Monitoring During Antiretroviral Therapy: Issues and Concerns

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With the rapid scale up of antiretroviral treatment programme in the public sector associated with availability of a large number of antiretroviral agents in the market and slashing of price by the Indian pharmaceutical industry, access to antiretroviral therapy (ART) has increased considerably in recent times in India. Due to the life-long nature of the treatment, monitoring of therapy demands serious attention.

Although, antiretroviral therapy should ideally be individualized as in the western world, yet the challenge before the low and middle income countries are to roll out the programme in a public health approach. Consequently, there are limited first-line, alternate first-line and second line regimens in the National ART programme.

A patient on ART should be monitored for efficacy of treatment, side-effects and toxicities of drugs, and adherence to therapy.

Efficacy of treatment can be assessed by clinical and laboratory (immunological and virological) parameters.

**MONITORING PATIENTS FOR EFFICACY OF TREATMENT**

All the patients, following initiation of ART, should be monitored by recording weight, BMI, functional status (working, ambulatory or bed-ridden), T-staging (WHO clinical staging while on ART), incidences of opportunistic infections, during all clinic visits\(^1\)\(^,\)\(^2\).

Review of concomitant use of other drugs to treat Opportunistic Infections, associated illnesses, is of paramount importance since drug interactions involving ARVs with prescription as well as non-prescription drugs are protean particularly with protease inhibitors and non nucleoside reverse transcriptase inhibitors. This has to be reviewed on each visit\(^1\)\(^,\)\(^2\).

**CD4 COUNT**

CD4 count has to be done routinely every 3 - 6 months and additionally, if needed, to identify treatment failure or diagnose Immune Reconstitution Inflammatory syndrome (IRIS) \(^3\). One must be aware of the variability of CD4 test results. Results that are inconsistent with prior trends should be repeated. Factors that influence CD cell count include analytical variation, seasonal & diurnal variation (with lowest value at 12.30 PM and highest at 8.30 PM), Intercurrent illnesses, corticosteroids, Interferon therapy etc. Modest decrease is noted following major surgery and certain acute infections. High dose corticosteroid administration has got a dramatic impact with sharp decline in count over short period. Deceptively high Cd4 count is observed following splenectomy and in HTLV - 1 co-infection \(^3\), CD4 percentage is preferred in children below 5 years of age. CD 4 count should ideally be estimated from the same laboratory on all occasions to avoid assay variation. The standard methods for determination of CD4 count include FACSCount, FACSCalibur, CyFlow etc. and the results are expressed as number of CD4 cells/µL of blood.

**VIRAL LOAD**

Although viral load is not essential in deciding when to start antiretroviral therapy, it is the most sensitive indicator to monitor treatment outcome. Typically, after the initiation
of antiretroviral therapy, the viral load is reduced by a factor of 1 $\log_{10}$ at 2 weeks and by 4 - 6 months, it becomes undetectable. Viral load is repeated every 3 - 6 months. Changes of < 0.5 $\log_{10}$ are not considered to be significant. Small, transient rise of viral loads, known as ‘blips’ are of no significance and probably represent statistical variation. There are three approved assays to measure HIV - 1 viral load: Reverse Transcription-Polymerase Chain Reaction (RT-PCR), branched-chain DNA (bDNA) and Nucleic Acid Sequence-Based Amplification (NASBA). These methods differ in levels of detection and in the linear range within which measurement is reliable or reproducible. Considerable differences exist between various methods and one should estimate the viral load for a particular patient by the same method. Details of different viral load measurement methods are given in Table I.

Routine tests that are done at 6-months interval include haemogram, LFT, urea, creatinine, lipid profile. For patients on PI-based therapy FBS, PPBS and routine urinalysis (TDF-based regimens) every 6 months is also recommended.

**MONITORING FOR SIDE-EFFECTS AND TOXICITIES OF ANTIRETROVIRAL DRUGS**

Side-effects and toxicities to antiretroviral agents should actively be sought for during all clinic visits. This include asking about common side-effects of drugs like tingling, numbness, pain in lower extremities, lassitude, fatigue, palpitation, effort intolerance, pain abdomen, vomiting, diarrhea, rash, jaundice etc. Thorough clinical examination should include looking for pallor, jaundice, absent ankle jerks, loss of vibration sensation in lower limbs, lipodystrophy, rash etc. (See Table II)

Routine laboratory tests employed to identify toxicities of antiretroviral drugs include frequent estimation of Hb% (for Zidovudine recipients), LFT (at least serum ALT), serum creatinine, blood sugar, lipid profile, routine urinalysis. Additionally, when suspected, further tests like serum amylase, lactate, electrolytes, abdominal imaging etc. are needed.

**MONITORING PATIENTS FOR ADHERENCE TO TREATMENT**

Adherence to antiretroviral drugs is crucial to the successfulness of ART. It has to be assessed during all clinical consultations by self-report by patient, re-call of ART ingestion events of 3-7 days, pill count (where feasible), and by biological parameters like CD4 count & plasma HIV viral load assay (wherever available). Adherence to Cotrimoxazole prophylaxis should also be emphasized.

**IDENTIFICATION OF TREATMENT FAILURE**

Treatment failure is first manifested either by failure to suppress the HIV viraemia to undetectable level after 4-6 months of ART OR rebound of detectable viraemia after initial suppression to undetectable level. This is followed usually by immunological failure and clinical failure.

Immunological failure is defined by occurrence of any of the following three conditions:

- a) Fall of CD4 count to below the baseline level
- b) Fall of CD4 count of > 50% of on-treatment peak value
- c) Failure of CD4 count to rise > 100 cell/µL after 1 year of continuous ART

Clinical failure is defined by occurrence of any WHO stage 4 conditions. However, it has to be remembered that certain stage 3 conditions like pulmonary TB and severe bacterial infections may be indicative of treatment failure.

**ART MONITORING STRATEGY**

Depending on the resources available, ART monitoring strategies can be of 3 types.

a) Clinical monitoring

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**Table I. Methods of measurement of HIV - 1 viral load**

<table>
<thead>
<tr>
<th>Test</th>
<th>Technology</th>
<th>Detection Limit (copies/ml)</th>
<th>Linear range (copies/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COBAS TaqMan HIV - 1 Test</td>
<td>RT-PCR</td>
<td>20</td>
<td>20 - 10,000,000</td>
</tr>
<tr>
<td>Versant HIV - 1 RNA 1.0 Assay</td>
<td>RT-PCR</td>
<td>37</td>
<td>37 - 11,000,000</td>
</tr>
<tr>
<td>Abbott Real Time HIV - 1</td>
<td>RT-PCR</td>
<td>40</td>
<td>40 - 10,000,000</td>
</tr>
<tr>
<td>Versant HIV - 1 RNA 3.0 Assay</td>
<td>bDNA</td>
<td>65</td>
<td>50 - 500,000</td>
</tr>
<tr>
<td>NucliSENS EasyQ HIV Version 2.0</td>
<td>NASBA</td>
<td>250</td>
<td>25 - 7,900,000</td>
</tr>
</tbody>
</table>
**Table II. Methods of measurement of HIV - 1 viral load**

<table>
<thead>
<tr>
<th>Name of antiretroviral drug</th>
<th>Side-effects &amp; toxicities</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors</strong></td>
<td></td>
<td></td>
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<tr>
<td>Zidovudine</td>
<td>Anorexia, nausea, vomiting, headache, insomnia, anaemia, neutropenia, nail discoloration, myopathy, hepatic steatosis with or without hepatomegaly, rash</td>
<td>Anaemia common during the first 3 - 6 months of ART initiation; monitoring Hb% at 1, 2, 3, 6 months needed</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Peripheral neuropathy, lipoatrophy, pancreatitis, lactic acidosis, dyslipidaemia, hepatic Steatosis with or without hepatomegaly, ascending neuromuscular weakness mimicking Guillain Barre Syndrome (rarely)</td>
<td>Vibration sense and ankle jerks should be monitored in each visit to detect peripheral neuropathy at the earliest</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Hypersensitivity reaction is manifested by fever, skin rash (maculopapular or urticarial; ~ 70%), fatigue, malaise, GI symptoms (nausea, vomiting, diarrhoea, abdominal pain), arthralgia, cough, dyspnoea</td>
<td>Most well tolerated NRTI in adults; sudden withdrawal in HIV/HBV co-infected patients may precipitate hepatic flare</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Most well tolerated NRTI in adults; sudden withdrawal in HIV/HBV co-infected patients may precipitate hepatic flare</td>
<td>It has the lowest genetic barrier for development of resistance. Because of reduced replicative capacity of Lamivudine mutant viruses (M 184V) and favorable interaction between M184 V, K65R and TAMs, it is often used in 2nd line despite development of mutation</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Similar to Lamivudine, may cause hyperpigmentation over palms &amp; soles; sudden withdrawal in HIV/HBV co-infected patients may precipitate hepatic flare</td>
<td>HLA B5701 screening eliminates risk of hypersensitivity; Re-challenge with Abacavir may be fatal.</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Pancreatitis, peripheral neuropathy, lipodystrophy, hyperuricaemia, hepatic Steatosis with or without hepatomegaly</td>
<td>Avoid with alcohol</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Flatulence, diarrhea; rarely renal impairment with Fanconi like syndrome with hypophosphataemia, hypouricaemia, proteinuria, normoglycaemic glycosuria &amp; rarely ARF; sudden withdrawal in HIV/HBV co-infected patients may precipitate hepatic flare</td>
<td>Effective against HBV, so sudden withdrawal may cause flare due to HBV; Serum creatinine &amp; routine urinalysis every 6 months should be done</td>
</tr>
<tr>
<td><strong>Non Nucleoside Reverse Transcriptase Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Rash, hepatitis</td>
<td>Hepatitis is expected to occur in higher frequency if baseline CD4 is &gt; 250/µL in female and &gt; 400/µL in male; increased incidence in HBV &amp; HCV co-infection &amp; other chronic liver diseases; frequent monitoring of ALT is required.</td>
</tr>
</tbody>
</table>
**Name of antiretroviral drug** | **Side-effects & toxicities** | **Comments**
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**Non Nucleoside Reverse Transcriptase Inhibitors**
Efavirenz | CNS symptoms are common; vivid dreams, nightmare, insomnia, dizziness, headache, inability to concentrate, agitation, confusion, depression, hallucination (rare), suicidal ideation (rare); typically starts on 1st / 2nd night but usually subsides by 2 to 6 weeks; Teratogenic (neural tube defects among newborns) | Ruling out pregnancy is needed before prescribingEfavirenz to a woman with child-bearing potential who is not on any contraceptives. CNS symptoms should be discussed with patients before prescribing Efavirenz and patient should be counseled to continue as most would come out of the symptoms by 2 - 6 weeks and the discontinuance rate is low.

**Protease Inhibitors** *
Indinavir, Nelfinavir, Saquinavir, Lopinavir, Atazanavir, Darunavir | All the protease inhibitors can cause diarrhea, lipodystrophy, dyslipidaemia (particularly hypertriglyceridaemia), glucose intolerance, diabetes mellitus, osteopenia, osteonecrosis, avascular necrosis of head of humerus and femur, increased bleeding episodes in haemophiliacs. Indinavir and Atazanavir can cause unconjugated hyperbilirubinaemia & renal calculus. | Diarrhoea is often self-limiting (can be controlled by loperamide in severe cases); monitoring of blood sugar, lipid profile every 6 months needed.

**Integrase Strand Transfer Inhibitors**
Raltegravir | Well tolerated |  |

**CCR5 Receptor Antagonist**
Maraviroc | Diarrhoea, nausea, headache, fatigue, postural hypotension; rarely hepatotoxicity, rash | Requires phenotypic assay to determine the receptor tropism of the HIV isolate to know efficacy of Maraviroc. It is effective against R5 tropic virus but ineffective against R4 or ‘Duo/Mixed’ tropic virus. Phenotypic assays are costly, currently unavailable in India

**Fusion Inhibitor**
Enfuvirtide | Injection site reaction, Increased incidence of bacterial pneumonia |  |

* All PIs are boosted with Ritonavir except Nelfinavir

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b) Clinical and immunological monitoring
c) Clinical, immunological and virologic monitoring
Randomized, control studies like HBAC [Home based AIDS Care] ⁶ and DART [Development of Antiretroviral therapy in Africa] ⁷ have shown that clinical monitoring alone, in comparison to combined immunological and clinical monitoring or to combined virological, immunological and clinical monitoring, is associated with increased mortality, disease progression, unnecessary switches but no significant difference in serious drug toxicities. The HBAC trial also documented that there was no significant difference in mortality, disease progression, unnecessary switches, or virologic treatment failures between the two strategies of combined immunological & clinical monitoring, and combined virological, immunological and clinical monitoring.
Viral load (VL) is considered a more sensitive and reliable indicator of treatment failure as compared to immunologic and clinical indicators. Viral load may be used in a targeted or routine strategy. In routine VL strategy, viral load is estimated before initiation of ART and thereafter every 4-6 months. Objective of this strategy is to detect virologic failure early to help in adherence intervention and change in therapy to limit ongoing viral replication, to reduce risks of accumulation of resistance mutations, and to protect drug susceptibility of 2ndline & subsequent therapies. However, this is associated with earlier & frequent switches to 2ndline ART. In settings with availability and accessibility of all the licensed antiretroviral drugs and drug resistance testing facility (genotypic drug resistance test), this strategy is best used.

Targeted viral load strategy, on the other hand, is aimed to confirm suspected clinical and immunologic treatment failure. This maximizes clinical benefits of 1st line ART and reduces unnecessary switches to 2nd line ART. This is ideal for settings with limited treatment options like in public health approaches of ART scale up.

**KEY POINTS**
- Patients on ART should be monitored regularly for treatment effectiveness, toxicities & side-effects and adherence
- Clinical and immunological monitoring is to be done for all patients on ART
- Targeted viral load monitoring strategy is appropriate for resource restricted settings with limited second line options
- Treatment failure should ideally be confirmed by viral load assay
- Switch to second line ART is to be guided by documented virologic failure

**REFERENCES**
1. Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach - 2010 revision (WHO)