 140 monotherapy, given weekly for three weeks at an intravenous dose of 5 mg/kg or a subcutaneous dose of 324 mg, rapidly suppressed viral load in patients whose HIV was exclusively R5 tropic (48, 49). Anti-PRO 140 antibodies have developed in some patients but do not appear to affect pharmacokinetics, antiviral responses, or the likelihood of adverse events, which are quite infrequent. PRO 140 is being studied as a weekly maintenance monotherapy for patients whose baseline HIV was CCR5 tropic and as salvage therapy for patients with viremia on their current antiretroviral regimen. Like maraviroc, this drug can only be used in patients previously demonstrated as infected exclusively with CCR5-tropic HIV-1. The drug was recently granted Orphan Drug status by the FDA and is progressing toward approval for heavily treatment-experienced patients with multidrug-resistant HIV.

Albuvirtide

Albuvirtide is a 32-amino acid synthetic peptide analog of the fusion region of HIV gp-41, similar to enfuvirtide (T-20). It has the advantage of a much longer plasma half-life than enfuvirtide (12–14 days) but is expensive to manufacture and must be given parenterally. At present, this drug is being developed exclusively in China. In an open-label phase III trial, 389 treatment-experienced patients were randomized to receive either lopinavir/ritonavir plus albuvirtide 320 mg intravenously once weekly or lopinavir/ritonavir plus WHO-recommended NRTIs. After 48 weeks of treatment, 80% of albuvirtide recipients had a viral load of <50 copies/mL, compared to 66% of controls (difference 14.4%, 95% CI −3.0 to 31.9) (50). To date, albuvirtide appears to be quite well tolerated. A subcutaneous formulation is in development that would allow self-administration every 2–4 weeks, and there are plans to study the drug in additional countries.

4′-Ethynyl-2-Fluoro-2′-Deoxyadenosine

Novel agents suitable for long-acting or extended release formulation need to have high potency to provide a reasonable mass of the active pharmaceutical ingredient per dose. In addition, the active pharmaceutical ingredient or its active metabolite should have slow systemic clearance to support infrequent dosing. 4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EFdA, MK8591) is a highly potent nucleoside reverse transcriptase inhibitor (NRTI) that, unlike any other currently approved NRTI, retains its 3′-hydroxyl group. EFdA has higher affinity than other NRTIs for the HIV reverse transcriptase active site, contributing to its potency (51). The incorporation of EFdA-monophosphate into the enzyme active site blocks primer translocation and halts replication without causing direct chain termination because the drug contains a 3′-hydroxyl group. The halogen (fluorine) substitution at the second position of the adenine ring impairs degradation by adenosine deaminase and contributes to the long intracellular half-life of EFdA-triphosphate, estimated at >72 h (52). EFdA is safe and well tolerated in animals, and it has remarkable potency in treating or preventing HIV using doses as low as 0.1 mg/kg/day (53). Like lamivudine and emtricitabine, the major resistance mutation associated with EFdA use is *M184V*, although achievable concentrations of the drug in vivo are generally high enough to suppress replication of HIV isolates harboring this mutation (54).

A particular attraction of EFdA is its suitability for incorporation into polymer implants similar to those used for hormonal contraception (55). Two EFdA-containing polymer implants produced an apparent plasma half-life in rats of nearly 100 days (56), suggesting the possibility of eventual development of human implants that could have a dosing interval of one year or longer. EFdA implants could be used for HIV PrEP or combined with other antiretrovirals for HIV primary

treatment or maintenance therapy. Phase I clinical studies of oral EFdA have been completed in human subjects, and phase IIb studies are in progress (52).

Broadly Neutralizing Antibodies

HIV broadly neutralizing antibodies (bNABs), originally isolated from HIV-infected individuals with high-level anti-HIV neutralizing activity, target specific antigens on the HIV external membrane glycoprotein 120, and several of these bNABs have reached clinical development for both HIV treatment and prevention, including VRC01, 3BNC117, and 10–1074 (57, 58). Early clinical studies demonstrated the bNABs were generally well tolerated, were associated with virologic activity, and enhanced immune function. Although bNABs must be given parenterally, a two-amino acid substitution (called LS for the substituted amino acids) introduced into the crystallizable fragment domain increases the serum half-life of bNABs by two- to threefold, conferring the potential for infrequent dosing (59). Pilot clinical studies of combination bNABs are currently under way, and plans for clinical studies with a combination of a bNAB (e.g., VRC01) and a long-acting antiretroviral (e.g., CAB) also are in progress.

LONG-ACTING ANTIRETROVIRAL DRUGS FOR HIV TREATMENT AND PREVENTION IN PRECLINICAL DEVELOPMENT

Existing Antiretroviral Drug Classes

Tenofovir, elsulfavirine, atazanavir, ritonavir, and raltegravir are derived from drugs or prodrugs in existing antiretroviral drug classes. Some of these agents are already approved as oral formulations; others are investigational.

Nucleoside reverse transcriptase inhibitors: tenofovir. Tenofovir (TFV) is a widely used antiretroviral NRTI with a long history of safety and tolerability. Because its intracellular active metabolite, TFV diphosphate, has an estimated half-life of 60–100 h, TFV could be administered infrequently while maintaining antiviral activity (60). The newer oral TFV prodrug tenofovir alafenamide (TAF) is 10 times more potent than the originally approved prodrug tenofovir disoproxil fumarate (TDF) (61). In phase III clinical trials, TAF was less toxic to kidneys and bone than TDF, possibly because it produces much lower plasma concentrations of TFV (62). A polyvinyl alcohol TAF implant produced measurable plasma concentrations of TFV in beagles for more than six weeks after insertion of a single implant, delivering TFV at a nearly constant rate for up to 40 days (63). In these animal studies, the intracellular concentrations of TFV diphosphate were at least tenfold higher than those associated with effective PrEP in humans taking standard daily doses of oral TDF. Like TAF, the nucleotide prodrug GS-9131 also has a favorable toxicity, resistance, and pharmacokinetic profile, suggesting that it may be a promising candidate for long-acting formulation (64). The availability of more long-acting NRTI formulations will greatly facilitate combination therapy or maintenance regimens for patients already fully suppressed with daily pills.

Nonnucleoside reverse transcriptase inhibitors: elsulfavirine. Elsulfavirine (VM1500A) is an HIV NNRTI that as an oral drug in a combination antiretroviral regimen showed safety and efficacy comparable to efavirenz-based regimens in clinical studies (65). The drug was approved recently for the treatment of HIV infection in Russia (66). A long-acting injectable formulation of

elsulfavirine with the potential for monthly injection recently was reported in preclinical studies (67), and clinical studies are planned.

Protease inhibitors: atazanavir and ritonavir. Atazanavir is an HIV protease inhibitor that was approved in its oral form for the treatment of HIV infection on the basis of safety, tolerability, and virologic suppression (68, 69). When boosted with the HIV protease inhibitor and potent CYP3A4 inhibitor ritonavir, it is considered an alternative drug as part of HIV treatment regimens (US Department of Health and Human Services, European AIDS Clinical Society, World Health Organization). A nanoformulated long-acting combination of atazanavir and ritonavir was injected subcutaneously or intramuscularly to mice and monkeys and achieved levels many times higher than oral administration in plasma and target tissues, including macrophages that may promote sustained drug release (70).

Integrase inhibitors: raltegravir. Raltegravir (RAL), an HIV integrase inhibitor, was approved in its oral form for the treatment of HIV infection on the basis of safety, tolerability, and virologic suppression (71) and is commonly used for HIV treatment. RAL is also recommended as part of a postexposure prophylaxis regimen to prevent the acquisition of HIV infection following exposure (4–6). A new long-acting preparation of RAL, targeted for HIV treatment and prevention, demonstrated favorable pharmacokinetic properties in rhesus macaques and potent antiretroviral activity in infected humanized BLT (bone marrow–liver–thymus) mice with a functional human immune system as well as long-term protection from repeated vaginal HIV challenges in uninfected BLT mice (72).

Newer Antiretroviral Drug Classes

Combinectin and capsid inhibitors are examples of newer mechanistic class agents.

Entry inhibitors: combinectin. Combinectin (GSK 3732394, BMS-986197) is an investigational drug with three different synergistic mechanisms of action and the potential for a long-acting formulation (73, 74). Adnectins are small proteins derived from a domain of human fibronectin and have modifiable binding loops similar to an antibody. Combinectin was developed to contain an anti-CD4 adnectin, an anti-gp41 adnectin, and a fusion inhibitor peptide with the potential for weekly subcutaneous dosing.

Capsid inhibitors. HIV capsid assembly is a novel antiviral target for which no antiretrovirals are yet approved. GS-CA1 is a highly potent HIV-1 capsid assembly inhibitor with a **50% effective concentration** of 140 pM in vitro that is active against all major HIV-1 clades (75). Although some resistance mutations in the HIV capsid gene can be selected in vitro by GS-CA1, preexisting resistance mutations could not be detected in 137 treatment-naive patients and 14 heavily treatment-experienced patients with virologic failure (76). This suggests that GS-CA1 resistance mutations may reduce the fitness of HIV isolates. Both the pharmacokinetic and physicochemical properties of GS-CA1 indicate that it will be an excellent candidate for long-acting formulation.

CHALLENGES AND OPPORTUNITIES FOR HIV TREATMENT AND PREVENTION

Although LA/ER formulations hold great promise for long-term treatment and prevention of HIV infection, these approaches also carry important challenges. Management of possible

drug-associated adverse effects is particularly challenging if the formulation is not removable or reversible, as is the case with intramuscular injections. For CAB LA and RPV LA, this issue was dealt with by selecting agents that were already known to be exceedingly well tolerated in studies using oral formulations of the same drugs. Oral RPV was already FDA approved before studies of its long-acting counterpart began. The main reason for requiring an oral lead-in phase in studies of these two formulations is to ensure tolerability before starting injections.

Other challenges include what to do if recipients become pregnant and how to manage HIV-infected patients who miss visits required for intramuscular or intravenous administration of these formulations. Subcutaneous formulations could be self-administered, but no subcutaneous formulations of any LA/ER antiretrovirals have been approved. Injected formulations are associated with an extended half-life and a long low-level tail if dosing is not repeated at regular intervals. At present, research participants who are receiving these agents for treatment or prevention are required to begin taking daily oral antiretrovirals for a period of several months when they stop therapy to prevent the emergence of drug resistance. For treatment indications, it is important to be able to combine two or more active agents, but the only formulations with reasonably matched pharmacokinetic profiles are CAB LA and RPV LA. Several investigational formulations that could alleviate this problem are in preclinical development (see the section titled Long-Acting Antiretroviral Drugs for HIV Treatment and Prevention in Preclinical Development), and there is also the possibility of combining long-acting versions of bNABs with small-molecule formulations.

A potential solution to many of the drawbacks of intramuscular formulations is subcutaneous implants that can deliver drug systemically. Advantages of this technology 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 a lower drug dose per day because of potency and formulation properties. If there is concern about a prolonged low-level pharmacokinetic tail, the device can simply be removed. Although implants have some advantages over injectable formulations, they also have disadvantages. These include the need for insertion and removal by trained personnel using sterile techniques. Because these devices can be removed in the case of adverse effects, novel agents developed for this indication may not require the availability of an oral formulation or oral lead-in period.

New drug delivery technologies also hold promise. These include biodegradable implants (77), microneedle patches for transdermal drug delivery (78), and slowly dissolving gastric reservoirs (79). Many of these technologies allow coformulation such that two or more antiretrovirals, or a combination of an antiretroviral for HIV prevention and a hormonal contraceptive, could be combined in the same device. Despite their promise, these new formulations should be developed while also considering those with the greatest need in the HIV epidemic, such as those living in low- and middle-income countries, infants, children, adolescents, and pregnant women. Of the two LA/ER antiretroviral formulations in phase III clinical development, RPV LA requires refrigeration and therefore may not be appropriate for use in many low- and middle-income countries.

IMPLICATIONS FOR OTHER DISEASES

Long-acting antimicrobial preparations could be used to treat or prevent other infectious diseases, and much can be learned in the development of LA/ER formulations for HIV that can be applied to other microbes. Tuberculosis remains one of the world's greatest preventable causes of death, and the main reason for treatment failure is the inability to complete a nine-month or longer course of oral therapy. A modeling exercise based on physicochemical properties found that rifabutin, rifapentine, delamanid, and bedaquiline all have properties similar to other long-acting small

molecules, but other antituberculosis drugs do not (80). This finding, combined with recent data demonstrating the efficacy of a one-month combination regimen to prevent tuberculosis, support the feasibility of such an approach (81).

Long-acting formulations of antimalarials could be used to prevent malaria infection and in chemoprophylactic campaigns could be used in place of a malaria vaccine. For example, a nanoformulated version of atovaquone protected mice from challenge with *Plasmodium berghei* for up to four weeks after a single intramuscular injection (82). Widespread use of such a formulation could effectively block transmission of malaria in humans.

The chronic hepatitis C virus (HCV) infection is now responsible for more US deaths annually than HIV. Despite the availability of curative oral regimens, the prevalence of chronic HCV is unchanged in many parts of the world. There is concern that oral antivirals alone may not be sufficient as a global public health measure. A test-and-treat strategy for HCV could theoretically end this epidemic if there were an effective two-drug injectable long-acting formulation that could deliver antiviral therapy for 8–12 weeks, as is feasible with current nanoformulations of CAB.

The management of other noncommunicable diseases will also benefit from long-acting agents to promote adherence to treatment, including asthma (83), diabetes (84), and hyperlipidemia (85).

CONCLUSIONS

Current HIV treatment and prevention regimens are potent, safe, tolerable, and convenient with one-pill, once-daily dosing. However, adherence is critical for long-term efficacy, and new long-acting regimens have the potential to improve convenience over the standard current oral regimens. Although only one long-acting antiretroviral drug is approved to date, many investigational long-acting formulations of drugs both in existing antiretroviral drug classes (reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors) and newer classes (entry inhibitors, capsid inhibitors) are under investigation in preclinical and clinical studies. Even though long-acting antiretroviral regimens appear promising, the challenges of managing side effects, drug-drug interactions, pregnancy, and long-lasting drug concentrations that could lead to the development of drug resistance exist. Further progress in the treatment and prevention of HIV infection will result from development of these long-acting formulations.

DISCLOSURE STATEMENT

R.G. is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. C.F. reports serving as a paid consultant for Cipla Pharmaceuticals, Janssen Pharmaceuticals, Merck Laboratories, Mylan Pharmaceuticals, and ViiV Healthcare, and received research grant support from Gilead Sciences paid to his university.

LITERATURE CITED

1. Samji H, Cescon A, Hogg RS, et al. 2013. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLOS ONE* 8:e81355
2. May MT, Gompels M, Delpech V, et al. 2014. Impact on life expectancy of HIV-1 positive individuals of $CD4^+$ cell count and viral load response to antiretroviral therapy. *AIDS* 28:1193–202
3. Lohse N, Obel N. 2016. Update of survival for persons with HIV infection in Denmark. *Ann. Intern. Med.* 165:749–50
4. US Dep. Health Hum. Serv. Antiretroviral Ther. Guidel. Panel. 2018. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*. AIDSinfo, US Dep. Health Hum. Serv. **https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0**

5. Günthard HF, Saag MS, Benson CA, et al. 2016. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. *JAMA* 316:191–210
6. EACS (Eur. AIDS Clin. Soc.). 2016. *Guidelines, Version 8.1*. Eur. AIDS Clin. Soc., Brussels, Belg. **http://www.eacsociety.org/files/guidelines_9.0-english.pdf**
7. WHO (World Health Organ.). 2016. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Geneva: WHO. 2nd ed. **http://www.who.int/hiv/pub/arv/arv-2016/en/**
8. Molina JM, Capitant C, Spire B, et al. 2015. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N. Engl. J. Med.* 373:2237–46
9. McCormack S, Dunn DT, Desai M, et al. 2016. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 387:53–60
10. Amico KR. 2012. Adherence to preexposure chemoprophylaxis: the behavioral bridge from efficacy to effectiveness. *Curr. Opin. HIV AIDS* 7:542–48
11. Swindells S, Flexner C, Fletcher CV, et al. 2011. The critical need for alternative antiretroviral formulations, and obstacles to their development. *J. Infect. Dis.* 204:669–74
12. Williams J, Sayles HR, Meza JL, et al. 2013. Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients. *Nanomedicine* 8:1807–13
13. Weld ED, Rana MS, Dallas R, et al. 2017. Readiness of youth living with HIV for long-acting antiretrovirals. In *9th International AIDS Society Conference on HIV Science*, July 23–26, Paris (Abstr. TUPEB0460). **http://programme.ias2017.org/Abstract/Abstract/245**
14. Jacobson JM, Flexner CW. 2017. Universal antiretroviral regimens: thinking beyond one-pill-once-a-day. *Curr. Opin. HIV AIDS* 12:343–50
15. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. 2017. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 390:1499–1510
16. Winner B, Peipert JF, Zhao Q, et al. 2012. Effectiveness of long-acting reversible contraception. *N. Engl. J. Med.* 366:1998–2007
17. Mäkäräinen L, van Beek A, Tuomivaara L, et al. 1998. Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. *Fertil. Steril.* 69:714–21
18. Rattan J, Noznesky E, Curry DW, et al. 2016. Rapid contraceptive uptake and changing method mix with high use of long-acting reversible contraceptives in crisis-affected populations in Chad and the Democratic Republic of the Congo. *Glob. Health Sci. Pract.* 4(Suppl. 2):S5–20
19. Fok WK, Blumenthal PD. 2017. HIV and contraception. *Curr. Opin. Obstet. Gynecol.* 29:419–26
20. Scarsi KK, Darin KM, Nakalema S, et al. 2016. Unintended pregnancies observed with combined use of the levonorgestrel contraceptive implant and efavirenz-based antiretroviral therapy: a three-arm pharmacokinetic evaluation over 48 weeks. *Clin. Infect. Dis.* 62:675–82
21. Morris MT, Tarpada SP. 2017. Long-acting injectable paliperidone palmitate: a review of efficacy and safety. *Psychopharmacol. Bull.* 47:42–52
22. Plosker GL, Brogden RN. 1994. Leuprorelin. A review of its pharmacology and therapeutic use in prostatic cancer, endometriosis and other sex hormone-related disorders. *Drugs* 48:930–67
23. Kalra A, Rehman H, Khera S, et al. 2017. New-generation coronary stents: current data and future directions. *Curr. Atheroscler Rep.* 19:14
24. Yoshinaga T, Kobayashi M, Seki T, et al. 2015. Antiviral characteristics of GSK1265744, an HIV integrase inhibitor dosed orally or by long-acting injection. *Antimicrob. Agents Chemother.* 59:397–406
25. Karmon SL, Mohri H, Spreen W, Markowitz M. 2015. GSK1265744 demonstrates robust in vitro activity against various clades of HIV-1. *J. Acquir. Immune Defic. Syndr.* 68:e39–41
26. Stellbrink HJ, Hoffmann C. 2018. Cabotegravir: its potential for antiretroviral therapy and preexposure prophylaxis. *Curr. Opin. HIV AIDS* 13:334–40
27. Spreen W, Min S, Ford SL, et al. 2013. Pharmacokinetics, safety and monotherapy antiviral activity of GSK1265744, an HIV integrase strand transfer inhibitor. *HIV Clin. Trials.* 14:192–203

28. Spreen W, Ford SL, Chen S, et al. 2014. GSK1265744 pharmacokinetics in plasma and tissue after single-dose long-acting injectable administration in healthy subjects. *J. Acquir. Immune Defic. Syndr.* 67:481–86
29. Markowitz M, Frank I, Grant RM, et al. 2017. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. *Lancet HIV* 4:e331–40
30. Landovitz R, Li S, Grinsztejn B, et al. 2017. Safety, tolerability and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected women and men: HPTN 077. In *9th International AIDS Society Conference on HIV Science*, July 23–26, Paris (Abstr. TUAC0106LB). **http://programme.ias2017.org/Abstract/Print/?abstractid=5481**
31. Cohen CJ, Andrade-Villanueva J, Clotet B, et al. 2011. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 378:229–37
32. Molina JM, Cahn P, Grinsztejn B, et al. 2011. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 378:238–46
33. Williams PE, Crauwels HM, Basstanie ED. 2015. Formulation and pharmacology of long-acting rilpivirine. *Curr. Opin. HIV AIDS* 10:233–38
34. Ferretti F, Boffito M. 2018. Rilpivirine long-acting for the prevention of HIV infection. *Curr. Opin. HIV AIDS* 13:300–7
35. Verloes R, Deleu S, Niemeijer N, et al. 2015. Safety, tolerability and pharmacokinetics of rilpivirine following administration of a long-acting formulation in healthy volunteers. *HIV Med.* 16:477–84
36. Jackson AG, Else LJ, Mesquita PM, et al. 2014. A compartmental pharmacokinetic evaluation of long-acting rilpivirine in HIV-negative volunteers for pre-exposure prophylaxis. *Clin. Pharmacol. Ther.* 96:314–23
37. Penrose KJ, Parikh UM, Hamanishi KA, et al. 2016. Selection of rilpivirine-resistant HIV-1 in a seroconverter from the SSAT 040 Trial who received the 300-mg dose of long-acting rilpivirine (TMC278LA). *J. Infect. Dis.* 213:1013–17
38. McGowan I, Dezzutti CS, Siegel A, et al. 2016. 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* 3:e569–78
39. Bekker L-G, Li S, Tolley E, et al. 2017. HPTN 076: TMC278 LA safe, tolerable and acceptable for HIV pre-exposure prophylaxis. In *Conference on Retroviruses and Opportunistic Infections*, February 13–16, Seattle, WA (Abstr. 421LB). **http://www.croiconference.org/sessions/hptn-076-tmc278-la-safe-tolerable-and-acceptable-hiv-preexposure-prophylaxis**
40. Margolis DA, Brinson CC, Smith GHR, et al. 2015. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. *Lancet Infect. Dis.* 15:1145–55
41. Spreen W, Williams P, Margolis D, et al. 2014. Pharmacokinetics, safety, and tolerability with repeat doses of GSK1265744 and rilpivirine (TMC278) long-acting nanosuspensions in healthy adults. *J. Acquir. Immune Defic. Syndr.* 67:487–92
42. Burkly LC, Olson D, Shapiro R, et al. 1992. Inhibition of HIV infection by a novel CD4 domain 2–specific monoclonal antibody. *J. Immunol.* 149:1779–87
43. Kuritzkes DR, Jacobson JM, Powderly WG, et al. 2004. Antiretroviral activity of the anti-CD4 monoclonal antibody TNX-355 in patients infected with human immunodeficiency virus type 1. *J. Infect. Dis.* 189:286–91
44. Jacobson JM, Kuritzkes DR, Godofsky E, et al. 2009. Safety, pharmacokinetics and antiretroviral activity of multiple doses of ibalizumab (formerly TNX-355), an anti-CD4 monoclonal antibody, in HIV-1 infected adults. *Antimicrob. Agents Chemother.* 53:450–57
45. Emu B, Fessel J, Schrader S, et al. 2018. Phase 3 study of ibalizumab for multidrug-resistant HIV-1. *N. Engl. J. Med.* 379:645–54
46. Murga J, Franti M, Pevear DC, et al. 2006. Potent antiviral synergy between monoclonal antibody and small-molecule CCR5 inhibitors of human immunodeficiency virus type 1. *Antimicrob. Agents Chemother.* 50:3289–96

47. Jacobson JM, Saag MS, Thompson MA, et al. 2008. Antiviral activity of single-dose PRO 140, a CCR5 monoclonal antibody, in HIV-infected adults. *J. Infect. Dis.* 198:1345–52
48. Jacobson JM, Lalezari JP, Thompson MA, et al. 2010. Phase 2a study of the CCR5 monoclonal antibody PRO 140 administered intravenously to HIV-infected adults. *Antimicrob. Agents Chemother.* 54:4137–42
49. Jacobson JM, Thompson MT, Lalezari JP, et al. 2010. Anti-HIV activity of weekly or bi-weekly treatment with subcutaneous PRO140, a CCR5 monoclonal antibody. *J. Infect. Dis.* 201:1481–87
50. Wu H, Yao C, Zhang T, et al. 2016. Efficacy and safety of long acting HIV fusion inhibitor albuvirtide in antiretroviral-experienced adults with HIV-1: interim 48 week results from the randomized, controlled, phase 3, non-inferiority TALENT study. In *HIV Drug Therapy*, Glasgow, UK, Oct. 23–26 (Abstr. O336). **http://www.natap.org/2016/GLASGOW/GLASGOW_38.htm**
51. Markowitz M, Sarafianos SG. 2018. 4′-Ethynyl-2-fluoro-2′-deoxyadenosine, MK-8591: a novel HIV-1 reverse transcriptase translocation inhibitor. *Curr. Opin. HIV AIDS* 13:294–99
52. Bernatchez JA, Paul R, Tchesnokov EP, et al. 2015. Derivatives of mesoxalic acid block translocation of HIV-1 reverse transcriptase. *J. Biol. Chem.* 290:1474–84
53. Stoddart CA, Galkina SA, Joshi P, et al. 2015. Oral administration of the nucleoside EFdA (4′-ethynyl-2-fluoro-2′-deoxyadenosine) provides rapid suppression of HIV viremia in humanized mice and favorable pharmacokinetic properties in mice and the rhesus macaque. *Antimicrob. Agents Chemother.* 59:4190–98
54. Oliveira M, Brenner BG, Xu H, et al. 2017. M184I/V substitutions and E138K/M184I/V double substitutions in HIV reverse transcriptase do not significantly affect the antiviral activity of EFdA. *J. Antimicrob. Chemother.* 72:3008–11
55. Flexner C. 2018. Antiretroviral implants for treatment and prevention of HIV infection. *Curr. Opin. HIV AIDS* 13:374–80
56. Grobler JA, Friedman E, Barrett SE, et al. 2016. Long-acting oral and parenteral dosing of MK-8591 for HIV treatment or prophylaxis. In *Conference on Retroviruses and Opportunistic Infections*, Feb. 22–25, Boston, MA (Abstr. 98)
57. Cohen YZ, Caskey M. 2018. Broadly neutralizing antibodies for treatment and prevention of HIV-1 infection. *Curr. Opin. HIV Aids* 13:366–73
58. Koup R. 2018. New-generation high-potency and designer antibodies: role in HIV treatment. *Annu. Rev. Med.* 69:409–19
59. Gautam R, Nishimura Y, Gaughan N, et al. 2018. A single injection of crystallizable fragment domain–modified antibodies elicits durable protection from SHIV infection. *Nat. Med.* 24:610–16
60. Chen J, Flexner C, Liberman RG, et al. 2012. Biphasic elimination of tenofovir diphosphate and nonlinear pharmacokinetics of zidovudine triphosphate in a microdosing study. *J. Acquir. Immune Defic. Syndr.* 61:593–99
61. Ruane PJ, DeJesus E, Berger D, et al. 2013. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J. Acquir. Immune Defic. Syndr.* 63:449–55
62. Sax PE, Wohl D, Yin MT, et al. 2015. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 385:2606–15
63. Gunawardana M, Remedios-Chan M, Miller CS, et al. 2015. Pharmacokinetics of long-acting tenofovir alafenamide (GS-7340) subdermal implant for HIV prophylaxis. *Antimicrob. Agents Chemother.* 59:3913–19
64. Mackman RL, Ray AS, Hui HC, et al. 2010. Discovery of GS-9131: design, synthesis and optimization of amidate prodrugs of the novel nucleoside phosphonate HIV reverse transcriptase (RT) inhibitor GS-9148. *Bioorg. Med. Chem.* 18:3606–17
65. Murphy R, Kravchenko AV, Orlova-Morozova E, et al. 2017. Elsulfavirine as compared to efavirenz in combination with TDF/FTC: 48-week study. In *Conference on Retroviruses and Opportunistic Infections*, Feb. 13–16. Seattle, WA. (Abstr. 452LB)
66. Al-Salama ZT. 2017. Elsulfavirine: first global approval. *Drugs* 77:1811–16
67. Rogovoy B, Koryakova A, Karapetian R, et al. 2017. Preclinical development of elsulfavirine/VM1500A long acting injectable formulations. In *16th European AIDS Conference*, European AIDS Clinical Society, Oct. 25–27, Milan. (Abstr. PE7/3)

68. Murphy RL, Sanne I, Cahn P, et al. 2003. Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS* 17:2603–14
69. Squires K, Lazzarin A, Gatell JM, et al. 2004. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J. Acquir. Immune Defic. Syndr.* 36:1011–19
70. Gautam N, Roy U, Balkundi S, et al. 2013. Preclinical pharmacokinetics and tissue distribution of long-acting nanoformulated antiretroviral therapy. *Antimicrob. Agents Chemother.* 57:3110–20
71. Lennox JL, DeJesus E, Lazzarin A, et al. 2009. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 374:796–806
72. Kovarova M, Swanson MD, Sanchez RI, et al. 2016. A long-acting formulation of the integrase inhibitor raltegravir protects humanized BLT mice from repeated high-dose vaginal HIV challenges. *J. Antimicrob. Chemother.* 71:1586–96
73. Wensel D, Sun Y, Li Z, et al. 2017. Discovery and characterization of a novel CD4-binding Adnectin with potent anti-HIV activity. *Antimicrob. Agents Chemother.* 61:e00508–17
74. Krystal M, Wensel D, Sun Y, et al. 2016. HIV-1 Combinectin BMS-986197: a long-acting inhibitor with multiple modes of action. In *Conference on Retroviruses and Opportunistic Infections*, Feb. 22–25, Boston, MA. (Abstr. 97)
75. Tse WC, Link JO, Mulato A, et al. 2017. Discovery of novel potent HIV capsid inhibitors with long-acting potential. In *Conference on Retroviruses and Opportunistic Infections*, Feb. 13–16, Seattle, WA. (Abstr. 38)
76. Perrier M, Bertine M, Le Hingrat Q, et al. 2017. Prevalence of gag mutations associated with in vitro resistance to capsid inhibitor GS-CA1 in HIV-1 antiretroviral-naive patients. *J. Antimicrob. Chemother.* 72:2954–55
77. Kalra A, Rehman H, Khera S, et al. 2017. New-generation coronary stents: current data and future directions. *Curr. Atheroscler. Rep.* 19:14
78. Moffatt K, Wang Y, Raj Singh TR, Donnelly RF. 2017. Microneedles for enhanced transdermal and intraocular drug delivery. *Curr. Opin. Pharmacol.* 36:14–21
79. Kirtane AR, Abouzid O, Minahan D, et al. 2018. Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy. *Nat. Commun.* 9:2
80. Swindells S, Siccardi M, Barrett SE, et al. 2018. Long-acting formulations for the treatment of latent tuberculous infection: opportunities and challenges. *Int. J. Tuberc. Lung Dis.* 22:125–32
81. Swindells S, Ramchandani R, Gupta A, et al. 2018. One month of rifapentine/isoniazid to prevent TB in people with HIV: BRIEF-TB/A5279. In *Conference on Retroviruses and Opportunistic Infections*, Mar. 4–7, Boston, MA. (Abstr. 37LB)
82. Bakshi RP, Tatham LM, Savage AC, et al. 2018. Long-acting injectable atovaquone nanomedicines for malaria prophylaxis. *Nat. Commun.* 9:315
83. McCracken JL, Veeranki SP, Ameredes BT, Calhoun WJ. 2017. Diagnosis and management of asthma in adults: a review. *JAMA* 318:279–90
84. Genovese S, Mannucci E, Ceriello A. 2017. A review of the long-term efficacy, tolerability, and safety of exenatide once weekly for type 2 diabetes. *Adv. Ther.* 34:1791–814
85. Pucci G, Cicero AF, Borghi C, Schillaci G. 2017. Emerging biologic therapies for hypercholesterolaemia. *Expert Opin. Biol. Ther.* 17:1077–87