API Consensus Guidelines for use of Antiretroviral Therapy in Adults (API-ART Guidelines)

Endorsed by the AIDS Society of India

SB Gupta*, SN Pujari**, SR Joshi***, AK Patel+, For expert panel of Guidelines Development Committee#

With rational use of antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection has been transformed into a chronic manageable illness like diabetes and hypertension. These guidelines provide information on state of art, evidence based approach for use of ART in Indian context.

When to initiate ART?
Antiretroviral therapy is indicated for all asymptomatic HIV infected persons regardless of CD4 counts and plasma viral load (PVL) levels. In asymptomatic patients, ART should be offered when the CD4 counts < 200/mm³ and should be considered in patients with CD4 counts between 200-250/mm³. Therapy is not recommended for patients with CD4 count more than 350/mm³. Involvement of 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 for antiretroviral naive patients. The choice between nevirapine and efavirenz is based on differences in adverse events profiles; cost and availability of convenient fixed dose combinations and need for concomitant use of rifampicin. A backbone of 2-nucleoside reverse transcriptase inhibitors (NRTIs) is combined with the NNRTI. 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 at 6 months after initiation of first-line ART is strongly recommended. Yearly estimation of lipid profile has been recommended.

How to identify and manage ART failure?
The guidelines recognize the issue of identifying ART failure late if only CD4 counts are used for monitoring. 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.

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 < 200/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 used with rifampicin. In pregnancy use of single dose nevirapine for reducing risk of mother to child transmission of HIV is not recommended, because of the risk of development of resistance. For post-exposure prophylaxis taking 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 advanced human immunodeficiency virus (HIV) disease in both the developed and developing world.1-5 Generic manufacturers of antiretrovirals (ARVs) have made ART more affordable and accessible. In order to provide optimal quality care, physicians need to have knowledge about 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-one antiretrovirals approved by US FDA, currently fourteen are available in India (Zidovudine (ZDV), Stavudine (d4T), Lamivudine (3TC), Didanosine (ddI), Zalcitabine (ddC), Abacavir (ABC), Tenofovir (TDF), (Nucleotide RTI), Nevirapine (NVP), Efavirenz (EFV), Nelfinavir (NFV), Lopinavir (LPV/r), Saquinavir (SQV), Indinavir (IDV), Ritonavir (RTV)). Rational use of ART is critical for prevention of drug resistant HIV epidemic in India in future. The objectives of these guidelines are:
WHEN TO INITIATE ART?

With currently available therapeutic options, eradication of HIV cannot be achieved. However, with the advent of potent antiretroviral therapy, 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. transmission of HIV from infected mother-to-child (MTCT), after occupational post-exposure prophylaxis (PEP) and non-occupational exposures. Theoretically a reduction in viral load is likely to lead to reduction in the risk of sexual transmission of HIV.

Since use of ART is lifelong, 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 adverse events, commitment to high levels of adherence, development of resistance to ARVs and affordability and patient's readiness for therapy. An algorithm summarizing when to initiate ART is illustrated in Fig. 1.

Antiretroviral treatment is indicated for all patients who are symptomatic with an AIDS-defining illness, irrespective of CD4 counts or viral load levels. Patients with AIDS have higher rates of mortality unless treated with ART. In addition patients with non-AIDS defining illness like recurrent oral candidiasis, oral hairy leukoplakia may have a risk of rapid progression, and therapy is indicated in these patients if CD4 count is <350/mm³.

There is a limited HIV natural history data 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 those with CD4 counts > 350/mm³.

Between CD4 250-350 mm³, therapy is considered for patients with one or more of the following criteria:
1. A rapidly declining CD4 count- more than 100 cells/year. CD4 counts should be monitored every 3-6 months to identify this.

When to initiate ART?

- 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
- To balance science with feasibility to provide quality care to HIV infected persons

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 specialty necessitating periodic updating. Most issues relating to use of ART in the Indian context will be addressed by the guidelines updated every three months on the Web. The Web Version is available on www.japi.org These guidelines will be reviewed on an annual basis.

Art is effective even in patients with advanced immunosuppression (CD4<50/mm³), and should be offered. However, the risk for development of IRIS is higher at this stage and should be closely monitored for.

Therapy may not be offered to asymptomatic patients with CD4 counts >350/mm³. The risk of progression to AIDS in these patients is very low. Initiating ART at this stage would mean longer exposure to the drugs resulting in increased costs, potential for development of short and long term adverse events and development of drug resistance in cases of sub-optimal adherence. For example the risk of developing fatal hepatitis due to nevirapine is higher at this stage.

Initiation of ART in asymptomatic patients whose CD4 count ranges between 200-350/mm³ is debatable. 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. Treatment can be considered in patients with CD4 count <250/mm³, especially if this value is confirmed with a repeat estimation 2-4 weeks apart. This is based on the rationale that this cut off is close to the 200/mm³ range and would also be the upper bound of the 30% physiologic variation in the CD4 counts.
success. The following points should be discussed with the patient prior to ART initiation is crucial for long-term success. 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.
4. Awareness of short and long term adverse events.
5. Awareness of drug-drug interactions.

It is also recommended that patient be provided some time to think. Therapy should never be initiated on the first visit and patients should be encouraged to involve at least one family member in making the decision.

**Baseline Evaluation**

A standard clinical and laboratory evaluation is recommended prior to initiation of ART. It is intended to establish the baseline status for future comparison, individualizing ART according to patient’s clinical status and preferences, and ruling out active OIs.

**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 ART regimen), sexual partners ARV use, ARV use during pregnancy and use of any alternative (e.g. herbal) preparations.

**Physical examination**

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

1. Body weight, height, Body Mass Index
2. Temperature/Lymph-node
3. Dermatological/Oral cavity: oral candidiasis, oral hairy leukoplakia
4. Genital/Pelvic (women)
5. Systemic examination
6. Fundus examination

**Laboratory evaluation**

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

**Essential**

1. Confirm HIV infection: A pre-requisite prior to ART initiation, it also is needed 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 OIs
3. CD4 counts: Estimated by flow-cytometry. Alternative low cost technologies are becoming available, however further evidence is needed to recommend its routine use in clinical practice.
4. CBC: Baseline Hemoglobin and WBC counts are needed to monitor hematological toxicity on Zidovudine (ZDV).
5. LFTs: Necessary to find evidence of hepatitis, particularly when NVP use is contemplated.
6. Urine routine: To evaluate proteinuria and sugar (necessitate estimation of blood glucose)
7. Creatinine: Dose of some nucleoside reverse transcriptase inhibitors (NRTIs) has to be adjusted according to creatinine clearance.
8. HBsAg: To rule out concomitant hepatitis B infection, this can influence choice of ARV regimen. Additionally, abrupt stopping of anti-HBV drugs like lamivudine and tenofovir is not recommended in patients with chronic hepatitis B co-infection since it may result in hepatitis B flare.
9. Chest X-ray: To rule out TB or other pulmonary infection
10. VDRL/TPHA
11. Pap smear: Helps in earlier diagnosis of cervical intraepithelial neoplasia (CIN)

**Cautions With Interpretation Of CD4 Counts And PVL**

- Standard methods
  - CD4 counts: Flow cytometry
  - PVL: Amplicor 1.5 , Branched DNA assay
- The laboratory should have quality assurance program
- Inter-current illnesses 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.
- Physiologic variations
  - 30% changes especially at higher CD4 counts
  - Diurnal variations: A practice to draw blood
for CD4 counts around same time during follow up 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.25
□ PVL: plasma separated within half an hour of specimen withdrawal
◆ PVL: Currently validated for HIV-1, not for HIV-2

**What To Start?**

Currently, antiretroviral agents of four classes are approved by US FDA for use in HIV infected patients (Table 1). These four classes include the nucleoside and nucleotide reverse transcriptase inhibitors (NRTI/NtRTI), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (Pis), and entry inhibitors.

The terminology “highly active antiretroviral therapy” (HAART) refers to use of combinations of three antiretroviral agents for treatment of HIV infection. 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 (1 PI + 2 NRTI), and triple NRTI-based regimens. Most experience in India is with NNRTI based regimens.

### Table 1 : Antiretrovirals approved for use

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Entry inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (ZDV)</td>
<td>Nevirapine (NVP)</td>
<td>Saquinavir (SQV)</td>
<td>Enfuvirtide* (T-20)</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Efavirenz (EFV)</td>
<td>Indinavir (IDV)</td>
<td></td>
</tr>
<tr>
<td>Lamivudine (d3T)</td>
<td>Delavirdine* (DLV)</td>
<td>Ritonavir (RTV)</td>
<td></td>
</tr>
<tr>
<td>Didanosine (dDI)</td>
<td>Nelfinavir (NFV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zalcitabine* (ddC)</td>
<td>Lopinavir (LPV/r)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Atazanavir* (ATV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine * (FTC)</td>
<td>Amprenavir* (APV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>Fos-amprenavir* (FPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Nucleotide RTI)</td>
<td>Tipranavir (TPV)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Drugs not available in India

### Initial Regimen for ART-naïve HIV-1 Infected Patients in India

Regimen selection should be individualized, taking into consideration a number of factors including: co-morbidity 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; gender; and pregnancy potential.

An NNRTI based regimen is recommended as first line therapy for most ART-naïve HIV infected patients. Recommended regimen for initial therapy in treatment naïve patients are depicted in Table 2.

NNRTI-based regimens are potent and have shown comparable efficacy to unboosted PI based regimens and are superior to 3 NRTI based regimens.21,22 NNRTI-based regimens have the advantage of lower pill burden and are cheaper compared to most of the PI-based regimens. Use of NNRTI-based regimens as initial therapy can preserve the Pis for later use, reduce or delay patient exposure to some of the adverse events more commonly associated with Pis.

The major disadvantage of currently available NNRTIs is their low genetic barrier for development of resistance. These agents only require a single mutation to confer resistance (mutations at codons 103, 181, 106, see section on treatment failure), and cross-resistance often develops across the entire class.21 As a result, patients who fail this initial regimen may lose the utility of other NNRTIs and/or may transmit NNRTI-resistant virus to others.

The major short-term adverse event associated with efavirenz is CNS disturbances. Usually these are self-limiting and wane off within two to four weeks and do not warrant discontinuation of efavirenz.21 Patient should be forewarned about these before initiating treatment. 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, as it is associated with neural tube defects in the baby.

Nevirapine may be used as an alternative to efavirenz for the initial NNRTI-based regimen in adult females with pre-treatment CD4+ T cell counts <250 cells/mm³ or adult males with pre-treatment CD4+ T cell counts <400 cells/mm³.21 Symptomatic, sometimes serious or life-threatening hepatic events were observed with higher frequency in women with pre-treatment CD4+ T cell counts >250/mm³ and men with pre-treatment CD4+ T cell counts >400/mm³.21 Nevirapine should be used with caution in patients already having background liver disease like hepatitis B and C co-infected patients. When starting nevirapine, a 14-day lead-in period at a dose of 200mg once daily should be prescribed before increasing to the maintenance dose of 200mg twice daily.

Efavirenz is the only NNRTI, which can be concomitantly used with rifampicin. An efavirenz-based regimen is recommended in HIV infected 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 between nevirapine and efavirenz based first line regimens, although there were differences in safety profile.21 Hence the choice between using NVP and EFV is based on toxicity concerns.22

**Patients Intolerant to NNRTI**

Patients who develop severe adverse events to nevirapine and Efavirenz should be treated with ritonavir boosted protease inhibitors (IDV/r, SQV/r, LPV/r) combined with 2NRTIs. Nelfinavir as a sole PI along with 2NRTI may be used in case of lack of storage facility for ritonavir or if patients can’t afford a ritonavir boosted PI or while providing treatment during...
Six nucleoside/nucleotide HIV-1 reverse transcriptase inhibitors (NRTI’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 and delays development of thymidine-associated mutations (TAMs) which are responsible for ZDV and d4T resistance.48

The choice of another NRTI to be combined with lamivudine depends on cost, adverse event profiles and availability of fixed dose combinations, which potentially improves adherence. Another important issue would be the sequencing potential and availability of other NRTI’s to be used in future regimens. Randomized controlled trials have shown no difference in the potency between zidovudine + lamivudine and stavudine + lamivudine along with a PI.49,50 However, stavudine is significantly associated with long-term adverse events and is recommended only as an alternative in patients who cannot be initiated on ZDV (due to anaemia) and cannot afford tenofovir. A combination of Zidovudine + lamivudine is recommended NRTI backbone for majority of the patients.

Another strategy may be to start with stavudine + lamivudine backbone (in patients who are anaemic) 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.

Tenofovir is an NRTI with once daily convenience and a good tolerability. When combined with lamivudine it has shown comparable efficacy with other NRTI backbones.41 However, there is very limited data on the use of tenofovir in the developing world. 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.51,52 When NVP based regimens are contemplated, consideration should be given to using fixed dose combinations (FDCs) of ZDV+ 3TC + NVP and d4T + 3TC +NVP which improves adherence due to low pill burden. It also reduces prescription errors and in a large observational cohort from India has shown effectiveness and tolerability.53

Though boosted protease inhibitors based regimens are extremely potent as first line therapy, they are only recommended in patients who can’t tolerate both NVP and EFV. Boosted PI based regimens are costly, complex, with high pill burden, associated with long term adverse events like dyslipidemia and diabetes. The advantage for boosted PI based regimens is their high genetic barrier to resistance and patients failing these regimens usually do not have PI resistant mutations.

**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. Monotherapy and dual nucleoside therapy: These regimens are not recommended because they have not demonstrated potent and sustained antiviral activity.45
2. Tenofovir + d4t + NNRTI is not recommended as an initial regimen due to reports of early virological and immunological failure.46
3. 3-NRTI regimen of abacavir + tenofovir + lamivudine and didanosine + tenofovir + lamivudine should be avoided due to high rates of virological failure.47 These combinations should not be used as a 3-NRTI regimen in any patient.
4. 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. In general, 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.48
5. Stavudine + zidovudine: Combination regimens containing these two NRTIs should be avoided due to the demonstration of antagonism in vitro and in vivo
6. Unboosted PIs should be avoided if possible due to poor bioavailability and higher pill burden.
7. Do not alter dosages or schedules of ARV drugs.
8. Efavirenz should be avoided in pregnancy or in women who plan pregnancy
9. Nevirapine should be avoided in women with CD4 count>250/mm^3 and in men with CD4 count>400/mm^3.

**Antiretroviral strategies, which are not recommended**

1. Induction-maintenance: Initiation of three drug ART and then reducing it to a combination of two ARV drugs is not recommended
2. Sequential adding 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 adverse events

**FOLLOW UP AFTER INITIATING ART**

Table 3 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. Once a patient is on an effective and stable regimen at 6

---

**Table 3: Recommended follow up scheme after initiation of ART**

<table>
<thead>
<tr>
<th></th>
<th>2 wks</th>
<th>1 mo</th>
<th>2 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>Every 3 mo</th>
<th>Every 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical and Adherence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CD4 counts</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PVL</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ALT</td>
<td>Yes (NVP)</td>
<td>Yes (NVP)</td>
<td>No</td>
<td>No</td>
<td>Yes (&lt;LLD*)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CBC</td>
<td>Yes (ZDV)</td>
<td>Yes (ZDV)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (d4T, CAD risk EFV, PI)</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* lower limit of detection

© JAPI • VOL. 54 • JANUARY 2006 www.japi.org 61
months, quarterly follow up is recommended.

Estimation of CD4 count is recommended at 6 months to document immunological improvement on ART and every six months thereafter. A caveat in following up with CD4 counts only 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. The lower limit of detection of PVL can be 400 copies/ml or 50 copies/ml.

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 may not be always known, and history of ARV treatment taken by sexual partners may not be known. In either instance prior 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 herbas (many patients taking herbas may not disclose that they take them)

If a patient can afford to do PVL, then it may be recommended every 6 months since it can identify failure earlier and reduce accumulation of resistant mutations.

After initiation of a NVP based regimen ALT measurement is recommended in the first month to detect drug-induced 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 d4T, EFV or PIs. In these patients and in patients with significant risk factors for coronary artery disease a fasting lipid profile should be done at 6 months, otherwise yearly estimations suffice.

**Discontinuation of OI prophylaxis on ART**

With ART induced immune reconstitution, the incidence of most OIs have reduced dramatically. It is possible to discontinue primary and secondary prophylaxis for most OIs when CD4 counts improve and sustain for at least 3-6 months. Table 4 summarizes indications for starting and discontinuation of OI prophylaxis.

**Adherence To ART**

One of the most important determinants of successful 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.

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:

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

During the era of unboosted PIs an adherence rate of more than 95% was recommended for successful ART outcome. However, with use of more potent drugs (e.g. boosted PIs) in regimens, this cut off of 90% may be slightly reduced. Additionally, the longer half-life of NNRTIs may actually prevent development of resistance because of continued exposure to the drug even after missing the dose. 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.

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. 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 accepts missing doses then the reasons for doing the same should be explored and tried to address. Indirect markers of good adherence are keeping appointments and getting prescription refills. Another marker of adherence on a thymidine-based regimen (ZDV or d4T) is evidence of macrocytosis on a hemogram, 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 to develop 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 for the patient to think.
- **Emphasize adherence before starting:** Explaining the patient that a high level of adherence is needed, and that the treatment is lifelong is crucial. Patient’s comprehension must be ascertained.
- **Demonstrate how to take drugs (e.g. NVP):** Many patients make mistakes during the initial lead-in dose phase of nevirapine, as it can be quite confusing. 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:** 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.

<table>
<thead>
<tr>
<th>OI</th>
<th>Primary prophylaxis</th>
<th>Drug of choice</th>
<th>Discontinued when CD4</th>
<th>Discontinued primary prophylaxis</th>
<th>Discontinued secondary prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>&lt;200</td>
<td>TMP-SMX 1 DS qd</td>
<td>&gt;200</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxo</td>
<td>&lt;100</td>
<td>TMP-SMX 1 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>
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 follow up 3-4 days before their drug stock are exhausted.

Remind every time during follow up: During follow up apart from assessing adherence the importance of achieving good adherence should be re-emphasized.

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 higher frequencies.

Anticipate and treat adverse events efficiently: Patients miss doses when they develop adverse events, which can be quite distressing. It is essential to inform patients about anticipated ARV adverse events, identify them early when they do occur and manage them efficiently. This is particularly important with the CNS side effects of elavirenz or with GI intolerance of PIs, 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.

Involvement of spouse, a family member in treatment education and adherence issues only after the patient consents for the same.

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.

Table 6 : Common drug-drug interactions with ARVs

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Problem Drug</th>
<th>Consequence</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine (NVP)/ PIs</td>
<td>Rifampicin</td>
<td>Reduce NVP levels</td>
<td>Use efavirenz Non-PI-based ATT?</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Fluconazole</td>
<td>Increase NVP levels- hepatitis</td>
<td>Monitor ALT closely</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Citalopram</td>
<td>Alter citalopram/sertraline levels</td>
<td>Fluoxetine Doxepin</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Sertraline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Phenytoin</td>
<td>Reduce NNRTI levels</td>
<td>Close monitoring Gabapentin</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Carbamazepine</td>
<td>Reduce anticonvulsant levels</td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Phenobarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Valproate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs/Elavirenz</td>
<td>Midazolam</td>
<td>Increase benzodiazepine levels</td>
<td>Lorazepam Temazepam</td>
</tr>
<tr>
<td>PIs</td>
<td>Triazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td>Simvastatin</td>
<td>Increase statin levels- increased toxicity</td>
<td>Pravastatin Fluvastatin Atorvastatin (with caution)</td>
</tr>
<tr>
<td>PIs</td>
<td>Lovastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs/NRTIs</td>
<td>Oral contraceptives</td>
<td>Increase or decrease levels according to the agent</td>
<td>Use indinavir Avoid OCPS and recommend alternative contraception methods</td>
</tr>
</tbody>
</table>

Knowledge of interactions between ARVs and other commonly used concomitant medicines in HIV infection is essential. The NNRTIs and the PIs are metabolized by the cytochrome P-450 3A4 group of enzymes in the liver and this enzyme is either induced or inhibited by other drugs. This can either decrease or increase the levels of NNRTIs or PIs with resulting decrease in blood levels and development of toxicity respectively.

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 a potent inhibitor of cytochrome P450 3A4 enzyme systems. When administered with other PIs, which are metabolized through this pathway, increased blood levels of the co-administered PIs are achieved. This helps reduce the dose and modify schedules of the concomitant PI. Table 5 summarizes the recommended doses of ritonavir boosted PIs.

Drugs like rifampicin are potent inducers of the cytochrome enzyme systems. Concomitant administration of NNRTIs and PIs with rifampicin can lead to reduction of blood levels of the former and development of resistance and failure of ART. Table 6 summarizes commonly used drugs and their interactions with ARVs in clinical practice.

The use of alternative medicines including herals is very common amongst patients in India. St Johns Wort has been documented to reduce PI levels when administered concomitantly. 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 drug interactions at the back of mind. Checking for the same can be done at the website: www.hiv-druginteractions.com.

Drug schedules and relationship 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 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.

**ARV Adverse Events**

ARV drugs may be associated with acute and long-term adverse events (AEs). Recognizing and managing these are essential because they may compromise adherence or sometimes necessitate switching of drugs, which may result in exhausting treatment options. Additionally, many of the concomitant drugs used for treating OIs are also associated with overlapping toxicities, making it difficult to identify the true offending agent. Patients should also be educated about these so that they are recognized early since many long term AEs may not reverse or may take years to improve.

The etiology of long term NRTI AEs involves cellular mitochondria. By inhibiting mitochondrial DNA polymerase enzyme gamma, NRTIs can induce reduction in respiratory chain function. Most of the long term AEs like lactic acidemia, pancreatitis, peripheral neuropathy, lipoatrophy and hepatitis may be caused in this way.

Table 7 and 8 summarize the common acute and long term adverse events 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. 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 HAART is immunopathological rather than protective. These conditions are therefore labeled as immune restoration inflammatory syndrome (IRIS). IRIS is defined as occurrence or worsening of clinical and/or laboratory parameters despite a favorable outcome in HIV surrogate markers (CD4 counts and PVL). These immune responses can be elicited against infective or non-infective agents. The temporal association between commencement of HAART (or change from a previously failing regimen) and the development of an unusual clinical phenomenon often provides a strong clue to the diagnosis of IRIS.

The following points help in diagnosis of IRIS

1. Temporal association between starting HAART regimen and subsequent development of clinical phenomena (the majority within 3 months).
2. Unusual clinical manifestations in patients responding to HAART. 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, with exclusion of other causes
   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 7 : Acute adverse events 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</td>
<td>Nausea, vomiting</td>
<td>Taking with or after food</td>
<td>Mostly self-limiting</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>Diarrhea, abdominal distress</td>
<td></td>
<td>Symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td>All PIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>NVP</td>
<td>Diffuse maculopapular with/without pruritus</td>
<td>Always use NVP in lead-in dose</td>
<td>Mild-moderate rash: antihistamine</td>
</tr>
<tr>
<td></td>
<td>ABC</td>
<td>Severe reaction: with fever and hepatitis or mucus membrane involvement (SJS)</td>
<td>Do not do double NVP dose when rash present</td>
<td>Severe rash: Discontinue* and never rechallenge</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td></td>
<td></td>
<td></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</td>
<td>Self limiting, resolve in 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>NVP</td>
<td>Nausea, anorexia, vomiting</td>
<td>Monitoring ALT/AST.</td>
<td>Symptomatic: discontinue permanently</td>
</tr>
<tr>
<td></td>
<td>All PIs</td>
<td></td>
<td>Avoid NVP in women with CD4&lt;250 &amp; men with CD4 &gt;400 Careful use of NVP in HBV/HCV co-infected patients</td>
<td>Asymptomatic:ALT &gt;&gt;5 times discontinue</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>Sometimes jaundice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>ABC</td>
<td>Fever, rash, malaise, worsens with continuation of ABC</td>
<td>Higher incidence with od dose</td>
<td>Discontinue and never rechallenge</td>
</tr>
<tr>
<td>reaction (HSR)</td>
<td></td>
<td></td>
<td></td>
<td></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 backbone 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. Unexpected clinical course.
4. Exclusion of alternative explanations—e.g., drug hypersensitivity reactions, drug resistance, non-compliance with treatment for the opportunistic infection.
5. Evidence of preceding immune restoration—e.g., a rise in blood CD4 lymphocyte count; restoration of cutaneous hypersensitivity to mycobacterial antigens (PPD); increased in-vitro T-cell proliferative responses to PPD.
6. Histopathological or cytological appearances of unexpectedly florid cell-mediated immune response within tissue samples.
7. Decline of plasma viral load by > 1 log (> 10 fold) from baseline value.

### Risk factors for IRIS

**Identified risk factors for infectious IRIS are**

1. An active or sub-clinical infection by opportunistic pathogens.
2. The antigens of non-viable micro-organisms (e.g., Cryptococci and CMV) are all possible targets for an immunopathological response.
3. Cd4 T count below 50 / mm³ prior to initiation of HAART is a major risk factor for IRIS.
4. Being ART naive is an important risk factor for development of IRIS.
5. Starting ART in close proximity to the diagnosis & initiation of treatment for an OI.

### Risk factors for IRIS

**Table 8 : 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</td>
<td>Discontinue and never re-challenge. Transfusion or growth factors for severe anemia</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>d4T, ddl</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 academia</td>
<td>d4T, ddl, ZDV</td>
<td>Nausea, vomiting, abdominal distress, fatigue progressing to breathlessness when acidosis develops</td>
<td>Identify early</td>
<td>Discontinuation No specific treatment for acidosis, riboflavin and thiamine can be tried</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>d4T, ddl</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>Lipatrophglycemia</td>
<td>d4T, ZDV PIs</td>
<td>Fat loss in face, extremities, buttocks Increase visceral fat in abdomen</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>Dyslipidemia</td>
<td>d4T EFV All boosted PIs (except ATV)</td>
<td>Increase in total cholesterol and triglycerides</td>
<td>Avoid these drugs when possible. Identify early by measuring fasting lipids as recommended in follow up</td>
<td>Life style modification Lipid lowering agents Switching to less offending agents</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, insulin</td>
</tr>
</tbody>
</table>

**Table 9 depicts various types of IRIS seen in clinical practice.**

Non-infectious IRIS includes GBS, autoimmune thyroiditis and sarcoidosis. The differential diagnosis for IRIS includes active OI, ARV drug failure, ARV drug toxicity or failure of anti-microbial 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 antimicrobial 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 HAART. In the majority of cases, HAART can be safely continued without need for interruption. In general, most clinicians prefer to continue ART if CD4 count is <100/µL or if IRIS manifests months after initiation of HAART.

On the other hand, 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 B 19, polyomavirus JC causing PML) or if ART toxicity is the main differential diagnosis (e.g. hepatitis).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are also helpful in controlling inflammation and fever associated with IRIS. However, in severe IRIS a short 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.
Table 9: Types of IRIS

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Manifestation</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTB</td>
<td>Clinical: 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>BT</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>Meningitis, palsy, lymphadenitis, abscess, cavitary pneumonia.</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>Pneumocystis</td>
<td>Pneumonitis</td>
<td>Severe hypoxia, ARDS</td>
</tr>
<tr>
<td>Hep B/Hep C</td>
<td>Hepatitis</td>
<td>Biopsy often characteristic of viral hepatitis; variable response of Hepatitis B &amp; C virologic markers</td>
</tr>
<tr>
<td>VZV</td>
<td>Herpes zoster</td>
<td>Few lesions; usually late</td>
</tr>
<tr>
<td>CMV</td>
<td>Retinitis, vitritis, cystoid macular edema, immune recovery uveitis, CNS, pancreas, lung, colon, skin</td>
<td>Inactive CMV retinitis in affected eye in case of IRU</td>
</tr>
<tr>
<td>JCV</td>
<td>PML</td>
<td>Contrast enhancing inflammatory lesion on MRI. On biopsy perivascular inflammatory cellular infiltration</td>
</tr>
<tr>
<td>HIV</td>
<td>Demyelinating leucoencephalopathy</td>
<td>Large numbers, increase in size of existing lesions Focal</td>
</tr>
<tr>
<td>HPV</td>
<td>Inflamed warts molluscum</td>
<td></td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Encephalitis</td>
<td></td>
</tr>
</tbody>
</table>

**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 problems relating to adherence and development of IRIS.66

**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.67 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.68-70 In patients with slow response (cultures positive at 2 months) 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?**

CD4 cell count is important in deciding when to start ART in HIV/TB co-infected patients.

1. HIV/TB with CD4 cells > 200/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 < 200/mm³: Delaying ART can result in HIV related morbidity and even mortality due to risk of occurrence of other OIs. In such situations ART should be initiated as soon as anti-TB medicines are tolerated and patient has shown clinical improvement. One should closely monitor for 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 PIs and NNRTIs and reduces exposure of PIs by 75-95% and NNRTIs nevirapine by 31% & efavirenz up to 20%,71-74 Sub-optimal exposure to these drugs may lead to development of drug resistance.

Unfortunately, of all available PIs and NNRTIs, rifampicin may be used only with full dose ritonavir or with efavirenz.75 Though some experts recommend increasing the dose of EFV to 800 mg when using with rifampicin, studies in developing countries have documented good efficacy with a dose of 600 mg.75,76

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.77

Therapeutic strategies for concomitant use of ART and ATT include:

1. Using Efavirenz + 2NRTIs: Efavirenz based HAART when used at standard dosages in HIV/TB patient-receiving rifampicin has demonstrated good clinical, immunological & virological outcome.75-77 Although EFV is more expensive than NVP, it should be used at least until the duration of TB therapy. After the completion of ATT, patients may be switched back to NVP based regimen in order to make the regimen less expensive. However, before the NNRTI switch it is necessary to document good virologic control of the EFV based regimen (PVL<400 copies/ml). The hepatic induction
effect of rifampicin continues for up to 2 weeks after discontinuation. The switch from EFV to NVP should be made after 2 weeks of ART completion. A lead in dose is not necessary when NVP is switched for EFV. 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 some PIs, but it is currently not available in India. If rifabutin is used, the dose should be reduced with PIs to avoid ocular and other toxicities.

3. When TB develops in patients on ART, the regimen should be changed to EFV based to make it compatible with TB treatment, provided efficacy of the ARV regimen is not compromised. 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 relapse.73

**TREATMENT OF HIV AND HBV/HCV COINFECTED PATIENTS**

**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 workout, which includes LFTs, PT, HBeAg and HBV-DNA (results should be expressed in international units/ml). Consider liver biopsy (if no contra-indications) to measure stage of fibrosis and of necroinflammatory activity and to exclude other causes of chronic liver disease. 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 rarely be achieved in clinical practice. 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).86 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.87

Interferon alpha is the preferred option for HBeAg +ve patients and adefovir in HBeAg –ve patients with an HBV-DNA >10^6 copies/ml in patients who don’t qualify for HIV treatment (here the indication to initiate ART is a CD4<500/mm^3). Early results suggest that adefovir does not select for resistance to HIV and therefore compromise future use of tenofovir.88 Peg-IFN-2a (180µg once weekly) for treatment of HBV should be given for 48 weeks, independently of HBeAg/anti HBe status. When using standard INF, 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.89

When ART is indicated for HIV-HBV co-infected patients include lamivudine and/or tenofovir (agents also active against HBV) as a part of ART. Withdrawal of lamivudine may result in an acute exacerbation of hepatitis that may be sufficient to precipitate liver decompensation.21,25 Table 10 summarizes recommendations for management of HIV-HBV co-infection.

<table>
<thead>
<tr>
<th>Table 10 : Summary of HIV/HBV treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only HBV treatment indicated</td>
</tr>
<tr>
<td>Only HBV treatment indicated</td>
</tr>
</tbody>
</table>

**HCV co-infection**

Hepatitis C virus co-infected patient should have additional baseline workup, which includes LFTs, PT, 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 non-immune. Patients should be advised abstinence from alcohol.

Hepatitis C co-infection increases the risk of developing hepatotoxicity with antiretroviral treatment.86 Physicians must be alert to this possibility. However, majority of patients with HCV are able to tolerate antiretroviral treatment. Physicians should carefully monitor liver enzymes for hepatotoxicity while patients are started on nevirapine based antiretroviral treatment, or use alternatives to nevirapine.87,88

**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.89,90 Initiating anti-HCV therapy should be related to the status of both HCV and HIV infection in the individual patient. HCV disease should be treated first if the HIV infection is felt to be stable and not requiring treatment, whereas HIV disease should be treated prior to Hepatitis C if patients qualify for HCV treatment as per guidelines and HCV therapy should be considered after CD4 cell counts increase to more than 350/mm². 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 sustained virological response (SVR) defined as undetectable HCV RNA 24 weeks after the end of therapy-evaluated using sensitive molecular tests.90 Pegylated interferon (PEG INF) + ribavirin is the current treatment of choice for HCV in monoinfected and HIV/HCV co-infected patients.91,92 Dosage of PEG-INF alpha 2a is 180µg subcutaneous per week or PEG-INF alpha 2b 1.5µg/kg per week along with ribavirin 800 – 1000 mg/day. Duration of anti HCV therapy should be one year, not based on HCV genotype similar to monoinfected patients (24 weeks for genotype 2 and 3 and 48 weeks for genotype 1 and 4). There are initial reports to suggest higher relapse rates in HIV/HCV coinfection compared to monoinfected patients.

AZT and ddI should be avoided in patients receiving ribavirin due to additional risk of marrow toxicity with AZT and steatohepatitis/ lactic acidosis and increased risk of decompensated liver disease with ddI.93

**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-
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 assessment of indications for therapy and drug selection is 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 avoided because of possible teratogenic effects in first trimester of pregnancy
3. Combination of d4T + ddI should be avoided because of risk of development of fatal lactic acidosis.
4. Do not use NVP as part of ART regimen if mother’s CD4 count > 250/mm³ due to risk of fetal hepatotoxicity.

Hence, a HIV infected pregnant women with CD4 counts <250/mm³ should be offered an NVP-based regimen; which should be continued even after delivery.

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 continuing of ART are reduction in risk of resistance development 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 or exclusive breast-feeding.

Antiretroviral therapy reduces viral load in the mother can thus reduce the risk of MTCT, although it is only one factor responsible for the same. The risk of fetal toxicity has to be considered in using ARV drugs during pregnancy. Most ARV drugs are 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 MTCT rates. 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. 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. Hence, as far as possible 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) who can afford and therapy can be closely monitored, a combination of standard 3 drug ART is recommended for reducing risk of MTCT. This 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. 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.

The choice of ARV drugs depends on ART treatment history of the infected mother and her husband. The husband’s treatment history is important to evaluate possibility of 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 PIs are otherwise recommended, in pregnancy most experience relates to nelﬁnavir use. Nelfinavir should be used in the doses of 1250 mg bid to account for changes in pharmacokinetics during pregnancy. Evidence on the risk of prematurity in women using PI is still conflicting. However, blood glucose levels need to be monitored periodically in these women. Infants born to such mothers should receive ZDV 4 mg/kg bid for 6 weeks.

In women who cannot afford a standard 3-drug regimen following option may be recommended:

- ZDV from 28 weeks of pregnancy plus single dose of NVP during labor and single dose NVP and one week ZDV for the infant. This approach has shown to be highly effective.

Mode of delivery also impacts MTCT rates. Elective cesarean section (ECS) is an efficacious intervention among HIV infected mothers not taking ARVs or on ZDV monotherapy alone. The risk of post-partum morbidity is slightly higher than vaginal delivery but lower than emergency cesarean section. 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 mothers viral load around delivery is < 1000 copies/ml. 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.

Transmission via breast-feeding is an important risk for transmission of HIV to infants and mothers should be informed about the same. The choice of whether to breast-feed or not finally should be made by the mother after the risks and benefits of the same are clearly explained to her. The benefits of breast-feeding are obvious and the risk of morbidity associated with top feeding may be significant. This study was conducted in a public sector hospital where access to safe top feeds may be limited. Exclusive breast-feeding is another option, where in the baby is fed only mothers milk. Studies have demonstrated that mixed feeding is the riskiest for MTCT. 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. Fig. 2 summarizes approach for managing an HIV infected pregnant woman.

Fig. 2 : Approach to use of ART in a HIV-infected pregnant woman.
HOW TO IDENTIFY AND MANAGE ART FAILURE?

Identifying failure

Development of resistance to ARV drugs is a common cause of ART failure. Resistance is the ability of the virus to replicate in the presence of ARV drugs. Additionally, 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 also 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 regime leading to development of further cross resistance and compromising the efficacy of the second-line regimen.104 Hence, if patients can afford, PVL determinations are recommended every 6 months to identify virological failure early.

The following definitions of ART failure are used:

**Virological failure**: Incomplete suppression of the virus on ART. It is defined as PVL value of >400 copies/ml at 6 months after ART initiation. Additionally, viral rebound after being undetectable is also considered as virological failure. Low-level viral rebound (<500-1000 copies/ml), termed blips, usually indicates statistical variation in PVL determinations and is not an indication to alter therapy.106

**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. 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.107-109 A drop of CD4 count in the presence of virological suppression can occur with underlying malignancies (e.g. NHL), superinfection with HIV-2, or CD4) after 4-8 weeks of intensive adherence counseling should be done. The reasons for non-adherence need to be explored. Unless these reasons are identified, a patient may also find it difficult to adhere to the second-line regimen.

**Clinical failure**: Progression of disease with occurrence of OIs or malignancies occurring after 3 months or more of ART initiation is defined as clinical failure. Within 3 months, differentiating between IRIS and OIs occurring because of inadequate CD4 improvement is difficult.

Fig. 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, a patient may also find it difficult to adhere to the second-line regimen.

b. Drug-drug interactions: Assessing whether the patient is concomitantly taking medications which interfere with ARV activity is important. Many patients may not reveal that they take 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 can be designed for the patient. The goal of second-line ART is to achieve optimal virological suppression (PVL <50 or <400 copies/ml at 6 months post initiation). Potent regimens are needed to achieve this goal.

NNRTIs (NVP, Efavirenz) used in the first-line regimen have a low genetic barrier to resistance (a single mutation leads to high level resistance). Resistance is the ability of the virus to replicate in the presence of ARV drugs. When a patient fails a first-line regimen of 2 NRTIs+1 NNRTI, resistance to NNRTI should be expected and the other NNRTIs cannot be used in the second-line regimen. Thus a protease inhibitor (PI) based regimen is recommended.

PI based regimens are recommended to be boosted with ritonavir (except nevirapine). Ritonavir is a potent inhibitor of the CYP250 3A4 enzyme in the liver and gut, the major pathway for metabolism of PIs. Concomitant use of low dose ritonavir increases Cmax, Cmin and AUC concentrations of the other PIs thus increasing drug exposure. Also doses can be reduced and schedules can be altered with co-administration. Use of non-boosted PIs 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 boosted PI needs to be given with 2 NRTIs to address NRTI cross-resistance and make the second-line regimen more robust. Three boosted PIs are currently available in India: lopinavir/ritonavir, saquinavir/ritonavir and indinavir/ritonavir. 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. A new formulation of SQV (500 mg) will be soon available which will make the pill burden similar with all the three boosted PIs (3 cap/tab bid). All the three are also 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 PIs itself causes resistance to NNRTI should be expected and the other NNRTIs cannot be used in the second-line regimen. Thus a protease inhibitor (PI) based regimen is recommended.

A new formulation of SQV (500 mg) will be soon available which will make the pill burden similar with all the three boosted PIs (3 cap/tab bid). All the three are also 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 PIs itself causes resistance to NNRTI should be expected and the other NNRTIs cannot be used in the second-line regimen. Thus a protease inhibitor (PI) based regimen is recommended.
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{115} In spite of resistance associated with lamivudine resistance, some studies have shown resistance, due to its low genetic barrier. M184V is the mutation was used in the first-line, then the virus is expected to develop resistance. TAMs can accumulate if the failing regime 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{116} 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. Genotypic resistance testing helps identify these mutations and can help optimize the choice of drugs to be used in a second-line regimen. In one meta-analysis, evidence for benefit of antiretroviral resistance testing was sparse and limited to small short-term improvements of virologic response.\textsuperscript{117} 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.

Table 11 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. Current formulation of ritonavir needs refrigeration; recently a tablet formulation of lopinavir/ritonavir has been approved that does need refrigeration.
5. 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 emphasize that patient involvement and discussion is important before initiation of second-line regimens. 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. But with use of second generation PIs and entry inhibitors it is possible to achieve undetectable PVL levels in significant number of patients. However, these drugs are not available in India and are extremely expensive.

**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 reinstate the first-line regimen or change to a second-line regimen should be considered accordingly. If the decision to reinstate 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.

### Table 11: 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>ZDV or d4T + 3TC</td>
<td>ddI + ABC</td>
<td>LPV/τ</td>
</tr>
<tr>
<td>TDF + ABC</td>
<td>SQV/τ</td>
<td></td>
</tr>
<tr>
<td>TDF + ZDV</td>
<td>IDV/τ</td>
<td></td>
</tr>
<tr>
<td>ZDV + ddI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF + 3TC</td>
<td>ZDV + ddI</td>
<td>LPV/τ</td>
</tr>
<tr>
<td>ddI + ABC</td>
<td>SQV/τ</td>
<td></td>
</tr>
<tr>
<td>ABC + 3TC</td>
<td>TDF + ZDV</td>
<td>LPV/τ</td>
</tr>
<tr>
<td>ZDV + ddI</td>
<td>SQV/τ</td>
<td></td>
</tr>
<tr>
<td>d4T + 3TC</td>
<td>TDF + ZDV</td>
<td>LPV/τ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IDV/τ</td>
</tr>
</tbody>
</table>

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

\* Efficacy of second line NRTIs depends on early identification of first line regimen failure. For e.g. if failure on TNF + 3TC is diagnosed late, resistance to TNF (K65R) may also be expected and this can compromise use of ddI in the second-line.

### 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 advisable to follow universal precautions strictly, considering 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 needle-stick or cut with a sharp object): The risk is approximately 0.3% (95% CI 0.2-0.5).\textsuperscript{118}
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:119

- 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 the high and intermediate low 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. This reduces inoculum size and 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:
   a. Empirical treatment with ARVs till risk assessment is done, or
   b. Thorough risk assessment and then initiate ARVs 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.). Source patient should be tested for HIV by rapid test. If source patient’s status is unknown local epidemiological and clinical evidence should be considered. Direct virus assays (e.g. PCR) is 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 doesn’t occur immediately after an exposure, leaving a brief window of opportunity during which post exposure antiretroviral intervention might modify or prevent viral replication.

**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 should be discouraged 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 naive, 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 Tables 12 and 13.

**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

---

### Table 12: Post exposure prophylaxis after percutaneous exposure

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Source HIV +ve, low risk</th>
<th>Source HIV +ve, high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less severe (e.g., solid needle and superficial injury)</td>
<td>Recommend 2 drug PEP</td>
<td>Recommend 3 drug PEP</td>
</tr>
<tr>
<td>More severe (e.g., large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient’s artery or vein)</td>
<td>Recommend 3 drug PEP</td>
<td></td>
</tr>
</tbody>
</table>

### Table 13: Post exposure after mucous membrane or non-intact skin exposure

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Source HIV +ve, low risk</th>
<th>Source HIV +ve, high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small volume (i.e., a few drops)</td>
<td>Consider 2 drug PEP</td>
<td>Recommend 2 drug PEP</td>
</tr>
<tr>
<td>Large volume (i.e., major blood splash)</td>
<td>Recommend 2 drug PEP</td>
<td>Recommend 3 drug PEP</td>
</tr>
</tbody>
</table>

*Low risk: Asymptomatic or viral load <1500 copies/ml

**High risk: Symptomatic HIV, AIDS, acute seroconversion and/or high viral load

NRTIs combination therapy. Three drugs PEP include 2 NRTI +1boosted PI or EFV.**118 Nevirapine (NVP) is contraindicated for PEP because of the risk of severe hepatotoxicity. Efavirenz and d4T+d4l 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 and d4T + 3TC) 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 and explained about universal precautions, immediate local wound care and they may consume one tablet of two nucleosides combinations after local wound management in case of occupational exposure. HCWs should then approach expert who can evaluate the severity and decides further treatment.

**Acknowledgement**

Sagar Galwankar, University of South Florida, Tampa, USA. for his comments.

These guidelines was possible due to unrestricted educational grant from Cipla Ltd., India.

**REFERENCES**


Announcement

DIABETIC FOOT

Live Workshop on Diabetic Foot on 26th March 2006.

Practical demonstration of diabetes foot management by faculties of national and international repute For the first time in central India, Organized by Diabetes Association of India, Nagpur Branch.

Only limited registrations on first come first basis. Kindly register yourself by sending DD/Cheque of Rs. 250/- in favour of “Diabetes association of India, Nagpur”.

(Please add Rs. 50/- for outstation cheques).

Dr. Sharad Pendse, Organising Chairman
Dr. Pramod Gandhi, Organising Secretary, 18 – Shreevvardhan Complex, Wardha Road, Ramdaspeth, Nagpur - 440010, (MS)
Ph.: 0712-2560302 / 09823042258; E Mail: drpdgandhi1@yahoo.co.in

74

www.japi.org © JAPI • VOL. 54 • JANUARY 2006