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# Trends in the Treatment of HIV Infection

Reginald P. Sequeira, Ph D, FCP*

**During the last decade several advances in understanding and management of human immunodeficiency virus (HIV) have resulted in optimism among clinicians and hope for patients. Research into areas of viral pathogenesis has made a direct impact on the clinical management of HIV-infected patients and has led to the development of new and more potent antiviral agents, regimens, and approaches to antiretroviral therapy (ART). These highly active antiretroviral therapies (HAART) have dramatically altered the natural progression of infection and significantly improved the quality of life for many HIV-infected patients[1]. As a result there has been a substantial decline in reported number of AIDS-related opportunistic infections and deaths[2,3].**

**Despite these remarkable advances, several concerns should be addressed. Although many will benefit from new and potent regimens, up to 50% of patients show treatment failure[4], and approximately 40% change therapeutic regimens during the first year because of drug-related adverse events[5]. The development of drug resistance, long-term toxicities, patient compliance, the management of HAART failures, and the method to control and prevent the spread of HIV are major challenges. Hope for a cure for HIV infection was dampened by the discovery of a latent form of the virus that persists within the resting $CD_4$ cells[6], perhaps as a result of survival advantage to T- cell from anti HIV-genes[7].**

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An understanding of viral pathogenesis and its implications on clinical practice is essential for clinicians managing HIV-infected patients. Consensus panel recommendations have been published which can be used for clinical decision making[8,9]. Pharmacotherapy of HIV has been directed at inhibiting key steps of the HIV life cycle[10].

A great deal of research has focused on agents that target inhibition of the reverse transcriptase enzyme. Nucleoside / nucleotide reverse transcriptase inhibitors (NRTI) (Table 1) inhibit this enzyme by incorporating false nucleic acids into the newly produced proviral DNA[11]. This results in a DNA strand that cannot continue elongation. Non-nucleoside reverse transcriptase inhibitors (NNRTI) inhibit reverse transcriptase by binding to the enzyme itself[12]. Agents that target the viral protease enzyme inhibit actively by binding to the catalytic site of the enzyme resulting in the production of immature, non-infectious virions[13]. Unlike reverse transcriptase inhibitors, the protease inhibitors (PI) interfere with viral replication in infected cells regardless of the current stage of HIV replication within that cell. In contrast, NRTI can protect newly infected cells only before formation and insertion of proviral DNA into the host genome. Hence NRTI provide no benefit for those infected cells that are actively producing new strains of virus.

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* Professor
Dept. of Pharmacology & Therapeutics
Arabian Gulf University
Kingdom of Bahrain.

HIV entry inhibitors include co-receptor antagonists and the fusion inhibitors. Fusion inhibitors (FI) bind the helical region in the gp41 subunit of the viral envelope protein and prevent conformational changes required for membrane fusion. The helical region appears to become accessible to FI (e.g.: enfuvirtide) after envelope binds $CD_4$, whereas co-receptor binding is thought to induce the final conformational changes that lead to membrane fusion. The sensitivity of HIV-1 to entry inhibitors correlate with envelope/ co-receptor affinity, receptor density, and fusion kinetics[14,15]. These are the only class of antiretroviral drugs that act extracellularly. Other areas under investigation include development of agents that prevent binding of HIV to the $CD_4$ receptor blockers (e.g.: via $CCR_5$ and CXCR-4 blockade), neutralizing antibodies against $CD_4$ and co-receptors, inhibition of the integrase enzyme, and altered translation and transcription of proviral DNA (e.g.: Tat Inhibitors, antisense oligonucleotides).

The possibility of eradicating HIV from infected patients would require a complete inhibition of viral replication in all cell lines and body stores where HIV resides[16]. Some cell lines such as peripheral T cells have a much shorter half-life (~ 1-2 days) in contrast to macrophages (~ 14 days). Long-lived infected T cells with half-lives lasting 6–44 months have also been identified[17,18], implying that complete suppression of HIV would require decades to eradicate infection[6]. Another complicating factor is the potential for HIV to reside in sanctuaries such as the brain and testes, that are less accessible to antiretroviral agents. Once therapy is discontinued, these sites could theoretically release infectious virions which could then repopulate the host. As a result of these observations, research has shifted toward immune-based therapies that can target HIV-infected cells.

**Antiretroviral Therapy**

The decision to initiate ART should consider the potential benefits of therapy versus the potential risks, including the short-term and long-term adverse events, and the potential for the development of drug resistance. ART should be offered to any patient who is symptomatic, regardless of T-cell count and viral load. In patients who are asymptomatic, assessment of patients' surrogate markers (T-cell count, viral load), concurrent medical condition, medication adherence history, if any, and motivation to start therapy are necessary[1].

The Department of Health and Human Services (DHHS), USA, guidelines provide a general framework to initiate ART in an antiretroviral naïve patient; however, these are not absolute. Antiretroviral drugs may improve the quality of life and life expectancy in patients, but these are not without significant risks and problems. Once therapy is initiated, ART should be continued for life. The fear of adverse events and perhaps alterations in life style may provide for barriers to initiate appropriate therapeutic interventions. Establishing a therapeutic contract with patients is crucial for the successful outcome of therapy. The decision to initiate therapy should not be taken lightly nor should it be based solely on surrogate markers.

**Goals of Treatment**

The major goals of ART include (a) the preservation and strengthening of the immune system; (b) prevention of the development of resistance to preserve future treatment options; (c) selection of a regimen that patient will adhere to, and (d) minimizing both the short-term and long-term serious adverse drug events.

The general rules of therapy include:

1. Initiate therapy when potential clinical benefits outweigh the potential risks. Several of the current HAART regimens have shown to reduce viral replication to below detection levels in most of the treated patients and have resulted in durable treatment responses[2,9,18].

2. Select an appropriate ART. The use of HAART is preferred as initial therapy. An initial regimen should contain two NRTI and either a NNRTI or a ritonavir-boosted or unboosted protease inhibitor[2]. Monotherapy should be avoided because it is clearly inferior to combination therapies. Also, the use of dual NRTI-only containing regimens should be avoided because initial viral suppression may not be sustained[8,9,19,20]. Two types of initial HAART strategies – NNRTI or PI-based can be considered.

Clinical trials have confirmed that NNRTI-based strategy to be superior to single PI-based HAART, and have achieved long-term treatment responses[21]. The choice of agent between nevirapine and efavirenz is based on adverse effects and drug-drug interaction potentials. The use of triple NRTI-only regimens[22] minimizes patient exposure to multiple classes of antiretroviral drugs, thereby preserving future treatment options, and perhaps minimizing adverse events. Since the above regimen has limited potency, it is generally reserved for patients with lower viral loads (<100,000 copies/mL), and for patients in whom therapeutic adherence may be an issue; zidovudine, lamivudine and abacavir are available as fixed dose combination formulation (Table 1); for patients with high viral load, a more aggressive strategy using four or more antiretrovirals (triple nucleosides + lopinavir / ritonavir or an NNRTI) has been evaluated with good response[23].

**Assessment of Response to ART**

The clinical assessment, surrogate marker response and regimen – tolerability are used to evaluate the short-term response to treatment. Initiation of an appropriate ART often results in resolution of constitutional symptoms, and improvement in overall general health. In all patients, regardless of clinical status, T-cell count and viral load should be determined. Maximal response to therapy in suppressing the viral load often takes 3-4 months. If the response is inadequate at the end of this period, development of drug resistance and/or increased viral seeding from tissue sanctuaries should be considered. It is recommended to determine the response at midpoint (4-8 weeks). Therapy with an effective regimen should result in a 3-10 fold (0.5 – 1 log) decrease in viral load by 4-8 weeks; the viral load should continue to decline over 12 – 16 weeks, and in most patients, becomes undetectable within 16 – 24 weeks of therapy in treatment - naïve patients[8,9,24]. However, maintenance of excellent treatment response is highly variable. Predictors of long-term virologic success include (a) potency of antiretroviral regimen; (b) adherence to treatment regimen; (c) low baseline viremia; (d) higher baseline $CD_4$ counts; and (e) rapid (i.e., 1 log in 1-4 months) reduction of viremia in response to ART.

The long term response to ART correlates with the magnitude of viral suppression upon initiation of ART: the greater the suppression, the longer the durability of the response[25]. In

response to declining viral replication, T-cell destruction slows, and subsequently $CD_4$ counts improve. Given that T cell changes are expected to improve gradually, a repeat count should be obtained at the end of 3-4 months follow-up visit[2].

Failure of either surrogate markers or clinical improvement of symptoms can be due to several reasons such as subtherapeutic drug levels, emergence of drug resistance and drug interactions. It is important to consider drug compliance, exposure to other drugs including those used as complementary medications[26].

Resistance testing continues to be an important component of optimizing drug therapy after therapeutic failure. However, its role in previously untreated patients is less clear. Although there is growing sense that such applications are of value, there is little evidence to guide such use in routine clinical practice[2].

Patients who have been infected for 10 or more years may have been treated with several antiretroviral regimens and available treatment options may be limited[19,20,22,27]. Many of these patients exhibit diminished response to ART and the durability of viral suppression often is not sustained[8]. This may reflect the development of resistant viral isolates that display cross-resistance to antiretroviral drugs[28]. Patients who have taken several antiretrovirals over the years also can have other therapeutic considerations such as decreased tolerability to medications[19,29,30], drug interactions and altered bio-availability of drugs[31]. Therapeutic drug monitoring can be helpful in circumventing some of these dilemmas.

In recent years, plasma drug level and phenotypic drug resistance data has been increasingly used to calculate a virtual phenotypic $IC_{50}$ value and then compare this with reference population drug levels and resistance data to obtain normalized value[32].

**Treatment interruptions**

Structured treatment interruptions (STI) and target controlled interventions are explored to minimize the risk of long-term adverse events, provided that the intervention does not cause immunologic deterioration. Two strategies have been explored: STI and $CD_4$ / viral load guided discontinuation of therapy. The impact of these interventions on decreasing long-term adverse events is also lacking[28]. STI interventions involve starting and stopping HAART at controlled time points in hopes of minimizing drug exposure, maintaining immunologic control, and minimizing drug resistance. Various dosing schedule have been tried with mixed results[33,34,35]. There is concerns about acute retroviral syndrome when therapy is restarted[34,36]. Furthermore, there is the potential risk of promoting antiretroviral drug resistance with STI strategies[36,37]. Recent clinical trials have failed to confirm that a significant proportion of patients with primary HIV infection can maintain suppression of viremia after STI[38,39].

In contrast to STI, target controlled therapy involves a strategy in which patients have their therapy discontinued and re-initiated only when certain target $CD_4$ counts (above 350 cells/mL) are reached. Others have also included viral load measurements. These approaches are not suitable for patients who have experienced severe immune damage before initiating HAART for concerns over a further rapid deterioration in immune function once therapy is interrupted. This strategy may be considered only in patients in whom careful follow-up can be assured.

According to 'autovaccination hypothesis' reexposure to HIV during treatment interruptions may stimulate the HIV-specific immune response and lead to low viremia after withdrawal of HAART. Results of a recent prospective study, however, do not favour autovaccination hypothesis. Treatment interruptions for two weeks did not provoke clinical complications and

there was little drug resistance[35]. Nevertheless, comparative trials are yet to demonstrate what benefit, if any, is associated with intermittent, as opposed to continuous ART.

**Chemoprophylaxis of HIV infection**

A. **Prophylaxis for occupational exposure to HIV**

Effective prophylaxis for infection with HIV is important for health care workers at risk for exposure to infected blood and body fluids. The average risk for percutaneous exposure is 0.3 percent, but exposure involving a high titer of HIV or a large volume of infectious material are apt to be much riskier. Treatment with zidovudine after percutaneous exposure appears to reduce the odds of infection by almost 80 percent.. Given the emergence of antiretroviral drug resistance among source patients, zidovudine plus lamivudine is recommended for prophylaxis for a period of 4 weeks. Use of indinavir or other protease inhibitors is recommended when the source patient is likely to harbor resistant virus or when exposure is especially hazardous[40].

B. **Postexposure prophylaxis after sexual, injection-drug use, or other non-occupational exposure (nPEP) to HIV**

For ethical and logistical reasons, a randomized, placebo-controlled clinical trials of nPEP probably will never be performed. Data from animal studies, perinatal clinical trials, and studies on health care workers receiving prophylaxis after occupational exposure, and observational studies suggest that nPEP can reduce the risk for HIV after non-occupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV infected, a 28-day course of HAART is recommended. ART should be initiated as soon as possible after exposure. For persons seeking care $\geq$ 72 hours after nonoccupational exposure, no recommendations are made for the use of nPEP. The risk and benefit on a case-by-case basis may be considered. Risk reduction counseling and indicated intervention services should be the focus for risk reduction for recurrent exposures. No evidence indicate that any specific antiretroviral medications is optimum for nPEP. On the basis of empirical evidence preferred regimens include efavirenz and lamivudine or emtricitabine with zidovudine or tenofavir (as a NRTI-based regimen), and lopinavir/ritonavir combination (Kaletra®) and zidovudin with either lamivudine or emtricitabine. There is no evidence to suggest that a three-drug HAART regimen is more likely to be effective than a two-drug regimen[2,41].

C. **Perinatal prophylaxis**

Preventing mother-to-child transmission of HIV: Mother-to-child transmission (MTCT) of HIV continues to be a major cause of infant morbidity and mortality in resource-poor settings[42]. Reduction in maternal viral load during late pregnancy, labour, and delivery seems to be a major factor in the effectiveness of reducing mother-to-child HIV transmission[43,44,45,46]. A high maternal plasma concentration of virus is a risk factor for the transmission of HIV-1 from an untreated mother to her infant[47]. Low transmission rates were noted in studies in which intrapartum and postpartum zidovudine was given[47]. Nevirapine also lowers the risk of HIV-1 transmission[48]. Since combination HAART has greatest efficacy in preventing HIV transmission[49], zidovudine in combination with lamivudine has also been recommended[48,50]. The efficacy and safety of potential alternative to zidovudine such as stavudine for use in pregnant women with HIV infection, has been confirmed[51]. Nelfinavir and nevirapine containing HAART regimens are well tolerated

during pregnancy, although side effects are more common in pregnant than in non-pregnant women[52].

Effective caesarian section reduces perinatal transmission in patients with or without monotherapy, but has not shown a benefit in patients on triple HAART therapy[45,49,50.] Currently there is no evidence of an effect of vaginal disinfection with intrapartum ART on the risk of MTCT of HIV[53]. Intrapartum change from oral to intravenous zidovudine or nevirapine further lowers the risk of perinatal HIV transmission during the first 14-16 weeks of life in breast-fed infants[48]. There is evidence that following a single dose nevirapine for prevention of MTCT, the risk for HIV-1 resistance mutation is high[54]. Selection of nevirapine resistant HIV can be reduced with short-course post-partum combination antiviral cover[42,55]. The efficacy of various short-course regimens have shown to reduce significantly post-partum transmission of HIV in both breast-fed and non-breast-fed population in resource constrained settings[56,57,58].

Although combination regimens, especially short course zidovudin and single dose nevirapine has shown a dramatic reduction in perinatal transmission of HIV[59,60], its large scale application has been problematic in field studies[60,61,62]. The need for a multifaced approach to prevention of MTCT has to be emphasized.

In children exposed *in utero* to zidovudine, mitochondrial dysfunction has been detected[63,64]. Furthermore, the risk of febrile seizure in neonates increases with perinatal exposure to antiretrovirals[65]. There is also evidence that perinatal exposure to antiretrovirals affects growth in children during first 18 months of life[46]. Nevertheless, current recommendations for zidovudine use for preventing MTCT should be maintained, and further assessment of the toxic effects of these drugs is warranted. Also, because of potential teratogenicity of efavirenz, it should not be used in any nPEP regimen during pregnancy or in women of childbearing age at risk for becoming pregnant during the course of antiretroviral prophylaxis. PI or NRTI based regimens may be considered in these circumstance[41]. Only few of the anti-retrovirals have been approved by the FDA for pediatric use (Table 1).

**Adverse Effects**

Adverse effects have been reported with all antiretroviral classes of drugs and are the primary cause for treatment discontinuation, medication nonadherence and/switching of treatment regimens. Female patients seem to have a greater risk for developing Stevens – Johnson syndrome and hepatotoxicity due to nevirapine, and lactic acidosis due to NRTI. Comorbidity such as alcoholism, hepatitis B or C infection also increases the risk of toxicity. Adverse effects due to antiretroviral drugs can be classified as (a) potentially life threatening and serious events; (b) adverse events leading to long-term consequences; and (c) adverse events presenting as clinical symptoms that may affect overall quality of life and compliance to medications[2].

Differentiating between complicating consequences of HIV infection and toxicities of drugs used in the management of HIV infection is challenging. Several distinct categories of adverse effects can include:

1. Mitochondrial dysfunction (including lactic acidosis, hepatotoxicity, pancreatitis and peripheral neuropathies)

2. Metabolic abnormalities (such as fat maldistribution and body habits changes; hyperlipidemia, hyperglycemia and insulin resistance, and osteopenia, osteoporosis and osteonecrosis)

3. Hematologic adverse events from drug-induced bone-marrow suppression (anemia, neutropenia and thrombocytopenia) and

4. Allergic reactions (skin rashes and hypersensitivity reaction).

While individual antiretrovirals are associated with specific toxicities, interactions between antiretrovirals and other drugs used in the management of HIV/AIDS complications can result in pharmacokinetic alterations and additional toxicities[1].

Metabolic complications due to antiretroviral therapies including dyslipidemia and new onset diabetes mellitus, have been reported[66,67,68,69,70]. The precise cause for dyslipidemia is unknown but may be related to homologies between retroviral protease and host proteins[71]. It is estimated that up to 40% patients receiving PI-based HAART therapy can experience impaired glucose tolerance due to insulin resistance; insulin sensitizing antidiabetic drugs are effective in these patients[66,72,73].

The management of HAART-associated dyslipidemia should involve dietary modifications, regular physical exercise and pharmacologic interventions reserved for those patients at risk for complications. While statins are effective in managing dyslipidemia, statins and PI-inhibitors both are metabolized by hepatic $P_{450}$ enzymes, thus producing drug interaction potentially resulting in an increased risk of myopathy and hepatotoxicity. There is a significant risk for developing lipodystrophy in patients treated with HAART and the underlying mechanism is uncertain. There is growing evidence that lipodystrophy, myopathy including cardiomyopathy, anemia, lactic acidosis, pancreatitis are mediated by mitochondrial toxicity, probably as a result of the inhibition of gamma-polymerase, the enzyme involved in replicating and repairing of mitochondrial DNA[74,75]. Since both insulin resistance and lipodystrophy have been implicated to involve mitochondrial dysfunction resulting from HAART, a common molecular mechanism may underlie the basis for these adverse drug effects[75,76]. As a general rule, nucleoside analogs are believed to be responsible for lipo-atrophy and PI are responsible for lipo-accumulation, in particular, visceral abdominal fat[69,71,72]. The actual effect of ART on this adverse drug effect may be determined by drug- combination used, and is unpredictable.

## CONCLUSION

The management of HIV infection is a constantly evolving process. The wealth of new data emerging has made staying informed about current issues and new developments a daunting task. Despite significant advances made in the management of HIV-infected persons a cure is still out of reach. Mortality in HIV-infected patients has decreased dramatically since the introduction of HAART. However, the mortality in patients with successful initial response to HAART is still higher than in non-HIV infected individuals. In many developing countries one of the most common reason for discontinuing therapy is the cost of treatment (in addition to the adverse effects). Simplifying therapeutic strategies against HIV is important to optimize the clinical benefit of long-term antiretroviral treatments for patients and to improve compliance and quality of life. Another priority for simplified regimens is to enhance efficacy of antiretroviral therapy, decrease the risk of emergence of drug resistance and minimize the long term complications. Directly observed therapy (DOT) in which a health care provider observes the regimen of antiretroviral medication is being evaluated[80].

Several novel therapies with existing and newer classes of drugs are very promising. Protease inhibitors such as TMC 114 and GSK 640385 have potent activity against PI-resistant HIV-1. A newer NNRTI, TMC 278, seems to have activity against NNRTI resistant isolates of HIV-1 and excellent tolerability. Highly potent, orally bioavailable CCR5 inhibitor, TAK-652, indicates a possibility of once daily administration. It has also been shown to have activity against all recombinant HIV-strains with seven different subtype envelope proteins. Another CCR5 inhibitor, AK602/ONO4128/ GW873140 has unique activity against R5 HIV at subnanomoalr concentrations, and is being evaluated with other conventional antiretrovirals for synergistic activity. Since it has a very long intracellular half-life (>100 Hrs), a sustained effect is feasible. Another CCR5 antagonist, Maraviroc (UK-427857) does not inhibit any of the major $P_{450}$ isoenzymes and is unlikely to produce drug-drug interactions. A maturation inhibitor, PA457, blocks the conversion of the capsid precursor (P25) to mature capsid protein (P24), resulting in defective core condensation and the release of non-infectious virus particles. PA457 has a potent inhibitory activity on HIV replication and is synergistic when combined with approved drugs. Integrase inhibitor, L-000810810, a new class of drug prevents HIV from infecting new cells. These are some of the highlights on new anti-retroviral drug therapies that are emerging and offer much hope[77]. We can expect to have potent new combinations evolving in the next few years. HIV positive people who have become resistant to PIs, NRTIs and NNRTIs will likely benefit from fusion and entry inhibitors, especially the non-peptide fusion and entry inhibitors[78].

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Table 1

| Current Status | Nucleoside Reverse Transcriptase Inhibitors (NRTIs) | Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) | Protease Inhibitors | Entry & Fusion Inhibitors |
|---|---|---|---|---|
| FDA Approved (Single drug) | Abacavir (Ziagen®) *<br>Didanosine (Videx®) *<br>Emtricitabine (Emtriva®) *<br>Lamivudine (Epivir®) *<br>Stavudin (Zerit®) *<br>Tenofavir (Viread®)<br>Zalcitabine (Hivid®)<br>Zidovudine (Retrovir®) * | Dilavirdine (Rescriptor®)<br>Efavirenz (Sustiva®) *<br>Nevirapine (Viramune®) * | Amprenavir (Agenerase®) *<br>Atazanavir (Reyataz®)<br>Fosamprenavir (Lexiva®)<br>Indinavir (Crixivan®)<br>Nelfinavir (Viracept®) *<br>Ritonavir (Norvir®) *<br>Saquinavir (Invirase®)<br>Tipranavir (Aptivus®) | Enfuvirtide (Fuzeon®) * |
| FDA Approved (Combination drugs) | Abacavir + Lamivudine + Zidovudine (Trizivir®)<br>Abacavir + Lamivudine (Epzicom®)<br>Emtricitabine + Tenofavir (Truvada®) | Nil | Lopinavir + Ritonavir (Kalestra®) * | Nil |
| Investigational drugs | AVX 754<br>Alovudine<br>Amdoxavir<br>DPC 817 (Reverset®)<br>Elvucitabine, Recivir. | Calanolide A<br>Capravirine<br>TMC 125 | TMC 114 | AMD 070, BMS 488043,<br>GSK-873, 140 (Aplaviroc®)<br>PRO 542, Peptide T,<br>SCH-C, SCH-D (Vicriviroc®)<br>TNX-355<br>UK- 422,857 (Maraviroc®) |

* Approved for pediatric use.

Table 2.1

| Regimens | Preferred | Alternatives | Not Recommended |
|---|---|---|---|
| **Protease-Inhibitor Based** | Lopinavir / Ritonavir + Zidovudine + Lamivudine / Emtricitabine | • Altazanavir / Fosamprenavir / Ritonavir boosted Indinavir / Nelfinavir or Ritonavir boosted Saquinavir + Zidovudine / Stavudine / Tenofavir / Abacavir / Didanosine + Lamivudine / Emitricitabine | • Unboosted Indinavir<br>• Unboosted Saquinavir<br>• Ritonavir boosted Tipranavir<br>• Ritonavir as sole PI |
| | **Advantages:**<br>• Sustained viral suppression<br>• Improved immunologic function<br>• Prolongation of patient survival. | **Disadvantages:**<br>• Pharmacokinetic variations<br>• Propensity for drug interactions<br>• Adverse reactions due to mitochondrial dysfunction. | |

Table 2.2

| Regimens | Preferred | Alternatives | Not Recommended |
|---|---|---|---|
| **Non-Nucleoside Reverse Transcriptase Inhibitor - Based** | Efavirenz + Zidovudine / Tenofavir + Lamivudine / Emtricitabine | • Efavirenz + Didanosine / Abacavir / Stavudine + Lamivudine / Emitricitabine<br>• Nevirapine-based regimen in adult females with $CD_4$ cell counts $\leq$ 250 cells/$mm^3$, and in adult males with $CD_4$ cell counts $\leq$ 400 cells/$mm^3$. | • Delaviridine<br>• Nevirapine for adult females with $CD_4$ cell counts $\geq$ 250 cells/$mm^3$, and adult males with $CD_4$ cell counts > 400 cells/$mm^3$. |
| | **Advantages:**<br>• Lower pill burden<br>• Preserving PI-based regimens for later use<br>• Reducing or delaying PI adverse effect | **Disadvantages:**<br>• Low genetic barrier for development of drug resistance resulting from a single mutation; cross-resistance.<br>• Not suitable for use during pregnancy and in women of childbearing age group. | |

Table 2.3

| Regimens | Preferred | Alternatives | Not Recommended |
|---|---|---|---|
| **Tripple Nucleoside Reverse Transcriptase Inhibitor -Based** | Abacavir + Zidovudine + Lamivudine (only for patients in whom PI-based o NNRTI-based regimen cannot be used due to drug-interactions in treatment – naïve patients). | None | • Abacavir + Tenofavir + Lamiivudine<br>• Didanosine + Tenofavir + Lamivudine. |
| | **Advantages:**<br>• Fewer drug interactions<br>• Low pill burden due to availability of fixed – dose combinations.<br>• Sparing the adverse effect of NNRTI or PI-based regimens. | **Disadvantages:**<br>• Less potent antiretroviral activity.<br>• Risk of non-response and virologic failure. | |