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Review Article

Revolutionising HIV Care: Emerging Strategies and Therapeutic Breakthroughs - A Literature Review

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A B S T R A C T

HIV-AIDS is a globally prevalent disease largely managed by the use of anti-retroviral therapy, however, during the treatment, a significant proportion of patients experience various drug-induced toxicities, thus causing failure to comply with the treatment regimen. With recent advancements in the field of medicine and HIV care many new and effective treatment modalities have surfaced and have been tested on humans giving promising results with a very significant reduction in the viral load. Given that millions of people worldwide are affected by HIV it is crucial now more than ever to explore innovative approaches. Our review paper delves into providing strong evidence based on existing literature of new emerging drugs as well injectables that cater to the needs of the patient and help in improving adherence to therapy. Cutting-edge genetic techniques such as gene editing and monoclonal antibodies are also highlighted as methods with the potential to eliminate HIV at its core. As research advances the collective efforts of researchers and healthcare professionals provide hope for a future where HIV is no longer a disease. This review emphasises the importance of research and innovation in our fight, against HIV and our pursuit of a cure.

Keywords: HIV, Pharmacotherapy, Anti-viral Medication, Novel Therapy, HIV-AIDS

Introduction

HIV or Human Immunodeficiency Virus remains a global health challenge, with UNAIDS 2023 estimates indicating that between 33.1 million and 45.7 million people are currently living with the virus. In 2022, 1.3 million new HIV cases were reported, and AIDS-related deaths reached 630,000. The most significant prevalence rates are observed in Eastern and Southern Africa, underscoring the ongoing impact of the virus on this region.[1] The present modality of treatment of HIV revolves around the use of Highly Active Antiretroviral Therapy (HAART) or Anti-Retroviral Therapy (ART) which currently employs the use of various classes of drugs like Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI), Nucleoside Reverse Transcriptase

Inhibitors (NRTI), protease inhibitors, entry inhibitors, CCR5 antagonists, fusion inhibitors and integrase inhibitors which are administered by oral route. However, challenges like noncompliance, and adverse effects like Zidovudine associated anaemia, stavudine-associated peripheral neuropathy, protease inhibitor-associated retinoid toxicity, NNRTI-associated hypersensitivity reactions, nausea, bloating and diarrhoea are highly observed in 30–70% of HIV patients receiving ART.[2] Treating older patients with HIV presents another challenge due to the association of drugs like abacavir and tenofovir with cardiovascular anomalies and renal disorders along with various drug interactions with their existing co-medications if any.[3] So despite the recent advancements in the pharmacotherapy of HIV, the disease remains incurable and the progression of the disease to AIDS can be prevented on a large scale by enhancing the patient's compliance to therapy. Over the last few years many new modalities of HIV treatment have emerged, giving hope to People living with HIV/AIDS and some even assuring a cure. The recent novel therapies include novel drugs, exosomes, latency-reversing agents, gene therapy, newer PEP and PrEP medications and stem cell transplants. The most notable report is the stem cell transplant that has become a cure for HIV in cancer patients.[4] Some other innovations that show potential as HIV treatment include the use of CRISPR-Cas-based gene editing technology along with other in vivo delivery gene editing tools.[5] Targeting of integrase protein seems to be another promising approach against HIV infection.[6] Long-acting injectables are a major area of focus because, unlike the currently used ART therapy which requires daily dosing, these injections are required to be taken only once a month which can lead to better disease rates.[7]

Our literature focuses on delving into the details of promising and advanced therapy modalities for treating HIV.

Drug Therapy

Recent development and drug discovery have opened more opportunities and modalities to treat patients suffering from HIV using novel drug molecules. Some of the novel drug molecules are as follows:

Doravirine

Second-generation NNRTI can be utilised clinically to treat HIV infections when resistance to Efavirenz is exhibited.[8] Doravirine marketed as Pifeltro was approved in August of 2018 by the US FDA as well as the European Union. In adult patients with virally suppressed HIV-1 infection with no prior antiretroviral treatment history, it is administered at a dose of 100 mg. A fixed-dose combination of three drugs marketed as Delstrigo, i.e., doravirine (100 mg), Lamivudine (300 mg) and Tenofovir (300 mg) is also approved for the treatment of HIV.[9] DRIVE-SHIFT phase 3 study concluded that the three-drug fixed-dose combination had lower dropout rates but was most frequently associated with 2 adverse reactions: nausea (4%) and headache (3%). Other common adverse reactions observed include insomnia, somnolence, rashes and fatigue.[9,10]

Bictegravir

It is an antiretroviral medication that inhibits integrase strand transferase and is marketed as Biktarvy tablet which is a combination of bictegravir (50 mg), emtricitabine (200 mg) and tenofovir (25 mg) for use in adults and in paediatric patients above 25 kg. It was approved by the FDA on February 7, 2018, and by the European Union in June 2018. A phase 3 study conducted by Sax et al. concluded that bictegravir had good virologic suppression and safety.[11] The BICSTaR cohort study found that 97% of treatment naïve patients were virologically suppressed.[12] Various clinical evidence also suggests the combination of bictegravir for HIV-1 positive patients had good effectiveness and was well tolerated.[13] Another notable benefit of Biktarvy is its efficacy against hepatitis B, demonstrated by the ALLIANCE trial.

Doravirine and bictegravir are known to have a significantly high genetic barrier, which infers the number of mutations in the virus required to develop resistance against these agents. Therefore, these drugs are resistant to the mutations that can render them ineffective and thus are therapeutically effective on their own and do not require the aid of another drug-pharmacological boosting.[8]

About PEP, PrEP and Long-Acting Injectables

The post-exposure prophylaxis medication should be taken by the patient within 2 hours of exposure and no later than 72 hours of suspected exposure, as viraemia follows within 72–120 hours (3–5 days) of virus inoculation. It involves a four-week or 28-day course. However, it is to be noted that in patients exposed to resistant HIV strains, PEP may not work. Similarly, PrEP is the treatment plan for those individuals who have a high chance of being exposed to HIV through sex or injection drug use. Medications used for PrEP& PEP can be the same. The only difference is in the way the drug is administered and its regimen. Initially, only tablet forms of the PEP, PrEP and HIV drugs were available, which were often accompanied by many drawbacks like difficulty in swallowing pills, tiredness of following long-term treatment plans, drug interactions with co-medications etc. To combat such shortcomings along with the issue of resistance of the virus to these drugs, the development of alternative dosage forms as well as newer drugs of ART, PrEP and PEP were likely needed, like long-acting injectables, which are discussed below.[14,15]

Cabenuva

Cabenuva is the first FDA-approved complete prescription injectable regimen that can be administered either monthly

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or twice monthly in patients above the age of 12 years. It obtained approval in January 2021.. Formulation exists as an intramuscular injection composed of Cabetogravir and Rilpivirine.[16] Randomised phase 3 trials, i.e., ATLAS and FLAIR trials conducted to assess the safety and efficacy of Cabenuva concluded that Cabenuva was non-inferior compared to the standard oral therapy in maintaining the viral load suppression.[17]

Lenacapavir

Lenacapavir is an HIV capsid assembly inhibitor, sold under the brand name "Sunlenca". It received FDA approval on December 22, 2022 as a twice-yearly treatment option for patients suffering from multi-drug resistant HIV-1 infection.[18] It was also approved by EMA, EU on August 22, 2022 in Europe followed by Canada in November 2022 and later approved by MHRA in the UK as well.[19–21] The competitive edge of this drug is its lack of in vitro cross-resistance with other drug classes and presently ongoing phase 3 clinical trials are being conducted to delve into utilisation of this drug in pre-exposure prophylaxis.[22,23]

The phase II/ III CAPELLA multicentre clinical trial was conducted to evaluate the efficacy and safety of this capsid inhibitor administered along with the failing standard regimen in 72 PLWH with multi-drug resistance. These subjects had high levels of the virus in their blood despite taking the ART. One group of subjects was randomised, double-binded to get either the Sunlenca or placebo while the other group received the open-labeled Sunlenca. The main aim was to look at how many patients would show a reduction in their virus levels in their first 14 days compared to the start. The lenacapavir injection group did much better (87.5%) than the group that took a fake treatment/ placebo (16.7%). Using Sunlenca with other drugs for 26 weeks, 81% of subjects had very low viral loads, which was continued with 83% still having less virus level even after 52 weeks.[24,25] The twice-yearly Sunlenca use in patients on the CAPELLA phase 3 trial confirmed an effect on health-related quality also, which was discussed in IAS 2023. 64 patients out of those 72 enrolled showed remarkable stability in the scores at baseline through week 52.[26]

Lenacapavir is currently still undergoing various clinical trials like PURPOSE 1, 2 & 5 to assess its use as prophylaxis in patients with high risk for HIV.[22,27,28] The drug is available to eligible patients with HIV but its use is limited to specific cases and clinical settings.[26,29] The predicted cost of tablet and injection of the drug is to be around $42,250 in the initial year of therapy and later yearly for $39,000.[30] The actual cost of the therapy for the patients can vary based on the financial help and insurance coverage promoted by the manufacturing company along with some external supporting programmes.[31]

Other Emerging Treatment Options

Maturation Inhibitors

The possible mechanism of action is by prevention of the breakdown of an HIV protein called "Gag" into small fragments which play an imperative role in the formation of the fully formed infective virus.[32] Drug candidates such as GSK3640254 are under ongoing phase 2 clinical trials for the treatment of HIV. However, the therapy poses a challenge with the development of resistance.

Broadly Neutralising Antibodies

A group of investigational bNabs including VRC01, 3BNC117, VRC01-LS and VRC07-523 LS have been ventured upon to find its role in the treatment of HIV infections. These drug candidates are antibodies targeting the CD-4 binding site and 10–1074 and PGT121, which target the glycan-rich V3 loop on the envelope of the virus.[33]

VRC01 was found to inhibit 90% of HIV strains in vitro. Currently, this drug is under Phase 2 of development for the treatment of HIV and has also been studied for prevention. VRC01-LS is the long-acting form of VRC01 which is also under clinical development. The Tatelo study helped in proving the safety and efficacy of a combination of VRC01 and 10-1074.[34]

Also under Phase 2 development for HIV treatment and prevention is 3BNC117. This drug also has long-acting versions being developed, namely 3BNC117-LS (also known as GS-5423 or teropavimab) and 3BNC117-LS-J. A phase 2 open-label study conducted in the United States showed that the drug was safe, well-tolerated as well as capable of delaying the resurgence of the virus. According to the "eCLEAR" study, the decrease in the viral load was found to be more rapid and the eradication of the viral cells was markedly enhanced with the early administration of 3BNC117.[35,36]

Similarly, VRC07-523 LS is in Phase 2 development for the treatment and prevention of HIV, including in people who do not have the virus.[37]

10-1074, also in phase 2 development, as well as its long-acting forms called GS-2872 or zinlirvimab and 10-1074-LS-J are being studied for their role in HIV treatment and prevention. There are multiple ongoing studies involving this drug, for instance, "RIO", the purpose of which is to find whether the dual therapy of the 2 bNABS, 3BNC117-LS and 10-1074-LS, have the capability of preventing viral rebound during a treatment interruption of ART. Another example of an ongoing study is "HIVACAR", the purpose of which is to prove the efficacy as well as safety of therapeutic HIV vaccines in combination with 10-1074 in the reduction of viral load during treatment interruption of ART.[38]

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PGT121 was isolated in 2011 from an African donor and was evaluated through a multicenter phase 1 clinical trial. The study ultimately demonstrated that this bNAb was able to block the HIV-1 RNA replication in infected persons in a potent and transient manner.[39]

However, these antibodies have their limitations as a therapeutic intervention i.e., insufficient potency leading to the transiency of viral suppression (i.e. for a short duration) at even high doses, emergence of resistance, unestablished impact on cell-associated HIV-1 reservoir and subpar potency in cell-to-cell transmission of viruses.[33]

Islatravir

Islatravir is another investigational drug undergoing phase 3 clinical trials in the treatment of HIV. The drug is planned to be formulated as a monotherapy as well as a fixed-dose combination with doravirine. The drug exhibits a longer half-life, making it a suitable candidate for extended-release formulations. The challenges associated with the drug were decreased total lymphocyte and CD4 cell counts at higher doses.[40]

Venetoclax

Venetoclax is an existing drug that the FDA approved on May 15, 2019 for the treatment of CLL & SLL and also later approved for the treatment of AML on October 16, 2020. The possible mechanism of action is BCL-2 antagonism. Various pre-clinical studies conducted across various institutes suggest its potency to kill the latent HIV-infected cells and delay reinfections. Other preclinical studies and models of HIV suggested that venetoclax delayed the reinfection by 2 weeks even without ART, also exhibiting the potency to antagonise and selectively kill the infected cells. However, the drug is still an ongoing candidate for Phase 1 and Phase 2 clinical trials.[41,42]

An in vivo study was conducted to check how long it takes the viral rebound to happen in the drug-treated vs control groups. Humanised mice were created and then infected with CCR5-tropic HIV-1, which after 3 weeks was established in their blood in stable levels. Mice with ART (three class ART of tenofovir/ emtricitabine/ rilpivirine/ raltegravir) in their foods, which effectively decreased their amount of viraemia within 7–8 weeks. While still on ART,8 of them were given venetoclax 100 mg/kg every weekday for 3 weeks and 6 were placed on placebo over 7 weeks. After administering the last dose of the drug, 2 weeks of ART was disrupted and resulted in viral rebound. Surprisingly, both groups showed viral rebound within 2 weeks and there was no significant difference in the rebound time between the two groups. There were no overt harmful effects found in drug-treated groups or any changes in immune cells seen.[43,44]

Another in vivo study showed that extended venetoclax can delay the viral rebound for up to 2 weeks. After treating the mice with venetoclax for 6 weeks, in 5 out of 8 mice the virus did not come back for 2 weeks after interrupting the ART, while in the other 2, the virus took 3 weeks to rebound post-ART. However, after 4 weeks post-ART discontinuation, no mice remained without the virus. Longer treatments with drugs could not be done further as they develop problems in their bone marrow. This shows that venetoclax significantly delayed the reappearance of the virus up to 3 times longer after stopping ART in this experimental model. This all indicates that targeting the protein BCL-2 with venetoclax may help in delaying the return of the virus which could act as a strategy to eliminate certain HIV-infected cells that persist even during ART.

Therefore instead of longer treatments with venetoclax, the study combined venetoclax with S63845 which targets MCL-1 protein that is important for T cell development and survival. S63845 used alone showed viral rebound within 2 weeks post-ART (25% of mice) similar to venetoclax. Both the drugs were treated in mice with drugs alone separately and others with the mentioned combination, which showed in most mice that were not treated with combination treatment viral rebound occurred within 1 week. While mice treated with both drugs, 2 out of 4 had rebound within 2 weeks post ART and in the other 2, viruses did not come back until 4 weeks after disruption of ART. There was a drift to lower viral loads in mice treated with combinations of the mentioned drugs during post-ART, but only observed until 19 weeks after infection. With just 3 weeks of combination therapy, the time of viral rebound was delayed up to 4 fold after cessation of ART in mice models which was not witnessed in venetoclax or S63845 drug treatment alone. The drug did not significantly deplete CD4+T cells in humanised mice, so researchers wanted to know the impact on different cell subsets in a controlled environment. Hence, they isolated CD4+ T cells from PLWH on ART & treated them with a concentration of venetoclax up to 100 nM. This study revealed that effector memory CD4+ T cells were quite sensitive to depletion and showed signs of cell death at the highest concentrations of the drug.[44]

For other indications, venetoclax can be accessed by patients and also has support programmes for patients who cannot afford it, but its use in HIV is yet to be approved and researched further.[45]

Obatoclax

It is another BCL-1 and MCL-1 inhibitor and also a member of BH3-mimetics, which was suggested to be better for curing HIV than venetoclax. It was designed for various

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types of cancers and has completed several phase II trials, but clinical phase III trials on lung patients were halted by the pharma company.[43,46] It can awaken the dormant HIV-1 cell lines in the lab (in vitro) and in the immune cells of HIV patients. It works by boosting the start and elongation of HIV-1 genetic activity through the NF-kB pathway. The drug activates caspase 8 but does not trigger phosphorylation of the cell-protecting BCL-2 in dormant HIV-1 cell lines. Crucially, it induces apoptosis in dormant infected cells. Its skills to awaken the latent infected cell along with inducing apoptosis makes it a promising candidate for further experiments and also as an Latency reversing agents with similar "shock & kill" approach strategy.[47] Several drugs were selected to see the reduction of certain cells with intact or defective provirus cells in an ex vivo experiment, in which obatoclax lowered the intact HIV viral DNA by 83%, but not the defective or total HIV DNA.[43,48]

Semzuvolimab

It was an investigational drug, formally known as UB-421 which elicits its action through CD4 attachment inhibition.[49] It targets the CD4+ receptor of T Cells prevents the binding of the virus to the receptor and inhibits its entry and multiplication, thereby reducing the viral burden in the body.[50]

A preclinical study of UB-421 showed that it can control the virus in PLWH as well as the PLWH with resistance to the current ART regimen.[51] A non-randomised open-label phase 2 trial of UB-421 was conducted to evaluate its efficacy as a weekly/ biweekly monotherapy during an 8 or 16-week period of ART discontinuation. This resulted in viral suppression (< 20 copies/mL) in all the subjects on the administration of the trial drug. No subjects viewed plasma virus relapse of more than 400 copies/mL.[50,52] In 2020, Taiwan FDA approved phase 1 of UB-421 subcutaneous injection formulation in HIV-1 infected treatment-naive patients.[53–55]

Another phase 2 multicentre study was aimed to evaluate the safety, tolerability and efficacy of this experimental drug along with the failing ART for the initial 1 week and 24 with the optimised background therapy(OBT) in the HIV-1 resistance patients which started in 2023 and is expected to complete around 5th month of 2024. The outcome measured the viral load log10 difference from the baseline.[56,57]

Finally, in January 2020, a phase III trial was started with the goal of finding this drug's effectiveness as monotherapy in HIV-infected patients.[57] Another randomised, double-blinded phase 3 trial began in 2023 with UB-421 vs placebo to measure the decline in the HIV RNA load in test subjects and is estimated to be completed around 2026.[58] Various Phase 2 and Phase 3 studies are still ongoing on the drug to evaluate its efficacy in treating multidrug-resistant HIV and also for the development of new dosage forms.[50,59]

Latency Reversing Agents

These drugs revive the latent or dormant virus present in the immune cells of the body, which can reactivate HIV viral gene expression in order to gain recognition by both the immune system and ART while maintaining cellular homeostasis without negative consequences.[60] The use of latency-reversing agents often termed as 'shock and kill' method so far has not effectively cleared viral reservoirs in humans. Amongst the existing classes of latency-reversing agents, PKC agonists and TLR agonists were found to be the most potent and gave reproducible results.[60,61]

PKC Agonists

From the reports, it is evident that, so far, the only PKC agonist to show effective results in the ex vivo experiment was Bryostatin-1. Bryostatin-1 has been under phase 2 clinical trials for cancers, but none has progressed to phase 3. Similarly, it is under extensive study for use in Alzheimer's disease. It has FDA orphan drug designation for the treatment of fragile X syndrome.[62] It was revealed that bryostatin-1 was safe when administered to 12 people in single-dose administration. However, the drug did not show much effect on transcription of latent HIV, due to low plasma concentrations. In phase 1 human in vivo study of the drug, dose-limiting toxicities like severe myalgia were reported.[61,63] Therefore, a recently proposed alternative to tackle the toxicities was to administer the compounds possessing PKC agonist-like action in their natural context. One such investigated compound was the *Euphorbia kansui* plant extract which has shown promising in vivo and ex vivo results.[61] Previous reports revealed that dichloromethane extracts of the roots of Euphorbia kansui can reactivate latent HIV 1 replication in cells. In addition, it can also activate ex vivo latent HIV 1 expression. Other plant-based derivatives like 'KnipholoneAnthrone' (KA) and its building block 'Anthralin' have high potential in reversing the viral latency at low micromolecular concentrations in multiple cell lines. The mechanism of action of these drugs is through oxygen free radicals and/ or by metal ions.[64] Clinical trials are yet to begin, in order to understand its use in HIV.

HDAC Inhibitors

HDAC inhibitors are able to trigger specific provirus integrations but result in numerous adverse effects at higher doses. One attractive mechanism is the stimulation of HIV reactivation through the activation of non-canonical NF-kB pathways using SMAC mimetic compounds.[60] Recently dCas 9 targeted chromatin and histone enrichment for mass spectroscopy (Catchet MS) led to the recognition of IKZF-1 targeting thalidomide analogues as novel latency reversal agents. Iberdomide, although under study for use in treating multiple myelomas, is one of the recent

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analogues having good potential along with FDA-approved analogues like lenalidomide and Pomalidomide for use as latency-reversing agents.[65] Lenalidomide has proven to have anti-tumour, pro-erythropoietic and immune augmenting action, because of which they have potential, in combination with Vacc-4X immunisation, to improve immune reconstitution in pts on ART. Similarly, phase 2 clinical trials of pomalidomide are undergoing to help us understand how well it works in treating patients with Kaposi sarcoma and human immunodeficiency virus (HIV) infection. Another development is the use of immune checkpoint blockers to activate dormant HIV in CD4 T cells.

TLR Agonist

TLR agonists are the next category showing high prospective as latency-reversing agents when used in combination with broadly neutralising antibodies or as adjuvants in HIV vaccines.[66] One of the significant TLR agonists in clinical trials is GS-9620 (Vesatolimod) under phase 1 trial which was found to be safe. So far there is no single latency-reversing agent that is able to lessen the latent HIV load and thus most recent studies have focused on developing and characterising combinations of compounds (shocktails) that produce synergistic action and exert a broader effect on latently infected populations.[67] (Table 1)

Table 1.A List of Drugs Used for the Treatment of HIV & Few Investigational Drugs

S.No.	Drug	Trial Name	Years of Study/ Status	Phase of Trial	RCT vs Placebo or Other Drugs	Outcome
1.	Doravirine	DRIVE FORWARD[68]	2014–2020	Phase 3	Comparison b/w doravirine & ritonavir-boosted darunavir, both combined with TDF/ emtricitabine (Truvada) or abacavir/ lamivudine (Kivexa)[68]	Both groups had undetectable viral loads proving doravirine to be non-inferior.
		DRIVE AHEAD[68]	2015–2020	Phase 3	b/w co-formulation of doravirine (100 mg), lamivudine (300 mg), and TDF (300 mg) and efavirenz (600 mg), emtricitabine (200 mg), and TDF (300 mg)[68]	Viral suppression rates similar proving doravirine as non-inferior
		DRIVE SHIFT[69]	2019	Phase 3	Switch to single-tablet doravirine (100 mg) with lamivudine 300 mg and TDF 300 mg[69]	The switch in therapy was found to be effective in controlling viral load and well-tolerated by patients.
2.	Bictegravir	ALLIANCE[70]	2018–2021	Phase 3	Comparison b/w Biktarvy & dolutegravir 50 mg + emtricitabine 200 mg/TDF 300 mg[70]	Biktarvy found to be effective in patients co-infected with hepatitis B
3.	Cabenuva	ATLAS[71]	2015–2018	Phase 3	Comparison b/w Cabenuva and regimen of 2 NRTIs and 3rd agent in HIV–1 patients who were virologically suppressed[71]	Cabenuva was found to be non-inferior
		FLAIR[71]	2016–2019	Phase 3	Comparison b/w Cabenuva and regimen of 2 NRTIs and 3rd agent in HIV–1 patients with no previous ARV exposure[71]	Cabenuva was found to be non-inferior

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4.	Lenacapavir	CAPELLA[24,25]	2019–2025	Phase II/ III	Combined with optimised ART & compared with placebo[24,25]	Lower viral loads (81%) and more were observed in twice-yearly treatment.
5.	GSK3640254	A phase IIb, randomised, double-blinded, parallel-group study comparing GSK3640254iin combination with dolutegravir along with dolutegravir+ lamivudine combination in HIV-1 infected ART-naive adults [DYNAMIC][72,73]	2021	Phase 2b	RCT on GSK3640254 with dolutegravir combination vs dolutegravir plus lamivudine[72,7]	The company had stopped the compound development. It is not due to safety or efficacy issues. It reflected the company strategy for portfolio progression.
6	VRC01	HVTN 703/ HPTN 081 AMP study-HIV Vaccine trial network 703/ HIV Prevention Trial network 081[74,75]	2016–2021	Phase 2	Multicenter, randomised, controlled, double-blind trial, evaluating the efficacy and safety of VRC01 in reducing the acquisition of HIV-1 in women of Sub-Saharan Africa[74,75]	VRC01 did not specifically protect the participants from acquiring HIV. There was a lack of efficacy due to the low percentage of VRC01-sensitive virus spreading in those regions where trials were conducted, but the effectiveness of VRC01 infusions for the prevention of HIV was 75%.
7.	Islatravir	ILLUMINATE HTE[40,76,77]	2020–2023	Phase III	Comparing the Anti-HIV action of islatravir, doravirine and also fixed doses of both vs placebo[40,76,77]	Viral suppression was attained and tolerated well through 49 weeks with DOR/ IST with the ART group. 48.6% of subjects had shown drug-related side effects and major side effects were related to doravirine/ islatravir.
8.	Venetoclax	AMBER[78,79]	Estimated to start in 2024	Phase I/ II	RCT[78,79]	Not yet out
9.	Obatoclax	Laboratory-based study to evaluate the effect of obatoclax on HIV-infected cells[43,48]	Not on any clinical trials yet	-	-	There was a reduction in the intact HIV DNA (83%) but not the defective HIV DNA.

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10.	Semzuvolimab/ UB-421	Randomised, double-blind, placebo-controlled trial[80]	Started in 2023, estimated to complete in 2026	Phase III	UB-421 vs placebo	Not yet out
11.	Bryostatin- 1	BRYOLAT[81]	2014–2015	I	Bryostatin-1 (10 mcg/m2) vs placebo (sodium chloride 0.8%)	Not yet out
12.	*Euphorbia kansui*	*Euphorbia kansui* in combination with ART for eradication of the latent HIV 1 reservoir, interventional study[82]	2020–(unknown status)	Phase 1	RCT	Not yet known
13.	Lenalidomide	i) A double-blind placebo controlled immunogenicity study of Vacc-4x + lenalidomide versus Vacc-4x with an initial open-label dose escalation assessment of lenalidomide in HIV-1-infected Subjects on ART[83]	2012–2014	Phase I/II	Lenalidomide capsules (2, 5, 10, 25 mg) vs lenalidome placebo capsules, with Vacc-4X & rhuGM-CF	Not yet known
		ii)ANRS 154 Lenakap trial[84]	2011–2014	Phase 2	Non- randomised, interventional study.	Not much improvement in patient responses was observed so further studies were not conducted.
14.	Pomalidomide	A phase II multicenter study of Pomalidomide monotherapy in HIV-positive individuals with Kaposi Sarcoma (KS) in Sub-Saharan Africa (SSA)[85]	2018–ongoing	Phase I/ II	RCT	It was well tolerated by patients and further studies are underway
15.	Vesatolimod (GS- 9620)	A phase 1b, randomised, blinded, placebo-controlled dose-escalation study of the safety and biological activity of GS-9620 in HIV-1 infected, virologically suppressed adults[86,87]	2017–2020	Phase 1	Vesatolimod vs placebo	Well tolerated and provided a rationale for future combination trials.

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Regenerative Medicine

Regenerative medicine is a technique adopted to replace damaged cells of our body with healthy cells from a donor[88,89]

Haematopoietic Stem Cell Transplantation

Stem cells are unspecialised cells that differentiate into any cell within our body and can multiply indefinitely thereby playing a major role in homeostasis and repair.[88,90,91] Haematopoietic stem cell transplant (HSCT) is a treatment modality that involves administering healthy haematopoietic stem cells in patients with deteriorated bone marrow function.[92] An allogeneic stem cell transplant involves the administration of healthy blood stem cells from a donor to a patient having bone marrow that fails to make adequate healthy blood cells. Stem cell transplantation is extensively used as an adjunct therapy in patients with critical autoimmune disorders.[93] This procedure augments bone marrow function and hence is used to treat malignant as well as non-malignant conditions, immunodeficiency syndromes, haemoglobinopathies, and other diseases.[94]

CCR5 and Δ32 Mutation

CCR5 is a chemokine co-receptor that functions like a door and allows HIV entrance into the cell.[95,96] Chemokine receptors regulate the initial stage of the HIV-1 virus's entry by acting on CD4, which is a pertinent receptor for HIV-1. Dendritic, T, monocyte, and macrophage cells all express the chemokine receptor CCR5, which is a gene product. The two types of HIV resistance that are currently in existence are caused by a genetic mutation called CCR5-delta 32. HIV is unable to enter immune cells when CCR5-delta 32 is present.

The mutation causes shrinkage of the receptor thereby preventing the expression of the receptor on the cell surface. Similar to a door that lets HIV enter a cell. HIV is kept out of cells by the CCR5-delta 32 mutation, which functions as a kind of "door lock".[97] This genetic mutation is seen in a tiny group of people with European ancestry that causes changes in CCR5 receptor mechanism, which results in increased resistance to HIV-1 infection.[98] Carriers of Δ32/Δ32 homozygous mutation of the CCR5 genes are resistant to HIV-1. A deletion in the coding area of CCR5 results in a shortened, nonfunctional receptor known as the delta 32 mutant (CCR5Δ32), which hinders infection in homozygous people and postpones the onset of AIDS in heterozygous people. Healthy cell transplantation from Δ32 donors shows promising results as the only possible cure for HIV according to various studies conducted and case reports obtained across the globe.[99,100]

These studies prove the absence of HIV-1 within the detectable limits, following complete donor chimerism, which suggests that donor cells were shielded from HIV-1 infection by ongoing ART administration, and had replaced latently infected host cells. Also, proviral HIV-1 DNA was easily found in Peripheral blood mononuclear cells (PBMC) after the conditioning regimen was administered and only became undetectable when full donor chimerism was established, which could be due to Graft versus Host Disease that significantly contributed to the reduction of the peripheral viral reservoir by clearing infected host cell (Figure 1)

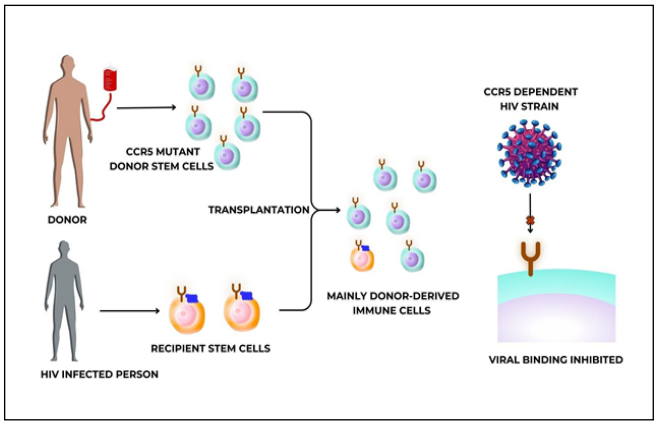

Figure 1.HIV-Infected Individual Receiving CCR5 Mutant Stem Cells from a Healthy Donor which Inhibits Viral Binding

CCR5 receptor antagonists like Maraviroc are available for HIV treatment which serve as allosteric competitive inhibitors of CCR5.[109] When CCR5 antagonists attach to the CCR5 receptor, they cause a conformational change in it that prevents the viral gp120's V3 loop from recognising and binding to it. Mutations in CCR5 result in Maraviroc resistance and failure of therapy.[110–113]

Genetic Approaches for HIV Treatment

CRISPR-Cas9 Editing

In several prokaryotes, there are CRISPRs (clustered regularly interspaced short palindromic repeats) which serve as an integral component of the adaptive immune system.[114] CRISPR/ Cas9 is the most versatile method lately used for proviral genome editing.Cas9 results in DNA breaks and triggers the DNA reconstructing process that alters the CCR5 gene.[115] Correct orientation removes the sgRNA target loci, but improper arrangement results in the regeneration of the sgRNA location. Rather than considering HIV-1 provirus genome editing as a stand-alone curative treatment, this technology might be one more tool in combination therapy. CRISPR/ Cas9 vectors, for instance, can be used as an adjuvant while antiretroviral therapy is ongoing. On the other hand, research using siRNA and CRISPR genome editing of the provirus has demonstrated that these technologies may work in concert to stop HIV-1 reproduction in cell lines.[116,117] (Table 2)

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Table 2.Few Evidences of Successful HSCT in HIV Treatment

City of Study	Patient's Age/ Gender	Diagnosis	Treatment
Berlin[100–102]	40Y/ male	AML and HIV	• Initially on ART-tenofovir, emtricitabine, efavirenz • The patient underwent two courses of induction chemotherapy and a single course of consolidation therapy, but his AML relapsed, necessitating HSCT. • HLA-identical donor homozygous for the CCR5Δ32 allele was identified and HSCT was carried out.
London[101,103]	-	Stage IVb (nodular sclerosing) Hodgkin's lymphoma, HIV	• Underwent chemotherapy and ART • HSCT done from a CCR5Δ32/Δ32 donor
Essen[103,104]	27Y/ male	HIV-1 infection and anaplastic large-cell lymphoma	HSCT from a donor having homozygous mutant CCR5 delta32 allele
Boston[105]	Male	Haematological tumours, HIV-1	Underwent allogeneic HSCT
Dusseldorf[106,107]	53Y/ male	AML and HIV-1	Allogeneic CCR5Δ32/Δ32 HSCT
Los Angeles[108]	Middle-aged female	AML and HIV-1	CCR5D32/D32 homozygous HSCT

Haplo-Cord Transplant

Healthy umbilical cord and bone marrow stem cells are transfused as a part of haplo-cord transplant therapy.[118] Few SCs are often present in cord blood transplants, and many transfusions are frequently needed to obtain a reconstituting dose. Complete immune reconstitution was obtained by CCR5D32/ D32 haplo-cord graft and the cells were HIV resistant. This transplant provides immunity to HIV strains and the viral load was undetectable after withdrawal of antiretroviral medication.[115] Overcoming the HLA barrier is a major obstacle in allogeneic transplantation, and a promising experimental strategy to address it is haplo-cord transplantation. The promising findings of preliminary research indicate sustained engraftment, very low rates of acute and especially chronic GVHD, and rapid engraftment.[120]

Engineered Immunity

B cells obtained by HSC can produce HIV neutralising antibodies which can protect against infection. Stem cell-based "engineered immunity" involves the genetic modification of HSCs to produce B cells that generate anti-HIV-specific neutralising antibodies against the virus.[121] T cell receptors can also be modified to confer immunity against HIV.[122]

Conclusion

With the rise of new techniques and drugs targeting HIV at its core, the road to an HIV cure is looking brighter. Drugs like doravirine, bictegravir, venetoclax, and islatravir, and novel drugs that reverse latency like PKC agonists and TLR agonists show great promise in reducing resistance and improving treatment efficacy. Long-acting injectables offer a more convenient option, addressing a key challenge, i.e. adherence, for HIV patients. Emerging genetic methods like gene editing and monoclonal antibodies have the potential to eliminate HIV at its source. The advancements in treatment modalities of HIV are now gaining traction and are not merely based on drug intervention but follow a more holistic approach. The literature provides information about recent advancements and innovations, opening more plethora of newer options with the safety of patients being the priority. In conclusion, these novel approaches give hope for a world where HIV is no longer an incurable disease.

Conflict of Interest: None

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