

Review Article

Optimising drug-resistant human immunodeficiency virus treatment in India: The potential of entry inhibitors

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ABSTRACT

Human immunodeficiency virus (HIV) entry inhibitors are potential treatments for drug-resistant HIV in India. HIV drug resistance is increasing globally and in India, necessitating new treatment options. The current management strategies for resistant HIV cases have limitations, including emerging resistance to dolutegravir. Four food and drug administration (FDA)-approved entry inhibitors are examined: Enfuvirtide, maraviroc, ibalizumab and fostemsavir. Their mechanisms of action, dosing regimens and efficacy from key clinical trials are presented. These inhibitors are effective against resistant strains and have a high genetic barrier to resistance. However, they also have limitations, such as parenteral administration requirements and high costs. Data suggest that despite higher initial costs, entry inhibitors can be cost-effective by reducing hospitalisations and long-term healthcare costs for managing drug-resistant HIV. HIV entry inhibitors have the potential to address drug resistance challenges and improve HIV treatment outcomes in India. Recommendations for India include considering the inclusion of enfuvirtide and maraviroc in national treatment guidelines for heavily treatment-experienced patients with resistant HIV.

Keywords: Antiretroviral therapy, Human immunodeficiency virus drug resistance, Human immunodeficiency virus entry inhibitors, Human immunodeficiency virus in India, Multidrug-resistant human immunodeficiency virus

INTRODUCTION

The far-reaching effects of human immunodeficiency virus (HIV) infection persist as a significant global health challenge, posing a formidable threat to public health systems worldwide. The advent of various antiretroviral drugs and treatment regimens has notably reduced HIV-related mortality and morbidity, dramatically improving survival rates since the early days of the HIV pandemic.^[1] By the end of 2021, antiretroviral therapy (ART) was being administered to 28.7 million people, representing about 75% of the global HIV-positive population. However, the increased use of these medications results in a parallel rise in HIV drug resistance (HIVDR) as well.^[2]

HIVDR AND ITS CLINICAL IMPLICATIONS

No definitive definition for multidrug-resistant HIV exists, but it generally refers to individuals with resistance to two or more antiretroviral (ARV) classes, failing three or more lines of treatment or having experience with three or more ARV classes.^[3]

Data from 2014 to 2019 revealed that transmitted HIVDR was most prevalent in North America at 14.2%, compared to 8.5% in Europe and 8.7% in high-income Asian countries.^[4] As per the

HIVDR Report 2021, pre-treatment HIVDR to nevirapine or efavirenz in populations initiating first-line ART exceeded 10% in 21 of 30 surveys reported to the World Health Organization (WHO). Amongst adults failing non-nucleoside reverse transcriptase inhibitors (NNRTIs)-based ART, resistance levels ranged from 50% to 97%, and nearly 50% of infants born to mothers with HIV had resistance to one or more NNRTIs.^[5]

In India, various studies have identified HIVDR mutations. For instance, the prevalence of HIVDR mutations in treatment-naïve populations from Northern India was found to be 2.9% in a study.^[6] Another study estimated drug resistance in 1.11% of untreated HIV patients, with the highest rates against nucleoside reverse transcriptase inhibitors (NRTIs) and NNRTIs. Amongst those previously on treatment, 25.7% showed resistance to tenofovir.^[7]

The clinical implications of HIVDR are substantial, affecting ART effectiveness and patient outcomes. HIVDR can lead to treatment failure, necessitating the use of more complex and costly ART regimens that may have more side effects and require stricter adherence. This increases the burden on healthcare systems and can lead to poorer health outcomes, including higher viral loads and increased risk of HIV transmission. The presence of drug-resistant HIV strains complicates HIV management, requiring regular HIVDR testing to guide appropriate ART choices. Studies indicate that HIV patients with multidrug resistance face a mortality risk at least 3 times that of the overall HIV-infected population.^[8]

CURRENT RECOMMENDATIONS FOR THE MANAGEMENT OF RESISTANT HIV CASES AND THEIR LIMITATIONS

In case of failure of first-line regimens, the WHO recommends a regimen of dolutegravir (DTG), an integrase strand transfer inhibitor, with two NRTIs, such as tenofovir and lamivudine. As an alternative to DTG, protease inhibitors such as darunavir, atazanavir, or lopinavir boosted with ritonavir can be used. For patients failing second-line therapy, a combination of DTG, darunavir and 1–2 NRTIs is considered the third-line treatment.^[9] National AIDS control organization (NACO) has adopted the regimen of DTG and two NRTIs as the second-line therapy in case of treatment failure or resistant cases. In case of failure of second-line therapy, the national programme recommends a combination of DTG and darunavir boosted with ritonavir as the treatment. For cases of drug resistance, the treatment approach includes monitoring viral load every 6 months and enhancing adherence counselling for patients with unsuppressed viral loads.^[10]

ART drugs used in second and third-line HIV treatment can cause various adverse effects. DTG may cause adverse

effects, including weight gain, insomnia and, in rare cases, neuropsychiatric symptoms.^[11] Tenofovir has been associated with renal toxicity and decreased bone mineral density.^[12] Lamivudine is generally well-tolerated but may cause headaches and gastrointestinal disturbances. Protease inhibitors such as darunavir, atazanavir and lopinavir can cause gastrointestinal issues, lipid abnormalities and increased cardiovascular risk. Ritonavir, used as a booster, may exacerbate these effects and cause additional drug interactions. Serious but rare adverse effects include hypersensitivity reactions, hepatotoxicity and lactic acidosis. It is crucial to monitor patients closely, especially during the initial months of therapy, and adjust treatment as needed to manage these potential side effects.^[13,14]

Since 2018, the WHO has recommended DTG as the treatment for first- and second-line HIV therapy across all demographic groups.^[15] DTG is favoured due to its higher effectiveness, simpler administration and fewer adverse events. In addition, DTG has a strong genetic barrier to the development of drug resistance.^[11] The reports from four surveys indicate that resistance to DTG varied from 3.9% to 8.6% overall. However, in a specific subgroup - patients who had been treated before and switched to a DTG-based treatment while their HIV viral loads were high - the resistance rate was much higher, approaching 20%.^[16] To date, only a limited number of countries have submitted survey data to the WHO.

The rising concerns over emerging resistance to DTG pose a significant threat to achieving the Sustainable Development Goals related to the HIV epidemic, which involve ending the HIV epidemic as a public health threat by 2030.^[17] The increasing resistance to conventional ART and the emergence of resistance to DTG highlight an urgent need to diversify treatment options for HIV.

HIV entry inhibitors are a newer group of drugs that offer several advantages over traditional ART due to their novel mechanism of action. All the entry inhibitors are approved for the treatment of individuals with multidrug-resistant strains or those who have experienced extensive prior treatment.^[18] Despite their potential benefits, these drugs have not yet been incorporated into the WHO guidelines for the management of HIV/acquired immune deficiency syndrome (AIDS). Similarly, the National AIDS Control Programme of India has not included any entry inhibitors in their treatment protocols.

Given the adherence challenges and the substantial HIV population in the country, the burden of HIVDR can also be substantial in India. In this narrative review, we aim to explore the efficacy of HIV entry inhibitors, the newer antiretroviral agents, in reducing viral load amongst multidrug-resistant HIV cases and their potential to optimise HIV treatment in India.

HIV ENTRY INHIBITORS

Since 2003, several HIV entry inhibitors such as fostemsavir, ibalizumab, maraviroc and enfuvirtide with different mechanisms of action have been approved for the treatment of patients with HIV who are heavily treatment-experienced.^[18] These drugs prevent HIV from entering and infecting host cells. Each inhibitor targets different stages of the HIV entry process. The mechanism of action and other properties of these drugs are given in Table 1.

RESULTS OF CLINICAL TRIALS

Enfuvirtide has shown significant effectiveness in highly treatment-experienced HIV-1 patients with multidrug-resistant virus. In the T-20 vs. Optimized regimen only study 2 (TORO 2) study, adding enfuvirtide to an optimised background regimen resulted in greater viral suppression and CD4+ cell count increases compared to the optimised regimen alone after 24 weeks.^[19] A cohort study done in

Mexico demonstrated high rates of viral suppression, with 81.4% of patients achieving HIV-1 ribonucleic acid (RNA) <400 copies/mL and significant CD4+ cell increases after 48 weeks of enfuvirtide-containing therapy.^[20]

The studies on maraviroc demonstrate its efficacy in both treatment-experienced and treatment-naive HIV-1 patients with CCR5-tropic virus. In treatment-experienced patients, maraviroc showed greater viral suppression and CD4 count increases compared to placebo, with 42–47% of patients achieving HIV-1 RNA levels <50 copies/mL after 48 weeks.^[21] For treatment-naive patients, maraviroc demonstrated similar efficacy to efavirenz at 96 weeks, with comparable viral suppression rates and greater CD4 count increases.^[22]

Ibalizumab has also demonstrated significant efficacy in treating multidrug-resistant HIV-1 infection across multiple studies. In a phase 2a study, ibalizumab combined with an optimised background regimen (OBR) showed durable

Table 1: Characteristics of approved entry inhibitors.

Drug	Year of FDA approval	Mechanism of action	Dose, route and frequency	Indications	Adverse effects
Enfuvirtide	2003	Fusion inhibitor - that binds to the gp 41 subunit of the HIV-1 envelope glycoprotein. This binding prevents the necessary conformational changes for the fusion of the viral membrane with the host cell membrane, effectively blocking the entry of the virus into the host cell.	90 mg subcutaneous twice daily	HIV-infected patients who have undergone multiple treatment regimens	Injection site reaction is a major adverse reaction
Maraviroc	2007	CCR5 antagonist - binds to the CCR5 co-receptor on the surface of CD4+T cells and blocks the interaction between CCR5 and the HIV-1 envelope glycoprotein gp 120	150/300/600 mg orally twice daily	Adults with CCR5-tropic HIV-1 infection, as a component of combination therapy	Cough, pyrexia, rash, rarely- hepatotoxicity
Ibalizumab	2018	Post-attachment inhibitor - a monoclonal antibody that binds to the CD4 receptor on host cells and interferes with the post-binding conformational changes necessary for the fusion of the viral and host cell membranes	2000 mg loading dose IV, followed by 800 mg IV every 2 weeks	Patients with multidrug-resistant HIV-1 infection, in combination with other ART drugs	Diarrhoea, dizziness and rash
Fostemsavir	2020	Pre-attachment inhibitor- binds to the gp120 subunit of the HIV-1 envelope glycoprotein. This prevents the conformational changes required for the virus to bind to the CD4 receptors on the surface of host cells, thereby blocking viral entry	600 mg orally twice daily	For heavily treatment-experienced patients living with multidrug-resistant HIV infection	Associated with increase in liver transaminases, QT prolongation is seen at high doses

HIV: Human immunodeficiency virus, CCR5: C-C Chemokine Receptor type 5, QT: QT interval

antiviral activity and significant CD4+ T cell count increases over 48 weeks.^[23] A phase 3 study of heavily treatment-experienced patients revealed that 83% achieved a viral load reduction of at least 0.5 log₁₀ copies/mL after 2 weeks, with 43% reaching <50 copies/mL by week 25.^[24]

In the BRIGHT E trial, fostemsavir with optimised background therapy (OBT) demonstrated sustained virologic and immunologic responses through 96 weeks. This phase 3 trial showed that fostemsavir significantly reduced HIV-1 RNA levels compared to placebo in the first 8 days, with 54% of patients in the randomised cohort achieving virologic suppression (<40 copies/mL) at week 48.^[25]

ADVANTAGES OF ENTRY INHIBITORS

- Unlike conventional ART that typically targets viral enzymes, entry inhibitors block the virus from entering host cells by targeting viral envelope proteins or host cell receptors. This unique approach has shown effectiveness in treating multidrug-resistant HIV cases, providing an effective option for patients with resistance to conventional ART and limited treatment alternatives.
- Entry inhibitors also present a higher barrier to resistance as they target more conserved regions of the virus, compared to drugs targeting reverse transcriptase or protease.
- Resistance to one class of entry inhibitors does not imply cross-resistance to other classes, enhancing their versatility.
- *In vitro* evidence supports the synergistic potential of combining entry inhibitors, which could improve treatment outcomes.
- These drugs are generally well-tolerated and have a different side effect profile with reduced drug–drug interactions, potentially offering patients an improved quality of life.^[18]

DISADVANTAGES OF ENTRY INHIBITORS

- Some inhibitors, such as maraviroc, exhibit a limited spectrum of activity, being effective only against CCR5-tropic HIV-1.
- Agents such as ibalizumab and enfuvirtide require parenteral administration, which is less convenient and can negatively impact patient adherence.
- Their limited availability and high cost restrict accessibility for many patients.^[18]
- Resistance to entry inhibitors in HIV treatment primarily develops through genetic mutations in the virus that alter the structure of target proteins, such as gp 120 and gp 41. For example, enfuvirtide resistance is often linked to mutations in the heptad repeat 1 (HR1) region of gp 41, while maraviroc resistance arises from changes in

the V3 loop of gp 120 that affect its interaction with the CCR5 co-receptor.^[26]

Even though the cost of these drugs is higher than conventional anti-retroviral agents, studies have shown that entry inhibitors, such as maraviroc and enfuvirtide, are particularly cost-effective as they effectively control the virus in patients with multidrug-resistant HIV and help avoid complications and additional healthcare costs associated with frequent regimen changes and advanced HIV-related illnesses. A study by Pialoux *et al.* (2011) demonstrated that patients treated with enfuvirtide experienced fewer hospitalisations and lower overall healthcare costs compared to those on standard ART regimens.^[27] Similarly, the cost-effectiveness analysis by Johnston *et al.* (2010) highlighted that maraviroc, when used in treatment-experienced patients, significantly reduces the long-term costs associated with managing HIV.^[28]

RECOMMENDATIONS AND FUTURE DIRECTIONS

To effectively manage and monitor resistance patterns, a nationwide HIV resistance survey should be conducted regularly to establish baseline resistance patterns and determine appropriate patient selection criteria. In addition, local clinical trials and studies should be actively promoted to evaluate the efficacy, safety profiles and pharmacokinetics of newer agents like entry inhibitors, specifically within the Indian population, assess population-specific adverse effects and determine optimal dosing strategies. By this stepped approach, evidence-based guidelines can be developed for dosing adjustments, appropriate monitoring protocols can be established, and comprehensive adverse effect management strategies can be implemented that are suitable for Indian healthcare settings.

We recommend a multi-phase research strategy that would include randomised controlled trials comparing entry inhibitors plus OBT versus standard of care in treatment-experienced patients with documented resistance; pharmacokinetic studies to assess drug metabolism in the Indian population; and real-world implementation studies to evaluate cost-effectiveness and healthcare delivery challenges.

After rigorous clinical evaluation and evidence generation in the Indian population, HIV entry inhibitors - particularly enfuvirtide and maraviroc - merit consideration for inclusion in national treatment guidelines for patients with resistant cases of HIV who are heavily treatment-experienced.

While oral administration (as with maraviroc) would be preferable, the parenteral route (as with enfuvirtide) should not be an absolute barrier to implementation, particularly for heavily treatment-experienced patients with limited therapeutic options. The benefit of achieving viral

suppression in cases where an effective regimen cannot be devised using currently available drugs may outweigh the challenges of parenteral administration in carefully selected patients. India has substantial experience in managing injectable treatments in drug-resistant cases, as evidenced by the successful implementation of injectable aminoglycoside-containing regimens in drug-resistant tuberculosis until oral bedaquiline-based regimens came in 2021.

A systematic economic evaluation and phased implementation strategy is crucial for the successful integration of entry inhibitors into the national programme. The initial phase should focus on patients with documented multi-drug resistance, prioritising more cost-effective options like maraviroc (oral administration) over agents requiring parenteral administration. This should be accompanied by a robust monitoring system to evaluate real-world cost-effectiveness in Indian settings.

To improve accessibility and economic feasibility, several approaches should be considered, such as negotiating preferential pricing agreements for low- and middle-income countries, exploring possibilities for domestic manufacturing to reduce costs and establishing a systematic monitoring system to track long-term economic benefits, including reduced hospitalisation rates and complications from drug resistance.

A comprehensive cost-benefit analysis specific to the Indian healthcare context should be conducted, considering the current burden of drug resistance in India and the economic impact of managing treatment failure and complications due to HIVDR.

These strategic approaches, combined with regular monitoring and evaluation, will help ensure the sustainable and effective implementation of entry inhibitors in India's HIV treatment programme, ultimately contributing to better patient outcomes and more efficient resource utilisation in HIV care.

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