Guidelines for Use of Antiretroviral Therapy for HIV Infected Individuals in India (ART Guidelines 2008)


EXECUTIVE SUMMARY

With the rational use of antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection has been transformed into a chronic manageable illness like diabetes and hypertension. Since these guidelines were last published, there has been new evidence addressing ART strategies and efficacy of new combinations. Additionally, many new antiretroviral drugs are now available in India. These guidelines update the previous version and provide information on state of ART, evidence based approach for use of ART in the Indian context.

When to initiate ART?

Antiretroviral therapy is indicated for all symptomatic HIV infected persons (Current WHO stage 4 and 3 conditions) regardless of CD4 counts and plasma Viral load (PVL) levels. In asymptomatic HIV infected individuals, ART is indicated if the CD4 count<350/mm³. Therapy is not recommended for asymptomatic individuals with CD4 count more than 350/mm³ except in HIV-HBV/HCV co-infected patients when treatment for HBV/HCV is indicated, HIV infected pregnant mothers for prevention of mother-to-child transmission of HIV and in patients receiving concomitant cytotoxic therapy (e.g. cancer chemotherapy). Involvement of the patient in all treatment decisions and assessing readiness is critical before initiating ART.

What to start with?

A non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen is recommended as initial therapy for antiretroviral naïve patients. The prevalence of primary NNRTI resistance amongst HIV infected patients in India is expected to be low. The choice between nevirapine and efavirenz is based on differences in adverse events profiles; cost, availability of convenient fixed-dose combinations and need for concomitant use of rifampicin. A backbone of 2-nucleoside reverse transcriptase inhibitors (NRTI’s) is combined with the NNRTI. In recognition of the short and long term toxicities of thymidine analog reverse transcriptase inhibitors (especially lipodystrophy, dyslipidemia, peripheral neuropathy, anemia and hyperlactataemia) and some evidence of inferior potency in the long term (mainly driven by treatment related toxicities) it is recommended that tenofovir or abacavir, in combination with lamivudine or emtricitabine, be preferred as the 2NRTI backbone. However, due to cost-related factors zidovudine may still be used as one of the NRTI backbone for initial treatment. Use of stavudine should be minimized in first line regimens and should be initiated if no other options can be accessed by the patient. Various combinations and ART strategies not to be used in clinical practice has been enlisted.

How to follow up?

Recommendations have been made for baseline evaluation and monitoring of patients on ART. These include guidelines on laboratory and clinical evaluation. A plasma viral load (PVL) at 6 months after initiation of first-line ART is strongly recommended. Furthermore PVL determination is recommended every six months (or at least yearly) to identify failure early and prevent development of broader cross resistance by persisting with a failing regimen. Twice-yearly estimation of lipid profile and blood sugar is recommended.

How to identify and manage ART failure?

The guidelines recognize the issue of identifying ART failure late if only CD4 counts/clinical markers are used for monitoring. Genotypic resistance testing, when available, should be used to determine resistance patterns, particularly if ART failure has been identified immunologically or clinically rather than virologically and if the patient has been continuing a failing regimen for a prolonged period of time. In the absence of resistance testing various second line regimens have been enlisted. A boosted protease-inhibitor based regimen is recommended in this situation to be combined with 2-NRTIs (with least likelihood of cross
resistance to the initially used NRTIs).

Special situations

Recommendations have been made for use of ART in HIV-TB, HIV-HBV, and HIV-HCV co-infected patients. In patients with active TB and a CD4 count < 350/mm³, initiation of ART is recommended as soon as the anti-TB treatment is tolerated. Efavirenz is the only ARV drug, which can be safely and effectively used with rifampicin. In pregnancy use of single dose nevirapine for reducing the risk of mother to child transmission of HIV is not recommended, because of the risk of development of resistance that can compromise mothers ART treatment especially if initiated within six months of receipt of the NVP dose. For post exposure prophylaxis taking the ART treatment history of the source patient is crucial in designing an effective regimen.

INTRODUCTION

Antiretroviral therapy (ART) has dramatically reduced morbidity and mortality rates in human immunodeficiency virus (HIV) disease in both the developed and developing world. Generic manufacturers of antiretrovirals (ARVs) from India have significantly reduced the cost of ART. Enhancing access to ARVs and ensuring quality care both in public or private sector in India is critical. In order to provide quality care, physicians need up to date and accurate information regarding ART including indications for its use, which drugs to choose and how to choose them, complications of therapy and managing special situations like HIV and tuberculosis (TB), HIV and pregnancy. Of the twenty-four antiretrovirals approved by US FDA, currently fourteen are available in India. Rational use of ART is critical for prevention of a possible epidemic of drug resistant HIV in India in future.

Most issues relating to use of ART in the Indian context will be addressed by the guidelines. The objectives of these guidelines are:

- To develop evidence-based, state-of-the- art guidelines for use of ART in India
- To develop guidelines which are simple to implement in clinical practice

The guidelines are designed to assist physicians in extending care to HIV infected individuals and establish a standard of clinical practice across India. HIV medicine is a rapidly changing field necessitating periodic updating. Physicians are encouraged to update themselves periodically. These guidelines will be reviewed on an annual basis.

WHEN TO INITIATE ART?

With use of available therapeutic options, eradication of HIV cannot be achieved. However, with the advent of potent ART, HIV infection has now been transformed into a chronic, manageable illness.

The goals of ART are:
1. To ensure maximal and durable suppression of the virus
2. To reconstitute and preserve immunologic quantity and function
3. To improve quality of life
4. To reduce morbidity and mortality due to HIV infection

Additionally, antiretroviral drugs can be used to reduce transmission of HIV in various situations, e.g. prevention of transmission of HIV from infected mother-to-child (pMTCT), after high risk occupational/ non-occupational exposures: post exposure prophylaxis (PEP). There is increasing interest in use of ARV for pre-exposure prophylaxis (PrEP), however pending further evidence this is not recommended in clinical practice. A reduction in plasma viral load is likely to lead to reduction in the risk of sexual transmission of HIV.

Since the use of ART is life-long, and associated with long-term adverse events, not all patients diagnosed with HIV infection need to be started on treatment. The decision to initiate ART is made after weighing the risk of progression to AIDS and other important determinants such as the incidence of short and long-term toxicities, commitment to high levels of adherence, possible development of resistance to ARVs and affordability and accessibility and patient’s readiness for therapy. Figure 1 summarizes recommendations about when to initiate ART.

Antiretroviral treatment is indicated for all patients who are symptomatic with an AIDS defining illness, irrespective of CD4 counts or viral load levels (or current WHO stage 4 and 3 conditions). Patients with AIDS have higher rates of mortality unless treated with ART. Patients with WHO stage 3 conditions have functional immunodeficiency and have a risk of rapid progression, and therapy is recommended in these patients especially...
Table 1: WHO Clinical staging system for adults and adolescents

<table>
<thead>
<tr>
<th>Clinical Stage 1</th>
<th>Asymptomatic</th>
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<tr>
<td>Persistent Generalized Lymphadenopathy</td>
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<tr>
<th>Clinical Stage 2</th>
<th>Moderate unexplained weight loss (under 10% of presumed or measured body weight)</th>
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<tr>
<td>Recurrent respiratory tract infections</td>
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<td>Herpes zoster</td>
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<td>Angular chelitis</td>
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<td>Recurrent oral ulcerations</td>
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<td>Papular pruritic eruptions</td>
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<td>Seborrheic dermatitis</td>
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<td>Fungal nail infections</td>
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<tr>
<th>Clinical Stage 3</th>
<th>Unexplained severe weight loss (&gt;10% of presumed or measured body weight)</th>
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<tbody>
<tr>
<td>Unexplained chronic diarrhoea &gt; 1 month</td>
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<tr>
<td>Unexplained persistent fever &gt; 1 month</td>
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<tr>
<td>Persistent oral candidiasis</td>
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<td>Oral hairy leucoplakia</td>
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<td>Pulmonary tuberculosis</td>
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<td>Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis)</td>
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<tr>
<td>Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis</td>
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<td>Unexplained anemia (&lt;8 g%), neutropenia (&lt;500), and chronic thrombocytopenia (&lt;50,000)</td>
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<tr>
<th>Clinical Stage 4</th>
<th>HIV wasting syndrome</th>
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<tr>
<td>Pneumocystis pneumonia</td>
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<tr>
<td>Recurrent severe bacterial pneumonia</td>
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<td>Chronic herpes simplex infection (orolabial, genital or anorectal of more than one months duration or visceral at any site)</td>
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<tr>
<td>Esophageal candidiasis</td>
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<td>Extrapulmonary tuberculosis</td>
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<td>Kaposi sarcoma</td>
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<td>Cytomegalovirus disease (retinitis or any other organ)</td>
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<tr>
<td>Central nervous system toxoplasmosis</td>
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<td>HIV encephalopathy</td>
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<td>Extrapulmonary cryptococcosis including meningitis</td>
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<td>Disseminated non-tuberculous mycobacterial infection</td>
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<td>Progressive multifocal leucoencephalopathy</td>
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<td>Chronic cryptosporidiosis</td>
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<td>Chronic isosporiasis</td>
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<td>Disseminated mycosis (histoplasmosis)</td>
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<tr>
<td>Recurrent septicaemia</td>
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<td>Lymphoma (cerebral or B cell Non-Hodgkins)</td>
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<td>Invasive cervical carcinoma</td>
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<tr>
<td>Atypical disseminated leishmaniasis</td>
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<tr>
<td>Symptomatic HIV associated nephropathy or cardiomyopathy</td>
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if CD4 count is <350/mm³.7-9  Table 1 enlists the WHO clinical staging system.

The exact time for initiating ART in the presence of an acute OI is unclear. A recent randomized strategy trial (ACTG 5164) demonstrated higher rates of clinical progression and more deaths especially in the first 6 months in patients who initiated ART after completion of OI treatment as compared to patients who initiated it within 14 days of starting acute OI treatment.3 However, virologic and immunologic outcomes between the two arms were similar at 48 weeks in this trial. Furthermore CD4 counts increased more rapidly in the immediate treatment group. While consideration should be given to early initiation of ART in patients presenting with an active OI, physicians should closely monitor for drug-drug interactions, additive toxicities and the emergence of immune reconstitution inflammatory syndrome (IRIS). It should also be noted that patients with TB were not included in the study and recommendations for the appropriate timing for initiation of ART in HIV patients with active TB is discussed below.

Certain AIDS defining illness like cryptosporidial diarrhea, progressive multifocal leucoencephalopathy (PML) and non-infectious complications like idiopathic esophageal ulcers, thrombocytopenia may be most effectively treated with ART induced immune reconstitution.10,11

There is a limited data on natural history of HIV infection from India, especially the risk of progression to AIDS at various CD4 counts and viral load levels. A retrospective analysis demonstrated that Indian HIV infected patients with CD4 counts <200/mm³ were 19 times more likely to die than were those with CD4 counts> 350/mm³.12 Since the risk of developing OI’s is significant when CD4 counts drop to less than 200/mm³, therapy is indicated for these patients, even if they are currently asymptomatic.7 At the same time it should be considered that ART is effective even in patients with advanced immunosuppression (CD4<50/mm³) and should always be offered.13,14 However, the risk for development of IRIS and certain short and long term toxicities is higher if ART is initiated at this stage and close monitoring is recommended.

Therapy is not indicated in asymptomatic patients with CD4 counts >350/mm³. The risk of progression to AIDS in these patients is very low.15 Initiating ART at this stage would mean prolonged exposure to the drugs resulting in increased costs, potential for development of short and long term toxicities and development of drug resistance in cases of sub-optimal adherence. For example the risk of developing fatal hepatitis due to nevirapine is significantly higher at this stage. Exceptions include patients who are co-infected with HBV or HCV in whom hepatitis treatment is indicated,16,17 pregnant mothers for prevention of mother to child transmission of HIV and patients initiating cytotoxic therapy.

Initiation of antiretroviral therapy is recommended in asymptomatic patients with confirmed CD4 counts<350/mm³ or CD4%<15%.17 There are no randomized controlled studies supporting this recommendation. However, observational studies have demonstrated a significant decline in mortality and morbidity when ART is initiated in this range rather than waiting until CD4 counts drop to below 200/mm³.15,16,12 Furthermore improvement in CD4 counts are better if ART is initiated.
before the CD4 counts fall to <200/mm³. The risk of occurrence of certain non-AIDS defining conditions (hepatic, cardiovascular, renal disease and non-AIDS defining malignancies) is also higher as compared to development of AIDS defining illnesses as CD4 falls to <350/mm³. High rates of early mortality on ART (within 6 months of initiation) has been demonstrated from ART programs in Africa that may be associated with advanced clinical and immunological disease at baseline in these patients. Finally there is emerging evidence to suggest lower rates of long term toxicities (peripheral neuropathy, anemia and renal toxicities) amongst patients who initiate ART at higher CD4 counts. All of this argues for earlier initiation of ART rather than waiting till the CD4 counts drop to less than 200. It should be remembered that women with CD4 counts 250-350/mm³ cannot be initiated on NVP based regimen because of concerns of life threatening hepatic toxicity.

Other surrogate markers like the total lymphocyte count (TLC) have been recommended for initiation of ART by some guidelines. However, the sensitivity and specificity of TLC are not sufficiently high to replace CD4 counts. Additionally, the use of TLC in monitoring response to treatment is unproven. Hence TLC is not recommended as a marker for decisions about initiation of ART.

The role of ART in primary HIV infection is controversial. Till further data is available treatment of primary HIV infection with ART is not recommended in routine clinical practice and should be restricted to clinical trial settings only.

Apart from the biological indications for therapy, assessing patient readiness prior to ART initiation is crucial for long-term success. The following points should be discussed with the patient prior to initiation:

1. Treatment is life-long, since viral eradication is not achievable.
2. Treatment is expensive.
3. High levels of adherence are needed and negative consequences of low adherence.
4. Education about short and long term adverse events.
5. Education about drug-drug interactions including herbals.
6. Counseling about the importance of safer sex practices.

Therapy should never be initiated during the first visit (unless advanced HIV disease) and patients should be encouraged to involve at least one family member in care.

Baseline Evaluation

A standard clinical and laboratory evaluation is recommended prior to initiation of ART. It is necessary to establish the baseline status for future comparisons, individualize ART according to patient’s clinical status and preferences, and rule out active OI’s.

History

Points to be elicited in history taking:

1. HIV specific symptoms- present and past
2. Genital ulcers and other sexually transmitted diseases
3. Personal history- smoking, alcohol, drugs
4. Past history of any coronary artery disease
5. High risk behavior- partner’s HIV sero-status if known
6. Women- Gynecological history, past pregnancies, contraception
7. Family history of coronary disease, hypertension, diabetes and hyperlipidemia
8. Treatment history: any past or current use of ARVs (useful for designing an ART regimen), sexual partners ARV use, ARV use during pregnancy (e.g. single dose NVP) and the use of any alternative (e.g. herbal) preparations.

Physical examination

A routine physical examination is essential prior to initiating ART. The following evaluation is recommended:

1. Body weight and BMI
2. Temperature
3. Blood pressure
4. Lymphadenopathy
5. Oral cavity: oral candidiasis, oral hairy leukoplakia
6. Dermatological
7. Genital
8. Systemic examination

Laboratory evaluation

The purpose of baseline laboratory evaluation is to stage HIV disease, rule out opportunistic infections and determine baseline safety parameters. The following tests are recommended:

Essential

1. Confirm HIV infection: A pre-requisite prior to ART initiation. This can be done by a supplemental ELISA or a Western Blot. A rapid HIV antibody test is recommended to rule out HIV-2 infection. Non-nucleoside reverse transcriptase inhibitor’s (NNRTIs) have no activity against HIV-2.
2. Specific investigations to rule out OI’s
3. CD4 counts: Determined by flow-cytometry. Alternative low cost technologies are becoming
available, however further evidence is needed to recommend its routine use in clinical practice.23

4. CBC: Baseline Hemoglobin and WBC counts are needed to monitor possible hematological toxicity due to Zidovudine (ZDV) use.

5. LFT’s: Necessary in evaluation of possible hepatitis, particularly when NVP use is contemplated; should be done if patient is co-infected with HBV/HCV.

6. Urine routine: To evaluate proteinuria and glycosuria (necessitate estimation of blood glucose)

7. Creatinine: Doses of nucleoside reverse transcriptase inhibitors (NRTI’s) except abacavir has to be adjusted according to Creatinine clearance. It is also essential to determine baseline creatinine prior to initiating tenofovir based regimens.

8. HbsAg: To rule out concomitant hepatitis B infection, this influences the choice of the ARV regimen. Abrupt stopping of anti-HBV drugs like lamivudine, emtricitabine and tenofovir is not recommended in patients with chronic hepatitis B co-infection since it may result in hepatitis B flare.24

9. Chest X-ray: to rule out TB or other pulmonary infections only if the patient is symptomatic

10. VDRL/TPHA

11. Pap smear

Optional

1. Fasting lipid profile: May be recommended in patients with established coronary artery disease risk factors or if stavudine, zidovudine, efavirenz, protease inhibitor (PI) use is contemplated.

2. Plasma viral load (PVL): A baseline PVL is not mandatory. With optimum adherence and a potent regimen, undetectable levels at 6 months after ART initiation should be achieved.25

3. Pregnancy test: EFV is contraindicated in first trimester of pregnancy and most ARVs are in FDA category B/C.

4. Anti HCV antibodies: The prevalence of HCV is low in HIV infected patients except, such as in northeastern states of India where the prevalence of injection drug use is high. It is also recommended in HIV infected hemophiliacs and thalassaemias or in HIV patients having any history of exposure to blood or blood products in the past.

5. Genotypic resistance testing: This is recommended in a patient with current history of sub-optimal exposure to ARVs (e.g. 2 drug therapy). Routine baseline genotypic resistance testing is not recommended at this time because it is presumed that the prevalence of transmitted baseline drug resistance may be low in the HIV-infected population in India.

Cautions with interpretation of CD4 counts and PVL

- Standard methods
  - CD4 counts: Flow cytometry
  - PVL: Amplicor 1.5 , Branched DNA assay. NASBA and Real time PCR

- The laboratory should have a quality assurance program

- Inter-current illnesses, concomitant steroid use, vaccinations may influence the CD4 counts and PVL values.

- Some evidence to suggest that CD4 counts in normal north Indians is significantly lower than the western population.26

- Physiologic variations
  - CD4 counts:
    - 30% changes especially at higher CD4 counts
    - Diurnal variations: The CD4 count is lowest at around 12.30 PM and highest at about 8.30 PM in the evening. A practice to draw blood for CD4 counts around the same time during follow up testing is necessary.
  - PVL: 0.3-0.5 log (2-3 fold change)

- Specimen processing
  - CD4 counts: within 18-24 hours of specimen withdrawal, ideally as soon as possible.27
  - PVL: plasma separated within half an hour of specimen withdrawal and store/transport at -20o, -70o Celsius.

- PVL: Currently available for HIV-1, not for HIV-2

**WHAT TO START?**

Antiretroviral agents of five classes are approved by US FDA for use in HIV infected patients (Table 2). These five classes include the nucleoside and nucleotide reverse transcriptase inhibitors (NRTI/NtRTI), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PI’s), entry inhibitors (fusion and chemokine inhibitors) and integrase inhibitors.

The terminology “highly active antiretroviral therapy” (HAART) refers to use of combinations of antiretroviral agents that achieve maximal and durable suppression of HIV. To date, most clinical experience with use of HAART in treatment-naïve individuals has been based on three types of combination regimens: NNRTI-based (1 NNRTI + 2 NRTI), PI-based (Ritonavir boosted PI + 2 NRTI), and triple NRTI-based regimens. There is emerging data about the use of raltegravir and maraviroc in initial treatment, however these drugs are not available at this time in India and will not be discussed.

Most experience in India is with use of NNRTI based regimens.

**Initial Regimen for ART-naïve HIV-1 infected patients in India**
Regimen selection should be individualized, taking into consideration a number of factors including: comorbidity or conditions such as tuberculosis, liver disease, depression or mental illness, cardiovascular disease, adherence potential; cost of treatment and affordability, dosing convenience including pill burden, dosing frequency, storage requirement, and food and fluid considerations; potential adverse events; drug-drug interactions, gender; and pregnancy potential.

An NNRTI based regimen is recommended as first line therapy for most ART-naïve HIV infected patients. NNRTI-based regimens are potent and have shown comparable efficacy to ritonavir boosted PI based regimens and are superior to 3 NRTI based regimens.31-33 NNRTI-based regimens have the advantage of a lower pill burden, no strict storage requirement and are cheaper when compared to PI-based regimens. Use of NNRTI-based regimens as initial therapy can preserve the PI’s for later use and reduce or delay patient exposure to some of the adverse events more commonly associated with PI’s. These regimens can still be positioned as first line treatment because the prevalence of primary resistance to NNRTIs may be presumed to be low in India.

The major disadvantage of currently available NNRTI’s is their low genetic barrier for development of resistance. These agents only require a single mutation to confer high level resistance (mutations at codons 103, 106, 181, 190 see section on treatment failure), and cross-resistance often develops across the entire class.34 As a result, patients who fail these initial regimens may lose the utility of other NNRTI’s and/or may transmit NNRTI-resistant virus. When patients fail an NNRTI based regimen 2-class resistance is more frequently seen, with accumulation of some mutations responsible for drug resistance to the NRTIs in the backbone.35 Furthermore, patients continuing on a failing NNRTI-based regimen may accumulate further resistance mutations that may compromise utility of second generation NNRTIs i.e. etravirine.36

The major short-term adverse event associated with efavirenz is CNS disturbances. Usually these are self-limiting and wane of within two to four weeks of therapy and do not warrant discontinuation of efavirenz.37 Patients should be forewarned about these before initiating treatment. Pre-existing psychiatric illness is not a contraindication for EFV use. Efavirenz should be avoided during pregnancy (especially during the first trimester) or in women who are planning to conceive or women who are not using effective and consistent contraception, because of concerns relating to teratogenicity.

Nevirapine may be used as an alternative to efavirenz for the initial NNRTI-based regimen in females with pre-treatment CD4+ T cell counts <250 cells/mm³ or males with pre-treatment CD4+ T cell counts <400 cells/mm³.38 Symptomatic, sometimes serious or life-threatening hepatic events were observed with greater frequency in patient with higher CD4 ranges than that mentioned above.38 Nevirapine should be used with caution in patients already having background liver disease like chronic hepatitis B and C co-infection. When starting nevirapine, a 14-day lead-in period at a dose of 200 mg once daily should be prescribed before increasing to the maintenance dose of 200 mg twice daily.

Efavirenz is the only NNRTI (and the only ARV drug), which can be effectively and safely used with rifampicin. Initiation with an efavirenz-based regimen is recommended in patients receiving rifampicin based antituberculous therapy (see section on drug-drug interactions and HIV and TB).

A large randomized controlled trial has shown similar efficacy of nevirapine and efavirenz based first line regimens, although there were differences in safety profile.40 Recently published Indian data also support the above finding.40 Hence the choice between using NVP and EFV is based on toxicity concerns with EFV having a better safety profile. Table 3 summarizes characteristics of EFV and NVP.

### Patients Intolerant to both NNRTIs

Patients who develop severe adverse events to both nevirapine and efavirenz should be treated with ritonavir boosted protease inhibitors (IDV/r, SQV/r,

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**Table 2: Antiretrovirals approved for use**

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Entry inhibitor</th>
<th>Integrase inhibitor</th>
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<tbody>
<tr>
<td>Zidovudine (ZDV)</td>
<td>Nevirapine (NVP)</td>
<td>Saquinavir (SQV)</td>
<td>Enfuvirtide (T-20)</td>
<td>Raltegravir*</td>
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<tr>
<td>Stavudine (d4T)</td>
<td>Efavirenz (EFV)</td>
<td>Indinavir (IDV)</td>
<td>Maraviroc*</td>
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<tr>
<td>Lamivudine (3TC)</td>
<td>Delavairidine * (DLV)</td>
<td>Ritonavir (RTV)</td>
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<tr>
<td>Didanosine (ddI)</td>
<td>Etravirine*</td>
<td>Naïve (NFV)</td>
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<tr>
<td>Zalcitabine (ddC)*</td>
<td></td>
<td>Lopinavir (LPV/r)</td>
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<td>Abacavir (ABC)</td>
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<td>Tenofovir (TDF)</td>
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<td>Fos-amprenavir* (FPV)</td>
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<td>(Nucleotide RTI)</td>
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<td>Tipranavir (TPV)</td>
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<td></td>
<td></td>
<td>Darunavir (DRV)*</td>
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* Drugs not available in India. Emtricitabine is available only as a fixed dose combination with tenofovir.
However, stavudine is associated with significant adverse event profiles and availability of other NRTI’s to be used in second line regimens. Randomized controlled trials have shown no difference in the potency between zidovudine + lamivudine and stavudine + lamivudine along with a PI. However, stavudine is associated with significant long-term toxicities and is recommended only as an alternative in patients who cannot be initiated on ZDV (due to anemia) and cannot afford tenofovir or abacavir.

Another strategy may be to start with stavudine + lamivudine backbone (in patients who are anemic) and then switch to zidovudine + lamivudine at 12-24 weeks, when hemoglobin improves. However, no randomized controlled trials have been undertaken to assess this strategy.

Thymidine analog NRTIs (i.e. ZDV and d4T) are associated with short and long term toxicities. Hence in patients who can afford, a non-thymidine analog NRTI / NtRTI (ABC, TDF) is recommended in combination with 3TC/FTC. Tenofovir is an NtRTI with the convenience of once daily dosing and a good safety profile. When combined with lamivudine/emtricitabine it has shown comparable efficacy with d4T/3TC based NNRRTI regimen and had better long term safety profile. In a randomized controlled trial (Gilead 934) at 96 weeks TDF/FTC/EFV was virologically and immunologically superior to ZDV/3TC/EFV. The difference in efficacy was driven mostly due to toxicity related discontinuations in the ZDV/3TC arm. The rates of body fat changes were also higher in the ZDV/3TC arm. The only important concern about TDF is renal toxicity although the incidence of the same is very low even at 4-5 years of treatment. Tenofovir has to be used cautiously in patients with background renal disease or potential for the same (e.g. diabetes, hypertension) and in patient on concomitant nephrotoxic medications e.g. amphotericin B, streptomycin. Creatinine clearance (calculated) and urinalysis is recommended to be done prior to and on TDF treatment. TDF/FTC/EFV is available as once a day pill which simplifies treatment.

Other non-thymidine based backbones using ABC, and ddI have the advantage of not being associated with long-term adverse events like lipodystrophy and dyslipidemia. ABC/3TC has shown similar virologic and immunologic efficacy as ZDV/3TC and TDF/FTC. However, physicians should watch for abacavir hypersensitivity reaction (HSR), which is more common in patients harboring the HLA B5071 genotype. A test to check for the presence of HLA-B5701 prior to ABC initiation is currently not available in India. Additionally, combining ABC with NVP during initiation is not recommended because of difficulty in identifying the offending agent should a hypersensitivity reaction occur. Didanosine is associated with pancreatitis and hyperlactataemia and is recommended as an alternative NRTI. One advantage is its availability as once a day kit along with 3TC and EFV. Recently the DAD study reported that current use of ABC and ddI may be linked to an increased risk of myocardial infarction. Further studies are needed to confirm this observation, and this should not preclude the use of ABC or ddI in HIV infected patients. Use of TDF or ABC in the initial regimen also provides for better sequencing options after treatment failure. Even if failure is identified late, K65R (with TDF) and L74V (with ABC) may be selected. Thymidine analogs would be effective backbone for second line regimens. Additionally further accumulation of mutations

**Table 3 : Choice of NVP vs EFV as initial NNRTI**

<table>
<thead>
<tr>
<th>Nevirapine</th>
<th>Efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>Expensive</td>
</tr>
<tr>
<td>Availability of FDCs</td>
<td>Once daily kits/FDC</td>
</tr>
<tr>
<td>Toxicity : Rash, hepatitis</td>
<td>Toxicity : CNS disturbances</td>
</tr>
<tr>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Men with CD4&gt;400</td>
<td>pregnancy (1st Tri)</td>
</tr>
<tr>
<td>Women with CD4&gt;250</td>
<td></td>
</tr>
<tr>
<td>Cannot be used with RMP</td>
<td>Used with RMP</td>
</tr>
<tr>
<td>Caution with HBV/HCV co-infection</td>
<td>Caution with pre-existing psychiatric illness</td>
</tr>
</tbody>
</table>

**Table 4 : Fixed dose combinations available in India**

<table>
<thead>
<tr>
<th>Two drugs</th>
<th>Three drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>D4T + 3TC</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>ZDV + 3TC</td>
<td>ZDV + 3TC + NVP</td>
</tr>
<tr>
<td>TDF + FTC</td>
<td>TDF + FTC + EFV</td>
</tr>
</tbody>
</table>

Selection of Dual Nucleoside/Nucleotide “Backbone” as Part of Initial Combination Therapy

Six nucleoside/nucleotide HIV-1 reverse transcriptase inhibitors (NRTI’s/NtRTI’s) are currently available in India. Lamivudine is a common second agent in these combinations because of its tolerability. Though lamivudine has a low genetic barrier to resistance (a single mutation M184V/I causes high level resistance), this mutation renders the virus less fit, renders the virus hypersusceptible to ZDV and TDF (see section: When to change) and delays development of thymidine-inhibitors (NRTI’s/NtRTI’s) are currently available in India. Lamivudine is a common second agent in these combinations because of its tolerability. Though lamivudine has a low genetic barrier to resistance (a single mutation M184V/I causes high level resistance), this mutation renders the virus less fit, renders the virus hypersusceptible to ZDV and TDF. However, stavudine is associated with significant long-term toxicities and is recommended only as an alternative in patients who cannot be initiated on ZDV (due to anemia) and cannot afford tenofovir or abacavir.

Another strategy may be to start with stavudine + lamivudine backbone (in patients who are anemic) and then switch to zidovudine + lamivudine at 12-24 weeks, when hemoglobin improves. However, no randomized controlled trials have been undertaken to assess this strategy.

Thymidine analog NRTIs (i.e. ZDV and d4T) are associated with short and long term toxicities. Hence in patients who can afford, a non-thymidine analog NRTI /
associated with cross resistance to other NRTIs seems to be less likely if a patient continues on a failing TDF based regimen.\textsuperscript{52} However if failure is identified late with ZDV or d4T based regimens, thymidine associated mutations (TAMs) may accumulate which can compromise use of all NRTIs in the second line regimen.\textsuperscript{53}

When NVP and EFV based regimens are contemplated, consideration should be given to using fixed dose combinations (FDCs) of ZDV/d4T+ 3TC + NVP and TDF/FTC/EFV respectively which improves adherence due to low pill burden. It also reduces prescription errors and has demonstrated effectiveness and safety in large cohort study from India.\textsuperscript{54} A combination of NVP with TDF/FTC will have a higher pill burden, but potentially a better safety profile. However NVP should not be used once daily with this combination because of higher incidence of unexplained virological failure.\textsuperscript{55}

Though boosted protease inhibitors based regimens are extremely potent as first line therapy, they are only recommended in patients who cannot tolerate both NVP and EFV. Boosted PI based regimens are costly, complex, with high pill burden, associated with long term adverse events like lipodystrophy, dyslipidemia and diabetes. The advantage in using boosted PI based regimens is their high genetic barrier to resistance and patients failing these regimens usually do not have PI resistant mutations thus restricting resistance to 1 class (i.e. to the backbone nucleosides).\textsuperscript{39} Recommended regimens for initial therapy in treatment naïve patients are summarized in Table 5.

### Antiretroviral Regimens Not Recommended

Some antiretroviral regimens or components are not recommended for HIV-1 infected patients due to sub-optimal antiviral potency, unacceptable toxicity, or pharmacological concerns. These are summarized below:

1. Mono-therapy and Dual nucleoside therapy: These regimens are not recommended because they have not demonstrated potent and sustained antiviral activity.\textsuperscript{56}

2. Tenofovir + ddI + NNRTI is not recommended as an initial regimen due to reports of early virological and immunological failure.\textsuperscript{55} Additionally a combination of TDF +ddI is usually avoided unless there are no options due to concerns of virologic and immunologic failure.\textsuperscript{9} The mechanism for this interaction is still unclear though intracellular antagonism has been postulated. When used concomitantly the 250 mg dose of ddI is recommended for use.

3. 3-NRTI regimens of abacavir + tenofovir + lamivudine and didanosine + tenofovir + lamivudine should be avoided due to high rates of virological failure.\textsuperscript{50}

4. NRTI sparing regimens (i.e. NNRTI+PI) is not recommended for initiation due to pharmacokinetic interactions, toxicities and resistance issues.

5. Boosted PI monotherapy esp. LPV/r is not recommended due to lower rates of virologic suppression.\textsuperscript{10}

6. Didanosine + stavudine: The combined use of didanosine and stavudine as a 2-NRTI backbone can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis. A combination containing didanosine and stavudine should be avoided unless other 2-NRTI combinations have failed or have caused unacceptable toxicities, and where potential benefits outweigh the risks of toxicities.\textsuperscript{59}

7. Stavudine + zidovudine: Combination regimens containing these two NRTIs should be avoided due to the demonstration of antagonism in vitro and in vivo.

8. Unboosted PI’s should be avoided due to poor bioavailability and higher pill burden.

9. Altering dosages or schedules of ARV drugs is not recommended. However, recently a meta-analysis has demonstrated equivalent efficacy of low dose stavudine (30 mg) for patients with > 60 kg weight.\textsuperscript{60} The World Health Organization has also recommended use of stavudine 30 mg bid for all patients needing ART irrespective of weight.

10. Efavirenz should be avoided in pregnancy or in women with pregnancy potential.

11. Tenofovir should be avoided during pregnancy because of possible risk of fetal bone loss.

12. Nevirapine should be avoided in women with CD4 count>250/mm\(^3\) and in men with CD4 count>400/mm\(^3\).

### Antiretroviral strategies that are not recommended

1. Induction-maintenance: Initiation of three drug regimens and then reducing it to a combination of two ARV drugs is not recommended.

---

\textsuperscript{a} Lamivudine can be used as an alternative to emtricitabine.

\textsuperscript{**} Stavudine is categorized as an alternative ARV because it is associated with a high incidence of adverse events including peripheral neuropathy, pancreatitis, hyperlactataemia and lipodystrophy and dyslipidemia that may not be reversible on treatment discontinuation.\textsuperscript{20,30}

\textsuperscript{***} ddI has to be taken on empty stomach and has higher risk of causing pancreatitis and symptomatic hyperlactataemia.

---

**Table 5** : Recommended NNRTI–Based Regimens (1-NNRTI + 2-NRTIs)

<table>
<thead>
<tr>
<th>Preferred</th>
<th>2NRTI</th>
<th>NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir + Emtricitabine*</td>
<td></td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Abacavir + Lamivudine</td>
<td></td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Zidovudine + Lamivudine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stavudine** + Lamivudine</td>
<td></td>
</tr>
<tr>
<td>Didanosine*** + Lamivudine</td>
<td></td>
</tr>
</tbody>
</table>
2. Sequential addition of drugs: A third drug, especially NNRTI should not be added to an on-going two drug regimen, as it can lead to rapid selection of resistance.

3. Structured treatment interruptions: Any form of treatment interruptions is not recommended in clinical practice unless a patient develops severe toxicities. CD4 guided treatment interruption as studied in the SMART trial was associated with more adverse outcomes (disease progression and non-AIDS events) in the treatment discontinuation (drug conservation) arm as compared to patients in the continuous therapy arm.61

**FOLLOW UP AFTER INITIATING ART**

Table 6 depicts the recommended follow up scheme after initiating ART.

Frequent follow up during the initial months is necessary to diagnose and efficiently manage acute adverse events, work with the patient on adherence issues, and diagnose clinical conditions like IRIS and acute OI’s. Most morbidity and mortality on ART in the developing world tend to occur within the first 3-6 months of initiation.62 Once a patient is on an effective and stable regimen at 6 months, quarterly follow up is recommended.

Determination of CD4 count is recommended initially at 6 months to document immunological improvement on ART and every six months thereafter. A caveat in following up with only CD4 counts is the risk of delayed detection of treatment failure (see section on identifying and managing failure).

A PVL at 6 months is essential to determine efficacy of the ARV regimen. With optimal adherence and a potent regimen PVL should be below the limits of quantification (undetectable) at 6 months.63,64 The lower limit of detection of PVL can be 400 copies/ml or 50 copies/ml depending on the assay used.

A PVL estimation at 6 months helps in the following:

1. Assess potency of the regimen
2. Assess adherence to the regimen: Objective marker to assess whether a patient has been taking medicines regularly as recommended
3. Past history of ARV treatment taken by the patient or by their sexual partners may not be always known. In either instance primary resistance may be present which can compromise efficacy of the ARV regimen
4. Ensure pharmacokinetics and pharmacodynamics of the regimen is optimal, particularly interaction with herbals (many patients may not disclose concomitant use of herbals)

Determination of viral load is recommended subsequently every 6 months (or at least once a year) since it can identify failure earlier and reduce accumulation of resistance mutations. This is more important if a patient is on ZDV or d4T based regimen to prevent ongoing accumulation of TAMs.

After initiation of a NVP based regimen ALT measurement is recommended in patients with clinical suspicion of hepatitis. With a ZDV based regimen it is important to monitor CBC for earlier detection of hematological toxicity. The prevalence of lipid abnormalities is significant on ART, particularly if a patient is on ZDV/d4T, EFV or PI's. In these patients and in patients with significant coronary artery disease risk factors; a fasting lipid profile and blood sugar estimation should be done every 6 months.

**Discontinuation of OI prophylaxis on ART**

With ART induced immune reconstitution, the incidence of most OI’s have reduced dramatically. It is possible to discontinue primary and secondary prophylaxis for most OI’s when CD4 counts improve and sustain for > 200/mm3 at least 3-6 months.65,66 Table 7 summarizes indications for starting and discontinuation of OI prophylaxis.

**ADHERENCE TO ART**

One of the most important determinants of success with ART is optimal adherence to drugs. The prevention of resistance to ARV drugs depends on adherence to and potency of the ARV drug regimen. Low levels of adherence to a standard regimen rapidly selects for drug resistant virus leading to therapy failure. There is strong evidence to suggest association of lower adherence with virological, immunological and clinical failure of ART.67,68

<table>
<thead>
<tr>
<th>Table 6 : Recommended follow up scheme after initiation of ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 wks</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Clinical and Adherence</td>
</tr>
<tr>
<td>CD4 counts</td>
</tr>
<tr>
<td>PVL</td>
</tr>
<tr>
<td>ALT</td>
</tr>
<tr>
<td>CBC</td>
</tr>
<tr>
<td>Lipid profile</td>
</tr>
</tbody>
</table>

* lower limit of detection
Adherence is the ability to take prescribed drugs in the recommended dosages and schedules and following any special instructions e.g. empty stomach. Adherence rate is calculated according the following formula:

\[
\text{Adherence rate} = \frac{\text{Number of pills expected to be taken} - \text{Number of pills missed}}{\text{Number of pills expected to be taken}} \times 100
\]

During the era of unboosted PI's an adherence rate of more than 95% was recommended for successful ART outcome. However with use of more potent drugs (e.g. boosted PI's) in regimens, this cut off of 95% may be too strict (making a regimen more forgiving). There is evidence to suggest that at least for an intermediate level of adherence (adherence rate 76%-99%), NNRTI based regimens may be more forgiving than PI based regimens. Nevertheless, physicians should encourage patients to achieve high rates of adherence to ART and work towards achieving the same. The patient should understand that more than 95% adherence for NVP based regimen would mean that he/she does not miss even two doses of fixed combination pills during a month.

Measuring adherence in clinical practice is difficult. Self-report is the easiest and cheapest method of assessing the same, they may be quite reliable. Pill counts and other objective markers of adherence measurement like MEMS caps are rarely possible in clinical set ups. Following up regularly (keeping clinic appointments) may also be an marker of good adherence. Patients should be asked whether they have missed doses over the last 4-7 days and over the last follow up period, rather than asking whether they have been taking drugs regularly. If a patient reports missing doses then the reasons for doing the same should be explored and addressed. Indirect markers of good adherence are keeping appointments and getting prescription refills. Another marker of adherence on a thymidine analog based regimen (ZDV or d4T) is development of macrocytosis, although it is not uniformly seen in all patients.

The physician should use various strategies to achieve good adherence. One of the most important aspects is developing a trusting relationship and rapport with the patient. Some of the strategies to achieve adherence are the following:

- Careful screening before starting: It is very important to screen for patient readiness before initiating ART. Cost is a major barrier to adherence in India and financial status of the patient should be assessed prior to prescribing ART. It may be worthwhile not to initiate therapy at the first visit and give some time to understand the commitment that a regimen would require, implications of being on treatment and to think about the strategies that s/he needs to evolve to overcome the challenges.

- Emphasize adherence before starting: Explaining to the patient that a high level of adherence is needed, and that the treatment is lifelong is crucial. Patient’s comprehension about drug adherence must be ascertained.

- Demonstrate how to take drugs (e.g. NVP): Many patients make mistakes during the initial lead-in dose of nevirapine. Demonstrating how to take the regimen and ensure that the patient has understood the same may be by asking him/her to repeat what has been explained.

- Using fixed dose combinations pills or combination packs: Using fixed dose combination of ARV drugs reduces the pill burden, potentially improving adherence. Additionally, using these combinations is associated with fewer prescription errors, and ensures that the patient takes all drugs in a regimen.

- Advice patients to buy monthly packs: Patients are more likely to take drugs regularly if they buy monthly packs. Buying loose pills on an as needed basis has a higher risk of missing doses.

- Follow up before supplies exhaust: One of the common reasons for missing doses is following up after the drug supplies are over. Patients should be encouraged to consult 3-4 days before their drug stocks are exhausted.

- Reminders every time during follow up: During follow up apart from assessing adherence the importance of achieving good adherence should be re-emphasized. This is also a good opportunity to reinforce safer sex messages.

- Using once daily regimens/user friendly regimens: There is evidence to suggest that adherence rates are higher if patients are prescribed once daily or twice daily drugs as compared to thrice per day or

---

**Table 7: Indications for starting and discontinuation of OI prophylaxis**

<table>
<thead>
<tr>
<th>OI</th>
<th>Primary prophylaxis</th>
<th>Drug of choice</th>
<th>Discontinued When CD4</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP [52]</td>
<td>&lt;200</td>
<td>TMP-SMX1 DS qd</td>
<td>&gt;200</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxo</td>
<td>&lt;100</td>
<td>TMP-SMX1 DS qd</td>
<td>&gt;200</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MAC</td>
<td>&lt;50</td>
<td>Azithromycin 1 gm/q wkly</td>
<td>&gt;100</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CMV</td>
<td>Not indicated</td>
<td>Secondary: Valganciclovir</td>
<td>&gt;100</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>Not indicated</td>
<td>Secondary: Fluconazole</td>
<td>&gt;100</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Not indicated</td>
<td>Secondary: Fluconazole</td>
<td>&gt;100</td>
<td>NA</td>
<td>Yes</td>
</tr>
</tbody>
</table>
importance to maintaining schedules and reduces variability in taking medicines along with interval between the doses.

- Anticipate and treat adverse events efficiently: Patients miss doses when they develop adverse events. It is essential to forewarn patients about ARV adverse events, identify them early when they do occur and manage them efficiently. This is particularly important with the CNS side effects of efavirenz or with GI intolerance of PI’s, which wane on their own after 2-4 weeks, and patients should be told not to discontinue the drug without informing the physician. Patients should be encouraged to contact the physician before contemplating any reduction of doses or changing of their ARV drugs due to any reasons.

- Reward the patient with positive feedback on
  - Declining Viral load
  - Improving CD4 counts

- Patients should be advised not to miss doses at work and to pack medications with them when they travel.

- Use of alarms in cell phones and wrist-watch to remind about the time to take medicine is a useful strategy

- Involvement of a spouse or a family member in treatment education and to remind is useful. However, this should be done in consultation with the patient as it requires sharing confidentiality that s/he is receiving antiretroviral drugs.

- Patients should have access to physicians or other members of the care team so that any problem can be sorted out without interfering with adherence.

- Studies have documented numerous predictors of poor adherence, depression being one of the most important. Identifying and managing depression is essential for successful ART outcome.72

- If patients cannot afford on-going therapy then referring the patient to a free ART program is a definite way to ensure continuation of ART. More information about free ART centers is available on www.nacoonline.org.

### Drug-Drug Interactions

Knowledge of interactions between ARV’s and other commonly used concomitant medicines in HIV infection is essential. Interactions occur between ARVs and other drugs and also occur between the ARVs themselves. The NNRTIs and the PI’s are metabolized by the cytochrome P-450 group of enzymes in the liver and these enzymes are either induced or inhibited by other drugs. This can either decrease or increase the levels of NNRTI’s or PI’s with resulting failure of treatment or development of toxicities respectively. Other sites at which interactions can occur include the gastrointestinal tract (absorption phase), and during excretion. Interactions can be bidirectional such that the levels of both the ARV and the concomitant drug are affected.

Use of ritonavir for boosting levels of concomitantly administered PI is the most common example of positive use of drug-drug interaction. Ritonavir used in low dose is inhibitor of cytochrome P450 3A4 enzyme systems. When administered with other PI’s, which are metabolized through this pathway, increased blood levels of the co-administered PI’s are achieved. This helps reduce the dose and modify schedules of the concomitant PI. In addition it reduces the chances of treatment failure and patients failing RTV boosted regimens usually do not develop primary PI mutations. Table 8 summarizes the recommended doses of ritonavir boosted PI’s.

Drugs like rifampicin are potent inducers of the cytochrome enzyme systems. Concomitant administration of NNRTIs and PI’s with rifampicin can lead to reduction of blood levels of both the ARV classes.73 This however is not clinically relevant for Efavirenz which can be used in standard doses.74 Table 9 summarizes commonly used drugs and their interactions with ARVs in clinical practice.

The use of alternative medicines including herbals is very common amongst patients in India. St John’s Wort has been documented to reduce PI levels when administered concomitantly.75 Until more data is available concomitant use of alternative therapy including herbals is strongly discouraged.

Before prescribing any concomitant medication in a patient on ART, the physician needs to keep possible

<table>
<thead>
<tr>
<th>Main PI</th>
<th>Naïve dose</th>
<th>boosted bid dose RTV/PI</th>
<th>boosted qd dose RTV/PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir</td>
<td>800 mg q8h, empty stomach</td>
<td>100/800 mg without food restrictions 100/400 mg, 200/800 mg</td>
<td>N/A</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>1200 mg tid</td>
<td>100/1000 mg</td>
<td>100/1600 mg</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>N/A</td>
<td>100/400 mg</td>
<td>200/800 mg (only treatment naive patients)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>400 mg od</td>
<td>N/A</td>
<td>100/300 mg od</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>750 mg tid or 1250 mg bid</td>
<td>Not boosted</td>
<td>Not boosted</td>
</tr>
</tbody>
</table>

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drug interactions at the back of mind. Checking for the same can be done at the website: www.hiv-druginteractions.org

Drug schedules and relationships with food intake should also be strictly followed since this helps in maintaining optimum drug levels. For example, ddi should always be administered on an empty stomach and Atazanavir and nelfinavir should be taken with food. In addition a difference of more than 1-2 hours around the dosing time should be avoided as much as possible.

Acid reducing agents (e.g. proton pump inhibitors) reduce absorption of atazanavir which can lead to sub-optimal blood levels and treatment failure.\textsuperscript{74}

Recommendations for use of these agents with atazanavir are summarized in Table 10.

### ARV Toxicities

ARV drugs may be associated with acute and long-term toxicities. Recognizing and managing these are essential because they may compromise adherence or sometimes necessitate substitution of drugs, resulting in exhausting treatment options. Additionally, many of the concomitant drugs used for treating OI’s are also associated with overlapping toxicities, making it difficult to identify the true offending agent. Patients should be educated about these so that they are recognized early.

### Table 9: Common drug-drug interactions with ARVs

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Class/Problem drug</th>
<th>Consequence</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>Anti-TB</td>
<td>Reduce NVP levels</td>
<td>Use rifabutin (with dose adjustments) Non-rifa based ATT?</td>
</tr>
<tr>
<td>(NVP)/ PIs</td>
<td>Rifampicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Antifungals</td>
<td>Increase NVP levels- hepatitis</td>
<td>Monitor ALT closely</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Decreased levels</td>
<td>Avoid with LPV/r and EFV. Use with caution with other PIs. Use fluconazole</td>
</tr>
<tr>
<td>Efavirenz/PIs</td>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Antidepressants</td>
<td></td>
<td>Fluoxetine, Paroxetine</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td></td>
<td>Doxepin, Amitryptiline</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Anticonvulsants</td>
<td>Reduce NNRTI levels</td>
<td>Close monitoring</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Reduce anticonvulsant levels</td>
<td>Gabapentin,Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td></td>
<td>levetiracetam</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td></td>
<td>Valproate with EFV</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs/ Efavirenz</td>
<td>Benzodiazepines</td>
<td>Increase benzodiazepine levels</td>
<td>Midazolam – single dose may be used for procedures with caution Lorazepam Temazepam</td>
</tr>
<tr>
<td></td>
<td>Midazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td>Lipid lowering</td>
<td>Increase statin levels</td>
<td>Pravastatin</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>- increased toxicity</td>
<td>Fluvastatin</td>
</tr>
<tr>
<td></td>
<td>Lovastatin</td>
<td></td>
<td>Atorvastatin (with caution, low doses)</td>
</tr>
<tr>
<td>PIs</td>
<td>Anti-hypertensives/</td>
<td></td>
<td>Use beta blockers (except carvedilol) with NNRTIs and PIs with caution.</td>
</tr>
<tr>
<td></td>
<td>Antianginals</td>
<td></td>
<td>All CCBs to be used with caution</td>
</tr>
<tr>
<td>PIs/NNRTIs</td>
<td>Oral contraceptives</td>
<td>Increase or decrease levels</td>
<td>Use indinavir.</td>
</tr>
<tr>
<td></td>
<td>according to the agent</td>
<td>according to the agent</td>
<td>Avoid OCPs and recommend alternative contraception methods. Use Depot Medroxyprogesterone acetate (DMPA)</td>
</tr>
<tr>
<td>PIs/NNRTIs</td>
<td>Antibacterials</td>
<td>Levels of both drugs increases</td>
<td>Monitor closely or use Azithromycin</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 10: Interaction of atazanavir and acid reducing drugs

<table>
<thead>
<tr>
<th></th>
<th>H\textsubscript{2} receptor antagonists (H\textsubscript{2} RAs)</th>
<th>Proton pump Inhibitors</th>
<th>Antacids &amp; buffered medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve</td>
<td>Treatment experienced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV</td>
<td>400 mg with food at least 2 hours earlier or at least 10 hours after H\textsubscript{2} RA</td>
<td>2 hours before or 1 hour after these medications</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>ATV/RTV</td>
<td>300/100 mg with food can be given simultaneously</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
since many long term toxicities may be irreversible or may take years to improve upon discontinuation of the offending agent.

The etiology of long term NRTI toxicities involves cellular mitochondria. By inhibiting mitochondrial DNA polymerase enzyme gamma, NRTIs can induce reduction in respiratory chain function.77 Most of the long term toxicities like lactic academia, pancreatitis, peripheral neuropathy, lipoatrophy and hepatitis are caused by mitochondrial dysfunction.

Table 11 and 12 summarize the common acute and long term toxicities associated with use of ARV agents

**IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)**

Antiretroviral therapy partially restores immune defects caused by chronic HIV infection. This typically includes restoration of protective pathogen-specific immune responses. This has resulted in a sharp decline in the incidence of opportunistic infections in HIV patients. 78 However, suppression of HIV viraemia by ART is accompanied by atypical OI manifestations or other inflammatory diseases in some patients. In these situations restoration of an immune response following ART is immunopathological rather than protective. These conditions are therefore labeled as immune reconstitution inflammatory syndrome (IRIS). IRIS is defined as a new occurrence or worsening of existing clinical conditions and/or laboratory parameters despite a favorable outcome in HIV surrogate markers (CD4 counts and PVL).79 These immune responses can be elicited against infective or non-infective agents. The temporal association between commencement of ART (or change from a previously failing regimen) and the development of an unusual clinical phenomenon often provides a strong clue in the diagnosis of IRIS.

The following points help in diagnosis of IRIS

1. Temporal association between starting a ART regimen and subsequent development of clinical phenomena (the majority within 6 months).
2. Unusual clinical manifestations in patients responding to ART. This includes
   a. Unexpected Localized disease, e.g. lymph nodes (new or enlargement &/or suppuration of lymph nodes), liver, spleen.
   b. Exaggerated inflammatory reaction, e.g. severe fever
   c. Painful lesions
   d. Atypical inflammatory response in affected tissues, e.g. granulomas, suppuration, necrosis
   e. Perivascular lymphocytic inflammatory cell infiltrate
   f. Progression of organ dysfunction or enlargement of pre-existing lesions
   g. Development or enlargement of cerebral space occupying lesions after treatment for cerebral cryptococcosis or toxoplasmosis
   h. Progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary MTB or PCP

### Table 11: Acute toxicities of ARV drugs

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Offending agents</th>
<th>Clinical presentation</th>
<th>Prevention</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI disturbance</td>
<td>ZDV, ddI, NVP, All PIs</td>
<td>Nausea, Vomiting, Diarrhoea, Abdominal distress</td>
<td>Taking with or after food</td>
<td>Mostly self-limiting, Symptomatic treatment</td>
</tr>
<tr>
<td>Rash</td>
<td>NVP, ABC, EFV</td>
<td>Diffuse maculopapular rash, Severe reaction: with fever and hepatitis or mucus membrane involvement (SJS)</td>
<td>Always use NVP in lead in dose, Do not double NVP dose when rash present. Do not use prophylactic steroids/antihistamines</td>
<td>Mild-moderate rash: antihistamine, Severe rash: Discontinue*, and never rechallenges</td>
</tr>
<tr>
<td>CNS symptoms</td>
<td>EFV</td>
<td>Drowsiness, abnormal dreams, impaired concentration</td>
<td>Educate patient Take 2-3 hrs before sleeping. Take on empty stomach</td>
<td>Self limiting, resolve in 2-4 weeks</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>NVP, All PIs, EFV</td>
<td>Nausea, anorexia, vomiting Sometimes jaundice</td>
<td>Monitoring ALT/AST. Avoid NVP in women with CD4 &gt;250 &amp; men with CD4 &gt;400 Careful use of NVP in HBV/HCV co-infected patients</td>
<td>Symptomatic: discontinue permanently, Asymptomatic: ALT&gt;5 times continue</td>
</tr>
<tr>
<td>Hypersensitivity reaction (HSR)</td>
<td>ABC</td>
<td>Fever, rash, malaise, worsens with continuation of ABC</td>
<td></td>
<td>Discontinue and never rechallenge</td>
</tr>
</tbody>
</table>

*While discontinuing NNRTIs, the long half life has to be taken into account to avoid functional monotherapy and development of resistance. Normally the NRTI backone is continued for at least 1 week after NNRTI discontinuation, or briefly a PI based regimen may be prescribed for the patient.
i. New onset or worsening of uveitis/vitritis after the resolution of CMV retinitis
j. Fever and cytopenia after treatment for disseminated MAC
3. Exclusion of alternative explanations—e.g., Drug hypersensitivity reactions, anti-microbial resistance, non-compliance with treatment for the opportunistic infection.
4. Evidence of preceding immune restoration—e.g., a rise in blood CD4 lymphocyte count; restoration of cutaneous hypersensitivity to mycobacterial antigens (PPD);
5. Histopathological or cytological appearances of unexpectedly florid cell-mediated immune response within tissue samples.
6. Decline of plasma viral load by > 1 log (> 10 fold) from baseline value.80

### Risk factors for infectious IRIS

Identified risk factors for infectious IRIS are
1. An active or sub-clinical infection by opportunistic pathogens.
2. CD4 T-cell count below 50 / mm³ prior to initiation of ART is a major risk factor for IRIS.80
3. Being ART naïve is an important risk factor for development of IRIS.81
4. Starting ART in close proximity to the diagnosis & initiation of treatment for an OI.82

Table 13 depicts various types of IRIS seen in clinical practice

Non-infectious IRIS includes Gullian Bare Syndrome, autoimmune thyroiditis and sarcoidosis. The differential diagnosis for IRIS includes active OI, ARV drug failure, ARV drug toxicity or failure of anti-microbial

### Table 12: Long term toxicities of ARV drugs

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Offending agents</th>
<th>Clinical presentation</th>
<th>Prevention</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia, leucopenia</td>
<td>ZDV</td>
<td>Fatigue, breathlessness, palpitations</td>
<td>Avoid in anemic patients And in patients with advanced disease. Monitor Hb levels as recommended</td>
<td>Discontinue and never re-challenge Transfusions or growth factors if severe</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>d4T, ddI</td>
<td>Numbness and pain in lower limbs</td>
<td>Identify early because sometimes irreversible Avoid using d4T/ ddI entirely Avoid using with pre-existing neuropathy</td>
<td>Early switching Symptomatics like gabapentin, carbamazepine</td>
</tr>
<tr>
<td>Lactic acidemia</td>
<td>NRTIs especially d4T, ddI, ZDV</td>
<td>Nausea, vomiting, Abdominal distress, fatigue progressing to breathlessness when acidosis develops High lactate levels</td>
<td>Identify early</td>
<td>Discontinue No specific treatment for acidosis, riboflavin and thiamine can tried.</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>d4T, ddI</td>
<td>Abdominal pain, nausea and vomiting High amylase/ lipase levels</td>
<td>Avoid in patients with h/o pancreatitis</td>
<td>Discontinue Medical management of pancreatitis</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td>d4T, ddI</td>
<td>Fat loss in face, extremities, buttocks</td>
<td>Avoid d4T as far as possible Identify early because can be irreversible</td>
<td>Discontinue offending agent No specific treatment available</td>
</tr>
<tr>
<td>Lipohypertrophy</td>
<td>d4T, ZDV</td>
<td>Increase visceral fat in abdomen</td>
<td>Avoid these drugs when possible Identify early by measuring fasting lipids as recommended in follow up</td>
<td>Life modification Lipid lowering agents Switching to less offending agents</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>d4T, EFV</td>
<td>All PI/r Increase in total and LDL cholesterol and triglycerides</td>
<td>Avoid offending agents Monitor sugar</td>
<td>Change offending agent Lifestyle modification Drugs: OHAs Insulin</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>d4T, PIs</td>
<td>Polyuria, polydipsia, polyphagia Increased fasting glucose</td>
<td>Avoid offending agents Monitor sugar</td>
<td>Change offending agent Lifestyle modification Drugs: OHAs</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>IDV, TDF</td>
<td>Increased serum creatinine, hydronephrosis (IDV) Hypoposphatemia (TDF) Fanconi syndrome</td>
<td>Hydration, Avoid other nephrotoxic drugs Monitor s. creatinine, urinalysis, s. potassium an phosphorus closely</td>
<td>Discontinue Usually reverses Supportive care and maintain electrolytes</td>
</tr>
</tbody>
</table>

Note: Discontinuing the offending agent would also mean substituting with an alternative drug to ensure efficacy of the regimen.

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therapy if patient is already on the same. Culturing the microorganism in body fluids may provide a clue for an active OI, which would warrant anti-microbial therapy.

Treatment of IRIS

There are no standard guidelines for treatment of IRIS. There is very limited information on the effectiveness of various interventions to manage IRIS, with lack of evidence from randomized clinical trials. Most cases will resolve without any additional treatment. Milder forms of IRIS resolve with continuing anti-infective therapy and ART.

Non-steroidal anti-inflammatory drugs (NSAIDS) may be helpful in controlling inflammation and fever associated with IRIS. However, in severe IRIS a course of oral prednisolone is required to alleviate symptoms. The dose and duration required is very variable and should be judged clinically. Severe disease will require at least 1–2 mg/kg of prednisolone. Thalidomide has also been tried effectively in some patients.

In the majority of cases, ART can be safely continued without need for interruption. Discontinuation of ART should be considered if inflammatory responses are considered life-threatening (e.g. intracranial IRIS leading to encephalitis, cerebritis, perilesional cerebral edema, pulmonary IRIS with ARDS etc), unresponsive to steroids, or if the involved pathogens are not amenable to specific antimicrobials (e.g. parvovirus B19, polyomavirus JC causing PML) or if ART toxicity is the main differential diagnosis (e.g. hepatitis).

### SPECIAL SITUATIONS

#### HIV AND TB

Tuberculosis (TB) is one of the commonest OI and is a leading cause of death amongst HIV infected patient in developing countries. Management of HIV and TB co-infection is complicated because of drug-drug interactions, overlapping toxicities, additional pill burden and development of IRIS.

#### Treatment of Tuberculosis

All HIV/TB patients should be treated with standard 4 drug anti-TB combinations as per TB treatment guidelines. Once weekly and twice weekly intermittent therapy should be avoided; especially in patients with advanced HIV infections. The rifampicin based regimen should be administrated daily (5-6 times a week) for at least the first 2 months of treatment amongst patients with advanced disease. Duration of anti-TB treatment in HIV is not well defined, but drug susceptible TB not involving the CNS should be treated with a 6 month regimen. In patients with slow response (cultures

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Table 13 : Types of IRIS

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Manifestation</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTB</td>
<td><strong>Clinical</strong>: High fever, lymphadenopathy, cough, dyspnoea, appearance of new effusion (commonly pleural and pericardial effusion occasionally), hepatosplenomegaly, ascites, oedema, epididymo-orchitis, abscess, inflammatory bowel perforation, psoas abscess etc.</td>
<td>Common during first 8 weeks. Caseating, granuloma, reactive changes; AFB smear &amp; culture usually negative; often associated with CD4 rise and PPD conversion.</td>
</tr>
<tr>
<td>MAC</td>
<td>Lymphadenitis, abscess (skin, endobronchial, abdomen) lung infiltrate, CNS.</td>
<td>Common during first 12 weeks. Localized; focal granulomatous lymphadenitis. Blood culture often negative; MAC may be isolated from lymph node culture.</td>
</tr>
<tr>
<td>M.Leprae</td>
<td>Cutaneous lesions</td>
<td>Variable occurrence from 1 week to 8 months. CSF pleocytosis, raised protein, India Ink &amp; culture --ve but Ag. +ve in low titer.</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>Meningitis, palsy, lymphadenitis, abscess, cavitary pneumonia.</td>
<td>Severe hypoxia, ARDS. Biopsy often characteristic of viral hepatitis; variable response of Hepatitis B &amp; C virologic markers.</td>
</tr>
<tr>
<td>Pneumocystis</td>
<td>Pneumonitis</td>
<td>Few lesions; usually late. Inactive CMV retinitis in affected eye in case of IRU.</td>
</tr>
<tr>
<td>Hep B/Hep C</td>
<td>Hepatitis</td>
<td>Contrast enhancing inflammatory lesion on MRI. On biopsy perivascular inflammatory cellular infiltration.</td>
</tr>
<tr>
<td>VZV</td>
<td>Herpes zoster</td>
<td>Large numbers, increase in size of existing lesions. Large numbers, increase in size of existing lesions.</td>
</tr>
<tr>
<td>CMV</td>
<td>Retinitis, Vitritis, iraeemia macular edema, Immune Recovery, Uveitis, CNS, Pancreas, Lung, Colon, Skin</td>
<td>Focal. Inflammatory lesions in skin.</td>
</tr>
<tr>
<td>JCV</td>
<td>PML</td>
<td>Focal. Inflammatory lesions in skin.</td>
</tr>
<tr>
<td>HIV</td>
<td>Demyelinating leucoencephalopathy</td>
<td>Focal. Inflammatory lesions in skin.</td>
</tr>
<tr>
<td>HPV</td>
<td>Inflamed warts molluscum</td>
<td>Focal. Inflammatory lesions in skin.</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Encephalitis</td>
<td>Focal. Inflammatory lesions in skin.</td>
</tr>
</tbody>
</table>
positive at 2 months) or when PZA is not used during the initial phase or cavitary TB with high bacillary loads treatment should be prolonged for a total of 9 months. Tuberculosis involving the CNS should be treated for 1 year.

Two important questions need to be answered while managing concomitant HIV and TB infections

When should ART be started?

Using ART in patients with tuberculosis and advanced HIV disease has been shown to reduce mortality and the risk of development of other OI’s. CD4 cell count is important in deciding when to start ART in HIV/TB co-infected patients.

1. HIV/TB with CD4 cells > 350/mm³: ART is delayed till the completion of TB treatment. The indications for ART initiation are the same as mentioned above.

2. Patients with CD4 cells ≤ 350/mm³: Delaying ART can result in HIV-related morbidity and even mortality due to risk of occurrence of other OI’s. In such situations ART should be initiated as soon as anti-TB medicines are tolerated and patient has shown clinical improvement (usually 2-4 weeks of initiation of ATT). One should closely monitor for the development of IRIS in patients initiating ART with baseline CD4<50/mm³.

Which combination antiretroviral regimen should be used?

There are limited options available for antiretroviral treatment in HIV/TB co-infected patients. Rifampicin, a critical component of antituberculous therapy interacts with PI’s and NNRTIs and reduces exposure of PI’s by 75-95% and NNRTIs nevirapine by 20-55% & efavirenz up to 20%. Sub-optimal exposure to these ARVs may lead to development of drug resistance.

Unfortunatley, of all available PI’s and NNRTIs, rifampicin can be concomitantly used only with full dose ritonavir or with efavirenz. Though some experts recommend increasing the dose of EFV to 800 mg when using with rifampicin, studies in developing countries have documented comparable antiretroviral effectiveness with a dose of 600 mg.

Ritonavir boosted saquinavir should not be used with rifampicin due to significant elevation (up to 20 x upper limit of normal) of serum transaminases in a Phase I study evaluating the pharmacokinetic interaction of this drug combination in healthy volunteers.

Therapeutic strategies for concomitant use of ART and ATT include:

1. Using Efavirenz + 2NRTIs: Efavirenz based ART when used at standard dosages in HIV/TB patient-receiving rifampicin has demonstrated good clinical, immunological and virological outcomes. Although EFV is more expensive than NVP, it should be used at least until the duration of TB therapy. After the completion of ATT, EFV may be substituted back to NVP in order to make the regimen less expensive. However, before the substitution it is necessary to document good virologic control of the EFV based regimen (PVL<400 copies/ml). The hepatic induction effect continues for up to 2 weeks after discontinuation of rifampicin. The substitution of EFV with NVP should be made after 2 weeks of rifampicin discontinuation. A lead in dose is not necessary when NVP is substituted for EFV in this situation. An additional concern is the risk of severe hepatitis in patients who are switched from EFV to NVP at higher CD4 counts, close monitoring is warranted.

2. Rifabutin has less pronounced interaction with PI’s, and it is currently available in India. If rifabutin is used, the dose should be reduced with PI’s to avoid ocular and other toxicities. With PI/r recommended dose of rifabutin is 150 mg every alternate day or thrice weekly.

3. Though nevirapine concentrations are affected by rifampicin, several cohort studies have demonstrated high rates of virologic suppression when both these drugs were concomitantly used. Nevirapine can be used as an alternative if there is absolute contraindication for use of efavirenz or the patient cannot afford rifabutin. Careful monitoring for hepato-toxicity is recommended in these situations.

4. When TB develops in patients already receiving ART, the regimen should be modified to EFV based to make it compatible with TB treatment. Following the completion of antituberculous therapy the EFV based regimen can be continued or changed in accordance with the clinical and immunological status of the patient. Anti TB treatment without rifampicin in HIV/TB co-infected patients is discouraged due to a significantly lower cure rate and higher incidence of TB relapses.

Treatment Of HIV And HBV/HCV Coinfected Patients

Liver related morbidity and mortality is very common amongst patients on ART. The commonest cause of liver related deaths is co-infection with hepatitis viruses (HBV, HCV). These deaths have been documented in patients even when they are on effective ART (virologically suppressed and having higher CD4 counts). Hence it is critical to diagnose these co-infections and manage them efficiently to improve clinical outcomes in patients on ART.

HBV co-infection

All HIV infected patients should be screened for HbsAg and if possible anti-HBc antibodies at baseline.
History of Hepatitis B vaccination should also be elicited. HBV co-infected patient should have additional baseline workup, which includes LFTs, PT, Serum proteins, HBeAg and HBV-DNA (results should be expressed in international units/ml). Consider liver biopsy (if no contra-indications) to measure the stage of fibrosis and of necroinflammatory activity and to exclude other causes of chronic liver disease. It is necessary to exclude co-infection with Hepatitis C. Patients should be advised abstinence from alcohol.

**Anti-HBV therapy in HIV/HBV co-infected patient**

The ideal goal of treatment for HBV is to achieve HbsAg clearance with anti-HBs seroconversion. However, this can be achieved only in minority of patients (less than 10% of HBV mono-infected patients receiving interferon treatment, and likely to be even less among HIV/HBV co-infected patients). A more realistic goal is to maximally suppress HBV DNA thus delaying progression of liver disease.

The optimal time for initiating anti-HBV therapy in co-infected patients has not been established but HBV-specific treatment should be considered for all patients who are HBeAg positive, or are HBeAg negative but with an abnormal LFT (ALT > 1.5x Upper Limit of Normal) and high HBV-DNA levels (HBV DNA >20,000 IU/ml for HBeAg positive and >2000 IU/ml for HBeAg negative patients). A histological evidence of active and/or advanced disease (Metavir ≥ A2 and/or ≥ F2) in patients with high HBV DNA levels is a strong indication for treatment. When initiation of ART is not indicated and HBV disease is mild and not (or slowly) progressing, the best current strategy may be to monitor the patients without treatment intervention.

Some anti-HBV drugs have anti HIV activity too (lamivudine/emtricitabine, tenofovir/adefovir and entecavir). Hence using them in sub-optimal combinations (e.g. mono or dual therapy) can result in development of drug resistant HIV. Treatment for HBV in co-infected patients depends on whether ART is indicated or not.

**ART and HBV treatment not indicated:** For this situation patients should be closely monitor for HIV and HBV diseases progression.

**ART indicated but HBV treatment not indicated:** A backbone of TDF + 3TC/FTC is preferred. Efavirenz is the NNRTI of choice to be combined with this backbone. Though NVP is not an absolute contraindication it should be avoided in patients with high ALT levels.

**ART not indicated but HBV treatment indicated:** Earlier initiation of ART may be warranted in these patients (CD4<500/mm³). When ART is initiated a backbone of TDF+3TC/FTC is recommended.

When CD4 is >500/mm³ and only HBV treatment is indicated avoid using drugs with anti-HIV activity (TDF or adefovir, FTC, and 3TC). Treatment with pegylated interferon is recommended in this situation. Response with pegylated interferon alpha 2a is good for HBV genotype A compared to HBV genotype D (common Indian HBV genotype). This should be given for 48 weeks, independent of HbeAg/anti Hbe status. When using standard interferon, HbeAg-positive patients should be treated with 5-6 MU/day or 10MU three times weekly for 4-6 months. HbeAg-negative patient should receive 3-6 MU three times weekly for at least 12 months [98]. Adefovir (10mg PO OD) is an alternative for HbeAg –ve patients. Early results suggest that adefovir does not select for resistance to HIV and therefore compromise future use of tenofovir. Entecavir (0.5mg PO OD for 3TC naive patients) is also effective for the treatment of chronic hepatitis B. However recent studies demonstrated the emergence of M184V (mutations leading to 3TC/FTC resistance however this was not selected for in patients on adefovir). Tenofovir (100mg PO OD) is an alternative for HbeAg –ve patients. Early results suggest that adefovir does not select for resistance to HIV and therefore compromise future use of tenofovir.

**HCV co-infection**

Hepatitis C Virus co-infected patient should have additional baseline workup, which includes LFTs, PT, Serum proteins, HCV-RNA and HCV genotype. Liver biopsy in co-infected patient is optional to assess disease severity and exclude other causes of chronic liver disease. At baseline exclude co-infection with Hepatitis B and vaccinate for Hepatitis B and Hepatitis A if patient is non immune. Patients should be advised abstinence from alcohol.

Hepatitis C co-infection increases the risk of developing hepato-toxicity with antiretroviral treatment. Physicians must be alert to this possibility. Physicians should carefully monitor liver enzymes for hepato-toxicity while patients are started on nevirapine based antiretroviral treatment, or use alternatives to nevirapine.

**Anti-HCV therapy in HIV/HCV co-infection**

HIV/HCV co-infected patients often require anti-HCV treatment due to accelerated progression of liver inflammation and fibrosis as compared to mono-HCV infected patients. Initiating anti-HCV therapy should be related to the status of both HCV and HIV infection in the individual patient. Chronic HCV should
be treated first if the patient does not qualify for anti-HIV treatment (the cut off for initiating ART is CD4 <500/mm³), whereas HIV disease should be treated prior to hepatitis C if patients qualify for HIV treatment and HCV therapy should be considered after CD4 cell counts increase to more than 350/mm³. Pre-treatment of HCV in co-infected individuals reduces the risk of liver toxicity associated with concurrent HIV therapy.

The primary goal of anti-HCV treatment is to achieve sustained virological response (SVR) defined as undetectable HCV RNA 24 weeks after the end of therapy-evaluated using sensitive molecular tests.77 Pegylated interferon (PEG INF) + ribavirin is the current regimen of choice for HCV in monoinfected and HIV/HCV co-infected patients.108-110 Dosage of PEG-INF alpha 2a is 180µ subcutaneous per week or PEG-INF alpha 2b 1.5µg/kg per week along with ribavirin 800 – 1000 mg/day. Regardless of genotype, duration of anti HCV therapy should be 48 weeks.111,112 There are some reports suggesting higher relapse rates in HIV/HCV co-infection compared to mono-infected patients.

AZT and ddI should be avoided in patients receiving ribavirin due to additional risk of marrow toxicity and steato-hepatitis/ lactic acidosis respectively and increased risk of decompensated liver disease with ddI.108

**HIV AND PREGNANCY**

Pregnancy is a special situation because it provides a unique opportunity for prevention of vertical transmission of HIV using various interventions. The risk of transmission of HIV from an infected mother is 14-32% if not breast-fed and is 25-48% if breast-fed.113 More than two-thirds of this transmission occurs during labor when the baby is exposed to maternal genital secretions. A significant proportion of transmission of HIV also occurs through breast-feeding.

**Antiretroviral therapy in pregnant women**

The goals of management of HIV in pregnancy are dual: managing the mother’s HIV status and prevention of mother to child transmission (MTCT) of HIV. The indications to start first line ART and the assessments required to initiate ART and basics of drug selection are similar to that in non-pregnant patients. However, in selection of a drug regimen the following points should be remembered:

1. Zidovudine should be included as one of the components of the regimen unless there are absolute contraindications for using the same.
2. Efavirenz should be not be used at least in the first trimester because of possible teratogenic effects.
3. Combination of d4T + ddI should be avoided during pregnancy as it is associated with development of potentially fatal severe lactic acidosis.
4. Do not use NVP as part of ART regimen if mother’s CD4 count >250/mm³ due to risk of fatal hepatotoxicity.
5. There is some controversy relating to use of TDF in pregnancy as it has been associated with bone abnormalities in rhesus monkeys.114 It should be used cautiously in pregnancy unless there are no other available options.

A HIV infected pregnant women with CD4 counts <250/mm³ should be offered an NVP-based three drug regimen; which should be continued even after delivery. However, in circumstances such as tuberculosis during pregnancy, efavirenz-based regimen may be initiated after 14 weeks of gestation.

In women who are already on antiretroviral therapy and become pregnant, benefits and risks of ART in the first trimester has to be discussed. The benefits of continuation of ART are prevention of emergence of drug resistance and reduction in risk of MTCT. The risk in continuation is the potential risk of ARV fetal toxicity, particularly during the first trimester of pregnancy.

**Interventions for reducing MTCT**

Interventions known to reduce risk of MTCT include: antiretroviral therapy for mother and baby, elective Caesarian section (ECS) and avoidance of breast feeding, exclusive breast-feeding or ARV prophylaxis to the baby during breast feeding.

Antiretroviral drugs reduce viral load in the mother, an important determinant in the risk of transmission of HIV to the baby. The risk of fetal toxicity has to be considered in using ARV drugs during pregnancy. Most ARV drugs are categorized as US FDA category B or C, but efavirenz is category D and is contraindicated in first trimester of pregnancy.

Various regimens have been studied for reducing risk of MTCT. Most of the studies have shown reasonable success using one or more ARV drugs (in women who do not need ART for their own HIV status) around delivery in reducing rates of MTCT.

A single dose of NVP at the onset of labor and within 72 hours of birth for the baby has been shown to reduce the risk of HIV transmission to the baby.115 However, there is evidence to suggest that resistance to single dose NVP is frequent and this can compromise the mother’s NVP based regimen in the future, especially if initiated within 6 months of the receipt of single dose NVP.116 Hence, single dose NVP should not be used for MTCT purposes. Even in the situation where the mother presents in labor a combination of ZDV+3TC should be added to single dose NVP and continued for 7 days after delivery to reduce risk of development of NVP resistance.

In mothers with CD4 counts>250/mm³ a combination of standard 3 drug ART is recommended for reducing risk of MTCT. The option termed as START (Short-term antiretroviral therapy) intends to treat mothers with
standard three drugs ART throughout the duration of pregnancy (except first trimester) and discontinuing shortly after delivery, if the pre-therapy CD4 counts were >350/mm³.³ The advantage of this approach is achieving maximal suppression of HIV and prevention of ARV resistance development, which would not compromise mother’s future therapeutic options. Such three drug combinations are known to reduce the risk of transmission up to 1.2%. It is also important to remember that NNRTI-based regimens should be avoided with this strategy. The long half life of NNRTI after discontinuation can lead to development of resistance.

The choice of ARV drugs depends on ARV treatment history of the infected mother and her husband. The husband’s treatment history is important to evaluate possibility of transmitted resistant virus should his viral load not be undetectable after 6 months of his own treatment.

Since NVP cannot be used in mothers with CD4 count > 250/mm³, and experience with the use of EFV after first trimester is limited, PI based regimens is recommended for START. Though standard boosted PI’s are otherwise recommended, in pregnancy most experience relates to use of nelfinavir.¹¹⁸ Unfortunately pregnancy alters the pharmacokinetics of PI’s, often leading to sub-optimal drug levels. With unpredictable levels, high pill burden and higher incidence of diarrhoea in the short term, nelfinavir based regimen should be avoided as far as possible.¹¹⁹ Studies have also shown significantly lower lopinavir exposure in third trimester of pregnancy versus non-pregnant women using the thrice daily capsule formulation, although this does not impact virologic suppression.¹²⁰ The tablet formulation may have better absorption and probably will have less pharmacokinetic impact in pregnancy. There is emerging evidence for safe use of atazanavir/ritonavir and saquinavir/ritonavir in pregnancy.¹²¹,¹²² Evidence on the risk of prematurity in women using PI is still conflicting.¹²³ Blood glucose levels need to be monitored periodically in these women. Infants born to such mothers should receive ZDV 4 mg/kg bid for 1 or 4 weeks.

**ART prophylaxis for the newborn**

Zidovudine (4 mg/kg bid) is the ARV of choice for this indication. Duration of administration of zidovudine to the baby depends on the duration of receipt of ART by mother. It is assumed that if the mother has received ART for over four weeks preceding delivery, effective reduction in viral load that reduces the risk of transmission to baby significantly has already occurred. If the mother has received at least four weeks of ART immediately before delivery, the neonate should receive zidovudine for one week only and if she has received it for less than four weeks, the neonate should receive zidovudine for four weeks.

In women who cannot afford a standard 3-drug regimen following option may be recommended:¹²⁴ ZDV from 28 weeks of pregnancy plus single dose of NVP during labor and ZDV/3TC for 1 week post-partum (to cover for the long half life of NVP). This approach has shown to be effective.¹²⁵ However the risk of development of NVP resistance cannot be entirely ruled out. Hence if a mother has received ZDV for more than 4 weeks then NVP use can be avoided during delivery.

**Mode of delivery**

The mode of delivery also impacts MTCT rates. Elective cesarean section (ECS) is an efficacious intervention among HIV infected mothers not taking ARVs, reducing the risk of MTCT by 51%. The risk of post partum morbidity with ECS is slightly higher than vaginal delivery but lower than emergency cesarean section.¹²⁶ The risk of MTCT according to mode of delivery in mothers with low viral loads (e.g due to potent ART) is less clear, but most experts would recommend a vaginal delivery if the mothers viral load around delivery is < 1000 copies/ml.¹²⁷ If viral load determinations are not possible, then an ECS is recommended for all women. ECS should be performed before the onset of labor and rupture of membranes.

**Breast feeding**

Breast-milk is an important mode of transmission of HIV to infants. Exclusive breast-feeding is an option, where in the baby is fed only mother’s milk. A study has demonstrated that mixed feeding enhances the risk of acquisition of HIV by almost two folds as compared to exclusive breast feeding.¹²⁸ According to a meta-analysis, six months of exclusive breast feeding is associated with minimal risk of transmission of HIV through breast milk without compromising immunologic and other well-known benefits of breastfeeding to the baby. The benefits of breast-feeding are obvious and the risk of morbidity associated with top feeding may be significant.¹²⁹ This study was conducted in a public sector hospital where access to safe top feeds may be limited.

The choice of whether to breast-feed or not finally should be made by the pregnant woman after the risks and benefits of the same are clearly explained to her, during antenatal period. She must be explained about care of breasts as mastitis and cracked nipple are known to enhance the risk of transmission of HIV to the baby through breast milk. Current UNAIDS/WHO/UNICEF recommendations stress avoidance of all breast-feeding if replacement feeding fulfills the key requirements of being affordable, feasible, acceptable, sustainable, and safe. The decision of breast-feeding or not should hence be individualized according to the mother’s circumstances. Figure 2 summarizes approach for managing an HIV infected pregnant woman.
ART: When and What to Change?

Once a patient is initiated on ART there may be various reasons to change current ART. Many studies have documented that at 1 year after initiating ART 40-50% patients had actually changed their first line regimen for various reasons. Changing ART can be broadly classified into 2 groups:

Substitution
Replacing a single/dual ARV drug by other drugs in a regimen for reasons other than ARV failure is referred to as substitution. There are various indications for substitution:

- **Toxicity:** Substituting a safer ARV drug for an offending agent e.g. TDF or ABC or ZDV for d4T (peripheral neuropathy, lipoatrophy, symptomatic hyperlactataemia), TDF or ABC or d4T for ZDV (anemia, GI intolerance).
- **Simplification:** Substituting for simplifying a complex regimen either for reducing pill burden or simpler scheduling e.g. bid to qd drugs (TDF for ZDV, ATV/r for other PI/r).
- **Cost:** Substituting a single agent for reducing cost of the regimen e.g. NVP for EFV (especially after TB treatment).
- **Proactive:** Substituting TDF or ABC for thymidine analogs (ZDV, d4T) anticipating long term adverse events.
- **Pregnancy:** Substituting ZDV for other NRTI and NVP for EFV for preventing MTCT and avoiding teratogenicity.
- **Drug-drug interaction:** e.g. Patient on NVP based regimen developing TB shifted to an EFV based regimen maintaining the same nucleoside backbones.

- **Preventing resistance:** When discontinuing an NNRTI based regimen, a PI may be substituted for NNRTI to cover for the long-half life while continuing the 2 nucleoside backbones.

Before substitution of a single drug it is important to establish evidence of virologic suppression and the effectiveness of current regimen. This can be done by determining a PVL if a patient has been on a stable regimen for more than 6 months. Within 6 months of initiating ART, the physician should clinically assess regimen effectiveness from adherence history.

If there is evidence that the regimen is not effective, resistance may be expected and substitution of a single drug is not recommended.

Switching
Changing an entire regimen for ART failure is referred to as switching.

Development of resistance to ARV drugs is a common cause of ART failure. Inadequate adherence to the prescribed regimen can lead to treatment failure. Hence assessment of treatment adherence when a patient is identified with treatment failure is crucial and a repeat determination (PVL or CD4) after 4-8 weeks of intensive adherence counseling should be done before altering therapy. Finally insufficient therapeutic blood levels due to poor absorption, drug-drug interactions or sub-optimal dosing can also lead to resistance and treatment failure. Acquisition of primary drug resistant virus or exposure to sub-optimal therapy (e.g. use of single dose NVP for MTCT) can lead to treatment failure.

Antiretroviral failure can be defined in 3 ways: virological, immunological or clinical, in most instances one following the other. There is a delay between virological and immunological failure risking exposure of HIV to a failing regimen leading to development of further cross resistance and compromising the efficacy of the second line regimens. Hence, if patients can afford, PVL determinations are recommended every 6 months (or at least yearly) to identify virological failure early, esp. if a patient is on ZDV or d4T to prevent sequential accumulation of thymidine associated mutations (TAMs).

The following definitions of ART failure are used:

**Virological failure:** It is defined as PVL value of >400 copies/ml or > 50 copies/ml at/or after 6 months of ART initiation. Viral rebound after being undetectable should be considered as virological failure. Low-level transient viral rebounds (<500-1000 copies/ml), termed blips, usually indicates statistical variation in PVL determinations and is not an indication to alter therapy.

**Immunological failure:** A drop of greater than 30% in CD4 counts from peak value or a return to pre-ART baseline or lower is defined as immunological failure. Non-improvement of CD4 counts>100 cells
at 1 year after ART initiation is also considered to be immunological failure. Some patients may have a disconnect phenomena where the PVL is undetectable and the CD4 may only have limited increase or there may be a fall in CD4 counts. Limited CD4 count reconstitution with optimal virological suppression can occur when the CD4 count is very low before initiating ART, in HCV co-infected patients, in elderly patients and rarely if a patient is on a ZDV based regimen.\textsuperscript{136-138} A drop of CD4 count in the presence of virological suppression can occur with underlying malignancies (e.g. NHL), superinfection with HIV-2, or in patients on concomitant cytotoxic or interferon therapy.

Virologic and/or immunologic failure should be confirmed by repeat determinations (after 4 weeks) of PVL and CD4 counts respectively before switching the patient to second line regimen. It is also important to confirm that the laboratory and PVL/CD4 determination is reliable.

**Clinical failure:** Progression of disease with occurrence of OI’s or malignancies after 6 months or more of ART initiation is defined as clinical failure. Within 6 months, differentiating between IRIS and OI’s occurring because of inadequate immunologic (CD4) recovery is difficult.

Figure 3 summarizes an approach to identifying failure on first line ART.

**Managing failure**

Identifying the cause of failure is important before deciding to modify the ART regimen. Following points need to be assessed:

a. Adherence: A detailed assessment of adherence needs to be done. The reasons for non-adherence need to be explored. Unless these reasons are identified and addressed, a patient may also find it difficult to adhere to the second-line regimens that are more complex. For e.g. a patient failing first line regimen because of sub-optimal adherence due to non-affordability is unlikely to afford second line regimens.

b. Drug-drug interactions: Assessing whether the patient is concomitantly taking medications which interfere with ARV activity is important. Many patients may not disclose taking herbal treatments along with the prescribed ART regimen.

c. Continuing high risk behavior: If a patient continues to practice high risk behavior, superinfection with a drug resistant virus may lead to treatment failure.

Once resistance is suspected a second line ART regimen should be designed for the patient. The goal of second-line ART is to achieve maximal and durable virologic suppression (PVL <50 or <400 copies/ml at 6 months post initiation). Potent regimens are needed to achieve this goal. The principal for constructing a second line regimen is to have a combination of three active (or at least 2 fully active) drugs with one drug from a new class (usually boosted PI) and a backbone of 2 active NRTIs (with least cross resistance to those used in the first line).

NNRTIs (NVP, EFV) used in the first line regimen have a low genetic barrier to resistance (a single mutation leads to high level resistance). These mutations (K103N, V106M, Y181C, G190A) emerge rapidly and confer cross-resistance between the NNRTIs.\textsuperscript{139} When a patient fails a first line regimen of 2 NRTIs+1 NNRTI, resistance to NNRTI should be expected and the other available NNRTIs cannot be used in the second line regimen. Hence a protease inhibitor (PI) based regimen is recommended.

PI based regimes should always be boosted with ritonavir. Ritonavir is a potent inhibitor of the CYP250 3A4 enzyme in the liver and gut, the major pathway for disposition of PI’s. Concomitant use of low dose ritonavir increases Cmin and AUC concentrations of the other PI’s thus increasing drug exposure. Hence PI doses can be reduced and schedules can be altered with ritonavir co-administration. Boosted PI does also have a high genetic barrier to resistance. Use of non-boosted PI’s in constructing a second line regimen is not recommended.

Another reason a boosted PI is recommended is because some NRTI (used in the first line) cross resistance is expected. A potent boosted PI needs to be given with 2 NRTIs to address NRTI cross-resistance and make the second line regimen more robust. Four boosted PI’s are currently available in India: lopinavir/ritonavir (LPV/r), saquinavir/ritonavir (SQV/r), indinavir/ritonavir (IDV/r) and atazanavir/ritonavir (ATV/r). LPV/r has better antiretroviral effects as compared to SQV/r and IDV/r, though this difference was driven by greater discontinuations in the in SQV/r and IDV/r arms due to inconvenience and adverse events.\textsuperscript{140,141} Except ATV all the other three are associated with significant short-term GI intolerance and long term dyslipidemia and insulin resistance. However there is evidence to suggest that the low dose ritonavir used to boost PI’s

![Fig. 3: Management of first-line ART regimen failure.](image-url)
itself causes rise in total cholesterol, LDL cholesterol, total/HDL cholesterol ratio and triglycerides which is amplified further by the concomitant PI.\textsuperscript{142} IDV/r is associated with clinically insignificant indirect hyperbilirubinemia and nephrolithiasis. Finally, the genetic barrier to resistance is high with all PI/r.\textsuperscript{143} Concomitant use of rifampicin is not recommended with all the boosted PI’s. Table 14 summarizes characteristics of currently available boosted PI’s.

Which 2 NRTIs need to be used with the boosted PI depends on which NRTIs were used in first line therapy. If lamivudine was used in the first line, then the virus is expected to develop resistance, due to its low genetic barrier. M184V is the mutation associated with lamivudine resistance. Some studies have shown that this mutation renders the virus less fit.\textsuperscript{144} In spite of resistance it may have some residual antiviral activity and this may be continued in the second line regimen for this replication advantage. However this may not be significant if full virologic suppression is achieved. This mutation delays development of TAMs (see below), which may be another reason to keep it in the second line regimen if ZDV or d4T is planned to be used. Additionally M184V causes hypersusceptibility to ZDV, d4T and TDF.\textsuperscript{145} For these reasons lamivudine may be continued in the second line regimen. M184V partially compromises the activity of abacavir and didanosine; however this may be clinically insignificant.

If zidovudine or stavudine have been used, some thymidine analog mutations (TAMs- positions 41, 67, 70, 210, 215, and 219) may be expected. Greater number of TAMs or a unique pathway (41,210,215) is associated with broader NRTI cross-resistance. TAMs may increasingly accumulate if the failing regimen is continued. If all TAMs accumulate then it signifies multi-NRTI resistance. It is interesting to note that M184V delays the accumulation of TAMs.\textsuperscript{146} Hence the choice of second-line NRTIs depends on the number of TAMs accumulated. With a combination of M184V and 3 or more TAMs abacavir activity is compromised. Tenofovir retains some activity in the presence of TAMs such as D67R, K70R, T215Y/F or K219Q/E. However if the three or more TAMs includes M41L or L210W, a reduced virological response can be expected.\textsuperscript{147}

If tenofovir or abacavir based regimen has been used K65R (with TDF) and K65R, L74V, Y115F, M184V, (with ABC) may be selected if failure is identified late. K65R compromises the activity of TDF, ABC and ddI. However partial activity with these drugs can always be expected. K65R causes hypersusceptibility to thymidine analogs (IC\textsubscript{50} is less than wild type HIV).\textsuperscript{148} Additionally K65R is also associated with reduced viral replication capacity.

Genotypic resistance testing identifies these mutations and can help optimize the choice of drugs to be used in a second line regimen. The importance of performing resistance testing in designing effective second line regimens have been documented in multiple studies.\textsuperscript{149} In India access to genotypic testing is extremely limited and when available is expensive. Expert advice is also advised for interpretation of resistance testing reports. When available, results of genotypic resistance testing should be incorporated in designing second line regimens.

Three types of resistance testing have been approved for use:

1. Genotypic resistance testing identifies specific mutations associated with resistance to ARV drugs by gene sequencing or allele specific PCR.
2. Phenotypic resistance testing measures the ability of recombinant virus from patients to grow in different concentration of ARV drugs.
3. Virtual phenotype uses genotype results to predict phenotypic susceptibility.

Genotypic testing is available in India in very few centers. Methods available include commercially approved (e.g. Viroseq) or home brew assays. Limitations of genotypic resistance testing include cost and turnaround time for results. They also cannot be reliably

### Table 14 : Characteristics of boosted PIs

<table>
<thead>
<tr>
<th></th>
<th>IDV/r</th>
<th>SQV/r</th>
<th>LPV/r</th>
<th>ATV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>++</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Convenience</td>
<td>3 bid</td>
<td>3 bid</td>
<td>3 bid</td>
<td>3 qd</td>
</tr>
<tr>
<td>2 bid?</td>
<td></td>
<td>2 bid*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Toxicity</td>
<td>GI intolerance, Retinoid, Ind. Bili</td>
<td>GI intolerance</td>
<td>GI intolerance</td>
<td>Ind Bili</td>
</tr>
<tr>
<td>Long Toxicity</td>
<td>Nephrolithiasis, Metabolic</td>
<td>Metabolic</td>
<td>Metabolic</td>
<td>Less metabolic</td>
</tr>
<tr>
<td>Resistance</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>RMP concomitant</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PPI</td>
<td>Safe</td>
<td>Safe</td>
<td>Safe</td>
<td>Caution</td>
</tr>
<tr>
<td>Food</td>
<td>Nil</td>
<td>w/in 2h full meal</td>
<td>Nil</td>
<td>With food</td>
</tr>
</tbody>
</table>

* For tablet version LPV/r
performed when the PVL is less than 1000 copies/ml. Finally, minority resistant variants (<20% of total viral quasi-species) may not be detected. Physicians should prescribe a resistance test only when the patient is currently still on a failing regimen or has discontinued them for no longer than 4 weeks.

Table 15 lists the recommended second-line regimens for patients failing first line ART regimen in India. However, second line regimens have the following disadvantages:

1. They are more expensive
2. High pill burden
3. Difficult to adhere to
4. Long term complications, particularly lipid abnormalities and insulin resistance, which may correlate with increased cardiovascular risk for HIV-infected patients.

It is also important to re-emphasize that patient involvement and discussion is important before initiation of second line regimen.

In patients who cannot afford second line regimens, careful consideration should be given to continuation of the failing regimen. The NNRTI component should be discontinued because of no residual activity and progressive accumulation of more NNRTI mutations that can compromise activity of second generation NNRTIs like etravirine. Consultation with an expert may also be advised in this situation.

**Managing treatment interruptions**

Often patients on stable ART miss doses or discontinue drugs. A careful adherence history needs to be taken to find out exactly how the doses were missed. Resistance development is more likely in a patient who takes drugs intermittently than in someone who discontinues therapy all together. Resistance may also be more likely when therapy interruptions occur early after treatment initiation rather than later on, particularly after the PVL has been undetectable. The decision to reintiate the first line regimen or change to a second line regimen should be considered accordingly. If the decision to reinitiate therapy is taken, VL estimation at the end of 3-6 months is recommended to assess effectiveness of therapy. Nevirapine has to be re-initiated in a lead-in dose if the interruption has been for more than 7 days.

**Managing second line failure**

This is a complex issue and should be done in consultation with an expert. The goal of treatment of a third line regimen depends on the availability of remaining options. Usually the goal of such treatment is to keep the CD4 counts up and PVL as low as possible, since achieving undetectable levels may be unrealistic with the available drugs in India. But with use of second generation PI's and entry and integrase inhibitors it is possible to achieve undetectable PVL levels in significant number of patients. However, these drugs are currently unavailable in India and are extremely expensive.

**POST EXPOSURE PROPHYLAXIS (PEP)**

Occupational transmission of HIV in health care settings has been documented although the incidence is very low. The best way for preventing occupational transmission is to prevent exposures with potentially hazardous body fluids. It is imperative to follow universal precautions strictly, and consider all patients to be potentially infectious. Routine testing for all patients is not recommended because the risk of HIV transmission is highest during window period, when HIV antibody testing is negative.

**Transmission in health care settings**

Transmission in health care settings can occur from
1. HIV infected patients to other patients
2. From an infected patient to a health care worker (HCW)
3. From an infected HCW to a patient: This is an exceedingly rare occurrence with only a couple of cases documented worldwide. HIV infected health care workers can continue to practice; exposure prone procedures should not be performed.

**Types of occupational exposure**

Exposures, which are considered to be risky, include
1) Percutaneous injury (e.g., a needlestick or cut with

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**Table 15: Recommended second line regimens**

<table>
<thead>
<tr>
<th>First line NRTI</th>
<th>Second line NRTI**</th>
<th>Boosted PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + 3TC/FTC</td>
<td>ZDV** + 3TC</td>
<td>ATV/r</td>
</tr>
<tr>
<td></td>
<td>ZDV+TDF + 3TC/FTC</td>
<td>LPV/r</td>
</tr>
<tr>
<td></td>
<td>ZDV + ddl + 3TC</td>
<td>SQV/r</td>
</tr>
<tr>
<td></td>
<td>ZDV + ABC + 3TC</td>
<td>IDV/r</td>
</tr>
<tr>
<td>ABC + 3TC/FTC</td>
<td>ZDV + TDF + 3TC/FTC</td>
<td>ATV/r</td>
</tr>
<tr>
<td></td>
<td>ZDV + 3TC</td>
<td>LPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SQV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IDV/r</td>
</tr>
<tr>
<td>ZDV + 3TC</td>
<td>TDF + ZDV +3TC/FTC</td>
<td>ATV/r</td>
</tr>
<tr>
<td></td>
<td>ABC + ddl + 3TC</td>
<td>LPV/r</td>
</tr>
<tr>
<td></td>
<td>ZDV + ddl + 3TC</td>
<td>SQV/r</td>
</tr>
<tr>
<td></td>
<td>TDF + FTC/3TC</td>
<td>IDV/r</td>
</tr>
<tr>
<td>ddI + 3TC</td>
<td>TDF + ZDV + 3TC/FTC</td>
<td>ATV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SQV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IDV/r</td>
</tr>
</tbody>
</table>

**NNRTIs used in first line regimen should not be recycled.**

*Choice should be individualized based on resistance patterns, CAD risk factors, pill burden.

**Efficacy of second line NRTIs depends on early identification of first line regimen failure. For e.g. if failure on ZDV + 3TC is diagnosed late, more number of thymidine analog mutations (TAMs) accumulate leading to limited utility of all NRTIs.

***D4T can be used for ZDV if there is absolute contraindication.
a sharp object): The risk is approximately 0.3% (95% CI 0.2-0.5).

2) Contact of mucous membrane or non-intact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other body fluids that are potentially infectious: The risk with mucus membrane exposure is 0.09% (95% CI 0.006-0.5).

3) Direct contact to concentrated virus in research laboratory.

Which body fluids are risky?
Body fluids have been categorized according to risk of transmission as follows:151

- High risk: Blood, plasma, sexual fluids, breast milk and any blood tinged body fluids
- Intermediate risk: Pleural, peritoneal, pericardial, CSF
- Low risk: Urine, feces, saliva, sweat, tears.

Risky exposure to high and intermediate risk body fluids may warrant PEP, while there is no need for PEP after exposure to low risks body fluids.

Management after high-risk exposure
Steps after high-risk exposure include:

1. Wound management: Immediate care of local wound/contaminated mucosal surfaces is very important in post occupational exposure care. Exposed skin area should be washed with soap and water and mucosal surfaces (conjunctiva and oral mucosa) should be irrigated with clear water. Soap is an effective disinfectant. There is no evidence of benefit for application of antiseptics or disinfectants and squeezing ("milking") puncture sites. Avoiding bleach or other agents caustic to skin is also recommended.

2. Risk assessment:
   Two approaches may be recommended:
   a. Empirical treatment with ARV’s till risk assessment is done, or
   b. Thorough risk assessment and then initiate ARV’s if indicated. Evaluation of HCW should include route of exposure, materials involved, timing and other risk factors (type of needle, size of needle, depth of injury, duration of contact, nature of procedure done etc.). The source patient should be tested for HIV by a rapid test. If the source patient’s status is unknown local epidemiological and clinical evidence should be considered. Direct virus assays (e.g. PCR) are not recommended to assess source patients HIV status.

The risk factors for seroconversion include deep injury, visible blood on device, needle placement in artery or vein and a source with late stage HIV infection.

Offering PEP
The rationale behind PEP is that systemic infection does not occur immediately after a potential exposure, leaving a brief window of opportunity during which post exposure antiretroviral intervention might modify or prevent viral replication and infection.

When to offer PEP?
PEP should be initiated as quickly as possible, preferably within 1 to 2 hours post exposure and up to 36 hours. PEP may not be effective if initiated more than 72 hours after exposure. It should be administered for 28 days.

Choosing ARV regimen
The source patient’s treatment history should be taken into account. If a patient is already on ARVs and likely to carry drug resistant viruses, the PEP regimen needs to be designed accordingly. If patient is antiretroviral naïve, then regimen selection is based on balancing the potential risk of transmission and risk of adverse events to ARVs.

Recommendations for prophylaxis are given in Table 16 and 17.

Choice of drugs in PEP regimen
Any combination of standard ARVs can be used in PEP regimens at the recommended dose. Two drugs
PEP include 2 NRTIs/NtRTIs combination therapy. Three drugs PEP include 2 NRTI/NtRTI +1 boosted PI or EFV.\textsuperscript{150} Nevirapine (NVP) is contraindicated for PEP because of the risk of severe hepatotoxicity. Efavirenz and d4T+ddI should be avoided during pregnancy. Checking for any existing medical conditions and any medications that an exposed HCW may be taking, in order to prevent toxicity and drug interactions is essential.

**Follow up schedule**

All HCW with occupational exposure to HIV should receive appropriate counseling and clinical follow up regardless of whether or not they have received PEP. HIV serology should be performed at the time of injury, and repeated at 6-8 weeks; 3 months and 6 months post exposure. The routine use of direct virus assay (HIV p24 antigen or tests for HIV-RNA) to detect infection in exposed HCW is not recommended. Laboratory tests to assess adverse events can be performed on a case-by-case basis according to the toxicity profiles of the drugs included in the PEP regimen. The HCW should be advised to practice safer sex or abstinence until serology is negative at 6 months post exposure. Temporary discontinuation of breast-feeding should be considered during antiretroviral therapy. Psychological support should be offered at any time during follow up.

One practical suggestion for PEP is at least two nucleoside combinations (AZT + 3TC, 4T + 3TC and TDF/FTC) should be available at emergency room, Operation Theater and wards offering nursing care or hospital pharmacy. This medicine should be accessible to all HCWs (medical and paramedical staff). All HCWs should be trained in issues related to universal precautions, immediate local would care and informed that they may consume one tablet of two nucleosides in combination after local wound management in case of any occupational exposure. HCWs should then approach appropriate experts who can then evaluate the severity and risk related to the exposure and decide regarding further treatment.

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