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## REVIEW ARTICLE

# Newer Long-acting Antiretroviral Drugs in Pre-clinical and Clinical development for HIV Prophylaxis and Management

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**ABSTRACT**
*Background The development of long-acting antiretroviral drugs (LA ARVs) has marked a significant advancement in HIV treatment, addressing issues such as adherence and drug resistance. Traditional antiretroviral therapies (ART), while effective in reducing HIV viral load and preventing progression, face challenges in settings with low adherence. LA ARVs, including drugs like cabotegravir and rilpivirine, offer extended dosing intervals, ranging from monthly to quarterly, which may improve adherence and clinical outcomes. This study reviewed the efficacy, tolerability, and potential of LA ARVs, particularly focusing on patient preferences and clinical applicability. Methods This research utilized a comprehensive review of clinical and preclinical data on various LA ARVs, assessing pharmacokinetic profiles, patient-reported outcomes, and adherence rates. Data from phase I to phase III trials were included to determine the clinical viability and patient acceptance of these treatments. Data source Preliminary data from multiple studies showed promising virologic suppression rates exceeding 80%, with patients reporting favorable preferences for monthly injections over daily oral regimens. Certain challenges, such as injection-site reactions and the need for specialized administration, were identified. Conclusion Long-acting antiretrovirals offer a compelling alternative for HIV management, potentially improving adherence and clinical outcomes. However, additional studies on safety, particularly in populations with co-morbidities, and cost-benefit analyses are necessary to guide widespread adoption.*
***Keywords**: HIV, Long-acting antiretroviral, Adherence, Cabotegravir, Rilpivirine*

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## INTRODUCTION

The recent antiretroviral medication (ART) reduces morbidity and mortality, inhibits HIV replication, maintains or restores CD4 cell counts and immunological function, preserves CD4 cell counts, and now extends survival to almost that of the general population.[1–3] Regardless of past disease, symptoms, indicators, HIV RNA level, or CD4 cell count, commencing antiretroviral therapy (ART) is recommended for everyone who is HIV-positive according to current treatment guidelines worldwide.[4–7] The three antiretroviral medications that make up the current first-line ART regimens are frequently formulated to allow for a one- pill, once-daily oral treatment regimen; both in clinical trials and in clinical cohorts, these regimens result in virologic suppression in more than 80% of HIV-infected patients.[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 Orally administered PrEP's effectiveness has also been limited by low adherence rates, however long-acting formulations may help to solve this problem as well.[10] Parenteral treatments might be useful clinically, even if administered only temporarily, in conditions where self-administration of oral medication may be challenging due to gastrointestinal, neurologic, or mental disorders.[11] Without patients' acceptance of these medication delivery methods, no long-acting therapy or preventative plan will be effective. Widespread and passionate support for formulated long-acting and extended-release (LA/ER) antiviral delivery strategies were discovered in many recently published patient surveys.

**Long-acting antiretroviral drugs:**

HIV can be well suppressed with oral antiretroviral regimens while presenting little risk of adverse effects. They provide the convenience of a single daily pill dosage. However, in situations when daily oral medicines are challenging to provide and/or where adherence may be insufficient, long-acting regimens with infrequent dosage, such as weekly oral or long- acting (LA) parenterally administered drugs, may be helpful for treatment or prevention. Alternatives to oral medication in such cases might just save lives and reduce the likelihood of illness spreading to others. For these innovative delivery methods to be successful, it is essential to understand patient preferences on receiving HIV prophylaxis or therapy via pills, injections, or implants. Patient opinions of long-acting antiretroviral dosage has been investigated in a number of surveys. Respondents expressed a lot of interest in LA antiretroviral treatment (ART) for prevention, with the major factors including convenience and extended duration of protection. A study of 400 patients conducted when LA ART was still in its very early phases of development showed remarkably high levels of support for the therapy.[12] A majority of respondents—more than 80%—said they would think about moving from oral to parenteral ART if injections were given once a month; interest was less with more frequent injections. Since then, a number of further studies have supported similar findings, some in particular populations such patients from largely minority neighborhoods,[15] adolescents,[14] and women with HIV infection.[13]

**HIV IN PREGNANCY:**

In 2016, there were 34.5 million HIV-positive individuals worldwide. Of them, 15.3 million (or 44%) were women of reproductive age. As a result, over half of the population may become pregnant while receiving antiretroviral medication (ART). The provision of ART to women before, during, and after pregnancy and nursing helps to enhance the health and survival of mothers,[16] which in turn helps to improve the health of their children.[17] The possibility to prevent MTCT with antiretroviral medications and the necessity to take into account the safety of the women themselves as well as the safety of their exposed fetus and children make pregnant women a distinct demographic from the standpoint of therapy.

**WHO recommendation:**

According to current WHO recommendations, first-line treatment should consist of a fixed dosage combination of tenofovir disoproxil fumarate, lamivudine, or emtricitabine, as well as the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz.[16] Dolutegravir, an integrase inhibitor, and 400 mg of efavirenz were recommended for first-line therapy in 2016, and the so-called "optimised antiretroviral regimens," which also include the protease inhibitor darunavir and the integrase inhibitor raltegravir, were recommended for second- or third-line therapy.[16] The goal of this transition is to adopt more regimens that are highly effective, safe for pregnant women, have minimal toxicity, and a strong genetic barrier to resistance. It also involves taking into account important optimisation criteria like cost, simplicity, and harmonisation. Since the majority of these exposures take place in low- and middle-income nations with no systematic monitoring of medication safety in pregnancy, gathering adequate data on the risk of birth malformations due to ART regimens presents one of the problems. In these situations, surveillance might be challenging due to uncertainties over the accuracy and scope of medical and pharmacy data, the prevalence of home births, and a lack of knowledge in recognizing birth defects. The WHO is organising a mechanism to aggregate these data to increase efficiency and accessibility. Recent initiatives by a number of African nations to establish birth monitoring showed early success.18 To guarantee that the health of women living with HIV and their families is improved, further implementation research is required.

**DRUGS IN PRE-CLINICAL AND CLINICAL DEVELOPMENT:**

**Long-acting antiretrovirals (for treatment and prevention) in clinical development: Cabotegravir**

Investigational HIV integrase inhibitor cabotegravir (CAB, GSK1265744) is structurally related to dolutegravir. It exhibits potent anti activity in vitro against all HIV subclades,[19] including those strains that are resistant to other integrase inhibitors.[20] For the treatment and prevention of HIV, the substance is being developed in both oral and long-acting injectable forms.[21] HIV-uninfected and -infected participants were given single and daily oral doses over the course of 10 days in Phase I and IIa studies, which had shown dose-proportional increases in drug concentrations, a prolonged mean plasma half-life of 31.5 h, and in HIV- infected subjects, a significant decrease in HIV RNA levels of 2.2–2.3 log10 copies/mL over the course of 11 days.[22] Although the majority of the individuals experienced moderate injection site reactions (discomfort, redness, and/or nodule development), CAB LA was generally well tolerated. An ongoing phase III non-inferiority research, HPTN study 083, NCT02720094, compared daily oral tenofovir/emtricitabine with injectable CAB administered every eight weeks for HIV PrEP in high-risk, HIV-uninfected males who have sex with men and transsexual women.

**Rilpivirine:**

Rilpivirine (RPV, TMC278) is an NNRTI that was approved for the treatment of HIV infection after phase III randomised trials,[23,24] showed it to be effective and safe when used as a component of an oral combination ART regimen. Due to the medication's physical, chemical and pharmacological characteristics, a long-acting injectable nanosuspension that can be dosed every 4 to 8 weeks can be created.[25,26] Long-acting rilpivirine (RPV LA, 300 mg/mL) showed plasma drug concentrations equivalent to those seen with the oral medication in a phase I investigation.[27] Another study looked at single doses of RPV LA for PrEP and discovered that RPV concentrations peaked at 6–8 days and lasted for 12 weeks in plasma, cervicovaginal fluid, vaginal and rectal tissue.[28]

**Combination Therapy with Cabotegravir and Rilpivirine**

In the LATTE study, 243 HIV-positive participants received dual nucleoside analogues along with either oral CAB (10, 30, or 60 mg daily) or efavirenz (control) for 24 weeks. If virological inhibition was attained, CAB was then continued along with either oral RPV 25 mg daily or continued dual nucleoside analogues along with efavirenz (control).[29] At 96 weeks, 68–84% of patients throughout the study regimens had HIV RNA levels below 50 copies/mL. Following trials will use CAB 30 mg, which has virologic activity comparable to efavirenz. In the first research using the combination of two long-acting injectable antiretrovirals, 40 HIV- uninfected subjects were randomised to receive parenteral regimens after receiving oral CAB 30 mg daily for a 14-day lead-in period.30 Injections were generally well tolerated and all parenteral dosing groups achieved the desired therapeutic drug plasma concentrations after 3 days of treatment with sustained exposure. The researchers came to the conclusion that a dual regimen of CAB LA and RPV LA for an all-injectable HIV therapy regimen should be further studied.

**Ibalizumab**

Ibalizumab is a humanised IgG4 antibody that prevents HIV-1 entry by attaching to the CD4 extracellular domain and blocking allosteric entry into CD4+ T cells.[31] The chance of immunosuppression is reduced since the ibalizumab binding site is different from the CD4 major histocompatibility complex sites. The US Food and Drug Administration (FDA) has authorized this medication for use in people with a multidrug-resistant HIV-1 infection who have received several treatments and are failing current therapy. Ibalizumab is administered intravenously in a single 2,000 mg loading dosage, with an additional 800 mg maintenance dose administered every two weeks after that. Ibalizumab demonstrated antiviral activity in clinical trials in individuals who had had antiretroviral treatment previously, although treatment was often associated to the early rebound of viremia and resistance.[32,33] Ibalizumab's limitations over other long-acting antiretrovirals in clinical use include intravenous administration and a biweekly dosage regimen. This drug's subcutaneous administration is being investigated.

**PRO 140**

A humanized monoclonal IgG4 antibody labeled PRO 140 binds to the CCR5 receptor's HIV-1 binding domain and inhibits CCR5-tropic viruses from attaching to and infiltrating cells.[46] The CCR5 antagonist maraviroc's binding site is different from PRO 140's, and PRO 140 works against viruses that are resistant to maraviroc.34 PRO 140 monotherapy quickly reduced viral load in individuals with HIV that was solely R5 tropic when administered once per week for three weeks at a dosage of 324 mg subcutaneously or 5 mg/kg intravenously.[35,36] Some individuals have acquired anti-PRO 140 antibodies, although they don't appear to have an effect on pharmacokinetics, antiviral responses, or the incidence of adverse events, which are quite rare. PRO 140 is being researched as rescue therapy for patients with viremia on their existing antiretroviral regimen and as a weekly maintenance monotherapy for patients whose baseline HIV was CCR5 tropic. Similar to maraviroc, this medication can only be administered in those who have already been shown to be HIV-1 CCR5-tropic infected. The FDA recently granted the medication orphan drug status, and it is now advancing toward clearance for patients with multidrug-resistant HIV who have had extensive therapy.

**Albuvirtide**

Similar to enfuvirtide, albuvirtide is a synthetic 32-amino acid peptide homologue of the fusion region of HIV gp-41 (T-20). Although it must be administered parenterally and is more expensive to produce than enfuvirtide, it has the benefit of having a substantially longer plasma half-life (12–14 days). This medication is currently only being developed in China. In a phase III open-label study, 389 patients who had previously received therapy were randomized to receive either lopinavir/ritonavir plus albuvirtide 320 mg intravenously once weekly or lopinavir/ritonavir plus WHO-recommended NRTIs. Albuvirtide seems to be well tolerated thus far. There are plans to investigate the medication in more locations, and a subcutaneous formulation that would enable self-administration every 2-4 weeks is now under development.

**Broadly Neutralizing Antibodies**

HIV broadly neutralising antibodies (bNABs) target specific antigens on the HIV external membrane glycoprotein 120 (gp120), and several of these bNABs have reached clinical development for both HIV treatment and prevention, including VRC01, 3BNC117, and 10-1074. bNABs were first isolated from HIV-infected individuals with high-level anti-HIV neutralising activity.[37,38] The results of early clinical investigations showed that bNABs were usually well tolerated, linked to virologic activity, and improved immune function. Even though bNABs must be administered parenterally, a two-amino acid substitution (referred to as LS for the substituted amino acids) added to the crystallizable fragment domain enhances the serum half-life of bNABs by two to three times, providing the possibility for infrequent administration.[39]

**Existing Antiretroviral Drug Classes**

Tenofovir, elsulfavirine, atazanavir, ritonavir, and raltegravir long-acting formulations are derived from drugs or prodrugs of recognized antiretroviral treatment classes. Some of these medications are currently on the market and have received approval for oral formulations.

**Nonnucleoside Reverse Transcriptase Inhibitors: Elsulfavirine.**

In drug trials, the HIV NNRTI elsulfavirine (VM1500A) showed safety and effectiveness that were equivalent to those of efavirenz-based regimens.[40] Russia recently authorized the use of the oral medication to treat HIV infection.[41] Recently, preclinical studies on an elsulfavirine long-acting injectable formulation with the capability for monthly injection were reported,[42] and clinical trials are anticipated.

**Protease Inhibitors: Atazanavir and Ritonavir**

In order to treat HIV infection, the HIV protease inhibitor atazanavir was approved for use in its oral form due to its virologic suppression, tolerance, and safety.[43,44] It is considered an alternate medication as part of HIV therapy regimens when combined with the HIV protease inhibitor and potent CYP3A4 inhibitor ritonavir. When administered subcutaneously or intramuscularly to mice and monkeys, a nano formulated long-acting combination of atazanavir and ritonavir achieved plasma and target tissue levels several times greater than oral dosing, including macrophages that may promote prolonged drug release.[45]

**Integrase Inhibitors: Raltegravir**

The HIV integrase inhibitor Raltegravir (RAL), which was licensed for use in oral form for the treatment of HIV infection on the basis of safety, tolerability, and virologic suppression [46] is frequently recommended for HIV. Additionally, the use of RAL is recommended as an element of a post - exposure prophylaxis programme to avoid acquiring HIV after exposure. A new long-acting RAL formulation for HIV prevention and treatment showed promising pharmacokinetic properties in rhesus macaques, potent antiretroviral activity in infected humanised BLT (bone marrow-liver-thymus) mice with a functional human immune system, and long-term protection from repeated vaginal HIV challenges in uninfected BLT mice.[47]

**Entry Inhibitors: Combinectin**

Combinetctin (GSK 3732394, BMS-986197) is an experimental drug with the potential for a long-acting formulation and three distinct synergistic modes of action.[48,49] Combinextin was designed with the ability for weekly subcutaneous dose and contains an anti-CD4 adnectin, an anti-gp [41] adnectin, and a fusion inhibitor peptide. Adnectins are small proteins synthesized from a portion of human fibronectin that have specific antibodies binding loops.

**Capsid inhibitors**

HIV capsid assembly is an antiviral drug target for which no antiretrovirals have yet received approval. GS-CA1 is an extremely potent HIV-1 capsid assembly inhibitor with an in vitro 50% effective concentration of 140pM that is active against all major HIV-1 clades.[50] Although GS-CA1 can select a few resistance mutations in the HIV capsid gene in vitro, preexisting resistance mutations were not found in 137 treatment-naive patients and 14 severely treated patients with virologic failure.51 This implies that GS-CA1 resistance mutations may affect the fitness of HIV isolates. The pharmacokinetic and physicochemical characteristics of GS-CA1 suggest that it will make a great long-acting formulation candidate.

## 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. Despite the fact that long-acting antiretroviral regimens seems promising, managing side effects, drug-drug interactions, pregnancy, and persistent drug concentrations that can result in the development of drug resistance presents challenges. Further progress in the treatment and prevention of HIV infection will result from development of these long- acting formulations.

**DECLARATION**

We hereby declare that the review article titled "Newer Long-acting Antiretroviral Drugs in Pre-clinical and Clinical Development for HIV Prophylaxis and Management" is an original work carried out by us, Jihana.M and Venkateswaramurthy.N, of the Department of Pharmacy Practice, JKKN College of Pharmacy, Kumarapalayam, Namakkal, Tamilnadu, India.

**AUTHOR CONTRIBUTIONS**

Jihana.M: Conducted the literature review, organized the data, and contributed to drafting and editing the manuscript.
Venkateswaramurthy.N: Supervised the study, provided critical revisions, and finalized the manuscript.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest in connection with this manuscript. We affirm that the content of this article is free from plagiarism, all sources of information and references have been duly acknowledged, and this work has not been published or submitted elsewhere for publication.

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