INTRODUCTION:
Though HIV has been known only for less than three decades, over 60 million people have been infected by the virus so far, nearly 27 million have died and nearly 33 million people globally are living with HIV. During the initial years of epidemic, major focus of attention was on preventive strategies and management of Opportunistic Infections (OIs). However, in last decade there have been significant advances in therapeutic options for treatment of persons infected with HIV. The ‘Highly Active Anti Retroviral Therapy’ (HAART) or ART has changed the HIV/AIDS from a ‘virtual death sentence’ to a ‘chronic manageable disease’.

The first drug effective against HIV, Zidovudine (AZT, ZDV) was approved as early as 1986. However, till early nineties, only Zidovudine (ZDV) & Didanosine (ddI) were available and were used as monotherapy. By the year 1995, results from several studies had demonstrated that use of two nucleoside analogue combined together (dual therapy) was quite effective in delaying the disease progression, showed impressive clinical improvements and increase in CD4 counts. The scenario changed dramatically in 1996 with the introduction of ‘Protease Inhibitors’ (PIs), which were very potent drugs and reduced the viral load by 10 – 100 times. As a result of effective triple combination therapy, hospitalisation rates of HIV infected individuals reduced dramatically, patients returned to work and opportunistic infections were reduced significantly. The drugs were no doubt quite efficacious but were associated with problems of significant toxicities, adherence to large number of pills (20 – 30 per day) and high costs.

Presently, we have 26 anti-retroviral agents approved by US FDA, of which 17 are currently available in India. The efficacy of drugs is well documented, options available are several and large numbers of patients are on ARV therapy. However, the management of HIV is becoming increasingly complex as problems of long term toxicities, drug-drug interaction and drug resistance are emerging. There are issues about wide availability of monitoring facilities like viral load, drug resistance testing, and second line ARV drugs.

GOALS OF ANTIRETROVIRAL THERAPY:
The currently available ARV drugs cannot eradicate the HIV infection from human body. This is so because a pool of latently infected CD4 cells is established during the earliest stages of acute HIV infection and persists with a long half-life, even with prolonged suppression of plasma viremia to < 50 copies/ml. The primary goals of antiretroviral therapy are maximal and durable reduction in plasma viral levels, restoration of immunological functions aimed at prolongation of life and improvement in quality of life. The reduction in viral load also leads to reduction in risk of sexual transmission.

The ARV drugs can also be used to reduce the risk of transmission of HIV from an infected mother to her child (MTCT), transmission after an accidental needle stick injury to a Health Care Worker from an infected person and in cases of sexual assault and rape etc.

PRINCIPLES OF ANTIRETROVIRAL THERAPY
A continuous high level of replication of HIV takes place in the body right from the early stages of infection. At least $10^{10}$ viral particles are produced and destroyed each day. The HIV destroys CD4 Cells, while body produces more CD4 cells. This balance is maintained for some years after which the rate of CD4 destruction becomes more than that of CD4 production. This progressive immune system damage results in susceptibility to different opportunistic infections (OIs), malignancies, neurological diseases, wasting and, ultimately, death.

Regular measurements of CD4 cell count and plasma HIV RNA levels (if possible) are necessary to determine the risk of disease progression in HIV infected patients and to determine when to initiate or modify ART regimens. The viral load levels indicate the magnitude of HIV replication while CD4 count indicate the extent of HIV induced immune damage.

The antiretroviral drugs act on various stages of replication of HIV in the body and interrupt the process of viral replication. Theoretically, these drugs can act at following steps in viral replication:

i. block binding of HIV to target cell (Fusion Inhibitors),

ii. block the viral RNA cleavage and one that inhibits reverse transcriptase (Reverse Transcriptase Inhibitors),

iii. block the enzyme integrase, which helps in the proviral DNA being incorporated into the host cell chromosome (Integrase Inhibitors).
Initiating Antiretroviral Therapy

A combination of at least three agents from different classes of ARV drugs is the regimen of choice as this gives maximal achievable suppression of HIV replication over a prolonged period of time.

ART has to be initiated as and when the patient becomes eligible according to the technical guidelines. However, before starting the ART, it is of utmost importance to ensure that the patient is well prepared for the therapy. The preparedness includes that the patient has an adequate understanding of the disease, is aware of the treatment regimens, importance of adherence to therapy and is willing to take the treatment. The adequate preparedness of the patient is critical in ensuring a high level of adherence to ART. Hence, the process of preparing the patient for ART should address the psycho social, financial, operational and other issues that can become potential barriers to adherence, and strategies to tackle these issues have to be tailored to the local situations and individual patient to ensure the long term adherence of the patient.

It is also important to have reliable laboratory services for investigations such as complete blood count and bio-chemistry, access to CD4 count and viral load facilities (if possible). One has to ensure reliable, affordable and uninterrupted access to quality antiretroviral drugs, and drugs to treat opportunistic infections and other related illness.

Prior to starting therapy, it is essential to have a detailed clinical evaluation, so as to assess the present stage of HIV infection, presence of any Opportunistic Infection (Present or Past) and identifying co-existing medical conditions like Hepatitis B & C infections, Liver diseases, presence of STDs and other concomitant treatment which may have a bearing on choice of drugs in the ART regimen etc.. The patient should have a detailed physical examination and should undergo investigations like complete blood count, chest X-Ray, renal and liver function, lipid levels, VDRL, Hepatitis B & C serology, pregnancy testing and urine for routine and microscopic examination and CD4 count. Major issues concerning ART for an individual are:

- When to start treatment?
- Which and how many agents to use? Choice of optimal regimen?
- How to monitor the therapy?
- How long to give therapy?
- When to change therapy and to what?
- Drug interactions involving antiretroviral therapy.

When to start treatment?

The guidelines on ART are issued and periodically updated by different expert groups like Department of Health and Human Services (DHHS), USA 2008, British HIV Association (BHIVA) 2006, Association of Physicians of India 2006 and National AIDS Control Organisation in India (NACO 2007).

WHO has also issued guidelines for initiating ART in resource limited settings. These guidelines are divided into two categories depending on whether CD4 count facilities are available or not. The total lymphocyte counts (TLC) can be used as a substitute for the CD4 count in symptomatic patients, and is not very useful in asymptomatic, although it is considered ‘less useful in asymptomatic patient’s as well as for follow up of patients on ART. The recommendations on starting treatment are based on WHO clinical staging, CD4 cell counts, and viral load, if possible.

The NACO guidelines on initiating therapy are also based on clinical staging and CD4 count. These guidelines have been revised in April 2009 as below.

Total lymphocyte count is no longer to be used for initiation or monitoring of ART.

The ART is effective even in patients with advanced immunosuppression (CD4 < 50/mm³) and should be offered though the rate of IRIS as well as mortality is higher than this stage. Some Indian data is now available showing that Indian HIV infected patients with CD4 count < 200/mm³ had 19 times higher mortality as compared to those CD count >350/mm³. It is also seen that certain AIDS defining illness like cryptosporidiosis and PML respond only to ART due to immune reconstitution induced by HAART.

The risk of progression to AIDS in patients with CD4 >350/mm³ is low and ART should not be offered to asymptomatic patients with CD4 >350/mm³. The decision to initiate ART between 200 to 350 CD4/mm³ in asymptomatic individuals is debatable. However, it is recommended that ART should be considered in all patients with CD4 count less than 250 cells/mm³ irrespective of symptoms. This value should be confirmed by a repeat test four weeks after initial tests.

What to start with?

It is recommended that all patients should be started with a three

<table>
<thead>
<tr>
<th>WHO Clinical Staging</th>
<th>CD4 (cells/cu.mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II</td>
<td>Treat if CD4 Count &lt; 250</td>
</tr>
<tr>
<td>III</td>
<td>Treat if CD4 Count &lt; 350</td>
</tr>
<tr>
<td>IV</td>
<td>Treat irrespective of CD4 Count</td>
</tr>
</tbody>
</table>

**Table 1: NACO guidelines on initiation of ART**

- I and II: Treat if CD4 Count < 250
- III: Treat if CD4 Count < 350
- IV: Treat irrespective of CD4 Count
Current Guidelines for Antiretroviral Therapy

A drug combination from two different classes, namely NRTI and NNRTI as follows:

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred first-line regimen</td>
<td>AZT+3TC+NVP</td>
<td>AZT may cause anaemia, which requires Hb monitoring, but is preferred over d4T because of d4T toxicity (lipodystrophy, lactic acidosis, peripheral neuropathy). Patients who develop severe anaemia while on an AZT-based regimen should not be re-challenged with AZT. In such cases, the patient should receive either d4T or TDF in place of AZT. For women with CD4 &gt; 250 cells/mm³, monitor for hepatotoxicity closely if started on the NVP-based regimen.</td>
</tr>
<tr>
<td>Alternative first-line regimens</td>
<td>AZT + 3TC + EFV</td>
<td>EFV is substituted for NVP in cases of intolerance to the latter or if patients are receiving rifampicin-containing anti-TB treatment. EFV should not be used in patients with grade 4 or higher elevations of ALT. If the patients have anaemia, a d4T-based regimen should be prescribed.</td>
</tr>
<tr>
<td></td>
<td>D4T + 3TC + (NVP or EFV)</td>
<td></td>
</tr>
</tbody>
</table>

At present, these regimens are recommended for use in India as first line drugs. The list of drugs is being expanded to include alternative first line regimen and second line regimens. First-line ART is the initial regimen prescribed for an ART naïve patient when the patient fulfills national clinical and laboratory criteria to start ART. Second-line ART is the next regimen used in sequence immediately after first-line therapy has failed.

Antiretroviral Components not recommended as part of an initial regimen in an Antiretroviral—Naïve patient

While selecting different combinations of ARV drugs, one must remember that a number of antiretroviral agents or ARV regimens are not recommended as part of an initial regimen in an antiretroviral-naïve patient. The reasons for not recommending their use as initial therapy are as follows:

1. **Modest antiviral activities**: delavirdine, combination of Zidovudine plus zalcitabine, Hydroxyurea
2. **High pill burden**: amprenavir (16 capsules per day) as sole PI, saquinavir soft gel capsule (18 capsules per day) as sole PI, combination of nelfinavir and saquinavir (16-22 capsules per day) as dual PI
3. **High incidence of toxicities**: ritonavir used as sole PI (600 mg twice daily) - gastrointestinal side effects, Didanosine + Zalcitabine, Didanosine + Stavudine - high toxicity
4. **Antagonistic in action**: Stavudine + Zidovudine
5. **High rates of virological failure**: Abacavir + Tenofovir + Lamivudine, Didanosine + Tenofovir + Lamivudine

Follow up of patients on ART:

The broad guidelines on follow up on patients on ART are depicted in Table below:

<table>
<thead>
<tr>
<th>Day 0 (baseline)</th>
<th>At 15 days</th>
<th>At 1 month</th>
<th>At 2 months</th>
<th>At 1 month</th>
<th>At 6 months</th>
<th>Consultation as needed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(symptom-directed)</td>
</tr>
<tr>
<td>Clinical and adherence counseling</td>
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<td>✓</td>
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<tr>
<td>Hb</td>
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<td>✓</td>
</tr>
<tr>
<td>ALT*</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Random blood sugar</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CD4</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Urinalysis</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pregnancy test for women with reproductive potential</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HIV and HCV screening</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Ref: ART Technical guidelines, NACO 2007

However, the ART guidelines by Association of Physicians of India recommended a determination of plasma viral load at six months to determine the efficacy of ARV regimen. This will help in assessing potency of regimen as well as adherence to regimen. A plasma viral load can identify failure earlier than CD4 count and reduces the accumulation of resistant mutations.

Adherence to ART:

The adherence to ART is one of the most crucial determinants of success of ART on long term basis. The adherence of 95% or more is crucial for patients to achieve desirable suppression of viral replication as depicted in figure below.
The adherence is determined by patients self report, pill count, appointments kept and refills obtained. The use of fixed dose combinations is an important part is improving adherence to ART. It is very important to adequately counsel the patients on adherence issues prior to start of therapy. Never start therapy on first visit, the patient needs to be adequately “prepared” to take it regularly on long term basis. The counselling must continue on every visit thereafter. One of the family members should be involved in treatment protocol and patient should be encouraged to join positive networks/visit drop in centres to interact with peer educators.

**Drug Interactions**

Potential drug-drug interactions should be taken into consideration while selecting an antiretroviral regimen and review of drug interaction potential should be undertaken when any new drug is to be added to an existing antiretroviral combination. A list of significant drug interactions with different antiretroviral agents should be available at ART Clinic for ready reference.

Most drug interactions with antiretroviral drugs are mediated through inhibition or induction of hepatic drug metabolism. All PIs and NNRTIs are metabolized in the liver by the cytochrome P450 (CYP) system, particularly by the CYP3A4 isoenzyme. All PIs are substrates and inhibitors of CYP3A4, with ritonavir having the most pronounced effect and saquinavir having the least potent inhibitory effect. The NNRTIs are also substrates of CYP3A4, and can be an inducer (nevirapine), an inhibitor (delavirdine), or a mixed inducer and inhibitor (efavirenz). Thus, these antiretroviral agents can interact with each other and with other drugs commonly prescribed for other concomitant diseases.

The list of drugs that may have significant interactions with PIs and/or NNRTIs is extensive and continuously expanding. Some examples of these drugs include medications that are commonly prescribed for HIV patients for other conditions, such as rifamycins (rifampicin), lipid-lowering agents (statins), benzodiazepines, calcium channel blockers, immunosuppressants (such as cyclosporine, and tacrolimus), neuroleptics, sildenafil, ergotamine, azole antifungals, macrolides, oral contraceptive and methadone.

Co-administration of PIs or NNRTIs with a potent CYP3A4 inducer, on the other hand, may lead to suboptimal drug concentrations and reduced therapeutic effects of the antiretroviral agents. These drug combinations should be avoided. If this is not possible, close monitoring of plasma HIV-RNA with or without antiretroviral dosage adjustment and/ or therapeutic drug monitoring may be warranted. For example, the rifamycins (rifampicin, and, to a lesser extent rifabutin) are CYP 3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs where ART and ATT is used concomitantly. As rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampicin for the treatment of tuberculosis when it is used with a PI- or NNRTI-based regimen despite the wider experience with rifampicin when used for this indication.

**Changing Therapy**

The reasons for changing an antiretroviral therapy regimen include:

1. Drug adverse effects,
2. Inconvenient regimens such as dosing/number of pills that may compromise adherence,
3. Treatment failure, (Clinical/immunological or virological)
4. Occurrence of active tuberculosis and
5. Pregnancy.

The decision to change regimen should be based on clinical history and physical examination; routine and relevant laboratory investigations, and changes in CD4 count. An assessment of adherence to medications should be made and remaining treatment options considered. Potential of initial viral resistance, drug interaction and diet also need to be considered.

**Change due to adverse effects/intolerance**

In a patient who experiences adverse effects or is intolerant to an otherwise successful regimen,” substitution” of the offending drug is reasonable. An example would be adverse effects of Zidovudine that can be replaced by Stavudine or skin reaction to nevirapine that should be substituted by efavirenz. For serious adverse effects, such as Abacavir hypersensitivity reactions and nevirapine related hepatic failure, rechallenge should not be attempted as this may lead to toxicity and death.

**Change due to treatment failure**

Treatment failure can be defined as clinical failure, immunologic failure and/or virological failure. Clinical failure is defined as occurrence or re-occurrence of HIV related events (after at least six months on an antiretroviral regimen), excluding immune reconstitution syndrome. Immunologic failure can be defined as fall of CD4 count to pre therapy baseline or below, 50% fall from the on treatment peak value or persistent CD4 below 100cell/cm^3. Virological failure can be defined as viral load of more than 10,000 copies/ml.

**Identifying Failure:- Clinical, Immunological and Virological Failures**

<table>
<thead>
<tr>
<th>Failure Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical failure</td>
<td>New or recurrent WHO stage 4 condition, after at least 6 months of ART</td>
</tr>
</tbody>
</table>
| Immunological failure | • Fall of CD4 count to pre-therapy baseline (or below)  
• 50% fall from the on-treatment peak value (if known)  
• Persistent CD4 levels below 100 cells/mm^3 |
| Virological failure | Plasma viral load > 10,000 copies/mL |

**Notes:**

i) Current event must be differentiated from IRIS.

ii) Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections) may indicate treatment failure and thus require second-line therapy to be considered.
vi) The optimal viral load value at which ARV drugs should be switched has not been defined. However, values of more than 10,000 copies/mL have been associated with subsequent clinical progression and an appreciable decline in the CD4 cell count.

The entire regimen should be “switched” from a first to a second line combination regimen in the case of treatment failure. A single drug should not be added or changed to a failing regimen. The new second-line regimen will need to use drugs, which retain activity against the patient’s virus strain and ideally include at least three new drugs, in order to increase the likelihood of treatment success. The table below is the second line regimens one could consider in adolescent and adults for each of the first-line regimens identified. NACO recommends the following second line drugs in the program.

TDF/3TC + LPV/r + ZDV is the standard regimen for all patients provided second line ART unless there is contraindication to ZDV such as hypersensitivity or anaemia from previous first line therapy use. In cases where the patient is anaemic and has prior history of intolerance to ZDV eg ZDV-related anaemia, the NACO regimen is TDF+3TC +LPV/r (without the ZDV).

### ARV drugs for 2nd line

<table>
<thead>
<tr>
<th>ARV drugs for 2nd line</th>
<th>Dosage</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + 3TC</td>
<td>Fixed dose combination of TDF 300 mg + 3TC 300 mg Once daily</td>
<td>1 – 0 – 0 (one tablet in the morning)</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Heat stable co-formulation of LPV 200mg + Ritonavir 50 mg</td>
<td>2 – 0 – 2 (two tablets in the morning and 2 tabs in the evening)</td>
</tr>
<tr>
<td>ZDV</td>
<td>Zidovudine 300 mg</td>
<td>1 – 0 – 1 (one tab in the morning and one tab in the evening)</td>
</tr>
</tbody>
</table>

Ref: Guidelines for second line ART in Adults Dec 2008, NACO

Nucleoside analogue cross-resistance is an increasing concern. When ZDV/3TC is used in the first-line regimen, nucleoside cross-resistance may compromise the potency of d4T/ddI in the second-line regimen, in particular in the presence of long-standing virological failure. In this regard, ABC/ddI might also be considered as the nucleoside backbone for a second-line regimen if the first line regimen did not include ABC. However, high-level ZDV/3TC resistance also confers diminished susceptibility to ABC.

The near complete cross resistance between EFZ and NVP means that a switch between these two agents in the setting of treatment failure is not advisable. In case of PIs, cross resistance among these agents is also common. A possible exception to this exists when nelfinavir (NFV) is the first PI employed. Therefore, in the case of treatment failure on a PI-based regimen, it is recommended that the PI be switched to an NNRTI.

Given the diminished potential of almost any second line nucleoside component, a ritonavir (RTV/r) enhanced PI component [indinavir (IDV)/r, lopinavir (LPV)/r, atazanavir/ritonavir, saquinavir (SQV)/r] is preferred to nelfinavir (NFV) in second line regimens because of its potency. NFV can be considered as an alternative for the PI component if a RTV-enhanced PI is not available or if there is a clinical contraindication to its use.

### ART and Tuberculosis

Due to a high prevalence of tuberculosis (TB) among HIV-infected individuals, many patients who are candidates for ART will have active TB. In addition, patients already receiving ART may develop clinical TB. Effective treatment and control of TB is a central priority when developing treatment strategies for co-infected patients. The management of HIV and TB co-infection is complicated because some antiretroviral agents produce unacceptable drug interactions with anti-tubercular agents and/or can increase toxicity of TB treatment. Tuberculosis treatment following the DOTS strategy should be initiated promptly in diagnosed cases of TB. The efficacy of DOTS in treating tuberculosis in HIV infected patients have been documented from some Indian publications also. The standard 6-8 months treatment using two drug regimen for two months intensive therapy followed by two drug for next four to six months as under the TB program is advocated for all. However, for those with CNS involvement, treatment for one year is recommended.

The two major issues in the clinical management of patients with HIV and TB are when to start ART and which regimen to use. Initiation of ART for TB patients at high risk for HIV disease progression and mortality is recommended, i.e., a CD4 count <200 cells/mm³, or extra pulmonary TB. For patients who develop TB with CD4 counts in the 50-200 cells/mm³ range or, in the absence of CD4 testing, have total lymphocyte counts <1200 cells/mm³, ART should be started after the first two months of TB therapy, because the toxicity of TB treatment is greatest during this period. In the subset of patients with very low CD4 cell counts (<50 cells/mm³) or those with other severe HIV disease, ART should be started as soon as TB therapy is tolerated. This group of patients should be specially monitored for development of IRIS. The NACO guidelines for management of HIV and TB infection are summarised in the following table (Revised April 2009).

### Type of TB | CD4 cell count (cells/ mm³) | Timing of ART in relation to start of TB treatment | ART recommendations
--- | --- | --- | ---
Pulmonary TB | CD4 < 350 | Start ATT first. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months) | Recommend ART. EFV containing Regimens
The first line treatment options include ZDV/3TC or d4T/3TC plus EFZ. All other NNRTIs and PI have significant interactions with rifampicin as discussed earlier. Alternatively, rifabutin can be used in place of rifampicin in the ATT regimen though this is not available under Revised National tuberculosis control program. EFV is the preferred drug as its potential to aggravate the hepatotoxicity of TB treatment appears less than with NVP.

Patients already receiving ART when they develop TB should adjust the regimen to be compatible with TB treatment (EFV based). Following completion of anti-tubercular therapy, the ART regimen can be continued or changed depending upon the clinical and immunologic status of the patient and affordability of drugs (EFV being more expensive than NVP). However, the National guidelines for India (NACO) recommend that the regimen should be changed from EFV to NVP once ATT is completed, and in such instances, NVP should be started as twice daily doses and not as once daily dose for 14 days.

**Important considerations before starting ART**

- No monotherapy or dual therapy is recommended.
- Starting ART in a patient not motivated enough to follow such treatment for indefinite period.
- Starting ART without providing adequate information about how and when to take the drugs, potential side effects and interactions with other drugs, when to stop the drugs, etc.
- Providing ART without the capacity to diagnose, treat or prevent opportunistic infections, emphasis on nutritional support.
- Providing ART without capacity to meet patient’s other needs such as sufficient nutritional support, adequate home care etc.

**Immune reconstitution Inflammatory Syndrome (IRIS)**

This is a spectrum of clinical signs and symptoms that occurs as a result of the body’s ability to develop an inflammatory response associated with recovery of the immune system. Antiretroviral therapy partially restores immune defects caused by chronic HIV infection, including the restoration of protective pathogen-specific immune responses. The protective response sometimes causes (atypical) inflammatory manifestations to concurrent infective or non-infective conditions, e.g., TB, MAC or CMV. Clinically, IRIS manifests itself as the occurrence or worsening of clinical and/or laboratory parameters, despite a favorable CD4 count (and viral load). The temporal association between the commencement of HAART (or change from a previously failing regimen) and the development of an unusual clinical phenomenon often provides a strong clue to the diagnosis of IRIS. Experience has shown IRIS can manifest itself in a variety of ways.

In India, the agreed practical definition of IRIS is the “occurrence of manifestations of new OIs or existing OIs within six weeks to six months after initiating ART; with an increase in CD4 count.”

The identified risk factors for infectious IRIS are

- An active or sub-clinical infection by opportunistic pathogens
- The antigens of non-viable microorganisms (e.g., Cryptococcus and CMV) are all possible targets for an immunopathological response
- A CD4 count of below 50/mm3 prior to the initiation of HAART
- Starting ART in close proximity to the diagnosis and initiation of treatment for an OI (should first treat and stabilize the OI, then start ART)

Non-infectious IRIS includes Guillain-Barre Syndrome, autoimmune thyroiditis and sarcoidosis. The differential diagnosis for IRIS includes active OI, ARV drug failure, ARV drug toxicity or failure of antimicrobial therapy if the patient is already on the treatment. Culturing the microorganism in body fluids may provide clues to an active OI, which would warrant antimicrobial therapy.

**FUTURE OPTIONS**

While antiretroviral drugs have done much to extend the lives of people infected with HIV, severe adverse effects and rising levels of drug resistance can limit their usefulness and hence, there is extensive effort to develop new anti-HIV medications. Progressive better understanding of the virus and the dynamics of replication has led to identification of new sites for the action of these drugs, as well as to the attempts in search for drugs that have different mechanism of actions. At least 24 new compounds are in pre approval clinical trials and six are in final stages. Some newer class of drugs like fusion inhibitors, integrase inhibitors etc. may just revolutionize the paradigms for how ART regimens are constructed. The newer group of drugs will offer freedom from cross resistance to pre existing classes. The new drugs that are under different stages of development include rilpivirin (second line NRTI), etravirine (newer NNRTI) and Tipranavir and Darunavir (new PI). The other new classes of drugs, in addition to the NRTI, NNRTI and PI that are showing promising options are:

**CONCLUSION:**

Antiretroviral therapy is quite effective in suppressing viral replication delaying the progression of disease and has changed the management of HIV disease dramatically, yet issues of adherence, toxicity, emerging resistance and cost of second line drugs dominate the scenario. The HIV care is still very complex and is rapidly evolving. The future options include new group of drugs, better strategies but the correct usage of these agents,
their timings of initiation and proper monitoring is of utmost importance if we want these drugs to remain effective. The therapy is no doubt panacea for those already infected, but HIV prevention messages and probably AIDS vaccines are the keys to halting the progression of the epidemic of this dreaded disease.

REFERENCES

12. WHO Guidelines on Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public health approach. 2006 Revision