



Draft - API Guidelines for HIV/AIDS 2007

Your suggestions are welcome on

shashank.sr@gmail.com

This is the second edition

**The first edition of this guidelines were published
in the January 2006 issue (Vol. 54 pgs. 57-74) of JAPI**

Suggestion can also be sent to

Dr. Shashank R Joshi

Hon. Editor, JAPI

No. 006 and 007, Turf Estate,

Dr. E. Moses Road,

Opp. Shakti Mill Compound,

Mahalaxmi (West),

Mumbai 400 011.

Guidelines for Use of Antiretroviral Therapy for HIV Infected Individuals in India (API ART Guidelines) 2007

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 versions and provides 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 symptomatic HIV infected persons (WHO stage 4 conditions) regardless of CD4 counts and plasma Viral load (PVL) levels. Furthermore, in patients with WHO stage 3 conditions (including pulmonary tuberculosis) ART is indicated when the CD4 count is $< 350/\text{mm}^3$. In asymptomatic individuals, ART should be offered when the CD4 counts fall below $200/\text{mm}^3$ and is recommended in patients with CD4 counts between $200\text{-}250/\text{mm}^3$. Therapy is not recommended for asymptomatic individuals with CD4 count more than $350/\text{mm}^3$. In asymptomatic individuals with CD4 counts between $250\text{-}350/\text{mm}^3$ various other criteria may help in the decision to initiate ART. 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 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 and dyslipidemia) and some evidence of inferior potency in the long term (mainly driven by treatment related toxicity) 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. 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 to identify failure early and prevent development of broader cross resistance by persisting with a failing regimen. Yearly estimation of lipid profile and blood sugar 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. 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. 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 $< 200/\text{mm}^3$, 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. 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.¹⁻³ 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-two 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 currently available therapeutic options, eradication of HIV cannot be achieved.⁴ 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. prevention of transmission of HIV from infected mother-to-child (pMTCT), after occupational-post exposure prophylaxis (PEP) and non-occupational exposures. There is increasing interest in use of ARV for pre-exposure prophylaxis (PrEP), however pending further evidence this is not routinely recommended in clinical practice. Theoretically 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. An algorithm summarizing when to initiate ART is illustrated in Figure 1.

Antiretroviral treatment is indicated for all patients who are symptomatic with an AIDS defining illness, irrespective of CD4 counts or viral load levels (WHO stage 4 conditions). Patients with AIDS have higher rates of mortality unless treated with ART.^{5,6} In addition patients with WHO stage 3 conditions have functional immunodeficiency and have a risk of rapid progression, and therapy is recommended in these patients if CD4 count is $<350/\text{mm}^3$.⁷⁻⁹ Table 1 enlists the WHO clinical staging system.

Adequate treatment of OIs with appropriate antimicrobial therapy and stabilizing patients is crucial before initiating ART. This helps to reduce pathogen load and prevent development of immune reconstitution inflammatory syndrome (IRIS), reduces pill burden, prevents additive toxicities and makes it easier to identify the offending drug in case of overlapping toxicities. Finally, certain AIDS defining illness like cryptosporidial diarrhea, progressive multifocal leucoencephalopathy (PML) 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 $<200/\text{mm}^3$ were 19

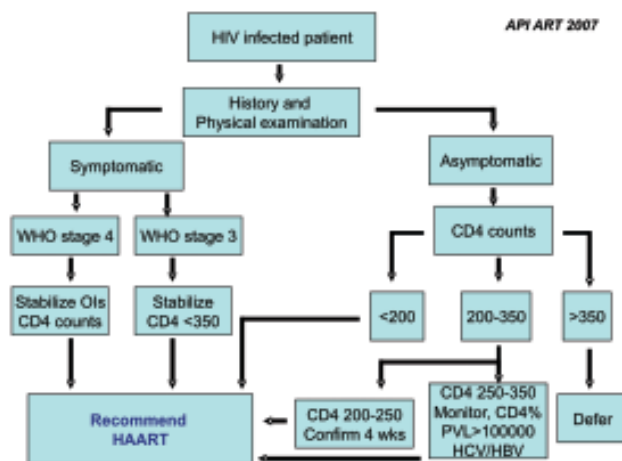


Fig. 1: Algorithm for when to initiate ART.

Table 1: WHO Clinical staging system for adults and adolescents

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

times more likely to die than were those with CD4 counts > 350/mm³.¹² Since the risk of developing OIs is significant when CD4 counts drop to less than 200/mm³, therapy is indicated for these patients, even if they are currently asymptomatic.⁵ At the same time it should be remembered that ART is effective even in patients with advanced immunosuppression (CD4<50/mm³) and should be always be offered.^{13,14} However, the risk for development of IRIS and certain short term toxicities is higher at this stage and should be closely monitored

for.

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.

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.^{15,16} 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 higher limit of the 30% physiologic variation in the CD4 counts.

In asymptomatic patients with CD4 250-350 mm³, therapy is considered for patients with one or more of the following criteria:

1. A rapidly declining CD4 count: CD4 counts should be monitored every 3 months to identify this.
2. A plasma viral load >100,000 copies/ml (5 logs).
3. A percentage CD4 count of <15%.¹⁷
4. Patient choice and readiness
5. Other clinical situations include

Conditions needing cyto-toxic therapy e.g. malignancies

HBV and HCV co-infection (when HCV treatment is planned)

HIV associated nephropathy^{18,19}

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.²⁰ 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.²¹ 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 complicating further therapy.
 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.

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 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 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 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
2. Temperature
3. Lymphadenopathy
4. Oral cavity: oral candidiasis, oral hairy leukoplakia
5. Dermatological
6. Genital
7. Systemic examination

8. Fundoscopic
9. Pelvic (women)

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 diagnose HIV-2 infection. Non-nucleoside reverse transcriptase inhibitor's (NNRTIs) have no activity against HIV-2.²²
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.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.
6. Urine routine: To evaluate proteinuria and glycosuria (necessitate estimation of blood glucose)
7. Creatinine: Dose of all nucleoside reverse transcriptase inhibitors (NRTI's) except abacavir has to be adjusted according to Creatinine clearance. Additionally it is also necessary prior to initiating a tenofovir based regimen.
8. HbsAg: To rule out concomitant hepatitis B infection, this can influence the choice of the ARV regimen. Additionally, 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 infection
10. VDRL/TPHA
11. Pap smear: Helps in earlier diagnosis of cervical intraepithelial neoplasia (CIN)

Optional

1. Fasting lipid profile: May be recommended in patients with established coronary 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 pregnancy

and most ARVs are in FDA category B/C.

4. Anti HCV: The prevalence of HCV is low in HIV infected patients except, such as in northeastern states of India where injection drug use is a risk factor. It is also recommended in HIV infected hemophiliacs and thalassaemics or any history of exposure to blood or blood products in the past.
5. Genotypic resistance testing: This is recommended in a patient with a previous history of sub-optimal exposure to ARVs (e.g. 2 drug therapy, exposure to single dose NVP in pregnancy). Routine baseline genotypic resistance testing is not recommended at this time because it is felt that the prevalence of transmitted baseline drug resistance may be low in the HIV-infected population.

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 a quality assurance program
- Inter-current illnesses, concomitant steroid use, vaccinations etc. 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
- PVL: Currently available 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 2). 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 (fusion 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 (Unboosted/boosted PI + 2 NRTI), and triple NRTI-based regimens. Most experience in India is with 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,

Table 2 : Choice of NVP vs EFV as initial NNRTI

Nevirapine	Efavirenz
Cheap	Expensive
Availability of FDCs	Once daily kits/FDC?
Rash, hepatitis	CNS disturbances
Contraindicated	Contraindicated
Men with CD4>400	pregnancy (1st Tri)
Women with CD4>250	
Cannot be used with RMP	Used with RMP
Caution with HBV/HCV co-infection	Caution with pre-existing psychiatric illness

Table 2 : Antiretrovirals approved for use

NRTI	NNRTI	PI	Entry inhibitor
Zidovudine (ZDV)	Nevirapine (NVP)	Saquinavir (SQV)	Enfuvirtide (T-20)
Stavudine (d4T)	Efavirenz (EFV)	Indinavir (IDV)	
Lamivudine (3TC)	Delavairidine * (DLV)	Ritonavir (RTV)	
Didanosine (ddI)		Nelfinavir (NFV)	
Zalcitabine (ddC)*		Lopinavir (LPV/r)	
Abacavir (ABC)		Atazanavir (ATV)	
Emtricitabine * (FTC)		Amprenavir* (APV)	
Tenofovir (TDF)		Fos-amprenavir* (FPV)	
(Nucleotide RTI)		Tipranavir (TPV)*	
		Darunavir (DRV)*	

* Drugs not available in India

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 unboosted PI based regimens and are superior to 3 NRTI based regimens.³¹⁻³³ NNRTI-based regimens have the advantage of a lower pill burden and are cheaper when compared to most 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 NNRTI's 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.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 to others. 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 in development.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 Patient should be forewarned about these before initiating treatment. Pre-existent 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, 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 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 higher frequency in women with pre-treatment CD4+ T cell counts >250/mm³ and men with pre-treatment CD4+ T cell counts >400/mm³.³⁹ 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 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.⁴⁰ Hence the choice between using NVP and EFV is based on toxicity concerns⁴¹ with EFV having a better safety profile. Table 3 summarizes the differences between EFV and NVP based first line ART regimen.

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, LPV/r, ATV/r) combined with 2NRTIs. Nelfinavir as a sole PI is not recommended due to concerns about sub-optimal potency.

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

Six nucleoside/nucleotide HIV-1 reverse transcriptase inhibitors (NRTI's/NtRTIs) 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-associated mutations (TAMs) which are associated with ZDV and d4T resistance⁴² Emtricitabine is similar to lamivudine except that it can be taken once daily and hyper pigmentation is an important adverse event. However, it is not available as a single agent but as a fixed dose combination with TDF or TDF/EFV (Table 4).

The choice of another NRTI to be combined with lamivudine depends on cost, short and long term 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.^{43,44} However, stavudine is associated with significant long-term toxicities and is recommended only as an

Table 3 : Fixed dose combinations available in India

Two drugs	Three drugs
D4T + 3TC	D4T + 3TC + NVP
ZDV + 3TC	ZDV + 3TC + NVP
TDF + FTC	TDF + FTC + EFV

Table 4 : Recommended NNRTI–Based Regimens (1- NNRTI + 2-NRTIs)

2NRTI	and	NNRTI
<p>Preferred</p> <p>Tenofovir + Lamivudine*</p> <p>Abacavir + Lamivudine</p> <p>Zidovudine + Lamivudine</p> <p>Alternative</p> <p>Stavudine** + Lamivudine</p> <p>Didanosine*** + Lamivudine</p>		<p>Efavirenz</p> <p>Nevirapine</p>

* Emtricitabine can be used as an alternative to lamivudine.

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.²⁸⁻³⁰ * ddi has to be taken on empty stomach and has higher risk of causing pancreatitis and symptomatic hyperlactataemia

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 affording patients a non-thymidine analog NRTI/NtRTI (TDF, ABC) is recommended in combination with 3TC/FTC. Tenofovir is an NtRTI with the convenience of once daily dosing and has a good safety profile. When combined with lamivudine/emtricitabine it has shown comparable efficacy with d4T/3TC based NNRTI regimen with better long term safety profile.⁴⁵ In a randomized controlled trial (Gilead 934) at 96 weeks TDF/FTC was virologically and immunologically superior to ZDV/3TC when combined with EFV. Furthermore there were more discontinuations due to toxicities in the ZDV/3TC arm. The frequency of body fat changes was also more in the ZDV/3TC arm.⁴⁶ 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.^{47,48} Hence TDF has to be used cautiously in patients with pre-existing potential for renal disease or in patient on concomitant nephrotoxic medications e.g. amphotericin B. Creatinine clearance (calculated) and urinalysis is recommended 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.⁴⁹ However, physicians should watch for abacavir hypersensitivity reaction (HSR), which is more common in patients

harboring the HLA B5071 phenotype. 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.^{50,51}

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 which would still leave the thymidine analogs for use in second line regimen. Additionally further accumulation of mutations associated with cross resistance to other NRTIs seems to be less likely if a patient continues on a failing TDF based regimen.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.⁵³

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.⁵⁴ This should be weighed against the risk of long term toxicity. 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 virological failure.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).³⁵ Recommended regimens for initial therapy in treatment naïve patients are depicted in Table 4.

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.⁵⁶

2. Tenofovir + ddi + NNRTI is not recommended as an initial regimen due to reports of early virological and immunological failure.⁵⁷
3. 3-NRTI regimen of abacavir + tenofovir + lamivudine and didanosine + tenofovir + lamivudine should be avoided due to high rates of virological failure.⁵⁸ 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.⁵⁹
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. However recently a meta-analysis has demonstrated equivalent efficacy of low dose stavudine (30 mg) for patients with > 60 kg weight.⁶⁰ The World Health Organization has also recommended use of stavudine 30 mg bid for all patients needing ART.
8. Efavirenz should be avoided in pregnancy or in women who plan pregnancy
9. Nevirapine should be avoided in women with CD4 count > 250/mm³ and in men with CD4 count > 400/mm³.

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.
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 adverse events) in the treatment discontinuation arm as compared to patients in the continuous therapy arm.⁶¹

FOLLOW UP AFTER INITIATING ART

Table 5 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. Most morbidity and mortality on ART in the developing world tend to occur within the first 3-6 months of initiation.⁶² Immune reconstitution inflammatory syndrome (IRIS) is the commonest cause of mortality during this phase. 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 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.^{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 may not be always known, and history of ARV treatment taken by sexual partners may not be known. In either instance primary resistance may

Table 5 : Recommended follow up scheme after initiation of ART

	2 wks	1 mo	2 mo	3 mo	6 mo	Every 3 mo	Every 6 mo
Clinical and Adherence	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CD4 counts	No	No	No	No	Yes	No	Yes
PVL	No	No	No	No	Yes (<LLD*)	No	Yes
ALT	Yes (NVP)	Yes (NVP)	No	No	No	No	Yes
CBC	Yes (ZDV)	Yes (ZDV)	No	Yes	Yes	No	Yes
Lipid profile	No	No	No	No	Yes (d4T, CAD risk)	No	Yes

* lower limit of detection

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 taking herbals may not disclose that they take them)

If a patient can afford PVL determination, then it is recommended every 6 months 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 the first month to detect drug-induced hepatitis, especially in symptomatic patients. 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 coronary artery disease risk factors; a fasting lipid profile and blood sugar estimation 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 > 200/mm³ at least 3-6 months.^{65, 66} Table 6 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}

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.⁶⁷ However with use of more potent drugs (e.g. boosted PIs) in regimens, this cut off of 95% may be reduced (making a regimen more forgiving). 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.⁶⁹ 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 should ensure that s/he 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.⁷⁰ 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 reports missing doses then the reasons for doing the same should be explored and be 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

Table 6 : Indications for starting and discontinuation of OI prophylaxis

OI	Primary prophylaxis Indicated when CD4	Drug of choice	Discontinued When CD4	Primary	Secondary
PCP [52]	<200	TMP-SMX1 DS qd	>200	Yes	Yes
Toxo	<100	TMP-SMX1 DS qd	>200	Yes	Yes
MAC	<50	Azithromycin 1 gm/q wkly	>100	Yes	Yes
CMV	Not indicated	Secondary:Valganciclovir	>100	NA	Yes
Cryptococcosis	Not indicated	Secondary:Fluconazole	>100	NA	Yes
Candidiasis	Not indicated	Secondary:Fluconazole	>100	NA	Yes

prior to prescribing ART.⁷¹ 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 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 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 higher frequencies.
- The physician should work out dose schedule in consultation with the patient. Instead of explaining a dose as twice a day (bd), it should be explained as 12 hourly doses. This approach emphasizes 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 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 efavirenz 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.
- 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

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 PIs 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 PIs with resulting failure of treatment or the development of toxicity 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 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. In addition it reduces the chances of treatment failure and patients failing RTV boosted regimens do not develop primary PI mutations. Table 7 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 both the ARV classes.⁷³ This however is not clinically relevant for Efavirenz which can be used in standard doses.⁷⁴ Table 8 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 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

Table 7 : Use of ritonavir in PI boosting⁷³

Main PI	Unboosted dose	boosted bid dose RTV/PI	boosted qd dose RTV/PI
Indinavir	800 mg q8h, empty stomach	100/800 mg without food restrictions 400/400 mg, 200/800 mg	N/A
Saquinavir	1200 mg tid	100/1000 mg	100/1600 mg
Lopinavir	N/A	100/400 mg	200/800 mg (only treatment naïve patients)
Atazanavir	400 mg od	N/A	100/300 mg od
Nelfinavir	750 mg tid or 1250 mg bid	Not boosted	Not boosted

Table 8 : Common drug-drug interactions with ARVs

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

maintaining optimum drug levels. For example, ddI and unboosted indinavir 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.

Acid reducing agents (e.g. proton pump inhibitors) reduce absorption of atazanavir which can lead to sub-optimal blood levels and treatment failure.⁷⁶ Recommendations for use of these agents with atazanavir are summarized in Table 9.

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 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 toxicities may be irreversible or may take years to improve.

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 acidemia, pancreatitis, peripheral neuropathy, lipoatrophy and hepatitis are caused by mitochondrial dysfunction.

Table 10 and 11 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

Table 9 : Interaction of atazanavir and acid reducing drugs

	H ₂ receptor antagonists (H ₂ RAs)		Proton pump Inhibitors	Antacids & buffered medications
	Treatment naïve	Treatment experienced		
ATV	400 mg with food at least 2 hours earlier or at least 10 hours after H ₂ RA	Not applicable	Do not co-administer	2 hours before or 1 hour after these medications
ATV/RTV	300/100 mg with food can be given simultaneously	300/100 mg with food at least 2 hours earlier or at least 10 hours after H ₂ RA	Do not co-administer	—

Table 10 : Acute toxicities of ARV drugs

Adverse event	Offending agents	Clinical presentation	Prevention	Management
GI disturbance	ZDV, ddI, NVP, All PIs	Nausea Vomiting Diarrhea Abdominal distress	Taking with or after food	Mostly self-limiting Symptomatic treatment
Rash	NVP, ABC, EFV	Diffuse maculopapular With/without pruritus Severe reaction: with fever and hepatitis or mucus membrane involvement (SJS)	Always use NVP in lead in dose Do not double NVP dose when rash present. Do not use prophylactic steroids/antihistamines	Mild-moderate rash: antihistamine Severe rash: Discontinue* and never rechallenges
CNS symptoms	EFV	Drowsiness, abnormal dreams, impaired concentration	Educate patient Take 2-3 hrs before sleeping. Take on empty stomach	Self limiting, resolve in 2-4 weeks
Hepatitis	NVP, All PIs, EFV	Nausea, anorexia, vomiting Sometimes jaundice	Monitoring ALT/AST. Avoid NVP in women with CD4 >250 & men with CD4 >400 Careful use of NVP in HBV/HCV co-infected patients	Symptomatic: discontinue permanently Asymptomatic: ALT>5 times discontinue
Hypersensitivity reaction (HSR)	ABC	Fever, rash, malaise, worsens with continuation of ABC	Higher incidence with od dose	Discontinue and never rechallenge

*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.

Table 11 : Long term toxicities of ARV drugs

Adverse event	Offending agents	Clinical presentation	Prevention	Management
Anemia, leucopenia	ZDV	Fatigue, breathlessness, palpitations	Avoid in anemic patients And in patients with advanced disease Monitor Hb levels as recommended	Discontinue and never re-challenge Transfusions or growth factors if severe
Peripheral neuropathy	d4T, ddI	Numbness and pain in lower limbs	Identify early because sometimes irreversible Avoid using d4T/ddI entirely Avoid using with pre-existing neuropathy	Early switching Symptomatics like gabapentin, carbamazepine
Lactic acidemia ²⁸	NRTIs especially d4T, ddI, ZDV	Nausea, vomiting, abdominal distress, fatigue progressing to breathlessness when acidosis develops High lactate levels	Identify early	Discontinuation No specific treatment for acidosis, riboflavin and thiamine can be tried
Pancreatitis	d4T, ddI	Abdominal pain, nausea and vomiting High amylase/lipase levels	Avoid in patients with h/o pancreatitis	Discontinue Medical management of pancreatitis
Lipoatrophy Lipohypertrophy ^{26,27}	d4T, ZDV PIs	Fat loss in face, extremities, buttocks Increase visceral fat in abdomen	Avoid d4T as far as possible Identify early because can be irreversible	Discontinue offending agent No specific treatment available
Dyslipidemia ²⁶	d4T EFV All boosted PIs (except ATV when used without RTV boosting)	Increase in total and LDL cholesterol and triglycerides	Avoid these drugs when possible Identify early by measuring fasting lipids as recommended in follow up	Lifestyle modification Lipid lowering agents Switching to less offending agents
Hyperglycemia	d4T PIs	Polyuria, polydipsia, polyphagia Increased fasting glucose	Avoid offending agents Monitor sugar	Change offending agent Lifestyle modification Drugs: OHAs Insulin
Nephrotoxicity	IDV TDF	Increased serum creatinine, hydronephrosis (IDV), Hypophosphatemia (TDF), Fanconi syndrome	Hydration, Avoid other nephrotoxic drugs Monitor s. creatinine, urinalysis, s. potassium and phosphorus closely	Discontinue Usually reverses Supportive care and maintain electrolytes

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

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 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 HAART (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 HAART regimen and subsequent development of clinical phenomena (the majority within 3-6 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

- 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, drug 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 HAART 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 12 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 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 HAART.

Non-steroidal anti-inflammatory drugs (NSAIDs) may be helpful in controlling inflammation and fever associated with IRIS.⁷⁹ However, in severe IRIS a short course of oral prednisolone is required to alleviate

Table 12 : Types of IRIS

Pathogen	Manifestation	Characteristic
MTB	<i>Clinical:</i> 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. <i>Radiological:</i> worsening pulmonary infiltrate or consolidation, intra-thoracic and intra-abdominal lymphadenopathy, development or enlargement of cerebral space occupying lesions.	Common during first 8 weeks. Caseating, granuloma, reactive changes; AFB smear & culture usually negative; often associated with CD4 rise and PPD conversion.
MAC	Lymphadenitis, abscess (skin, endobronchial, abdomen) lung infiltrate, CNS.	Common during first 12 weeks. Localized; focal granulomatous lymphadenitis. Blood culture often negative; MAC may be isolated from lymph node culture
M.Leprae	Cutaneous lesions	BT
Cryptococcus	Meningitis, palsy, lymphadenitis, abscess, cavitory pneumonia.	Variable occurrence from 1 week to 8 months. CSF pleocytosis, raised protein, India Ink & culture -ve but Ag. +ve in low titer Severe hypoxia, ARDS
Pneumocystis	Pneumonitis	Biopsy often characteristic of viral hepatitis; variable response of Hepatitis B & C virologic markers
Hep B/Hep C	Hepatitis	Few lesions; usually late
VZV	Herpes zoster	Inactive CMV retinitis in affected eye in case of IRU
CMV	Retinitis, Vitritis, cystoid macular edema, Immune Recovery Uveitis, CNS, Pancreas, Lung, Colon, Skin	
JCV	PML	Contrast enhancing inflammatory lesion on MRI. On biopsy perivascular inflammatory cellular infiltration
HIV	Demyelinating leucoencephalopathy	
HPV	Inflamed warts molluscum	Large numbers, increase in size of existing lesions
Parvovirus B19	Encephalitis	Focal

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, HAART 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 B 19, 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 problems relating to adherence and development of IRIS.⁸³

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.⁸³ 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.⁸⁴⁻⁸⁶ In patients with slow response (cultures positive at 2 months) or when PZA was not used during the initial phase 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 (usually 2-6 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 PIs and NNRTIs and reduces exposure of PIs by 75-95% and NNRTIs nevirapine by 31% & efavirenz up to 20%.⁸⁷⁻⁸⁹ 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 [90]. 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.^{91,92}

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.⁹³

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.^{91,94} 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 a 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 of rifampicin continues for up to 2 weeks after discontinuation. The substitution of EFV with NVP should be made after 2 weeks of ATT completion. A lead in dose is not necessary when NVP is substituted 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 already receiving HAART, the regimen should be changed 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.⁹⁵

TREATMENT OF HIV AND HBV/HCV COINFECTED PATIENTS

Liver related morbidity and mortality is very common amongst patients on HAART. The commonest cause of liver related deaths is co-infection with hepatitis viruses (HBV, HCV).⁹⁶ These deaths have been documented in patients even when they are on effective HAART (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 HAART.

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, 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).⁹⁷ 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.⁹⁷ When initiation of HAART 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/adeofovir and possibly 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 indicated for the patient

If HBV treatment is indicated ART is usually recommended to be started early (i.e. either CD4<350 or even CD4<500). 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

Avoiding using drugs with anti-HIV activity (TDF, FTC, and 3TC) is critical. Adeofovir and interferon alpha 2a are the options available. Interferon alpha (Pegylated interferon alpha 2a) is the preferred option for HBeAg +ve patients. PEG-INF 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.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.⁹⁹⁻¹⁰¹ Entecavir (0.5mg PO OD for 3TC naïve patients) is also effective for the treatment of chronic hepatitis B naïve and nucleoside experienced patients (1mg PO OD). However recent evidence suggests the emergence of M184V mutation in patients treated with entecavir that can compromise 3TC therapy.

Few important points about treatment for HBV include:

- The frequency of 3TC resistance is around 25% per year.
- Stopping HAART containing anti-HBV agents should be avoided because that can lead to sudden flaring of hepatitis.¹⁰²
- Duration of treatment is infinite
- Except interferon, all drugs can be used for treatment even when the patient has end stage liver disease (ESLD)

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 patient is non immune. Patients should be advised abstinence from alcohol.

Hepatitis C co-infection increases the risk of developing hepatotoxicity with antiretroviral

treatment.¹⁰³ Physicians must be alert to this possibility. Physicians should carefully monitor liver enzymes for hepatotoxicity while patients are started on nevirapine based antiretroviral treatment, or use alternatives to nevirapine.^{104,105}

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.^{106,107} 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, 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.⁹⁷

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 with AZT and steatohepatitis/ lactic acidosis 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 HAART and the assessments required to initiate HAART 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 not be used because of possible teratogenic effects in first trimester of pregnancy
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 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 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 fall in US FDA category B or C, but efavirenz falls in 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.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,¹¹⁶ especially if therapy is initiated within six months of receipt of the single

dose nevirapine.. 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) 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.¹¹⁷ 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 not be used in START. 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 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.¹¹⁸ Unfortunately pregnancy alters the pharmacokinetics of PIs, often leading to sub-optimal drug levels. With unpredictable levels, high pill burden and higher incidence of diarrhea 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. However, 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 6 weeks.

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 recommended¹²⁴:

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 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.

The 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.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-milk is an important mode for transmission of HIV to infants. Exclusive breast-feeding is another 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.^{130,131} Changing ART can be broadly classified into 2 groups:

Substitution

Replacing a single/dual ARV drug by another in a regimen 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 hyperlactetemia),^{132,133} 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 in 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 is referred to as switching. The commonest reason for switching is ART failure.

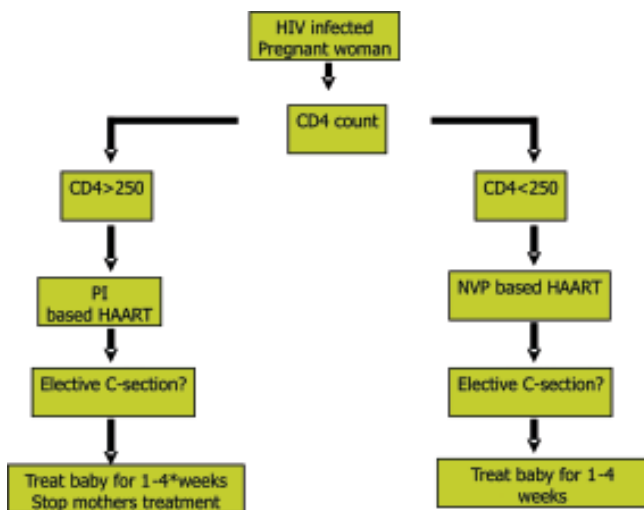
Development of resistance to ARV drugs is a common cause of ART failure. Additionally, inadequate adherence to the prescribed regimen can lead to treatment failure. Hence assessment of treatment adherence when a patient is identified with treatment failure is crucial and a repeat determination (PVL or 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 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.¹³⁴ Hence, if patients can afford, PVL determinations are recommended every 6 months 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 6 months after ART initiation. Additionally, viral rebound after being undetectable should be 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.¹³⁵

Immunological failure: A drop of greater than 30% in CD4 counts from peak value or a return to pre-ART



* 1 week therapy for baby is recommended if mother has received more than 4 weeks of ART.

Fig. 2: Approach to use of ART in a HIV-infected pregnant woman.

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.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 OIs or malignancies occurring after 6 months or more of ART initiation is defined as clinical failure. Within 6 months, differentiating between IRIS and OIs occurring because of inadequate immunologic (CD4) recovery 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:

- 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 regimens which are more

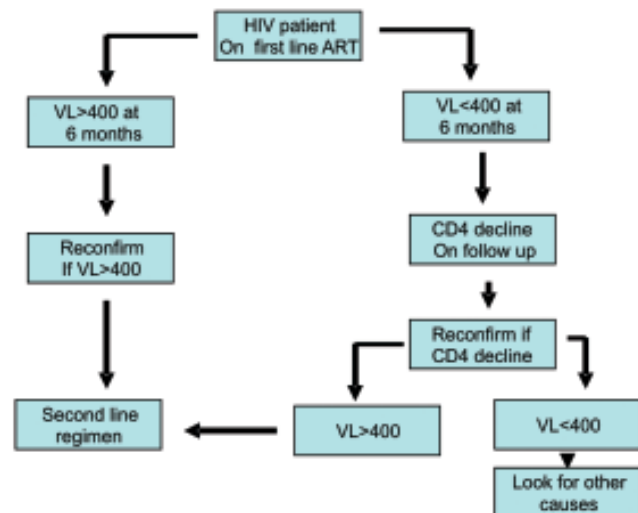


Fig. 3 : Management of first-line ART regimen failure.

complex.

- 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.
- 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 optimal virological 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 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.¹³⁹ 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. Hence a protease inhibitor (PI) based regimen is recommended.

PI based regimes should always be boosted with ritonavir (except nelfinavir). 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. Additionally boosted PIs have a high genetic barrier to resistance. 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 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 PIs 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.^{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 PIs itself causes

rise in total cholesterol, LDL cholesterol, total/HDL cholesterol ratio and triglycerides which is amplified further by the concomitant PI.¹⁴² IDV/r is associated with clinically insignificant indirect hyperbilirubinemia and nephrolithiasis. Finally, the genetic barrier to resistance is highest with LPV/r.¹⁴³ Concomitant use of rifampicin is not recommended with all the boosted PIs. Table 13 summarizes characteristics of currently available boosted PIs

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.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 using one of the thymidine analogs. Additionally M184V causes hypersusceptibility to thymidine analogs and tenofovir.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 in significant.

If zidovudine or stavudine have been used, some thymidine analog mutations (TAMs- positions 41, 67, 70, 210, 215, and 219) may be expected. The greater the 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.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.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 (IC₉₀ is less than wild type HIV).¹⁴⁸ Additionally K65R is also associated with reduced viral replication capacity.

Genotypic resistance testing helps identify 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.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.
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 performed when the PVL is less than 1000 copies/ml. Finally, minority resistant variants (<20% of total viral quaci-species) may not be detected. Physicians should always prescribe a resistance test only when the patient

Table 13 : Characteristics of boosted PIs

	IDV/r	SQV/r	LPV/r	ATV/r
Cost	+	++	+++	++
Convenience	3 bid2 bid?	3 bid	2 bid	3 qd
Short Toxicity	GI intolr Retinoid Ind. Bili	GI intolr	GI intolr	Ind Bili
Long toxicity	Nephrolithiasis Metabolic	Metabolic	Metabolic	Less metabolic
Resistance	Rare	Rare	Rare	Rare
Sequencing potential	Cross resist poss	Cross resist poss	Cross resist poss	UniqueProfile?
RMP concomitant	No	No	No	No
PPI	Safe	Safe	Safe	Caution
Food	Nil	w/in 2h full meal	Nil	With food

is currently on a failing regimen or has discontinued them for no longer than 4 weeks.

Table 14 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.

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 reinitiate 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.

Table 14 : Recommended second line regimens

First line NRTI	Second line NRTI*	Boosted PI
TDF + 3TC/FTC	ZDV + TDF + 3TC/FTC ZDV + ddI + 3TC/FTC ZDV + ABC + 3TC/FTC	ATV/r LPV/r SQV/r IDV/r
ABC + 3TC/FTC	ZDV + TDF + 3TC/FTC	ATV/r LPV/r SQV/r IDV/r
ZDV + 3TC	TDF + ZDV +3TC/FTC ABC + ddI + 3TC/FTC ZDV + ddI + 3TC/FTC	ATV/r LPV/r SQV/r IDV/r
ddI + 3TC	TDF + ZDV + 3TC/FTC	ATV/r LPV/r SQV/r IDV/r

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 ZDV + 3TC is diagnosed late, more number of thymidine analog mutations (TAMs) accumulate leading to limited utility of all NRTIs.

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. 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 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 a sharp object): The risk is approximately 0.3% (95% CI 0.2-0.5).¹⁵⁰
- 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. 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:

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.

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 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 15 and 16.

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 combination therapy. Three drugs PEP include 2 NRTI +1boosted PI or EFV.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

Table 15 : Post exposure prophylaxis after percutaneous exposure

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

Table 16 : Post exposure after mucous membrane or non-intact skin exposure

Exposure	Source HIV +ve, low risk*	Source HIV +ve, high risk**
Small volume (i.e., a few drops)	Consider 2 drug PEP	Recommend 2 drug PEP
Large volume (i.e., major blood splash)	Recommend 2 drug PEP	Recommend 3 drug PEP

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

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

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 in issues related to universal precautions, immediate local wound 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.

REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338:853-60.
2. Marins JR, Jamal LF, Chen SY, *et al.* Dramatic improvement in survival among adult Brazilian AIDS patients. *AIDS* 2003;17:1675-82.
3. Kumarasamy N, Solomon S, Chaguturu SK, *et al.* The changing natural history of HIV disease: before and after the introduction of generic antiretroviral therapy in southern India. *Clin Infect Dis* 2005;41:1525-8.
4. Finzi D, Blackson J, Siliciano JD, *et al.* Latent infection of CD4 cells provide a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med* 1999;5:512-17.
5. Mellors JW, Munoz A, Giorji JV, *et al.* Plasma Viral load and CD4+ lymphocytes as prognostic markers for HIV-1 infection. *Ann Intern Med* 1997;126:946-54.
6. Egger M, May M, Chene G, *et al.* Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;360:119-29.
7. Coogan MM, Greenspan J, Challacombe SJ. Oral lesions in infection with human immunodeficiency virus. *Bull World Health Organ* 2005;83:700-6.
8. Greenspan JS, Greenaspan D. The epidemiology of oral lesions of HIV infection in the developed world. *Oral Diseases* 2002;8 Suppl 2:34-9.
9. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents in resource limited settings: Towards universal access.
10. Smith HV, Corcoran GD. New drugs and treatment for cryptosporidiosis. *Curr Opin Infect Dis* 2004;17:557-64.
11. Roberts MT. AIDS-associated progressive multifocal leukoencephalopathy. *CNS Drugs* 2005;19:671-82.
12. Kumarasamy N, Solomon S, Flanigan TP, *et al.* Natural history of human immunodeficiency virus disease in southern India. *Clin Infect Dis* 2003;36:79-85.
13. Santos J, Palacios R, Ruiz J, *et al.* Study of patients diagnosed with advanced HIV in the HAART era—OMEGA Cohort. *Int J STD AIDS* 2005;16(3): 252-5.
14. Pujari S, Patel A, Naik E, *et al.* Quantitative immunologic response to HAART is similar even when initiated late: Experiences from an Indian cohort. 15th World AIDS Conference, Bangkok 2004; CD abstract.
15. Phillips AN, Staszewski S, Weber R, *et al.* HIV viral load response to antiretroviral therapy according to baseline CD4 count and viral load. *JAMA* 2001;286:2560-7.
16. Sterling TR, Chaisson RE, Keruly J, *et al.* Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study. *J Infect Dis* 2003;188:1659-65.
17. Moore DM, Hogg RS, Yip B, *et al.* CD4 percentage is an independent predictor of survival in patients starting antiretroviral therapy with absolute CD4 cell counts between 200 and 350 cells/microL *HIV Med* 2006;7:383-8
18. Clayton A, Mughal T. The changing face of HIV-associated lymphoma: what can we learn about optimal therapy in the post highly active antiretroviral therapy era? *Hematol Oncol* 2004;22:111-20.
19. Herman ES, Klotman PE. HIV-associated nephropathy: Epidemiology, pathogenesis, and treatment. *Semin Nephrol* 2003;23:200-8.
20. Schrelbman T, Freidland G. Use of total lymphocyte count for monitoring response to antiretroviral therapy. *Clin Infect Dis* 2004;38:257-62.
21. Fehr JS, Nicca D, Sendi P, *et al.* Starting or changing therapy - a prospective study exploring antiretroviral decision-making. *Infection* 2005;33:249-56.
22. Hightower M, Kallas EG. Diagnosis, antiretroviral therapy, and emergence of resistance to antiretroviral agents in HIV-2 infection: a review. *Braz J Infect Dis* 2003;7:7-15.
23. Balakrishnan P, Solomon S, Kumarasamy N, *et al.* Low-cost monitoring of HIV infected individuals on highly active antiretroviral therapy (HAART) in developing countries. *Indian J Med Res* 2005;121:345-55.
24. Bessesen M, Ives D, Condreay L, *et al.* Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis* 1999;28(5):1032-5.
25. Tuboi SH, Harrison LH, Spinz E, *et al.* Predictors of Virologic Failure in HIV-1-Infected Patients Starting Highly Active Antiretroviral Therapy in Porto Alegre, Brazil. *J Acquir Immune Defic Syndr* 2005;40:324-328.
26. Attili VS, Sundar S, Singh VP, *et al.* Validity of existing CD4+ classification in north Indians, in predicting immune status. *J Infect* 2005;51:41-6.
27. Mandy FF, Nicholson JK, McDougal JS. Guidelines for performing single platform absolute CD4 T-cell determinations, with CD45 gating for persons infected with human immunodeficiency virus. *MMWR* 2003;52(RR02):1-13.
28. Pujari SN, Dravid A, Naik E, *et al.* Lipodystrophy and dyslipidemia among patients taking first-line, World Health Organization-recommended highly active antiretroviral therapy regimens in Western India. *J Acquir Immune Defic Syndr* 2005;39:199-202.
29. Saghayam S, Chaguturu SK, Kumarasamy N, *et al.* Lipoatrophy is the predominant presentation of HIV-associated lipodystrophy in southern India. *Clin Infect Dis* 2004;38:1646-7.
30. Patel AK, Patel K, Patel J. Lactic acidosis in HIV-I infected patients receiving antiretroviral therapy. *J Assoc Physicians India* 2004;52:666-9.

31. Van Leeuwen R, Katalama C, Murphy RL, *et al.* A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003;17:987-99.
32. Staszewski S, Morales-Ramirez J, Tashima KT, *et al.* Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999;341:1865-73.
33. Gulick RM, Ribaud HJ, Shikuma CM, *et al.* Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004;350:1850-61.
34. Zhang Z, Hamatake R, Hong Z. Clinical utility of current NNRTIs, and perspectives of new agents in the class under development. *Antivir Chem Chemother* 2004;15:121-34.
35. Riddler SA, Haubrich R, DiRienzo G, *et al.* A prospective, randomized, phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection: ACTG 5142. Program and abstracts of the XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. Abstract THLB0204.
36. Woodfall B. Impact of NNRTI and NRTI resistance on the response to the regimen of TMC125 plus 2 NRTIs in the study TMC125-C227. International Congress on drug therapy in HIV infection Plenary 5/session 6, 14th Nov 2006.
37. Fortin C, Joly V. Efavirenz for HIV-1 infection in adults: an overview. *Expert Rev Anti Infect Ther* 2004;2:671-84.
38. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr* 2004;35:538-9.
39. Imperiale SM, Lanes SZ, Stern JO, *et al.* The Viramune (nevirapine) hepatic safety project: analysis of symptomatic hepatic events. *Antiviral Ther* 2002;7:L57.
40. van Leth F, Phanuphak P, Ruxrungtham K, *et al.* Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004;363:1253-63.
41. Carr A. Antiretroviral therapy for previously untreated HIV-1 infected adults: 2NN, or just one. *Lancet* 2004;363:1253-63.
42. Ait-Khaled M, Stone C, Amphlett G, *et al.* CNA3002 International Study Team. M184V is associated with a low incidence of thymidine analogue mutations and low phenotypic resistance to zidovudine and stavudine. *AIDS* 2002;16:1686-9.
43. Gulick RM, Meibohm A, Havlir D, *et al.* Six-year follow-up of HIV-1-infected adults in a clinical trial of antiretroviral therapy with indinavir, zidovudine, and lamivudine. *AIDS* 2003;17:2345-9.
44. Squires KE, Gulick R, Tebas P, *et al.* A comparison of stavudine plus lamivudine versus zidovudine plus lamivudine in combination with indinavir in antiretroviral naïve individuals with HIV infection: selection of thymidine analog regimen therapy (START 1). *AIDS* 2000;14:1591-1600.
45. Gallant JE, Staszewski S, Pozniak AL, *et al.* Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004;292(2):191-201.
46. Gallant JE, DeJesus E, Arribas JR, *et al.* Tenofovir DF, emtricitabine, and efavirenz versus zidovudine, lamivudine and efavirenz for HIV. *N Engl J Med* 2006;354:251-60.
47. Heffelfinger J, Hanson D, Voetsch A, *et al.* Renal impairment associated with use of tenofovir. Abstract 779, 13th CROI 2006, Denver.
48. Gallant JE, Parish MA, Keruly JC, *et al.* Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse transcriptase inhibitor treatment. *Clin Infect Dis* 2005;40:1194-8.
49. DeJesus E, Herrera G, Teofilo E, *et al.* Abacavir versus zidovudine combined with lamivudine and efavirenz for the treatment of antiretroviral naïve HIV infected adults: a randomized equivalence trial. *Clin Infect Dis* 2004;39:1038-46.
50. Maggiolo F, Ripamonti D, Gregis G, *et al.* Once-a-day therapy for HIV infection: a controlled, randomized study in antiretroviral-naïve HIV-1-infected patients. *Antivir Ther* 2003;8:339-46.
51. Landman R, Thiam S, Canestri A, *et al.* Long-term evaluation (15 months) of ddI, 3TC and efavirenz once-daily regimen in naïve patients in Senegal: ANRS 12-04/IMEA 011 study. In: Program and abstracts of the 9th Annual Retrovirus Conference; February 24-28, 2002; Seattle. Abstract 458.
52. Brandi CJ, Margot NA, Miller MD. Long-term follow-up of patients taking tenofovir DF with low-level HIV-1 viremia and the K65R substitution in HIV-1 RT. *AIDS* 2007;21:761-763
53. Gallant JE Drug resistance after failure of initial antiretroviral therapy in resource-limited countries. *Clin Infect Dis* 2007;44:447-52
54. Pujari S, Patel A, Eknath N, *et al.* Effectiveness of generic Fixed dose combinations of HAART for treatment of HIV infections in INDIA. *J Acq Immune Def Syndr* 2004;37:1566-1569
55. Rey D, Schmitt MP, Hoizey G, *et al.* Early virologic non-response to once daily combination of lamivudine, tenofovir, and nevirapine in ART-naïve HIV-infected patients: preliminary results of the DAUFIN study. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, California. Abstract 503
56. Hirsch M, Steigbigel R, Staszewski S, *et al.* A randomized controlled trial of indinavir, zidovudine and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis* 1999;180:659-75.
57. Torti C, Quiros-Roldon E, Regazzi M, *et al.* Early virological failure after tenofovir + didanosine + efavirenz combination in HIV-positive patients upon starting antiretroviral therapy. *Antivir Ther* 2005;10:505-13.
58. Gallant JE, Rodriguez A, Weinberg W, *et al.* Early non-response to tenofovir DF (TDF) + Abacavir (ABC) and lamivudine (3TC) in a randomized trial compared to efavirenz (EFV) + ABC + 3TC: ESS30009 unplanned interim analysis. Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 16, 2003. (Abstract H-1722a).
59. Moyle G. Double "d" drug danger. *AIDS Read* 2003;13:15-24.
60. Hill A, Ruxrungtham K, Hanvanich M, *et al.* Systematic review of clinical trials evaluating low doses of stavudine as part of antiretroviral treatment. *Expert Opin Pharmacother* 2007;8:679-88.
61. Strategies for management of Antiretroviral therapy study group, El Sadr WM, Lundgren JD, Neaton JD, *et al.* CD4 guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283-96
62. Etard JF, Ndiaye J, Therirry-Mieg M, *et al.* Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. *AIDS* 2006;20:1181-9.
63. Ghani AC, Ferguson NM, Fraser C, *et al.* Viral replication under combination antiretroviral therapy: a comparison of

- four different regimens. *J Acquir Immune Defic Syndr* 2002;30:167-76.
64. Maggiolo F, Migliorono M, Pirali A, *et al.* Duration of viral suppression in patients on stable therapy for HIV-1 infection is predicted by plasma HIV-1 RNA level after 1 month of treatment. *J Acquir Immune Defic Syndr* 2000;25:36-43.
 65. Benson CA, Kaplan JE, Masur H, *et al.* Treating opportunistic infections among HIV-infected adults and adolescents. *MMWR* 2004;53(RR15):1-154.
 66. Kumarasamy N, Vallabhaneni S, Cecelia AJ, *et al.* Safe Discontinuation of Primary Pneumocystis Prophylaxis in Southern Indian HIV-Infected Patients on Highly Active Antiretroviral Therapy. *J Acquir Immune Defic Syndr* 2005;40:377-378.
 67. Paterson DL, Swindells S, Mohr J, *et al.* Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000;133:21-30.
 68. Bangsberg D, Hecht F, Charlebois E, *et al.* Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS* 2001;15:1-2.
 69. Maggiolo F, Ravasio L, Ripamonti D, *et al.* Similar adherence rates favor different virologic outcomes for patients treated with Non-nucleoside analogs or protease inhibitors. *Clin Infect Dis* 2005;40:158-63.
 70. Nieuwkerk PT, Oort FJ. Self reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis. *J Acquir Immune Defic Syndr* 2005;38:445-8.
 71. Kumarasamy N, Safren SA, Raminani SR, *et al.* Barriers and facilitators to antiretroviral medication adherence among patients with HIV in Chennai, India: a qualitative study. *AIDS Patient Care STDS* 2005;19:526-37.
 72. Pujari SN, Sarna A, Sengar A, *et al.* Adherence to antiretroviral therapy (ART) and it's principal determinants in HIV infected adults in India. 12th Conf on retroviruses and OI, 2005, Boston, abstract no 627.
 73. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. *J Antimicrob Chemother* 2004;53:4-9.
 74. CDC notice on readers: Updated guidelines on the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. *MMWR* 2004;53:37
 75. Piscitelli SC, Burstein AH, Chaitt D, *et al.* Indinavir concentrations and St John's Wort. *Lancet* 2000;355:547-8.
 76. Roter hand brief Bristol Myers Squibb December 2004.
 77. Moyle G. Mechanisms of HIV and nucleoside reverse transcriptase inhibitor injury to mitochondria. *Antivir Ther* 2005;10 Suppl 2:M47-52.
 78. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, *et al.* Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003;362:22-29.
 79. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004;18:1615-27.
 80. Shelburne SA, Visnegarwala F, Darcourt J, *et al.* Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005;19:399-406.
 81. French MA, Lenzo N, John M, Mallal SA, McKinnon EJ, James IR, *et al.* Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med* 2000;1:107-15.
 82. Kumarasamy N, Chaguturu S, Mayer KH, *et al.* Incidence of Immune Reconstitution Syndrome in HIV/Tuberculosis-Coinfected Patients after Initiation of Generic Antiretroviral Therapy in India. *J Acquir Immune Defic Syndr* 2004;37:1574-1576.
 83. Centers for Disease Control and Prevention. Notice to Readers: Acquired Rifamycin Resistance in Persons with Advanced HIV Disease Being Treated for Active Tuberculosis with Intermittent Rifamycin- Based Regimens. *MMWR* 2002.;51:214-5.
 84. Sterling TR, Alwood K, Gachuhi R, *et al.* Relapse rates after short-course (6-month) treatment of tuberculosis in HIV-infected and uninfected persons. *AIDS* 1999;13:1899-904.
 85. Kassim S, Sassan-Morokro M, Ackah A, *et al.* Two-year follow-up of persons with HIV-1- and HIV-2-associated pulmonary tuberculosis treated with short-course chemotherapy in West Africa. *AIDS* 1995;9:1185-91.
 86. El-Sadr WM, Perlman DC, Denning E, Matts JP, Cohn DL. A review of efficacy studies of 6-month short-course therapy for tuberculosis among patients infected with human immunodeficiency virus: differences in study outcomes. *Clin Infect Dis* 2001;32:623-32.
 87. Moreno S, Podzamczek D, Blazquez R, *et al.* Treatment of tuberculosis in HIV infected patients: safety and efficacy of concomitant use of ritonavir and rifampicin. In: XIIIth International AIDS Conference, July 9-14, Durban, South Africa, 2000.2:49.
 88. Polk RE, Brophy DF, Israel DS, *et al.* Pharmacokinetic interaction between amprenavir and rifabutin or rifampin in healthy males. *Antimicrob Agents Chemother* 2001;45:502-508.
 89. Robinson P, Lamsom M, Gigliotti M, *et al.* Pharmacokinetic interaction between nevirapine and rifampin. International Conf on AIDS, 1998, Geneva, Switzerland pg 1115.
 90. Ramachandran G, Kumar AK, Rajashekar S, *et al.* Increasing nevirapine dose can reduce reduced bioavailability due to Rifampicin co-administration. The 3rd IAS Conference on HIV pathogenesis and treatment, Rio 2005, abstract no. WePe3.3CO2.
 91. Patel Atul K, Patel K, Patel J, *et al.* Study on safety and antiretroviral effectiveness of concomitant use of rifampicin (RMP) and efavirenz in antiretroviral naïve tuberculosis co infected HIV-1 patients in India. *J Acquir Immune Defic Syndr* 2004;37:1166-69
 92. Manosuthi W, Sangkanuparph S, Thakkinstain A, *et al.* Efavirenz levels and 24-week efficacy in HIV-infected patients with tuberculosis receiving highly active antiretroviral therapy and rifampicin. *AIDS* 2005;19:1481-6.
 93. U.S. Food and Drug administration. Medwatch alert. <http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Invirase> (accessed 20th Nov. 2005)
 94. Pedral-Samapio D, Alves C, Netto E, *et al.* Efficacy of efavirenz 600 mg dose in the ARV therapy regimen for HIV patients receiving rifampicin in the treatment tuberculosis. 10th Conference on Retroviruses and Opportunistic Infections, February 2003, Boston, MA. Abstract 784.
 95. Hwaken M, Nunn P, Gathua S, *et al.* Increased recurrence of tuberculosis in HIV-1 infected patients in Kenya. *Lancet* 1993;342:332-338.
 96. Martin-Carbonero L, Soriano V, Valencia E, *et al.* Increased impact of chronic viral hepatitis on hospital admissions and mortality amongst HIV infected patients *AIDS Res and Human Retroviral* 2001;17:1467-71.
 97. Alberti A, Clumeck N, Collins S, *et al.* Short statement of the first European consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005;42:615-24.
 98. Cooksley W. Treatment with interferons (including pegylated

- interferons) in patients with chronic hepatitis B. *Semin Liver Dis* 2004; 24 (suppl): 45-53.
99. Benhamou, Y, Bochet M, Thibault V, *et al.* Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet* 2001; 358: 718-23.
 100. Xiong S, Yang H, Westland C, *et al.* Resistance surveillance of HBeAg chronic hepatitis B patients treated for two years with adefovir dipivoxil. [Abstract]. *Hepatology* 2003;194(Suppl 2):182.
 101. Angus P, Vaughan R, Xiong S, *et al.* Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. *Gastroenterol* 2003;125:292-7.
 102. Bonacini M Kurz A, Locarnini S, *et al.* Fulminant hepatitis B due to a lamivudine-resistant mutant of HBV in a patient co-infected with HIV. *Gastroenterology* 2002;122: 244-5.
 103. Den Brinker M, Wit F, Wertheim-van Dillen PME, *et al.* Hepatitis B and C virus co-infection and the hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS* 2000;14:2895-2902.
 104. Martinez E, Blanco JL, Arnaiz JA, *et al.* Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001;15:1261-68.
 105. Sulkowski MS, Thomas DL, Mehta SH, *et al.* Hepatotoxicity associated with nevirapine of efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002;35:182-189.
 106. Benhamou Y Bochet M, Di Martino V, *et al.* Liver fibrosis progression in human immunodeficiency virus and hepatitis C co-infected patients. *Hepatology* 1999;30:1054-58.
 107. Lesens O Deschenes M, Steben M, *et al.* Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus positive hemophiliacs and should be treated as an opportunistic infection. *J Infect Dis* 1999;79:1254-58.
 108. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, *et al.* Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004;351:438-50
 109. Carrat F, Bani-Sadr, Pol S, *et al.* Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* 2004;292:2839-48.
 110. Chung R, Anderson J, Volberding P *et al.* Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-co-infected persons. *N Engl J Med* 2004;351:451-9
 111. Soriano V, Puoti M, Bonacini M, *et al.* Care of patients with hepatitis C and HIV co-infection. *AIDS* 2004;18:1-12.
 112. Rockstroh JK and Spengier U. HIV and hepatitis C virus co-infection. *Lancet Infectious Dis* 2004;4:437-44.
 113. Breast-feeding and HIV transmission study group. Late post natal transmission of HIV-1 in breast fed children: an individual patient meta-analysis. *J Infect Dis* 2004;189:2154-2166.
 114. Tarantal AF, Castilo O, Ekert JE, *et al.* Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys. *J Acquir Immune Defic Syndr* 2002; 29:107-20.
 115. Guay LA, Mosoke P, Fleming T, *et al.* Intrapartum and neonatal single dose nevirapine compared with zidovudine for prevention of MTCT of HIV-1 in Kampala, Uganda: HIVNet 012 randomized trial. *Lancet* 1999;354:795-802.
 116. Jourdain G., Ngo-Giang-Huong N., Le Coeur S, *et al.* Intrapartum Exposure to **Nevirapine** and Subsequent Maternal Responses to **Nevirapine**-Based Antiretroviral Therapy. *N Engl J Med* 2004;351:229-40.
 117. Moodley J, Moodley D. Management of human immunodeficiency virus infection in pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 2005;19:169-83
 118. Bryson Y, Stek A, Mirochnik M, *et al.* For the PACTG 353 team. Pharmacokinetics, antiviral activity and safety of nelfinavir in combination with ZDV/3TC in pregnant HIV-infected women and their infants. 9th Conf retroviruses and opportunistic infections, Seattle. Abstract no. 795-W.
 119. Read J, Best B, Stek A, *et al.* Nelfinavir pharmacokinetics (625-mg tablets) during third trimester of pregnancy and post partum. 14th Conf Retroviruses and opportunistic infections, Los Angeles Abstract no 740.
 120. Aweeka F, Tiereny C, Stek A, *et al.* ACTG 5153s: Pharmacokinetic exposure and virologic response in HIV-1 infected pregnant women treated with a PI. 14th Conf Retroviruses and opportunistic infections, Los Angeles Abstract no 739.
 121. Burger D, Eggink A, Van Der ende I, *et al.* The pharmacokinetics of saquinavir in the new tablet formulation + ritonavir (1000/100 mg twice daily) in HIV-1 infected pregnant women. 14th Conf Retroviruses and opportunistic infections, Los Angeles Abstract no 741
 122. Ripamonti D, Cattaneo D, Airoldi M, *et al.* Atazanavir based HAART in pregnancy. 14th Conf Retroviruses and opportunistic infections, Los Angeles Abstract no 742
 123. Szyld EG, Warley EM, Freimanis L, *et al.* Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. *AIDS* 2006;20:2345-53
 124. World Health organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection infants. Guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource limited settings. <http://www.who.int/hiv/pub/mctct/en/arvdrugswomenguidelinesfinal.pdf> (accessed Nov 20th 2005)
 125. Lallemand M, Jourdain G, Le Couer S, *et al.* Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004;351:217-28.
 126. Read J, Newell M. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. *Cochrane database syst rev.* 2005;4:CD005479
 127. Shapiro D, Tuomola R, Pollack H, *et al.* Mother-to-child transmission risk according to antiretrovirals, mode of delivery, and viral load in 2895 U.S. women (PACTG 357). 11th Conf on retroviruses and opportunistic infections 2004, San Francisco. abstract no.99.
 128. Iliff PJ, Piwoz EG, Tawengwa NV, *et al.* Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS* 2005;19:699-708.
 129. Phadke MA, Gadgil B, Bharycha KE, *et al.* Replacement-fed infants born to HIV-infected mothers in India have a high early postpartum rate of hospitalization. *J Nutr* 2003;133:3153-7.
 130. Mocroft A, Youle M, Moore A, *et al.* Resonance for modification and discontinuation of antiretrovirals: results from a single treatment center. *AIDS* 2001;15:185-94.
 131. Fatenkeheuer G, Rømer K, Cramer P, *et al.* High rates of changes of first antiretroviral combination regimen in an unselected cohort of HIV-1 infected patients. 8th ECCAT 2001, Greece, abstract no 50.
 132. Moyle G, Baldwin C, Langroudi B, *et al.* A 48 week randomized, open label comparison of three abacavir based

- substitution approaches in the management of dyslipidemia and peripheral lipotrophy. *J Acquir Immune Defic Syndr* 2003;33:22-28.
133. Moyle G, Sabin C, Carteledge J, *et al.* A 48 week randomized, open label comparative study of tenofovir DF vs abacavir as substitutes for a thymidine analog in persons with lipotrophy and sustained virologic suppression on HAART. 12th Conf on retroviruses and opportunistic infections 2005, Boston abstract no 44B.
 134. Kantor R, Shafer RW, Follansbee S, *et al.* Evolution of resistance to drugs in HIV-1-infected patients failing antiretroviral therapy. *AIDS* 2004;18:1503-11.
 135. Skalar PA, Ward DJ, Baker RK, *et al.* Prevalence and clinical correlates of HIV viremia ('blips') in patients with previous suppression below the limits of quantification. *AIDS* 2002;16:2035-41.
 136. Moore DM, Hogg RS, Yip B, *et al.* Discordant Immunologic and Virologic Responses to Highly Active Antiretroviral Therapy Are Associated with Increased Mortality and Poor Adherence to Therapy. *J Acquir Immune Defic Syndr* 2005;40:288-293.
 137. Zala C, Patterson P, Ochoa C, *et al.* The impact of the hepatitis C virus on CD4-T cell response post-initiation of HAART among patients enrolled in clinical trials. 11th Conference on Retroviruses and Opportunistic Infections. San Francisco, February 2004 abstract no. 817.
 138. Braitstein P, Asselin J, Montessori V, *et al.* Impact of the hepatitis C virus on CD4 response post initiation of highly active antiretroviral therapy among a population-based HIV treatment cohort. International AIDS Society Conference on HIV Pathogenesis and Treatment. Paris, France 2003 abstract 161.
 139. Zang Z, Hamatake R, Hong Z. Clinical utility of current NNRTIs and perspectives of new agents in this class under development. *Antivir Chem Chemother* 2004;15:121-34.
 140. Ulrik BD, Jan G, Mike Y, *et al.* A randomized trial to evaluate lopinavir/ritonavir versus saquinavir/ritonavir in HIV-1-infected patients: the MaxCmin2 trial. *Antivir Ther* 2005;10:735-43.
 141. Dragstead UB, Gerstoft J, Pedersen C, *et al.* Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus type 1-infected patients: the MaxCmin1 Trial. *J Infect Dis* 2003;188:635-42.
 142. Shafran SD, Mashinter LD, Roberts SE. The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations. *HIV Med* 2005;6:421-5.
 143. deMendoza C, Soriano V. Resistance to HIV protease inhibitors: mechanisms and clinical consequences. *Curr Drug Metab* 2004;5:321-8.
 144. Turner D, Brenner BG, Routy JP, *et al.* Rationale for maintenance of the M184V resistance mutation in human immunodeficiency virus type 1 reverse transcriptase in treatment experienced patients. *New Microbiol* 2004;27(2 Suppl 1):31-9.
 145. Underwood M, St Clair M, Ross L, *et al.* Cross resistance of clinical samples with K65R, L74V, and M184V mutations. 12th conf retroviruses and opportunistic infections 2005, Boston abstract no 714
 146. Mouroux M, Descamps D, Izopet J, *et al.* Low-rate emergence of thymidine analogue mutations and multi-drug resistance mutations in the HIV-1 reverse transcriptase gene in therapy-naïve patients receiving stavudine plus lamivudine combination therapy. *Antivir Ther* 2001;6:179-83.
 147. Antoniou T, Park Wyllie L, Tseng AL. Tenofovir: A nucleotide analog for the management of HIV infection. *Pharmacotherapy* 2003;23:29-43.
 148. White KL, Margot NA, Ly JK, *et al.* A combination of decreased NRTI incorporation and decreased excision determines the resistance profile of HIV-1 K65R RT. *AIDS* 2005;19:1751-60.
 149. Tural C, Ruiz L, Holtzer C, *et al.* Utility of HIV genotyping and clinical expert advice. 8th Conf on retroviruses and opportunistic infections 2001, Chicago abstract no 434.
 150. CDC, Updated U.S. Public health services guidelines for the management of occupational exposures to HIV and recommendations for Post exposure prophylaxis. *MMWR* 2005;54:RR9:1-17.
 151. Bell DM. Occupational risk of human immunodeficiency virus infection health care workers: An overview. *Am J Med* 1997;102:9-15.