

**INTRODUCTION**

There has been significant increase of universal access to antiretroviral therapy (ART) over the last three decades resulting in substantial reductions of morbidity and mortality and increase in life expectancy of people living with HIV/AIDS (PLHIV). While most of the present day guidelines (WHO, DHHS) recommend initiation of ART regardless of clinical stage and CD4 count, the current NACO guideline (2016) advocates the start of ART in patients with clinical stage 3 & 4 (irrespective of CD4 count) and in PLHIV with  $CD4 \leq 500$  cells/mm<sup>3</sup> in clinical stage 1 & 2. Following initiation of ART, in most of the patients, the plasma HIV-1 viral load becomes undetectable by 4-6 months associated with substantial rise of CD4 count. A sustained high degree of adherence is required to maintain long-term viral suppression. However, because of very high rate of HIV replication and error-prone reverse transcription, mutations and consequent development of HIV drug resistance is inevitable - leading to virologic rebound, immunologic decline and clinical disease progression. While HIV genotypic drug resistance testing is mandatory in the developed world prior to ART initiation and switch, in public health programs of middle & low income countries such testing facility is largely unavailable. Patients in the western world are monitored routinely by plasma HIV viral load & CD4 count every 3 - 6 months. In the National ART Program of India, the patients are monitored clinically every month and by CD4 tests every 6 months.

**DEFINITION OF ANTIRETROVIRAL TREATMENT FAILURE**

Failure on antiretroviral treatment can be categorized as virological failure, immunological failure and clinical failure.

**Virological Failure**

It is defined as HIV RNA viral load of 1000 copies/ml on two consecutive occasions after at least 6 months of ART (WHO) or repeated detection of HIV RNA level > 200 copies/ml (DHHS). Virologic failure should be differentiated from viremia 'blips' which is defined as viral suppression followed by transient/isolated low level detectable HIV RNA (typically < 200 copies/ml) and subsequent return to undetectable levels. Blips probably represent statistical variations and are not associated with the risk of subsequent virologic failures.

**Immunological Failure**

It is defined as suboptimal immunologic response to therapy or an immunologic decline while on therapy. The

decrease in CD4 cell count to pre-therapy baseline level, or >50% fall from on-treatment peak value or persistently low CD4 cell counts of < 100 cells/mm<sup>3</sup> even after 6-12 months of ART, constitute immunologic failure.

**Clinical Failure**

It is defined as occurrence or recurrence of a WHO stage 3 or 4 condition while on antiretroviral treatment. The progression of clinical disease should be differentiated from immune reconstitution inflammatory syndrome (IRIS).

Typically, virologic failure is the first even followed by immunologic & clinical failure.

While routine virologic monitoring is the standard of care in industrialized countries, targeted viral load testing is still practiced in resource-restricted settings to confirm immunologic &/or clinical failure before switching to second or third-line treatment. Although the targeted viral load approach is cost-saving, but it is associated with late diagnosis of treatment failure.

Causes of virologic failure are protean and include patient-related as well as regimen-related factors.

Patient-related factors include non-adherence, high baseline HIV RNA, low baseline or nadir CD4 count, comorbidities (active substance use, psychiatric illness, and neurocognitive disorders), transmitted/acquired drug resistance, prior treatment failure.

Among the ARV related factors the important ones are drug side-effects, sub-optimal pharmacokinetics, sub-optimal virologic potency, functional monotherapy, food requirement/restriction, pill burden & frequency, adverse drug-drug interactions with co-administered drugs and cost & affordability.

Evaluation of virologic failure should include an assessment of patient-related as well as ARV-related factors. Adherence is a key determinant of the degree and duration of virologic suppression. Considering the fact that non-adherence to ART is the strongest predictor for failure to achieve viral suppression, assessment of adherence is crucial and all attempts need to be taken to identify the cause of non-adherence and initiate focused adherence support measures.<sup>7</sup> Drug toxicities, drug-drug interaction, depression, and active substance use need to be looked for and addressed specifically. Assessment of recent clinical history and physical examination, adherence, remaining treatment options, potential resistance pattern from previous therapies and patient's

**Table 1: Preferred second-line ART regimens for adults & adolescents (WHO)**

First-line regimen	Second-line Regimen	Alternative second-line regimen
Zidovudine/stavudine + lamivudine + nevirapine/efavirenz	Tenofovir + lamivudine + ritonavir-boosted atazanavir or lopinavir	2 NRTIs + ritonavir-boosted darunavir
Tenofovir /abacavir + lamivudine + nevirapine/efavirenz	Zidovudine + lamivudine + ritonavir-boosted atazanavir or lopinavir	2 NRTIs + ritonavir-boosted darunavir

HBV-HIV co-infected patients failing tenofovir + lamivudine/emtricitabine + efavirenz based regimen should receive zidovudine + tenofovir + lamivudine/emtricitabine + ritonavir boosted atazanavir / lopinavir.

\* Raltegravir + ritonavir-boosted Lopinavir can be an alternative second-line regimen for selected patients with NRTI toxicities or resistance to all NRTIs.

**Table 2: Preferred second-line & third-line ART regimens for adults & adolescents (NACO)**

First-line regimen	Second-line Regimen	Third-line Regimen
Zidovudine/stavudine + lamivudine + nevirapine/efavirenz	Tenofovir + lamivudine + ritonavir-boosted atazanavir or lopinavir	Raltegravir + ritonavir-boosted darunavir*
Tenofovir /abacavir + lamivudine + nevirapine/efavirenz	Zidovudine + lamivudine + ritonavir-boosted atazanavir or lopinavir	Raltegravir + ritonavir-boosted darunavir*

\* In patients failing second-line ART with plasma HIV viral load > 100,000 copies/ml or CD4 count < 200 cells/mm<sup>3</sup>, in addition to raltegravir + ritonavir-boosted darunavir, the NRTI backbone of Zidovudine + lamivudine or Tenofovir + lamivudine need to be recycled.

understanding of consequences of new regimen are important before taking decisions regarding switching of ART regimen.

HIV drug Resistance (DR) testing should be done while the patient is still on the failing therapy or within 4 weeks of discontinuance of the same. If the test is done beyond 4 weeks of treatment discontinuation, some of the key HIV DR mutations may be missed. For most of the HIV DR assays, a minimal viral load of 500 – 1,000 copies/ml is essential.

#### Further treatment decision (Tables 1 & 2)

The goal of second/ third line regimen is to achieve an undetectable HIV viraemia. Ideally, the new ART regimen should contain at least two, preferably three fully active antiretroviral drugs. These active drugs are usually identified by HIV DR testing, patient's past ARV history, CCR5 tropism assay etc. As a rule single active drug should never be added to a failing regimen. In absence of HIV DR results, the ARV history, knowledge of the genetic barrier & common mutations associated with different classes as well as specific ARV drugs, help in formulating the subsequent (2<sup>nd</sup>/3<sup>rd</sup> line) regimens. The heavily treatment experienced patients, failing multiple classes with very few treatment options with the available drugs, may benefit from HIV phenotypic resistance test results.

For patients failing non-nucleoside reverse-transcriptase inhibitor-based first-line ART, it is recommended to switch to boosted protease inhibitor (PI)-based regimens with unused NRTI backbone. Some ARVs despite having drug resistance (e.g. NRTIs) contribute partial activity in new regimen, while others are not (e.g. NNRTI, INSTI, and Enfuvirtide). Of note, a new/unused drug may not be fully active due to potential cross resistance among

drugs of the same class. Maraviroc can only be used in patients harbouring CCR5 tropic virus as ascertained by genotypic/phenotypic co-receptor tropism assay.

According to WHO, the preferred third-line regimen should include new drugs with minimal risk of cross-resistance to previously used regimens, e.g. integrase inhibitors like dolutegravir or raltegravir, second-generation NNRTI (etravirine) and PI (darunavir). It also recommends if a patient is failing on a second-line regimen with no new ARV drug option, s/he should continue with a tolerated ARV regimen.

#### ISOLATED CENTRAL NERVOUS SYSTEM VIROLOGIC FAILURE

A rare form of virologic failure has been documented in a subset of patients having HIV breakthrough in CSF in presence of suppressed plasma HIV. They usually present with sub-acute onset of new CNS symptoms & signs. MRI brain usually shows abnormalities and CSF demonstrates lymphocytic pleocytosis. CSF HIV RNA is typically higher than plasma HIV RNA. The CSF-virus often demonstrates drug resistance. Antiretroviral regimens need to be switched according to the CSF HIV drug resistance report, if available. In absence of CSF HIV resistance testing, the regimen may be changed based on patient's ARV drug history and by selecting drugs with higher CNS Penetration Effectiveness (CPE) Score.

#### SUMMARY

Management of treatment-experienced patients requires judicious selection of subsequent regimens to achieve durable suppression of HIV. Review of past ARV history, side-effects & toxicities, drug-drug and drug-food interactions and assessment of adherence are crucial before switching to a new regimen. Identification of

barriers to adherence and adoption of remedial measures to improve adherence are of utmost importance.

## REFERENCES

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