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***Review Article***

# ANTI-HIV DRUGS: CHALLENGES, CONCERN AND CURRENT UPDATES

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**ABSTRACT**
Globally around 38 million adults and children are suffering from human immunodeficiency virus (HIV) infection and around 7000 new infection cases reported on daily basis. Till date 26 anti-HIV compounds under six classes has been approved. These compounds are generally used in different combinations to achieve highest benefit, tolerability and compliance. However the emergence of multiple drug resistant HIV strains remains a serious concern and demand for the development of novel anti-retrovirals (ARVs).

***Keywords:*** *HIV, ART, ARV, HAART*

## INTRODUCTION

The detailed understanding of human immunodeficiency virus (HIV) replication and pathogenesis helped in identification of variety of anti-retroviral (ARV) drugs that target at crucial stages of HIV life cycle. Antiretroviral therapy (ART) initially started with azidothymidine (AZT) which later evolved to combination of two ART and finally lead to highly active anti-retroviral therapy (HAART). HAART resulted in significant improvement of quality of life, better immune status and reduced morbidity and mortality associated with HIV infection (Hull & Montaner, 2011). Continued search of new ARVs, improvement in first line drugs and identification of novel ARVs proven boon for effective therapy for HIV patients. However, success of ART achieved on the cost of life threatening adverse drug reaction (ADR), drug-drug interactions, inconvenience of drug dosing and emergence of multi-drug resistance (MDR) HIV strains (Desai *et al,* 2012).Today the disease has been stepped into its 3$^{rd}$ decade where several treatment-experienced patients are living with severe ADRs and facing the threat for treatment failure due to emergence of MDR strains (Johnson *et al,* 2008). Now it is likely that newly infected patients harbor resistant strains of HIV against commonly used ARV drugs. These scenarios present multiple critical issues with ARV medicines that need a critical attention. The present article is an attempt to present the key issues with ARVs and discuss the newly approved ARV drugs in existing classes with the glimpse of novel ARV drugs under development.

### *Available Anti-HIV Drug Classes*

Currently total of 26 approved drugs available as anti-retroviral (ARV) agents as a single drug which targets four distinct classes of proteins viz. reverse transcriptase inhibitors, protease, integrase and host cell receptors. Conventional classes of anti-retroviral drugs are the protease inhibitors (PIs), Nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Non-conventional approved drug group includes chemokine co-receptor (CC) antagonist, integrase inhibitors and fusion inhibitors. Future promising ARV drugs include CD4 attachment inhibitors, capsid assembly inhibitors and maturation inhibitors (Desai *et al,* 2012).

### *I. Nucleoside reverse transcriptase inhibitors (NRTIs)*

The first approved anti-HIV drugs were NRTIs and they formed the backbone of anti-retroviral therapies (ARTs). NRTIs were preferred as first line of ARV due to their favorable pharmacokinetics, long intracellular half life, high oral bioavailability, convenient doses and low risk of drug interactions (Back *et al,* 2005).

However, continued usage of NRTIs were reported to accumulate genetic mutations that causes the emergence of resistant viral strains. NRTIS were also reported to be associated with bone marrow

suppression and severe mitochondrial toxicity. Long term usage of Stavudine (Table 1) was reported to cause severe and irreversible cytotoxicity. According to recent WHO guideline, Stauvidine is recommended for gradual wipe out for the ART but it remain widely used as first line of ARV drugs in developing countries due to low cost and ease of availability (Desai *et al*, 2012). Even Abacavir has also been suggested for less use due to hypersensitivity, cardiovascular risk and high virologic failure. The new promising compoundsof NRTIs class viz. Apricitabine, Elvucitabine and Amdoxovir are currently under evaluation against HIV-1 isolates which are resistant to conventional NRTIs.

### *II. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*

The first line of ART regimen consists of NNRTIs along with protease inhibitors and one or two NRTIs (Desai *et al*, 2012). Nevirapine or efavirenz is commonly used in developing countries due to their efficacy, convenient schedule and low cost. Nevirapine (Table 1) is safe in pregnancy and thus exploited to prevent vertical transmission. However, Nevirapine based ARTs was reported for hepatotoxicity and cutaneous hypersensitivity (Crane *et al*, 2007). In developed countries, efavirenz is preferred over nevirapine in initial ART regimen because of its dose availability as once a day or in suitable fixed dose combinations with tenofovir and emtricitabine. Though, efavirenz has short term effect on central nervous system (CNS) and is teratogenic. Similar to NRTIs, NNRTIs also exhibits low genetic barrier to drug resistance (Desai *et al*, 2012). Therefore, patients failed to respond one NNRTIs are not prescribed any other NNRTIs in future regimen.

### *III. Entry Inhibitors*

HIV-1 entry into host cell is a multifactorial event which involves interaction between HIV-1 glycoproteins gp120 with host CD4 receptor and CCR5 or CXCR4 co-receptors (Desai *et al*, 2012). These complex interactions between HIV and host cell brings their membrane in close proximity which results into membrane fusion. The knowledge of these molecular events leads to generation of fusion inhibitors and chemokine co-receptor antagonists.

#### *a. Fusion Inhibitors*

Enfuvirtide (Table 1) is the only available approved fusion inhibitor for the patients who failed to respond other ARTs. enfuvirtide is synthetic peptide which shows partial structural similarity to gp41 and thus it blocks the conformational changes in gp41 and thus blocks host cell and viral membrane fusion. It has shown a great decline in viral RNA load when used in combination with darunavir/ritonavir, zidovudine, tenofovir and tipranavir (Lalezari *et al*, 2003). Results from an evaluation study on the enfuvirtide for prevention of vertical transmission appear encouraging. However, patients on enfuvirtide based regimen failed to respond within few weeks due to mutation in HR1 and HR2 region of gp41 which indicates the low genetic barrier of drug. T1249 is second generation ARV agent which was found effective against enfuvirtide resistant HIV-1, HIV-2 and SIVs (Desai *et al*, 2012).

#### *b. Chemokine receptor inhibitor and antibodies*

Currently, only maraviroc is available approved chemokine receptor-5 (CCR5) inhibitor. In a study conducted on naïve patients, maraviroc (Table 1) showed high efficacy similar to efavirenz (Cooper *et al*, 2010). Therefore, it was approved in ART regimen for naïve patients who were infected with R5 tropic strain of HIV-1. This drug is well tolerated with minimal side effects. However, HIV-1 resistant to CCR5 inhibitors like maraviroc were observed to switch their tropism from R5 to X4. This resistant pattern is potentially alarming due to faster CD4 decline capabilities of CXCR4 tropic viruses.

PRO140 is approved humanized monoclonal antibody which inhibits CCR5 tropic HIV-1 by binding at CCR5 co-receptor and does not affect the physiological functions of CCR5. Since it binds on the surface of CCR5 co-receptor extracellularly, it inhibits subsequent infection of HIV in healthy host cells. In vitro studies indicated synergistic response of PRO140 with CCR5 inhibitors (Desai *et al*, 2012; Jacobson *et al*, 2008; Murga *et al*, 2006).

**Table 1: Available anti-HIV-1 Drugs**

| SN | NRTIs | NNRTIs | Entry Inhibitors | Integrase Inhibitors | Protease Inhibitors |
|---|---|---|---|---|---|
| 1 | Zidovudine | Nevirapine | Maraviroc | Raltegravir | Ritonavir |
| 2 | Stavudine | Delviradine | Enfuvirtide | Dolutegravir | Indinavir |
| 3 | Lamivudine | Efavirenz | | | Saquinavir |
| 4 | Didanosine | Rilpivirine | | | Nelfinavir |
| 5 | Zalcitabine | Etravirine | | | Amprenavir |
| 6 | Abacavir | | | | Fosamprenavir |
| 7 | Tenofovir | | | | Atazanavir |
| 8 | Emtricitabine | | | | Tipranavir |
| | | | | | Darunavir |

*NRTIs = Nucleoside Reverse Transcriptase Inhibitors, NNRTIs = Non Nucleoside Reverse Transcriptase Inhibitors*

***IV. Integrase inhibitors***

These pharmacological agents inhibit transfer of viral DNA to host cell DNA. Raltegravir was the first integrase which was approved for naïve as well as treatment experienced patients. Raltegravir (Table 1) showed significant anti-retrovial activity against HIV isolates which were resistant to multiple ARV agents like NRTIs, NNRTIs and protease inhibitors.Combinations of raltegravir, etravirine and darunavir/ritonavir were proven effective and exhibited significant decrease of HIV RNA counts in treatment-experienced patients. Raltegravir is recommended for anti-HIV treatment at stages in naïve and treatment-experienced patients due to short term safety, tolerability, significant ant-viral activity and fewer drug interactions (Desai *et al,* 2012; Lalezari *et al,* 2005).

***V. Protease inhibitors (PIs)***

This class of drugs shows high genetic barrier for drug resistance. Now low dosage of protease inhibitors like ritonavir is suggested as first line option in naïve patients who do not respond well to other initial ART regimen. However, emerging HIV mutant strains from the selection pressure of protease inhibitors grants cross-resistance. Except nelfinavir, most of other protease inhibitors are recommended with ritonavir boosting for first line ARTs by US department of health and human services and International AIDS society, USA (Desai *et al,* 2012; Hammer *et al,* 2008). The concept of low dosages of ritonavir boosting has not only enhanced the utility of protease inhibitors based regimen but also opened the possibilities for discovery of novel antiviral drugs (Desai *et al,* 2012).

Atazanavir (Table 1) is second-generation protease inhibitor and claimed to be around 20 times more potent than other known PIs. Tripanavir is another second generation PI which is approved to use in patients with PI resistant HIV strains. It is found to exhibit synergistic response with NRTIs, NNRTIs and enfuviritide. Darunavir is non-peptide based PI which was developed for treatment-experienced patients with PI resistant HIV strains (Desai *et al,* 2012).

***Challenges and concern with anti-HIV drugs***

Characteristics of HIV virus, ART drugs and HIV patients are major challenges for an effective long term HIV medications.

*I. HIV associated factors*

1. HIV (retrovirus with defective reverse transcriptase) multiplies massively (approx. $10^{10}$ copies/day) and commits multiple errors in its genome, resulting in the emergence of mutant viruses. These mutants poses a big challenge in the development of effective anti-HIV drugs (Williams & Loeb, 1992).
2. Upon infection, HIV becomes an integral part of host genome and survives throughout the life span of the host. Even after 6-12 months of ART treatment when viral load were undetectable in plasma, HIV remain detectable in seminal fluids and often these HIV particles are drug resistant. The existence of

HIV in the potential reservoirs are the major issues for effective ARTs and often relapse are reported on discontinuation of ARTs (Finzi *et al,* 1997; Perelson *et al*, 1996; Siliciano *et al*, 2003).

3. Emergence of multiple drug resistant HIVs in treatment-experienced patients are also big concern for effective ARV drugs (Martinez-Cajas & Wainberg, 2008).

*II. ART drug related factors*

1. Existing anti-retroviral treatments are unable to reach in effective concentration at latent reservoirs (Kulkosky & Bray, 2006).
2. All the known classes of ARVs has potential for toxicity, thus it's hard to use combinational ARTs for long term in HIV patients. These complicated treatments at time required to withdraw in serious life threatening reactions like cardiovascular and cerebrovascular disease (Carr *et al,* 1998).
3. Patients on ART show significant drug-drug interactions that complicate the treatment and adversely affect the patient care.These interactions generally remain incomplete during clinical trials and detected during treatment (Desai *et al,* 2012).
4. Undetectable levels of plasma viremia correlated with strict regimen of ART that includes administration of two or more drugs multiple times a day for lifetime of patients. These multiple pill count may lead to cellular toxicity, poor adherence to regimen and inconvenience to patients (Finzi *et al,* 1997).
5. All classes of ARV reported to produce resistant HIV strains in vivo. Drug resistance not only leads to failure of ART but also imposes a daunting task in drug development (Desai *et al*, 2012).
6. Safe alternatives of ARV and availability in developing countries adds another problem in ART management (Desai *et al,* 2012).

*III. Host associated factors*

1. Patients having pre-existing risks like fatty liver, psychiatric disorder, obesity, abnormal liver and altered renal functions are likely to have adverse drug reactions and needs close attention. Co-existing disease and health issues like diabetes mellitus, tuberculosis, anemia, hyperlipidemia may complicate therapies and enhance the chances of drug interaction and cellular toxicity (Desai *et al,* 2012).
2. Successful usage of highly active anti-retroviral therapies (HAART) enhanced significant life span of HIV patients. These highly treatment-experienced people are likely to expose to broad range of drug regimen along with ART which may pose them to risk of multiple metabolic disease.
3. A group of ARVs may be required for dose adjustment or modification in special group of patients like children and pregnant women. The safety and correct dosage of ARVs for children has not been appropriately established (Desai *et al,* 2012).
4. The counseling of HIV patients and their family members for proper understanding of disease, adherence to drug treatment regimen, changing of life style, regular follow-ups, and proper nutrition is key for effective treatment (Desai *et al,* 2012).

***Future promising anti-HIV drugs***

An array of drugs that belongs to different classes of ARV compounds are under multiple phases of clinical trials (Desai *et al*, 2012).

*I. Attachment inhibitors*

These investigational ARVs inhibit the interaction between gp120 and CD4. Ibalizumab is one such ARV humanized monoclonal antibody against CD4. It is designed in such a way that it does not interfere with the immunological functions of CD4. It appears to have potent antiretroviral activity with mild side effects (Desai *et al,* 2012; Jacobson *et al,* 2009).

*II. Drug boosters or enhancers*

These investigational compounds may not have direct anti-retroviral activity but they enhance the effect of ARTs. Cobicistat and SPI452 are such compounds, which do not have any known anti-HIV activity. Both of these drugs found to increase the plasma levels of protease inhibitors (Mathias *et al,* 2010).

*III. Capsid assembly inhibitors*

These compounds are known to disrupt interaction between capsids (structural protein) which may lead to compromised integrity and virus survival. PF-3450071 and PF-3450074 are such investigational compounds, act during early HIV replication and produced defective viruses (Desai *et al*, 2012).

*IV. Maturation Inhibitors*

Maturation inhibitors like bevirimat, which acts on last but important stage of HIV maturation before budding from host cells. The primary target of the drug is Gag polyprotein, required for assembly and budding of viral particles. This drug inhibits the cleavage of precursor polyprotein into mature capsid proteins, which resulted defective, immature and non-infectious HIV particles (Salzwedel *et al*, 2007).

## CONCLUSION

Though the presently available ARV drugs are highly effective, toxicity, drug-drug interaction, inconvenient life-long dosages and emergence of MDR HIV strains remained a big challenge. New members of existing ARV drug classes added new hope for treatment-naïve and experience HIV patients. These newly approved ARV agents offer the option of second line treatment for treatment-experienced patients. However, neither these new ARV agents offer complete eradication of virus nor are free from the ADRs. Thus there are urgent needs for development of novel ARV drugs and optimally utilize the existing ARTs to combat resistant HIV strains. Since ARVs significantly reduced the sexual transmission of HIV, they are recommended for pre-exposure prophylaxis to prevent HIV transmission through sexual route (Desai *et al*, 2012). Though multiple ARVs of novel classes are under investigation, development of effective ARVs or HIV vaccine remains a big challenge.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## REFERENCES

**Back DJ, Burger DM, Flexner CW, Gerber JG (2005).** The pharmacology of antiretroviral nucleoside and nucleotide reverse transcriptase inhibitors: implications for once-daily dosing. *Journal of acquired immune deficiency syndromes* **39 Suppl 1** S1-23, quiz S24-25.

**Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA (1998).** A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *Aids* **12** F51-58.

**Cooper DA, Heera J, Goodrich J, Tawadrous M, Saag M, Dejesus E, Clumeck N, Walmsley S, et al (2010).** Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. *The Journal of infectious diseases* **201** 803-813.

**Crane HM, Van Rompaey SE, Kitahata MM (2007).** Initiating highly active antiretroviral therapy with newer protease inhibitors is associated with better survival compared to first-generation protease inhibitors or nevirapine. *AIDS patient care and STDs* **21** 920-929.

**Desai M, Iyer G, Dikshit RK (2012).** Antiretroviral drugs: critical issues and recent advances. *Indian journal of pharmacology* **44** 288-298.

**Finzi D, Hermankova M, Pierson T, Carruth LM, Buck C, Chaisson RE, Quinn TC, *et al* (1997).** Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science* **278** 1295-1300.

**Hammer SM, Eron JJ, Jr., Reiss P, Schooley RT, Thompson MA, Walmsley S, Cahn P, Fischl MA, et al (2008).** Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. *Jama* **300** 555-570.

**Hull MW, Montaner J (2011).** Antiretroviral therapy: a key component of a comprehensive HIV prevention strategy. *Current HIV/AIDS reports* **8** 85-93.

**Jacobson JM, Kuritzkes DR, Godofsky E, DeJesus E, Larson JA, Weinheimer SP, Lewis ST (2009).** Safety, pharmacokinetics, and antiretroviral activity of multiple doses of ibalizumab (formerly TNX-355), an anti-CD4 monoclonal antibody, in human immunodeficiency virus type 1-infected adults. *Antimicrobial agents and chemotherapy* **53** 450-457.

**Jacobson JM, Saag MS, Thompson MA, Fischl MA, Liporace R, Reichman RC, Redfield RR, et al (2008).** Antiviral activity of single-dose PRO 140, a CCR5 monoclonal antibody, in HIV-infected adults. *The Journal of infectious diseases* **198** 1345-1352.

**Johnson VA, Brun-Vezinet F, Clotet B, Gunthard HF, Kuritzkes DR, Pillay D, Schapiro JM, Richman DD (2008).** Update of the Drug Resistance Mutations in HIV-1. *Topics in HIV medicine : a publication of the International AIDS Society, USA* **16** 138-145.

**Kulkosky J, Bray S (2006).** HAART-persistent HIV-1 latent reservoirs: their origin, mechanisms of stability and potential strategies for eradication. *Current HIV research* **4** 199-208.

**Lalezari JP, Bellos NC, Sathasivam K, Richmond GJ, Cohen CJ, Myers RA, Jr., Henry DH, et al (2005).** T-1249 retains potent antiretroviral activity in patients who had experienced virological failure while on an enfuvirtide-containing treatment regimen. *The Journal of infectious diseases* **191** 1155-1163.

**Lalezari JP, Henry K, O'Hearn M, Montaner JS, Piliero PJ, Trottier B, Walmsley S, Cohen C, et al (2003).** Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *The New England journal of medicine* **348** 2175-2185.

**Martinez-Cajas JL, Wainberg MA (2008).** Antiretroviral therapy : optimal sequencing of therapy to avoid resistance. *Drugs* **68** 43-72.

**Mathias AA, German P, Murray BP, Wei L, Jain A, West S, Warren D, Hui J, Kearney BP (2010).** Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity. *Clinical pharmacology and therapeutics* **87** 322-329.

**Murga JD, Franti M, Pevear DC, Maddon PJ, Olson WC (2006).** Potent antiviral synergy between monoclonal antibody and small-molecule CCR5 inhibitors of human immunodeficiency virus type 1. *Antimicrobial agents and chemotherapy* **50** 3289-3296.

**Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD (1996).** HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science* **271** 1582-1586.

**Salzwedel K, Martin DE, Sakalian M (2007).** Maturation inhibitors: a new therapeutic class targets the virus structure. *AIDS reviews* **9** 162-172.

**Siliciano JD, Kajdas J, Finzi D, Quinn TC, Chadwick K, Margolick JB, Kovacs C, Gange SJ, Siliciano RF (2003).** Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nature medicine* **9** 727-728.

**Williams KJ, Loeb LA (1992).** Retroviral reverse transcriptases: error frequencies and mutagenesis. *Current topics in microbiology and immunology* **176** 165-180.