**DRAFT GUIDELINES FOR NATIONAL ROLL-OUT OF SECOND LINE ART**
**April 2011**

# National Guidelines on Second-line ART for adults and adolescents

April 2011

NATIONAL AIDS CONTROL ORGANISATION, MINISTRY OF HEALTH &FW, GOVT OF INDIA

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## Acronyms and abbreviations

| | |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| AIDS | acquired immunodeficiency syndrome |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| ATV | atazanavir |
| ZDV | zidovudine (also known as ZDV) |
| bPI | boosted PI |
| CD4 count | CD4+ T-lymphocyte |
| COE | Centers of excellence |
| d4T | stavudine |
| ddI | didanosine |
| EC | enteric coated |
| EFV | efavirenz |
| FDC | fixed-dose combination |
| FTC | emtricitabine |
| Hb | haemoglobin |
| HIV | human immunodeficiency virus |
| IDV | indinavir |
| LPV | lopinavir |
| NFV | nelfinavir |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NVP | nevirapine |
| PI | protease inhibitor |
| PLWHA | people living with HIV/AIDS |
| /r | low-dose ritonavir |
| RTV | ritonavir |
| SACEP | State AIDS Clinical Expert Panel |
| SQV | saquinavir |
| TDF | tenofovir disoproxil fumarate |
| VL | viral load |

# Introduction and Preamble

## Introduction

The National ART programme launched on 1st April, 2004 in eight government hospitals in six high prevalence states has since been scaled up to 300 centres where in a total of 12,53,500 patients have been registered in HIV care and nearly 404882 are currently on ART as on March 2011. The major **targets** of national ART programme under NACP-III are:

1. To provide free ART to 300,000 adult and 40,000 paediatric PLHAs by 2012 through 250 ART centres and 650 Link ART centres
2. To involve inter-sectoral partners, NGOs and Private partners, so as to have a comprehensive national framework of ART programme.
3. To achieve and maintain a high level of drug adherence and minimise the number of patients lost to follow up, so that drugs are effective for longer period of time.
4. To provide comprehensive care, support and treatment through establishment of 350 CCCs by 2012.

In order to improve the quality of care offered to PLHAs, following activities have been undertaken in the last year.

1. Revision of technical and operational guidelines on ART, OI, CCC & Paediatric care
2. Revision of training modules for Doctors, Counsellors and nurses.
3. Appointment of Regional Coordinators for Care, Support & Treatment.
4. Tracking of Patients lost to follow up
5. Revision of Manpower at ART Centres
6. Strengthening the capacity of laboratories for CD4 testing
7. Constitution of Technical Resource Group on ART,CCC.Paeds care and Research
8. Strengthening of Supply Chain Management for ARV Drugs
9. Conceptualization and Operationalisation on Link ART Centres
10. Collaboration with intersectoral partners, NGOs & CII:
11. Establishing Community Care Centres and linking them to ART centres
12. Establishing ten Centres of Excellence in HIV care
13. Launch of National Paediatric HIV/AIDS initiative:

The national program at present provides only first line antiretroviral drugs. It has been seen from available data that nearly 2-3% patients on ART have developed treatment failure to the first line drug regimen as reported from a rapid survey of 38 ART centers conducted by WHO and NACO in Dec 2006.

The Technical Resource Group (TRG) on ART at NACO deliberated and formulated the technical and operational guidelines related to provision of second line ART. The TRG observed that for a roll out of second line drugs, it is essential to build the capacity of doctors as HIV/AIDS treatment is not a part of regular teaching in hospitals and many doctors may not be aware of technical protocols for second line drugs. Hence, a special training of health care providers is required prior to roll out of second line drugs. The group also recommended that institutional strengthening is necessary prior to the roll out, particularly laboratories for viral load testing essential for second line drugs initiation, but not routinely available in the hospitals. As the second line drugs have more side effects and tolerability of these drugs is much less compared to the first line drugs and the patient has to take 7-9 pills per day in the second line ART regimen compared to only 2 pills per day in first line ART necessitating strong systems to ensure patient adherence for a long term response. All these regulatory mechanisms need to be in place to minimize the chances of resistance due to wrong prescriptions as there is no third line. The second line drugs are almost ten times costlier than first line drugs and hence there are huge financial implications also

The TRG recommended that second line drugs should be provided in a phased manner, starting with a pilot project at 2 ART centers, viz. GHTM Tambaram and JJ Hospital, Mumbai. During the pilot roll out, only the patients who are on ART at these centers for at least 6 months were to be considered for second line ART. The experience gained at these two centers during the pilot phase was to be studied and used for further modification of protocols for replication at the 10 proposed “centers of excellence” across the country. The group also recommended that the second line drugs should be provided first to patients who are enrolled in the National ART programme from the beginning of their treatment and are now failing. The expansion should be in a phased manner and strictly monitored. The pilot was started in January 2008.

A team of experts visited both the pilot sites in July 2008, analyzed the patient case records in depth and visited the residence of patients started on second line to understand constraints in adherence to these drugs. The results were then shared with the TRG which recommended a phase expansion to 8 more centres starting with their own patients and then expanding the linkages to other ART centres in the country.

Currently second line ART is available at 10 COE wherein nearly 2000 patients are receiving free second line ART. It is being further extended to 8 ART plus centres now and another 13 centres in this year.

The national programme will also provide alternative first line ARV drugs for substitution in case of toxicity/intolerance to drugs presently available in first line therapy and also second line ARV regimen for patients with documented treatment failure following a public health approach.

# Section I:

# TECHNICAL GUIDELINES

## 1.1 FIRST LINE & SECOND LINE DRUG REGIMEN :

The working definition of first and second line regimen is as follows:

***First-line ART*:**

First-line ART is the initial regimen prescribed for an ART naïve patient when the patient fulfils national clinical and laboratory criteria to start ART.

*(Current NACO treatment guidelines for first-line ART recommends two classes of drugs for initial treatment ie 2 NRTI + 1 NNRTI.)*

***Second-line ART*:**

Second-line ART is the next regimen used in sequence immediately after first-line therapy has **failed.**

*(Current NACO treatment guidelines recommend that the protease inhibitor (PI) class is reserved for, and therefore characterizes second-line ART. Ritonavir-boosted protease inhibitors (bPIs) are recommended, supported by two agents from the NRTI class.)*

## 1.2 SUBSTITUTION VS SWITCH

Change of ARVs prescribed should be carefully distinguished between substituting a drug within a regimen and switching the entire ART regimen:

- Failure refers to the loss of antiviral efficacy and triggers the **SWITCH** of the entire regimen from first to second line. It is identified by clinical and/or immunological and/or virological monitoring.

- Single drug replacement of individual ARV (usually within the same class) refers to **SUBSTITUTION of individual drugs** for toxicity, drug-drug interactions, or intolerance; which does not indicate a second line regimen is being used.

Accordingly the following ART regimens have been designated as "**National ART regimen**" by National AIDS Control Organisation.

Table 1: National ART regimens

| National ART Regimen | Regimen | Remarks | To be made Available at |
|---|---|---|---|
| **Regimen I** | Zidovudine + Lamivudine + Nevirapine | "Preferred regimen" | |
| **Regimen I (a)** | Stavudine + Lamivudine + Nevirapine | For patients with Hb < 8 gm/dl | |
| **Regimen II** | Zidovudine + Lamivudine + Efavirenz | preferred for patients on anti-tuberculosis treatment and Hb > 8gm/dl | All ART centers |
| **Regimen II (a)** | Stavudine + Lamivudine + Efavirenz | for patients on anti-tuberculosis treatment and Hb < 8 gm/dl | |
| **Regimen III** | Tenofovir+ Lamivudine + Nevirapine | For patients not tolerating ZDV or d4T on a NVP-based regimen | Refer to SACEP for decision. |
| **Regimen III (a)** | Tenofovir + Lamivudine + Efavirenz | For patients not tolerating ZDV or d4T on a EFV-based regimen | |
| **Regimen IV** | Zidovudine + Lamivudine + Atazanavir/Ritonavir | For patients not tolerating both NVP and EFV, and Hb > 8gm/dl | |
| **Regimen IV (a)** | Stavudine + Lamivudine + Atazanavir/Ritonavir | For patients not tolerating both NVP and EFV and Hb < 8 gm/dl | Centers of excellence |
| **Regimen V** | Tenofovir + Lamivudine + Atazanavir/Ritonavir | | |

## 1.3 ALTERNATIVE ARV DRUGS FOR INTOLERANCE TO ZDV/D4T AND NVP/EFV: SUBSTITUTION

Substitution of ARV drugs for reasons of intolerance or toxicity or drug-drug interactions may be needed in following cases:

- Intolerance to both ZDV and d4T : in this case, TDF+3TC as fixed dose combination will be provided, after consultation with the SACEP. Drug supply mechanism to be decided.
- Intolerance to both NVP and EFV: in this case, ATV/r as a substitution ARV will be provided upon review and approved by the SACEP. The patient shall be managed and provided ATV/r by the COE for at least 6 months and then transferred back to the referring ART center.
  ***(Presently it has been decided that all patients on second line will continue to get drugs at COE only and decision to shift them back to referring ART centre shall be made on case to case basis depending on capacity of the ART centre. This shall be decided by NACO and communicated later)***
  *(*See section on Operational guidelines).

With reference to p36, section A9 NACO 2007 ART Guidelines for Adults and Adolescents, as a general principle, mild toxicities do not require discontinuation of ART or drug substitution. Symptomatic treatment may be given. Moderate or severe toxicities may require substitution of the drug with another of the same ARV class.

Table 2: Major Toxicities caused by first-line ARVs regimen and recommended drug substitutions

| Regimen | Toxicity | Drug substitution |
|---|---|---|
| **D4T/3TC/NVP** | • d4T related neuropathy or pancreatitis<br>• d4T related lipodystrophy<br>• NVP related severe hepatotoxicity<br>• NVP related severe rash(but not life threatening)<br>• NVP related life-threatening rash(Stevens-Johnson syndrome) | • Substitute with ZDV<br>• Substitute with TDF<br>• Substitute with EFV (except in first trimester of pregnancy)<br>• Substitute with EFV<br>• Substitute with PI |
| **ZDV/3TC/NVP** | • ZDV related persistent GI intolerance or severe hematological toxicity<br>• NVP related severe | • Substitute with d4T<br>• Substitute with EFV (except in pregnancy. |

| | | |
|---|---|---|
| | hepatotoxicity<br><br>• NVP related severe rash (but not life-threatening)<br>• NVP-related life threatening rash (Stevens Johnson Syndrome) | In this situation, switch to ATV/R<br>• Substitute with EFV<br><br>• Substitute with PI |
| **D4T/3TC/EFV** | • d4T related neuropathy or pancreatitis<br>• d4T related lipoatrophy<br>• EFV related persistent CNS toxicity | • Substitute with ZDV<br>• Substitute with TDF<br>• Substitute with NVP |
| **ZDV/3TC/EFV** | • ZDV related persistent GI intolerance or severe hematological toxicity<br>• EFV related persistent CNS toxicity | • Substitute with d4T<br><br>• Substitute with NVP |

**Notes:**

- *The general principle is that single drug substitution for toxicity should be made within the same ARV class eg substitution of d4T with ZDV or TDF (for neuropathy), ZDV with d4T or TDF (for anaemia) or EFV with NVP (for CNS toxicity or in pregnancy).*
- *Substituting d4T may not reverse lipodystrophy but may slow its progression. Besides ZDV and TDF, ABV or ddI are acceptable alternatives but these are not available in the national programme*
- *If a life-threatening toxicity occurs, all ART should be stopped until the toxicity has resolved and a revised regimen commenced when the patient has recovered.*

* ***It has been decided that 'triple NRTI approach' will not be used in the National programme until further data is available globally****

*(Source: Table 23, p38 NACO 2007 ART Guidelines for adults and adolescents)*

Experience has shown that in nearly 3-5 % of patients on ART in India, despite substitution from ZDV to d4T or from d4T to ZDV for toxicities, cannot tolerate either ZDV or d4T. Furthermore, some patients may not tolerate either NVP or EFV eg development of Steven Johnson Syndrome. In this minority of cases, the national programme will provide alternative drugs for substitution for reasons of toxicity as follows:

Table 3: Substituting with alternative first line ARV drugs

| **First line ARV causing the toxicity** | **Alternative substitute** | **Remarks** |
|---|---|---|
| **(a) Intolerance to both ZDV and d4T**<br><br>Patient should have been tried on ZDV **and** d4T with **documented intolerance** to both. TDF+3TC will be provided after review by the SACEP. Drug supply mechanism to be decided. | | |
| d4T + 3TC<br>ZDV + 3TC | TDF + 3TC | Continue the same NNRTI<br>(either NVP or EFV) |
| **(b) For intolerance to both NVP and EFV**<br><br>Patient should have been tried on both NVP **and** EFV (except for if history of Steven Johnson Syndrome is present) and **documented** as not tolerating, before requiring substitution for the NNRTI component | | |
| NVP or EFV | ATV/R | Continue with the same NRTI backbone ie ZDV/3TC or d4T/3TC if no problems |
| *Essentially this moves the patient to the PI-based regimen. Counsel for good adherence. If this regimen fails, there is no other optimal alternative/third line regimen.*<br>*These patients should be referred to the SACEP for review, then COE shall manage and provide ATV/R as substitution for intolerance to NNRTI.* | | |

*See annex IV : Severity grading of clinical and laboratory toxicities of ARVs*

## 1.4 MONITORING PATIENTS ON 1ST LINE ART FOR FAILURE

*(Reference: p39 Section A10, NACO 2007 ART Guidelines of adult and adolescents)*

**Good adherence is the key to maintaining the first line ART for longer duration**

**Good adherence is required for second line ART to ensure viral suppression and increase survival.**

The principles of monitoring patient on first line ART are:

- **Clinical monitoring and staging** at each visit as per NACO guidelines
  - Do clinical staging at each visit: use the T staging for clinical events (see Table 4 below).

- **Immunological monitoring:** Ensuring the routine monitoring lab tests are done eg. CD4 count every 6 months

- **Adherence support and monitoring** to ensure >95% adherence
  - Check for progress of improvement at each visit and weight
  - Screen for TB: ask for symptoms and signs of TB eg fever, weight loss, night sweats, haemoptysis
  - Determine if Cotrimoxazole is required or not, based on CD4 counts

Table 4: Example: use of the T clinical staging for monitoring patients on ART

| Visit | Symptoms and signs | WHO Clinical Stage to record on patient treatment card | Remarks |
|---|---|---|---|
| 1st visit | Oral thrush, chronic diarrhoea, PCP diagnosed | 4 | Treat OI, prepare patient and start first line ART |
| 2nd visit | Other symptoms improved but new herpes zoster | T 2 | Give symptomatic treatment |
| 3rd visit | Asymptomatic | T 1 | |
| 4th visit | Asymptomatic | T 1 | |

(Note: T refers to the staging event on treatment)

Development of a new or recurrent WHO Clinical stage 3 or 4 condition while on ART for at least 6 months, is considered functional evidence of the **progression of HIV disease**. An exception is pulmonary TB and some types of extra pulmonary TB which needs further evaluation and may not signify treatment failure (see below)

Table 4: Clinical staging events to guide decision making on switching

| New or recurrent event on ART[a] | Recommendations | Additional Management Options |
|---|---|---|
| Asymptomatic (T1) | Do not switch regimen | • Maintain schedule follow-up visits, including CD4 monitoring (if available)<br>• Continue to offer adherence support |
| Stage 2 event (T2) | Do not switch regimen[b] | • Treat and dmanage staging event<br>• Assess and offer adherence support<br>• Check if on treatment for at least six months<br>• Assess continuation of reintroduction of OI prophylaxis<br>• Schedule earlier visit for clinical review and consider CD–4 (if available)[c] |
| Stage 3 event (T3) | Consider switching regimen[bd] | • Treat and manage staging event and monitor response<br>• Assess and offer adherence support<br>• Check if on treatment for at least six months<br>• Check CD4 cell count (if available)[cd]<br>• Assess continuation of reintroduction of OI prophylaxis |
| Stage 4 event (T4) | Switch regimen[be] | • Treat and manage staging even and monitor response<br>• Check if on treatment for at least six months<br>• Assess continuation or reintroduction of OI prophylaxis<br>• Check CD4 cell count (if available)[c]<br>• Assess and other adherance support |

a Refers to clinical stages while on ART for at least six months (termed T1, T2, T3, T4)

b Differentiation of opportunistic infections from immune reconstitution inflammatory syndrome is necessary.

c Treat and manage the staging event before measuring CD4 cell count.

d Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections) may be indicators of tratment failure and thus require consideration of second-line therapy; response to appropriate therapy should be used to evaluate the need for switching of therapy.

e Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not be indicators of treatment failure and thus do not require consideration of second-line therapy, response to appropriate antimicrobial therapy should be used to evaluate the need to switch therapy.

TB can occur at any CD4 level and does not necessarily indicate ART failure. The response to TB therapy should be used to evaluate the need to switch ARV drugs. In the case of pulmonary TB and some types of extrapulmonary TB (e.g. simple lymph node TB or uncomplicated pleural disease), the response to TB therapy is often good and the decision to switch ARV drugs can be postponed and monitoring can be stepped up. This also applies if severe and/or recurrent bacterial infections (as stage 3 or 4 events) or oesophageal candidiasis respond well to therapy.

*(Source: Table 27, p42 NACO 2007 ART Guidelines for adults and adolescents)*

## 1.5 Identifying Treatment Failure

***High index of suspicion is required***

Look for the following among patients who have been receiving first line ART for at least 6 months:

- New OIs/recurrence/clinical events after 6 months on first line ART( after ruling out IRIS)
- Clinical deterioration in spite of good adherence to therapy
- Progressive CD4 count decline
- Slow/no clinical improvement over 6-12 months, associated with stationary CD4, despite good adherence

The NACO definitions of ART failure are in table 5 below:

Table 5: Clinical, immunological and virological definitions of treatment failure for first-line regimen.

| | |
|---|---|
| **Clinical failure**[i] | New or recurrent WHO stage 4 condition, after at least 6 months of ART[ii,iii] |
| **Immunological failure**[4] | • Fall of CD4 count to pre-therapy baseline (or below)<br>• 50% fall from the on-treatment peak value (if known)<br>• Persistent CD4 levels below 100 cells/mm[iii,v] |
| **Virological failure** | Plasma viral load > 10,000 copies/mL[vi] |

*Notes:*

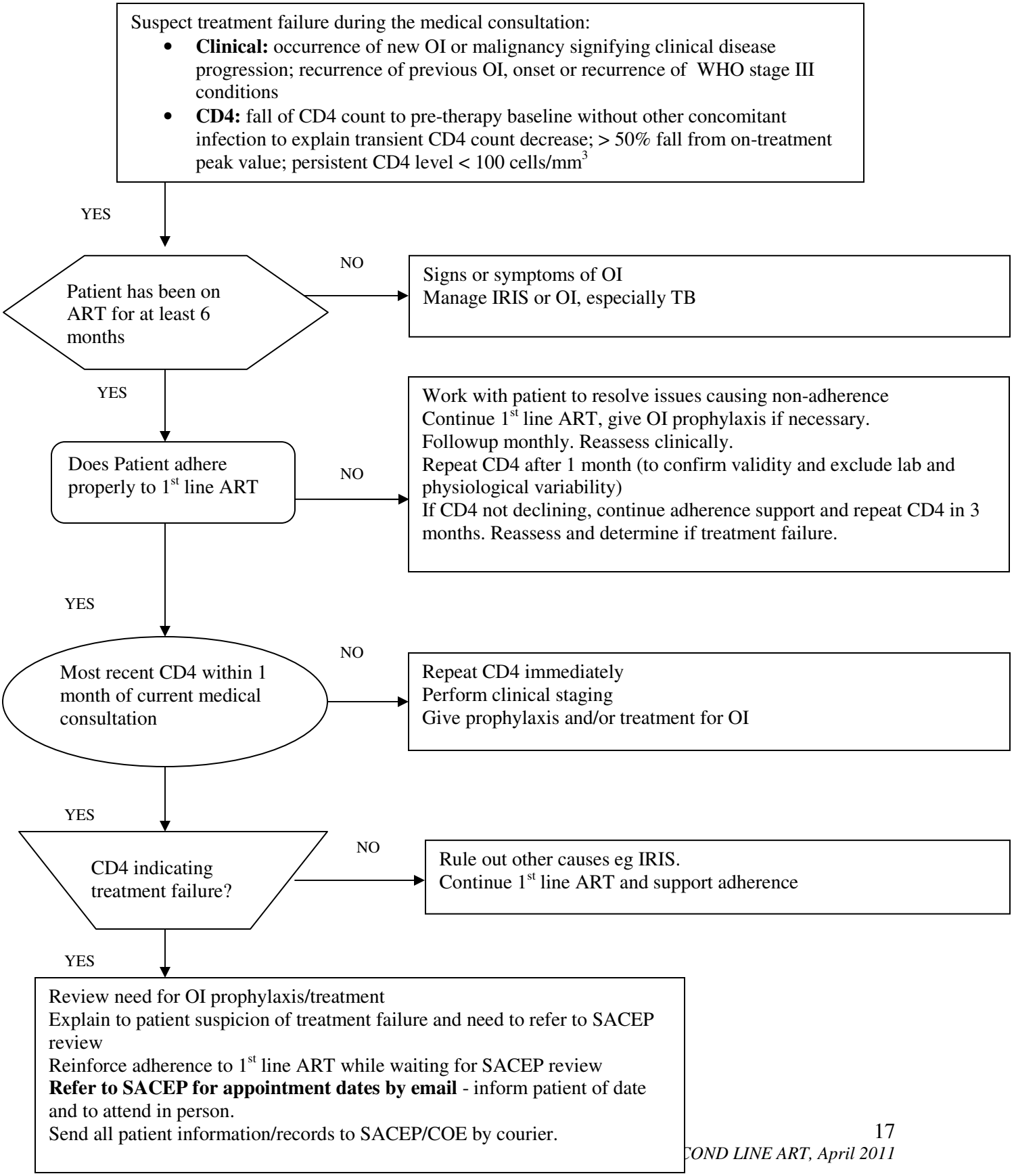
i) Current event must be differentiated from IRIS.
ii) Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections) may indicate treatment failure and thus requirsecond-line therapy to be considered.
iii) Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not indicate treatment failure and thus second-line therapy need not be considered.
iv) Without any concomitant infection causing transient CD4 cell count decrease.
v) Some experts consider persistent CD4 cell counts of below 50/mm³ after 12 months of ART to be more appropriate.
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.

*(Source: Table 25, p41 NACO 2007 ART Guidelines for adults and adolescents)*

At the ART center, "**suspicion of treatment failure"** depends on good clinical assessment backed up by use of CD4 counts. Before labeling as '**failure**' – ensure that the following has been done:

- Patient had a reasonable trial of first line ART for at least 6 months
- Assess adherence and support patient to improve this (reinforce)
- Screen and treat intercurrent OIs, exclude IRIS
- Provide Cotrimoxazole as per guidelines if necessary
- If TB is present: assess if this is reinfection or IRIS or a new infection. If the response to TB therapy is good, then the decision to switch therapy can be postponed and the patient re-evaluated again.
- CD4 count (most recent)

## 1.6 Protocol for determining ART failure (Protocol A1.1) at ART centers



Patients who are referred to SACEP for review should be accompanied with complete details of the history and all records. Any incomplete records will delay decisions to be taken by SACEP.
*(Refer to section 3 on operational guidelines for the SACEP functioning.)*

**Eligibility for enrollment into second line treatment :**

a) Free treatment and free viral load testing for all those below poverty line, Widows and children.
b) Patient under treatment in government ART centers continuously for at least two years, irrespective of income status.

This has now been revised and all patients who require second line ART shall be reviewed by SACEP as per laid down referral procedure, irrespective of the fact whether they started treatment in private sector or NACO centres and BPL etc. criteria as above have been removed.

The SACEP review will be based on the referral from the ART center providing first line ART to the patient suspected of treatment failure. *Each COE will have defined ART centres linked to it and patients* from these centres *only will be reviewed by a particular COE.*

When a patient is suspected to have treatment failure, the ART center must follow the NACO protocol in section 1.6 (Protocol A1.1) before referring to the SACEP. This is to ensure that appropriate referrals for 'suspect treatment failure' are made:

- Laboratory tests including Hb, LFT, RFT and CD4 and other symptom-directed testing should be done immediately if suspected of treatment failure.
- Most recent CD4 count should be within 2 months of the current medical consultation
- In the meanwhile, the patient is to be counseled for 100% adherence in a few sessions (and/or be optionally linked to the nearest Community Care Center for in-hospital stay and adherence support)
- Ensure use of cotrimoxazole prophylaxis if CD4 < 200 cell/$mm^3$.
- Continue with the 1$^{st}$ line ART regimen during this time.
- If OI or any intercurrent illness is present, treat for the specific OIs. If the OI treatment is not available in the institution then these patients can be referred to the COE for further management.
- Counsel and support adherence during this period of OI treatment as some patients may not adhere to taking ART when they feel ill.
- For suspected TB, refer to RNTCP services for treatment and monitor the response to TB therapy. If the response to TB therapy is good, the patient should be evaluated again for suspicion of treatment failure. Repeat CD4 counts 2 weeks after the OI has been treated, and for TB – after the

intensive phase (ie 8 weeks of ATT completed). Review the patient for suspected treatment failure as per protocol.
- If the diagnosis is IRIS, CD4 may not be necessary. It is imperative to use clinical judgment in this case.

On follow up after the confirmation/repeat of CD4 levels, if still suspect treatment failure by the immunological criteria (or clinical criteria):

- The referring ART center will inform and counsel the patient on the findings of 'suspected treatment failure', support psychosocial needs, counsel to continue 1st line ART until otherwise advised by the HIV physician; and with the informed consent of the patient for shared confidentiality to the SACEP/COE for referral.
- The ART center will send the request form **ANNEX VI** with the filled details together with a confirmed contact phone of the patient; and photocopies of the case sheets/patient treatment record to the COE.

## 1.7 Management protocol based on SACEP decision and viral load test results

Routine drug resistance testing is not part of the national protocol for second-line ART, however may be done for research/surveillance and monitoring purposes. Blood samples on **dried blood spots (DBS)**, shall be collected and stored for use at a later date for drug resistance genotyping.
(see Laboratory guidelines section below)

Details in the reporting and recording formats should be completed by the COE staff so that good documentation is present. This will enable the COE and the national programme to learn from the national rollout of second line ART.

Once patient has been referred to SACEP for evaluation according to the technical protocol, the SACEP will document its decision ie

- Provide 2nd line ART
- Not eligible for 2nd line ART
- Re-evaluate

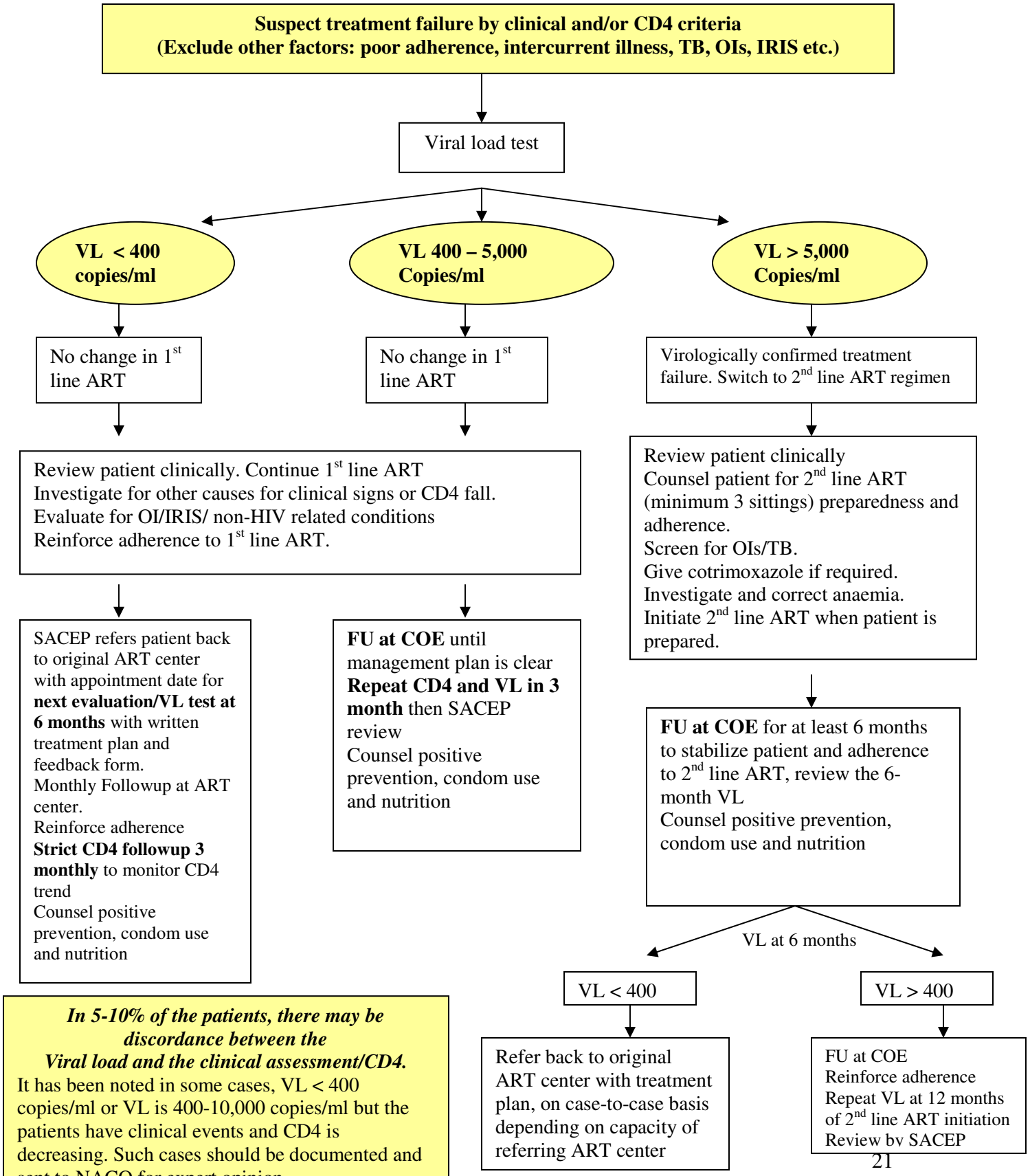
After the decision of the SACEP to provide 2nd line ART to the patient, the COE staff will ensure the necessary work to prepare the patient for initiation of second line ART as follows:

- Communicate the decision of the SACEP to the referring ART center for their reference, and ART center to 'transfer out' the patient to COE. (see M&E section)
- ensure linkage with NGO/CBO/FBO/positive network/CCC/ICTC for outreach and community/home based care

- treatment preparation: the patient should undergo a minimum of 3 counseling sessions for treatment readiness. Treatment supporter should ideally be present.
- Ensure all baseline laboratory and clinical screening is done and recorded before initiation of second line ART
- Consent form for 2nd line ART initiation signed – **ANNEX V**

Only the **nodal officer of the COE will be authorized to prescribe second-line ARV**s after approval of SACEP. The decision to switch from first line to second line therapy resides on the decision of the SACEP which will meet every Tuesday afternoon, to review the case history, order the viral load testing and approve initiation of second line ART for treatment failure and use of alternative regimens.

## Protocol A1.2 : SACEP Management according to viral load results



## 1.8 Initiating the standardized NACO second-line regimen

After the SACEP has approved the eligibility for second line ART for the patient, the clinical management shall be the responsibility of the COE and the patient will be 'Transferred out' from the referring ART center to the COE.

The provision of the second-line regimen assumes that 'late switching' occurs.

The objectives of the second-line are:

- To prolong survival of the PLHA

**The NACO standard second line regimen (TDF + 3TC + ATV/R) aims to achieve viral suppression for as long as possible, so that survival can be prolonged.**

Background on why this regimen is optimum for India:

The NACO technical resource group on ART had extensive discussions on the regimen which is optimum for the national setting. It is assumed that late switching occurs and the objective of second line is to maximize survival as long as possible for the PLHA. It is also assumed that by the time of switching to second line therapy, most patients will have multiple TAMs (thymidine analague mutations) and thus the effectiveness of other NRTIs such as ABC, TDF, ddI would be limited in the second line regimen.

The vast majority of patients receiving first-line therapy will be receiving either D4T/3TC or ZDV/3TC as their NRTI backbone. For these patients, the majority of patients with failure to first-line therapy will have the 3TC-related M184V mutation.

- Even in the presence of M184V, 3TC/FTC can exert anti-viral activity. Continuing 3TC or FTC in the second line will reduce viral fitness
- The presence of 3 or more TAMs can significantly reduce efficacy of TDF. M184V can mitigate (reduce) the effect of the TAMs on TDF to some extent.
- Increasing number of TAMs will reduce the efficacy of ZDV. M184V can mitigate/reduce the effect of TAMs on ZDV to some extent.

In second-line therapy, the concern is with the development of K65R as a result of TDF. Continuing ZDV and maintaining the AZT-related TAMs can preclude/antagonize the development of K65R. This has the potential to prolong the anti-viral potency of the second-line regimen, which is of significant use in the absence of any third/salvage options.

This is the rationale for including both TDF and ZDV along with 3TC in the NRTI backbone for second-line therapy. Some anti-viral activity out of both ZDV and 3TC/FTC will be present. Furthermore, the likelihood of developing K65R will be reduced thereby prolonging the efficacy of TDF by maintaining ZDV.

In this manner, the overall potency and durability of the second-line regimen will be improved and will help in prolonging the survival of PLHAs on second line.

For the minority of patients who receive TDF/3TC or TDF/FTC due to intolerability to both D4T and ZDV in the first line regimen: They are likely to develop M184V with treatment failure; and depending on when failure is diagnosed, may or may not have K65R. ZDV will still retain activity in this situation. ABC and DDI may retain *some* anti-viral activity also. The NRTI backbone, which would include ZDV, 3TC/FTC, and potentially another NRTI (ABC, DDI) will be discussed further.

| ARV drugs for 2nd line | Dosage | Dosing schedule |
|---|---|---|
| **TDF + 3TC** | Fixed dose combination of TDF 300 mg + 3TC 300 mg Once daily | 1 – 0 – 0 (one tablet in the morning) |
| **ATV/R** | Atazanavir 300mg, Ritonavir 100 mg Each Once daily | 1- Capsule and 1 tablet daily morning) |

NACO regimen V : TDF/3TC + ATV/R is the standard regimen for all patients provided second line ART .

Table 7 : Side effects related to the NACO second line regimen:

| ARV drug | Side effect/toxicity | Management |
|---|---|---|
| **ZDV** | Gastrointestinal intolerance including nausea, vomiting, diarrhoea;<br>Anaemia and neutropaenia which may present as acute bone marrow suppression within the first few weeks or present as a slow onset of progressive anemia over months<br>Hyperpigmentation of skins, nails and mucous membranes<br>Lactic acidosis (rarely)<br>Lipodystrophy and lipoatrophy (uncommon) | Symptomatic management of the minor side effects.<br><br>Monitor Hb close for first one month of therapy as per NACO lab monitoring protocol |
| **TDF** | **Usually well tolerated**<br><br>Minor: weakness and lack of energy, headache, diarrhea, nausea, vomiting and intestinal gas.<br>More serious side effects include liver or kidney failure and pancreas disease.<br><br>TDF can reduce bone mineral density | Symptomatic management of minor side effects<br><br>Monitor Liver and Renal function test as per NACO lab monitoring protocol<br><br>Calcium supplements may be used in patients with osteoporosis |
| **LPV/r** | Side effects include abdominal pain, abnormal stools or bowl movements, diarrhea, feeling weak/tired, headache and nausea. In addition, patients taking Lopinavir should be monitored for possible liver problems. People taking the drug who have liver disease, such as hepatitis B or hepatitis C, may experience a worsening of their liver condition. A small number of patients have experienced severe liver problems. | Symptomatic management of minor side effects<br>Supportive counseling and use of other drugs to manage GI effects should be done. These symptoms improve after a few weeks.<br><br>For HIV patients with history of blood transfusion, IDU and history suggestive of hepatitis – screen for HBV and HCV as per |

| | | |
|---|---|---|
| | | NACO guidelines. Monitor LFTs regularly |
| **3TC** | **Usually well tolerated**<br><br>Side effects may include cough, diarrhea, dizziness, headache, loss of appetite, mild stomach cramps or pain and trouble sleeping.<br>More serious side effects include burning, tingling, or pain in the hands, arms, feet, or legs; chills; ear, nose, or throat problems; fever; muscle aches; nausea; pale skin; severe stomach pain; skin rash; unusual tiredness or weakness; vomiting; and yellow eyes or skin. | Symptomatic management of minor side effects |

## 1.9 Drug-drug interactions

*Refer annex 5, p102 NACO 2007 ART guidelines for adults and adolescents*

*Drug information on second-line ARV drugs in Annex I*

## 1.10 Second-line ART and TB treatment

Tuberculosis is the most commonly detected serious opportunistic infection among PLHIVs in India. While tuberculosis has to be treated appropriately and on priority, in the context of second-line ART drug-drug interactions must to be considered. Rifampicin alters the metabolism of Protease Inhibitors, including lopinavir and ritonavir, and reduces effectiveness of standard doses. However, rifamycin-class drugs are highly efficacious in treatment of tuberculosis.

Another rifamycin, rifabutin, can be administered in the presence of PI-containing second line ART regimen without compromising the efficacy of ART or Anti TB treatment. Therefore NACP and RNTCP have recommended the substitution of rifabutin for rifampicin for the duration of TB treatment. In the presence of the boosting drug like Ritonavir (PI), rifabutin metabolism is altered, and less rifabutin is needed than would be without ritonavir. Therefore, the dosage of rifabutin during the administration of Second line regimen containing LPV/r shall be
150 mg thrice weekly for all patients >30 kg weight. The remainder of the TB treatment regimens, including dosing and duration, remain unchanged as per RNTCP guidelines.

As with all anti-TB treatment, **supervised treatment under DOTS is required.** The patients' DOTS provider should be informed and counseled regarding the substitution using rifabutin, by the treating medical officer.

**Rifabutin dose: 150 mg OD, three times a week**

Refer **ANNEX II**

Table 8 : Patient education on use of Rifabutin:

| **Ask** | | **Remarks** |
|---|---|---|
| **Ask for allergies** | Allergy to rifabutin, rifampicin, niacin, ethionamide | |
| **Ask for pregnancy or planning for pregnancy** | Pregnant or not? | Not enough evidence to show it is harmful or not. Consider risk-benefit to pregnant woman. |
| **Ask for use of other medications** | Especially anticoagulants ('blood thinners') such as warfarin , blood pressure or heart disease medication, diabetes medications, digoxin, methadone, oral contraceptives, zidovudine , itraconazole, and ketoconazole. Rifabutin may decrease the effectiveness of these medications some oral contraceptives; another form of birth control should be used while taking this drug. | Rifabutin reduces efficacy of these drugs<br><br>If using oral contraceptives, instruct to also use condom to prevent pregnancy. |
| **Inform about common side effects** | Skin, tears, saliva, sweat, urine, and stools may turn orange-brown. But, this side effect is normal and will stop when you finish taking rifabutin | Most common minor side effect, reassurance only. |
| | Chest pain, skin rash, | Rarely, Rifabutin may cause |

| | | |
|---|---|---|
| **Inform ART center if any of these symptoms are severe** | muscle aches, severe headache, fatigue, sore throat, flu-like symptoms, vision changes, unusual bruising or bleeding, nausea/vomiting, yellowing of the skin or eyes. | uveitis (photophobia, excessive tearing, blurred vision, eye pain) - treat with eye drops containing an anti-inflammatory drug (corticosteroid) and stop rifabutin. Once the inflammation has cleared up, rifabutin may be restarted.<br><br>The most serious side effect of rifabutin is **neutropenia**. |

**Anti-TB treatment should be initiated as soon as TB treatment is diagnosed.**

Initiation of 2nd line ART in patient already on anti-TB treatment

If a patient is already on anti-TB treatment, and needs to be initiated on second-line ART, then **substitute RIFABUTIN for rifampicin within the RNTCP regimen for 2 weeks prior to initiation of second-line ART**. This is to allow hepatic metabolism (induced by rifampicin) to normalize prior to initiation of PI-containing regimens. While the patient is counseled and prepared for initiation of 2nd line regimen, the patient should still be taking the 1st line ART regimen. Presuming the patient remains on an efavirenz-containing ART regimen, the dose of 1st line ART and use of efavirenz is not changed with the use of rifabutin during this overlap period.

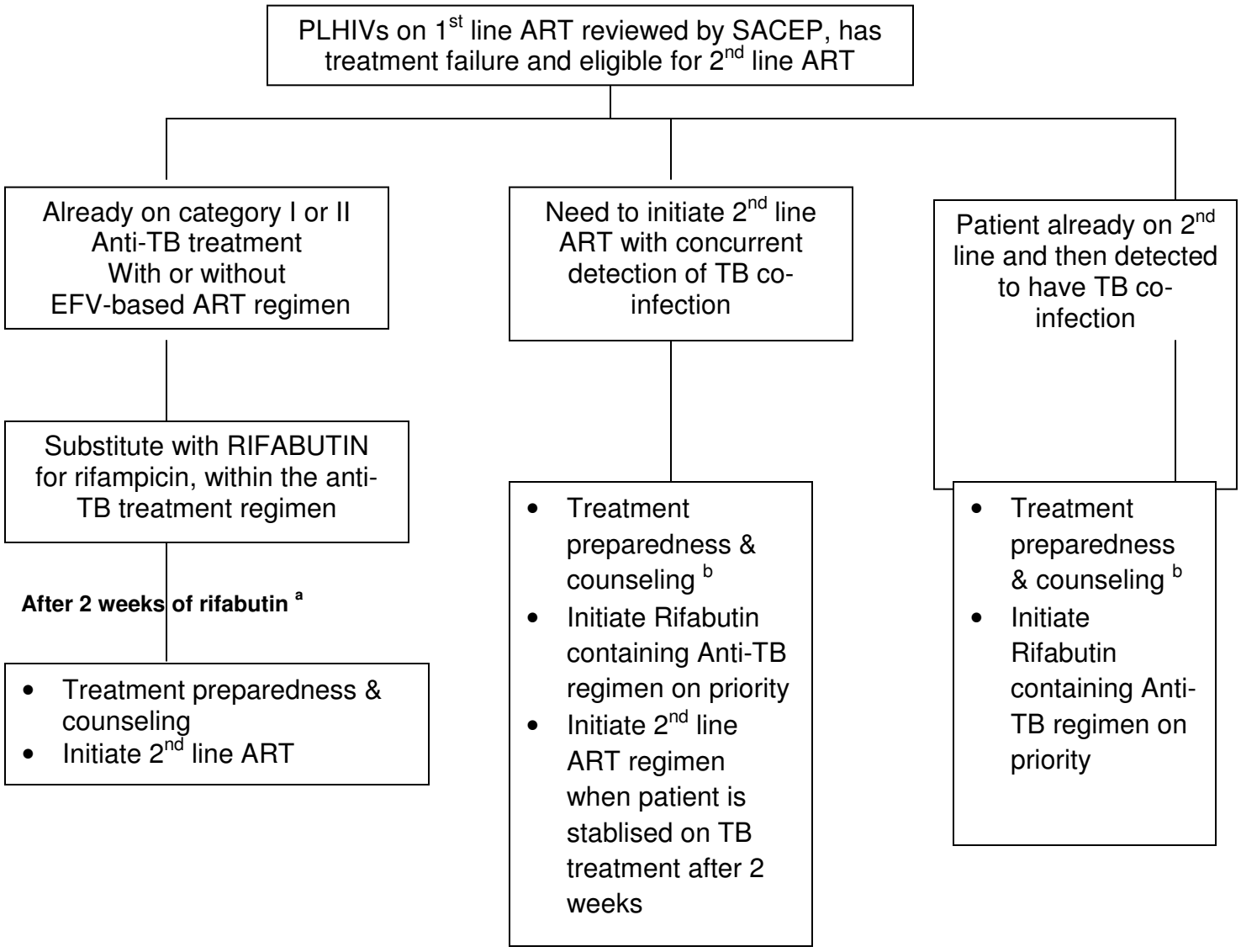
RNTCP recording and reporting: TB treatment categorization does not change with the use of rifabutin, which is a simple substitution for rifampicin. The substitution of rifabutin for rifampicin should be noted on the TB treatment card, and in the TB register "Remarks" column.

Initiation of Anti-TB treatment in patients already on 2ND line ART

If the patient is already on 2nd line ART (Lopinavir/Ritonavir containing treatment protocol), and detected to have TB, **subsitute with RIFABUTIN** for rifamipicin within the category I or II anti-TB regimen from the start of TB treatment.

Mechanism of drug supply for rifabutin to be communicated later.

**Initiation of Second line ART / Anti TB Treatment in the presence of TB co-infection (Protocol A 1. 3)**




**Note:**

a The 2 week period allows hepatic function to normalize after induction of P450 cytochrome enzymes by rifampicin

b Patient to be counseled well for both anti-TB and 2nd line ART. Pill burden is high. If patient is not started on 2nd line ART immediately, then to continue 1st line regimen until switch to 2nd line ART occurs.

## 1.11 Laboratory monitoring of patients on second line regimen

| Tests | Base-line 0 | Day 15 (if ZDV used in 2nd line) | 1 | 3 | 6 | 12 | 18 | 24 |
|---|---|---|---|---|---|---|---|---|
| **Hb, CBC** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | **then annually** | |
| **LFT** | ✓ | | | ✓ | ✓ | ✓ | | |
| **Renal function test** | ✓ | | | ✓ | ✓ | ✓ | **Then every 6 - monthly** | |
| **Fasting blood sugar** | ✓ | | | | | ✓ | **then annually** | |
| **Fasting lipid profile** | ✓ | | | | | ✓ | | |
| **Viral Load (VL)** | ✓ | | | | ✓ | Then no more VL unless indicated in protocol A1.2 | | |
| **CD4** | ✓ | Then every 6 monthly | | | | | | |

Note: Resistance testing is for operations research/ surveillance/monitoring only, under current national programme.

NACO will provide a baseline and annual checkup of fasting blood sugar and lipid profile. This is to understand the baseline and monitor the possible morbidities/side effects of PIs. However, the national programme will not be providing statins nor fibrates for treatment of dyslipidaemias.

## 1.12 Adherence and second-line ART

**NACO 2008 tools to support counseling and treatment adherence** for all patients and especially for patients who have difficulty with their first line ART and those taking second line ART:

1. Patient counseling diary (individual)
2. Use the Visual Analogue Scale (VAS) to help understand drug adherence
3. Patient education information leaflets for their prescribed regimens
4. Patient pill-taking monthly calender

Note: refer to attached CD for ART Counselling tools

Long term adherence continues to be challenge to PLHAs taking lifelong ART. The most common reason for HIV drug resistance is due to non-adherence and missed doses. Adherence approaching 100% is required for optimal viral suppression both in first line and second line ART.

The experience of the national programme to date is that in general, socio-demographic characteristics such as age, sex, social class, marital status or personality traits, race, religion and educational levels are poor predictors of adherence. Patients' beliefs, knowledge and expectations, sometimes shared by friends and community, strongly influence medical decision-making and willingness to begin and then adhere to prescribed treatments. Adherence is found to be greater when the person perceives the need for treatment, believes the treatment will be helpful and understands the purpose of the medications. Attitudes of friends, trust in physicians and confidence in one's own ability to follow the agreed-upon treatments are also associated with adherence. Lack of belief in the efficacy of treatment may lead to either treatment refusal, or inadequate adherence once initiated.

It is for this reason that the **initial conversations between doctors and patients** about combination therapy are crucial to later success: Simply telling the patient that it's time to begin antiviral therapy, writing out prescriptions and handing them to a patient who asks no questions and expresses no opinions is likely to lead to adherence problems and treatment failure. Occasionally, well-meaning physicians urge reluctant patients to start treatment, despite the patients' reservations. The more assertive patient may state that he or she is not ready to start, but others may acquiesce to a regimen that they consider of doubtful value or not compatible with their life circumstances. **Do not start second line ART if the patient is not ready to comply to adherence and follow up schedule.**

HIV/AIDS is associated with **neurocognitive problems** such as memory loss. This will cause adherence problems. Some patients may have trouble sorting their pills for the day or the week, while others may have trouble keeping track of the time, or may simply forget. Even among asymptomatic patients, memory problems are present. When memory is a significant problem, prescription of complex medical regimens is unlikely to succeed unless social (e.g., family member) or institutional (e.g., home attendant) resources are regularly available to help with the scheduling and taking of medications.

Psychiatric disorders also may constitute barriers to adherence. Even mild conditions such as depressed mood, as elicited on self-report rating scales, may be associated with medication nonadherence,either because of impaired

concentration, which is one of the criteria for diagnosing mood disorders, or because of feelings of hopelessness and despair. Among those with chronic and severe psychiatric disorders, noncompliance with psychotropic medication often contributes to relapse. When substance abuse is also present in HIV-infected patients with severe mental illness, many of whom live alone in unstable housing, the probability of effective management of combination therapy is poor.

When prescribing combination therapy, many physicians focus on potency and efficacy, ignoring the life circumstances of the particular patient. However, **the regimen really has to fit into the person's daily schedule.** If someone is working in a setting where others present who do not know about his or her HIV status, having to regulate mealtime around pill-taking may be extremely difficult. If an HIV-positive student has final examinations in two weeks, this may not be the moment to initiate combination therapy that is likely to induce significant, if transient, side effects at the outset of treatment. Overall, the match in terms of timing and lifestyle is a significant determinant of long-term adherence.

Although not invariably the case, those who live with others, who have friends and relatives who believe in and encourage medication adherence, and who have a fairly organized day are far more likely to succeed with the complex regimens that combination therapy demands. Community attitudes play an important role.

Two-way communication between the clinical team and patient is critical to the success of adherence. **The patient has to believe that combination therapy will make a profound difference in extending life, or else the regimen's burdens will outweigh the perceived rewards.** Initiating combination therapy is not usually regarded as an immediate need. If it takes extra time, or additional visits, for the clinical team to convince the patient that combination therapy should be initiated now, or for the patient to convince the doctor that his or her current life circumstances are simply not conducive to starting now, then extra time must be provided. However, there are a few urgent situations when immediate initiation may be considered imperative. One example is a patient with an essentially untreatable condition such as PML who is rapidly getting sicker. In this case, ART can lead to life-saving remission in certain cases of this sort. In less urgent situations, treatment can be safely put off while doctor-patient discussions continue.

At the outset, before even beginning combination therapy, it is helpful to **review anticipated problems and barriers to adherence, which then permits the patient to work out solutions on his or her own or with assistance.** For this purpose, some providers give their patients 1-2 weeks of cotrimozaxole and to use this time to reinforce adherence. Which doses are problematic? What are the circumstances? What is the patient thinking when errors occur? What is the patient's attitude about mistakes? Does he consider a fifteen-minute delay a catastrophe signifying irremediable failure? Alternatively, what do they think

about missing a weekend's worth of "medications"? Such rehearsal is often extremely helpful in anticipating and correcting potential pitfalls.

Some patients find it helpful to have a **written treatment plan** that shows the name of the medication, time of each dose, number of pills or capsules per dose and meal restrictions, if any, along with a telephone number to call with questions and for the next appointment date. Both doctor and patient should keep a copy of the plan for review at the next visit. Other techniques for promoting adherence include identifying daily activities that can be linked to pill-taking (e.g., a regular TV show), keeping a medication diary or log (preprinted forms can be prepared), preparing pills for the week at fixed times (e.g., Sunday evening), and otherwise relating pill-taking to the normal rhythms of daily life. Planning ahead for changes in routine or for weekends can forestall lapses at such times.

Mechanical aids are often useful. These range from pill boxes with dividers in which medications can be sorted by the week and time of day to timers, alarms, beepers that can be set to ring when it is time to take pills, to signs and checklists posted on refrigerators.

Social assistance can make a major difference, especially at the beginning of the regimen. Some people have a **family member/treatment supporter** who agrees to provide reminders every time medication is scheduled. Some ART centers have shown that providing a hotline staffed by nurse/counselor can make a major difference in getting patients started and continuing with ART. Sometimes children remind their mothers; sometimes mothers remind their adult children.

Over time, initial enthusiasm can dwindle as the incessant demands of scheduling persist. The media begin to relate stories about treatment failures and relapses. Friends taking the same medications get sick or die. As people feel better and return to work, new problems arise. Among these are maintaining confidentiality, arranging schedules to accommodate pill-taking, frequent trips to the bathroom (if taking medication that requires a high liquid intake), occasional days with significant side effects such as diarrhea, the constant reminder of illness and simply the ongoing burden of the regimen. We need to know in more detail about the hurdles, questions and worries that arise over time with ART, and we need to develop **individual interventions** to maintain adherence once therapy is established.

For patients who have difficulties with adherence to first line ART or who are suspected of treatment failure, or who will start second line ART, the objectives of adherence counseling are:

- To improve the adherence to medications so that ART is successful
- To encourage self management of medications
- To foster **honest communication** between provider and patient

- To respect patient choices and decision-making related to their HIV related medical care

***Patients don't want to disappoint their healthcare provider. The challenge is: how do you make it okay to say 'no' to doctors/counselors/nurses; or make it okay to say 'I can't do this'***

**See ANNEX III : Patient treatment education leaflets**

## ANNEX I: FAQ on drugs for second line regimen

### Tenofovir (TDF)

| | |
|---|---|
| **Class** | Nucleotide reverse transcriptase inhibitor (NtRTI) |
| **NACO Formulation** | Tablet TDF 300 mg + 300 mg 3TC (fixed dose combination) |
| **Contraindication** | Known sensitivity to TDF. Should not be administered to children < 18 years until further data known |
| **Safety in pregnancy** | No evidence of impaired fertility or harm to fetus due to TDF in animal studies. TDF should be used in pregnant women only if clearly required and with caution |
| **Precautions** | Impaired renal function: Dosing interval adjustment (300 mg every 2nd day) is required in all patients with creatinine clearance < 50 ml/min. The dose interval modifications are based on limited data. Therefore clinical response to treatment and renal function should be closely monitored in these patients.<br><br>Lactic acidosis/severe hepatomegaly with steatosis: have been reported with of all NRTI including TDF. In practical clinical experience, the risk with TDF is low. Monitor patients for hepatotoxicity and stop treatment if lactic acidosis occurs, |
| **Food** | Should be taken with food |
| **Interactions** | If ddI or antacids are administered, they should be taken at least 2 hours apart<br><br>TDF increases the level of ddI - TDF is preferably not co-administered with ddI . If ddI is to be co-administered with TDF, adjust dose of ddI – if weight > 60 kg, give ddI at 250 mg once daily; if weight < 60 kg, give ddI at 200 mg once daily.<br><br>TDF levels are increased by LPV/r but in clinical practice, this has little practical effects<br><br>TDF decreases blood levels of atazanavir (ATV). TDF should only be administered with boosted ATV (ATV 300mg/RTV 100mg).<br><br>TDF should not be administered to patients with renal insufficiency ie creatinine clearance < 60 ml/min<br><br>Tenofovir does not affect blood levels of **methadone, ribavirin** or **adefovir.** There is no known interaction between |

| | |
|---|---|
| | tenofovir and **buprenorphine.** |
| **Other information** | Three regimens containing tenofovir should normally <u>not be used:</u><br><br>• Tenofovir + abacavir + lamivudine<br>• Tenofovir + didanosine + lamivudine<br>• Tenofovir + didanosine + either efavirenz or nevirapine in patients new to ART with high viral loads.<br><br>Like 3TC, TDF has activity against hepatitis B, which may flare up when TDF is discontinued. While data is limited, TDF may have prolonged activity against hepatitis B even when resistant to 3TC. |
| **Adverse effects** | Headache, high blood pressure or general sense of feeling ill. These side effects are likely to get better or disappear over time<br><br>The most common TDF side effects are GI related: nausea, vomiting, loss of appetite.<br><br>TDF can reduce bone mineral density. Calcium or vitamin D supplements may be helpful especially in people with osteoporosis |
| **Storage** | Room temperature (15 – 30 degree C) |

**LPV/r drug-drug interactions**

| | |
|---|---|
| **Class** | Protease inhibitor (PI) |
| **NACO Formulation** | Heat stable tablet: 200 mg LPV + 50 mg RTV |
| **Contraindication** | LPV/r is contrindicated in patients with known hypersensitivity to LPV or RTV |
| **Safety in pregnancy** | No data on LPV/r in pregnant women. LPV/r should not be used during pregnancy and breastfeeding. |
| **Precautions** | Hepatic impairment – avoid if severe renal impairment, pregnancy; breastfeeding. |
| **Food** | Should be taken with food |
| **Interactions** | If ddI or antacids are administered, they should be taken at least 1 hour apart<br><br>LPV should not be taken with these drugs: amiodarone, astemizole, cisapride, ergotamine and similar alkaloids, |

| | |
|---|---|
| | flecanide, garlic supplements, lovastatin,midazolam, pimozide, propadenone, rifamipicin, simvastatin, St John's wort, terfenadine and triazolam<br><br>Rifamipicin should not be used in combination with LPV/r because co-administration may cause large decreases in LPV concentrations.<br><br>LPV levels are increased by delavirdine and Ritonavir (RTV)<br><br>LPV levels are decreased by amprenavir, carbamazepine, dexamethasone, Efavirenz, ketoconazole, nevirapine, Phenobarbital, St John's wort, phenytoin, rifamipicin and TDF.<br><br>LPV increases the levels of amiodaron, amprenavir, atorvastatin, bepridil, calcium channel blockers, clarithromycin, ketoconazole, indinavir, itraconazole, lidocaine (systemic), quinidine, rifabutin, saquinavir, sildenafil and TDF.<br><br>LPV decreases the levels of amprenavir, atovaquone and methadone.<br><br>LPV has potential interactions with anticonvulsants, statins, oral contraceptives, tricyclic antidepressants, oral anticoagulants and immunosuppressants. |
| **Adverse effects** | GI-related: diarrhoea, nausea, vomiting, colitis, abdominal discomfort, asthenia, headache, insomnia, rash.<br>Less frequently: drug mouth, hepatic dysfunction, pancreatitis, dyspepsia, dysphagia, oesophagitis, influenza-like syndrome, appetite changes, hypertension, palpitations, thrombophlebitis, vascultitis, chest pain, dyspnoea, agitation, anxiety, ataxia, hypertonia, confusion, depression, dizziness, dyskinesia, parasthesia, peripheral neuritis, somnolence; Cushing syndrome, hypothyroidism, sexual dysfunction, anaemia, leucopenia, dehydration, oedema, lactic acidosis; arthralgia, myalgia, abnormal vision, otitis media, taste disturbances, tinnitus, acne, alopecia, drug skin, pruritis, skin discoloration, nail disorders, sweating; Lipodystrophy and metabolic effects, raised bilirubin and lowered sodium,low platelet and low neutrophil counts also reported in children. |
| **Storage** | Room temperature (below 30 degrees) |

**Zidovudine (AZT, ZDV)**

| | |
|---|---|
| **Class** | Nucleoside reverse transcriptase inhibitor (NsRTI) |
| **NACO Formulation** | Tablet 300 mg |
| **Contraindication** | Hypersensitivity to ZDV<br>ZDV should not be given to patients with low neutrophil counts (< 0.75 x 10 9/litre) or anaemia < 7.5 g/dl) |
| **Safety in pregnancy** | ZDV is indicated for use in HIV-positive pregnant women and their newborn infants to reduce mother-to-child transmission |
| **Precautions** | Haematological toxicity, vitamin B12 deficiency (increased risk of neutropaenia), renal impairment, hepatic impairment, risk of lactic acidosis<br><br>Hepatic disease: potentially life-threatening lactic acidosis and severe hepatonegaly with steatosis have been reported; therefore caution in liver disease. |
| **Food** | Can be taken with or without food |
| **Interactions** | Should not be used with ribavirin and d4T (antagonistic)<br><br>Methadone levels are not affected by ZDV. Methadone increases ZDV concentration significantly thus monitor for ZDV toxicity. |
| **Adverse effects** | Common- anaemia (which may require transfusions), neutropaenia, leucopenia<br><br>Also common- hyperlactaemia.<br><br>Rare- lactic acidosis, hepatitic steatosis,anorexia, Lipodystrophy.<br><br>Others- nausea, vomiting, abdominal pain, dyspepsia, diarrhoea, flatulence, taste disturbance, pancreatitis, liver disorders including fatty change and raised bilirubin and liver enzymes; chest pain, dyspnoea, cough, influenza-like syndrome, headache, fever,parasthesia, neuropathy, convulsion, dizziness, somnolence, insomnia, anxiety, depression, loss of mental acuity, malaise, anorexia, asthenia, myopathy, myalgia, pancytopenia, thrombocytopenia, gynaecomastia, urinary frequency, rash, pruritis, pigmentation of nails, skin and oral mucosa. |
| **Storage** | Room temperature (15-30 degrees C) |

**Lamivudine (3TC)**

| | |
|---|---|
| **Class** | Nucleoside reverse transcriptase inhibitor (NsRTI) |
| **NACO Formulation** | Combined as fixed dose combination as TDF/3TC at dose of 300 mg once a day |
| **Contraindication** | Known sensitivity to 3TC |
| **Safety in pregnancy** | Limited data available on safety of 3TC in human pregnancy |
| **Precautions** | Renal impairment<br>Hepatic impairment: potentially life-threatening lactic acidosis and severe hepatomegaly reported, caution in liver disease. Recurrent hepatitis may occur in patients with chronic hepatitis B infection on discontinuation of 3TC |
| **Food** | Can be taken with or without food |
| **Interactions** | Rare |
| **Adverse effects** | Nausea, vomiting, diarrhea, abdominal pain, cough, headache, fatigue, insomnia, malaise, fever, rash, alopecia, muscle disorders, nasal symptoms; peripheral neuropathy reported; rarely pancreatitis; neutropenia, anaemia, thrombocytopenia; lactic acidosis/hepatic steatosis; raised liver enzymes and serum amylase |
| **Storage** | Room temperature (15-30 degrees C) |

**Rifabutin**

| | |
|---|---|
| **Class** | Anti-tuberculous agent |
| **NACO Formulation** | tablet 150 mg<br>Concurrent use with LPV/r (no change) , Rifabutin dose 150 mg once daily 3x/wk<br>Rifabutin AUC ↑ by 303% |
| **Contraindication** | Allergy to rifampicin |
| **Safety in pregnancy** | Limited data in pregnancy. Not teratogenic in rats/rabbits |
| **Precautions** | Allergy to rifamipicin |
| **Food** | none |
| **Interactions** | Rifabutin reduces levels of warfarin, barbiturates, benzodiazepines, beta-blockers, chloramphenicol, clofibrate, oral contraceptives, corticosteroids, cyclosporine, diazepam, dapsone, digitalis, dozycycline, haloperidol, oral hypoglycaemics, ketoconazole, methadone, phenytoin, quinidine, theophylline, trimethoprim, verapamil.<br><br>Drugs that inihibit cytochrome P450 and prolongs the half life of Rifabutin: PIs and Delavadine, erythromycin, clarithromycin (56% increase), and azoles (fluconazole, itraconazole, ketoconazole). |

| | |
|---|---|
| **Adverse effects** | Common: brown-orange discoloration of secretions: urine,tears, saliva, sewat, stool, skin. Infrequent: Rash, GI intolerance, neutropenia. Rare: flu-like illness, hepatitis, hemolysis, headache, thrombocytopenia, myositis.<br>Uveitis is dose-related (usually> 450 mg/day) or with standard 300mg/day combined with drugs that increase rifabutin levels (most PIs, clarithromycin, fluconazole) |
| **Storage** | Room temperature (15-30 degrees C) |

**ANNEX II : Recommendations for Coadministering Antiretroviral Drugs with RIFABUTIN – 2007**

| ***Non-nucleoside reverse-transcriptase inhibitors*** | | | |
|---|---|---|---|
| | **Antiretroviral dose change** | **Rifabutin dose change** | **Comments** |
| **Efavirenz** | No change | to 450-600 mg (daily or intermittent) | Rifabutin AUC □ by 38%. Effect of efavirenz + protease inhibitor(s) on rifabutin concentration has not been studied. Efavrirenz should not be used during the 1st trimester of pregnancy. |
| **Nevirapine** | No change | No change (300 mg daily or thrice-weekly) | Rifabutin and nevirapine AUC not significantly changed. |
| **Delavirdine** | Rifabutin and delavirdine should not be used together | | Delavirdine AUC □ by 80%; rifabutin AUC by 100%. |
| **Etravirine** | No change | No change (300 mg daily or thrice-weekly) | No clinical experience; etravirine Cmin □ by 45%, but this was not thought to warrant a change in dose |
| ***Single protease inhibitors*** | | | |
| | **Antiretroviral dose change** | **Rifabutin dose change** | **Comments** |
| **fos-Amprenavir** | No change | □ to 150 mg/day<br>or<br>300 mg 3x/week | No published clinical experience |
| **Atazanavir** | No change | □ to 150 mg every other day or 3x/week | No published clinical experience. Rifabutin AUC by 250% |
| **Indinavir** | 1000 mg every 8 hours | □ to 150 mg/day | Rifabutin AUC by 170%; indinavir concentrations □ bv 34% |

| | | | |
|---|---|---|---|
| | | or<br><br>300 mg 3x/week | |
| **Nelfinavir** | No change | □ to 150 mg/day<br>or<br>300 mg 3x/week | Rifabutin AUC by 207%; insignificant change in nelfinavir concentration |
| ***Dual protease inhibitor combinations*** | | | |
| | **Antiretroviral dose change** | **Rifabutin dose change** | **Comments** |
| **Lopinavir / ritonavir (Kaletra □)** | No change | □ to 150 mg every other day or 3x/week | Rifabutin AUC by 303%; 25-O-des-acetyl rifabutin AUC by 47.5 fold. |
| **Ritonavir (any dose) with saquinavir, indinavir, amprenavir, fos-amprenavir, atazanavir, tipranavir or darunavir** | No change | □ to 150 mg every other day or 3x/week | Rifabutin AUC and 25-O-des-acetyl rifabutin AUC , by varying degrees. |
| ***CCR-5 receptor antagonists*** | | | |
| **Maraviroc** | No change | No change | No clinical experience; a significant interaction is unlikely, but this has not yet been studied |
| ***Integrase inhibitors*** | | | |
| **Raltegravir** | No change | No change | No clinical experience; a significant interaction is unlikely, but this has not yet been studied |

From CDC Dec 2007, available online at: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm.

**Annex III : Patient education card for second line ART (available from SACS)- to be changed according to new regimen. The one given below is no longer to be used.**

ADULT

# TREATMENT EDUCATION INFORMATION

**TDF + 3TC + LPV/r**

## REGIMEN – Va

| TDF + 3TC + LPV/r | | |
|---|---|---|
| **Tenofovir (300mg)** | **Lamivudine (150mg)** | **Lopinavir/ritonavir (200mg/50mg)** |

| Daily | | |
|---|---|---|
|  | Morning | |
| | Tenofovir + Lamivudine<br>Lopinavir/ritonavir | 1 tablet<br>2 tablets |
|  | Evening | |
| | Lopinavir/ritonavir | 2 tablets |

## REMEMBER THAT

- If you miss doses (even 2 dose in a month) **FURTHER DRUG RESISTANCE** will develop. This is bad for you as these second line drugs will stop working.
- Drugs must be taken as prescribed with food, and do not miss any dose.
- If you forget a dose, do not take a double dose.
- If you stop taking the ART, you will become ill within months.
- Do not share any of the drugs with your spouse, family or friends.
- If you find it difficult to take your pills, go back to the ART center and discuss this with the doctor and counselor. Ask for support from your treatment supporter, family, friends, NGO and positive network.

**Remember: Adherence is under your control**

Note: The color, shape and size of ARV drugs may be different due to different supplier each year.

It is common to have side effects. They will usually go away in a few weeks. You can ask the doctor to give you some medication to help you make it better. If you have side effects, do the following:

| If you have | Do the following |
|---|---|
| Nausea | Take the ARV pills with food. |
| Diarrhoea | Keep drinking and eating, do not eat spicy food/chillies. |
| Muscle pain, fatigue | These will go away. |

If nausea or diarrhoea persists or gets worse, report to the ART center.

**Seek care urgently if:**

- Yellow eyes with high fever, headache, running nose and body ache.
- Missed periods/possibility of pregnancy.
- Severe abdominal pain.
- Extreme paleness of face, hands or eyes.
- Fatigue and shortness of breath.

Note: Remember to take your cotrimoxazole prophylaxis tablet every day, if the doctor prescribes it.
Always use condom during sex.
Do not stop any drugs by yourself.

Phone: _____ Call ART centre if you have any questions or problems. (9 AM –4 PM)

Phone: _____ After 4 PM, contact the Hospital Emergency number.

Phone: _____ Call the local positive network number for support.

**National AIDS Control Organisation**
Ministry of Health & Family Welfare
Government of India, 9th Floor, Chandralok Building
36, Janpath, New Delhi – 110001, India
Tel: 011-23325343, 011-23731774, 011-23731778, Fax: 011-23731746
E-Mail info@nacoonline.org

**ANNEX IV:**

## SEVERITY GRADING OF SELECTED CLINICAL AND LABORATORY TOXICITIES

(Source: Division of AIDS, National Institute of Allergy and Infectious Diseases, USA – modified.)

For abnormalities NOT found elsewhere in the toxicity table use the scale below to estimate grades of toxicity.

GRADE 1 Transient or mild discomfort; no limitation of activity; no medical intervention/ therapy required.

GRADE 2 Mild to moderate limitation of activity; some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3 Marked limitation of activity; some assistance usually required; medical intervention/therapy required; hospitalization possible.

GRADE 4 Extreme limitation of activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care.

| HAEMATOLOGY | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| Haemoglobin | 8.0 – 9.4 g/dl **OR** 80 – 94 g/l **OR** 4.93 – 5.83 mmol/l | 7.0 – 7.9 g/dl **OR** 70 – 79 g/l **OR** 4.31 – 4.92 mmol/l | 6.5 – 6.9 g/dl **OR** 65 – 69 g/l **OR** 4.03 – 4.30 mmol/l | <6.5 g/dl **OR** <65 g/l **OR** <4.03 mmol/l |
| Absolute neutrophil count | 1000 –1500/ $mm^3$ **OR** 1.0 – 1.5/G/l* | 750 – 999/ $mm^3$ **OR** 0.75 – 0.99/G/l* | 500 – 749/ $mm^3$ **OR** 0.5 – 0.749/G/l* | <500/$mm^3$ **OR** <0.5/G/l* |
| Platelets | 75000 – 99000/$mm^3$ **OR** 75 – 99/ G/l* | 50000 – 74999/$mm^3$ **OR** 50 – 74.9/G/l* | 20000 – 49999/$mm^3$ **OR** 20 – 49.9/G/l* | <20000/$mm^3$ **OR** <20/G/l* |
| CHEMISTRIES | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
| SODIUM | | | | |
| Hyponatraemia | 130 – 135 meq/l **OR** 130 – 135 mmol/l | 123 – 129 meq/l **OR** 123 – 129 mmol/l | 116 – 122 meq/l **OR** 116 – 122 mmol/l | <116 meq/l **OR** <116 mmol/l |
| Hypernatraemia | 146 – 150 meq/l **OR** 146 – 150 mmol/l | 151 – 157 meq/l **OR** 151 – 157 mmol/l | 158 – 165 meq/l **OR** 158 – 165 mmol/l | >165 meq/l **OR** >165 mmol/l |

| CHEMISTRIES | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| POTASSIUM | | | | |
| Hyperkalaemia | 5.6 – 6.0 meq/l **OR** 5.6 – 6.0 mmol/l | 6.1 – 6.5 meq/l **OR** 6.1 – 6.5 mmol/l | 6.6 – 7.0 meq/l **OR** 6.6 – 7.0 mmol/l | >7.0 meq/l **OR** >7.0 mmol/l |
| Hypokalaemia | 3.0 – 3.4 meq/l **OR** 3.0 – 3.4 mmol/l | 2.5 – 2.9 meq/l **OR** 2.5 – 2.9 mmol/l | 2.0 – 2.4 meq/l **OR** 2.0 – 2.4 mmol/l | <2.0 meq/l **OR** <2.0 mmol/l |
| BILIRUBIN | | | | |
| Hyperbilirubin-aemia | >1.0 – 1.5 x ULN | >1.5 – 2.5 x ULN | >2.5 – 5 x ULN | >5 x ULN |
| GLUCOSE | | | | |
| Hypoglycaemia | 55 – 64 mg/dl **OR** 3.01 – 3.55 mmol/l | 40 – 54 mg/dl **OR** 2.19 – 3.00 mmol/l | 30 – 39 mg/dl **OR** 1.67 – 2.18 mmol/l | <30 mg/dl **OR** <1.67 mmol/l |
| Hyperglycaemia (nonfasting and no prior diabetes) | 116 – 160 mg/dl **OR** 6.44 – 8.90 mmol/l | 161 – 250 mg/dl **OR** 8.91 – 13.88 mmol/l | 251 – 500 mg/dl **OR** 13.89 – 27.76 mmol/l | >500 mg/dl **OR** >27.76 mmol/l |
| Triglycerides | 200 – 399 mg/dl **OR** 2.25 - 4.51 mmol/l | 400 – 750 mg/dl **OR** 4.52 – 8.47 mmol/l | 751 – 1200 mg/dl **OR** 8.48 – 13.55 mmol/l | >1200 mg/dl **OR** >13.55 mmol/l |
| Creatinine | >1.0 – 1.5 x ULN | >1.5 – 3.0 x ULN | >3.0 – 6.0 x ULN | >6.0 x ULN |
| TRANSAMINASES | | | | |
| AST (SGOT) | 1.25 – 2.5 x ULN | >2.5 – 5.0 x ULN | >5.0 – 10.0 x ULN | >10.0 x ULN |
| ALT (SGPT) | 1.25 – 2.5 x ULN | >2.5 – 5.0 x ULN | >5.0 – 10.0 x ULN | >10.0 x ULN |
| GGT | 1.25 – 2.5 x ULN | >2.5 – 5.0 x ULN | >5.0 – 10.0 x ULN | >10.0 x ULN |

| CHEMISTRIES | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| TRANSAMINASES | | | | |
| Alkaline phosphatase | 1.25 – 2.5 x ULN | >2.5 – 5.0 x ULN | >5.0 – 10.0 x ULN | >10.0 x ULN |
| Pancreatic enzymes | | | | |
| Amylase | >1.0 – 1.5 x ULN | >1.5 – 2.0 x ULN | >2.0 – 5.0 x ULN | >5.0 x ULN |
| Pancreatic amylase | >1.0 – 1.5 x ULN | >1.5 – 2.0 x ULN | >2.0 – 5.0 x ULN | >5.0 x ULN |
| Lipase | >1.0 – 1.5 x ULN | >1.5 – 2.0 x ULN | >2.0 – 5.0 x ULN | >5.0 x ULN |
| Lactate | <2.0 x ULN without acidosis | >2.0 x ULN without acidosis | Increased lactate with pH <7.3 without life-threatening consequences | Increased lactate with pH <7.3 with life-threatening consequences |
| GASTRO-INTESTINAL | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
| Nausea | Mild **OR** transient; reasonable intake maintained | Moderate discomfort **OR** intake decreased for <3 days | Severe discomfort **OR** minimal intake for ≥3 days | Hospitalization required |
| Vomiting | Mild **OR** transient; 2–3 episodes per day **OR** mild vomiting lasting <1 week | Moderate **OR** persistent; 4–5 episodes per day **OR** vomiting lasting ≥1 week | Severe vomiting of all foods/fluids in 24 hours **OR** orthostatic hypotension **OR** intravenous Rx required | Hypotensive shock **OR** hospitalization for intravenous Rx required |

| GASTRO-INTESTINAL | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| Diarrhoea | Mild **OR** transient; 3–4 loose stools per day **OR** mild diarrhoea lasting <1 week | Moderate **OR** persistent; 5–7 loose stools per day **OR** diarrhoea lasting ≥1 week | Bloody diarrhoea **OR** orthostatic hypotension **OR** >7 loose stools/day **OR** intravenous Rx required | Hypotensive shock **OR** hospitalization required |
| **RESPIRATORY** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Dyspnoea | Dyspnoea on exertion | Dyspnoea with normal activity | Dyspnoea at rest | Dyspnoea requiring $O^2$ therapy |
| **URINALYSIS** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Proteinuria | | | | |
| Spot urine | 1+ | 2+ or 3+ | 4+ | Nephrotic syndrome |
| 24-hour urine | 200 mg to 1 g loss/day **OR** <0.3% **OR** <3 g/l | 1 g to 2 g loss/day **OR** 0.3% to 1.0% **OR** 3 g to 10 g/l | 2 g to 3.5 g loss/day **OR** >1.0% **OR** >10 g/l | Nephrotic syndrome **OR** >3.5 g loss/day |
| Gross haematuria | Microscopic only | Gross, no clots | Gross plus clots | Obstructive |
| **MISCELLANEOUS** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Fever (oral, >12 hours) | 37.7 – 38.5 °C **OR** 100.0 – 101.5 °F | 38.6 – 39.5 °C **OR** 101.6 – 102.9 °F | 39.6 – 40.5°C **OR** 103 – 105 °F | >40.5 °C **OR** >105 °F for ≥12 continuous hours |

| MISCELLANEOUS | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| Headache | Mild; no Rx required | Moderate **OR** non-narcotic analgesia Rx | Severe **OR** responds to initial narcotic Rx | Intractable |
| Rash hypersesnitivity | Erythema, pruritus | Diffuse maculopapular rash **OR** dry desquamation | Vesiculation **OR** moist desquamation **OR** ulceration | **ANY ONE OF**: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, exfoliative dermatitis |
| Fatigue | Normal activity reduced by <25% | Normal activity reduced by 25–50% | Normal activity reduced by >50%; cannot work | Unable to care for self |

**Annex V : Consent form for patients starting second line ART – at COE**

# Consent form for patients starting second line ART

I, (name)……, (address) ……
CONSENT / NOT CONSENT to sharing all information necessary in the medical management of my health status and HIV/AIDS with the service providers who will be part of the management of myself

And

I AGREE / NOT AGREE to receive the second line antiretroviral therapy.

I fully understand the information that has been provided by the health care staff in the following:

- That second line ART is not an emergency and thus will be started as per the medical decision of the doctor
- That receiving second line ART involves shared confidentiality with other service providers such as CBO/NGO/positive network who may conduct outreach and home-based care activities with myself at home
- That second line ART requires 100% adherence to taking the drugs
- That there is no third line ART at the moment, thus second line ART is the best chance to prolong my survival/life
- That I understand the Side effects of second line ART
- That I shall not stop the drugs on my own accord and will return to the ART center if there are problems
- That the national programme shall collect and store my blood to test if the ART medicines are working against the HIV virus at a later date. This will not affect my current treatment. This will help the doctors improve the care and treatment of all patients undergoing treatment at this clinic, and possibly at other clinics in the country.

…….
Signature of patient
And date

……
signature of witness
(doctor/nurse/counsellor)
And date

## Annex VI: Request/ Reply form to SACEP for review of patients suspected of treatment failure (to be sent with patient records)

**Request form to SACEP/ COE for Review**

Dear Dr …….  Referral date…….
Center of Excellence……

I would like to refer this patient for review by the SACEP for ☐ Alternative first-line ARV drugs
☐ Suspect Treatment Failure
☐ Others…….

Name…….. Gender/Age ……..
Address……ART center no….....
Contact phone/mobile……

The following is attached with this request form:

- Photocopy of the NACO patient treatment record
- Photocopy of all lab tests including CD4
- Photocopy of all other relevant material
- Address proof with photo

The following sections summarises the patients antiretroviral therapy history:

A: Summary of the case history of the patient (pre-ART; ART; suspected treatment failure)
……..
……..

B. Summary of adherence history and other psychosocial issues
……
……

C. Summary of relevant laboratory tests including CD4/viral load (if available)
……..
……..
Thank you

……..
Name of Nodal Officer referring
ART center/ contact number/email

**Reply Form: from SACEP/COE to ART center**

Dear Dr …… Date…….
ART center……..

Patient name……Gender/Age……
Address…….. ART center no……
Referred for……on Date……

Findings/ investigation results:…….
……
……
Treatment/follow-up Plan:…….
……..
……
Thank you

……..
Name of Nodal Officer
COE/ contact number/email

# Section II

# Operational Guidelines

## 2.1 State AIDS Clinical Expert Panel (SACEP)

**State AIDS Clinical Expert Panel (SACEP)** has been established at each centre of excellence. The SACEP shall consist of

1. Nodal Officer of COE/ART centre,
2. One more ART expert (panel to be formed by NACO, preferably not from the same ART center)
3. Regional Coordinator/Jt Director (CST) / Consultant (CST) at SACS,

In addition to the above, there would be observers from central level regularly for monitoring purposes.

The Terms of reference of SACEP are :

- Review and decide on all cases referred by the referring ART center for second-line ART provision – both for eligibility for viral load testing and starting second line or alternative first-line ART regimen
- Review referred cases for alternative first line ARV drugs
- Meet at the COE to review cases every Tuesday afternoon (next working day in case of a holiday). This is to ensure that there is no delay in review and processing of the case referred for review of suspected treatment failure. A maximum of 15-20 patients shall be reviewed at each meeting (old and new). However if there are too few patients, the meeting may be deferred to the next week.
- Mentoring and ensure high quality case management of the PLHA on second-line ART by the referring ART center
- Document the registration and monitor progress of all patients suspected of treatment failure sent for SACEP review

The SACEP will follow the technical protocols as laid out by NACO in section I.

The ART plus centre have a similar structure called **DACEP** (**District AIDS Clinical Expert Panel)**

## 2.2 Eligibility and criteria for provision of second line ART

a) Free treatment and free viral load testing for all those below poverty line, Widows and children.
b) Patient under treatment in government ART centers continuously for at least two years, irrespective of income status.

This has now been revised and all patients who require second line ART shall be reviewed by SACEP as per laid down referral procedure, irrespective of the fact whether they started treatment in private sector or NACO centres and BPL etc. criteria as above have been removed.

The SACEP review will be based on the referral from the ART center providing first line ART to the patient suspected of treatment failure. *Each COE will have defined ART centres linked to it and patients* from these centres *only will be reviewed by a particular COE.*

Criteria for provision of second line ART:

- Referred by the NACO ART center following the NACO protocol on determining treatment failure (section 1.6)
- Reviewed by the SACEP and determined to be medically eligible as per the NACO protocol for second line provision
- Has been assessed by counselor/nurse/doctor for adherence and is prepared for second line treatment
- Should have family support/ treatment supporter, and linked to NGO/CBO/CCC/ICTC for outreach/community/home based care services and monitoring of adherence

Furthermore, the patient to be provided second line ART shall need to sign a consent form for informed consent **(ANNEX E)** for home visits/followed at the community by link worker/NGO/positive network/ICTC which will support the adherence at community level for second line provision.

The COE shall coordinate the meeting of the SACEP to be held at the COE meeting room. The COE will request for the ART center referring physician to attend and/or the patient to be physically present for the review panel.

## 2.3 Protocol for referral by ART centre to SACEP

**See also M&E section**

Protocol for referral by ART center to SACEP

| | |
|---|---|
| Step 1 | ART center shall follow **Protocol A1.1** for suspect treatment failure. ART center shall email details (brief ART history, clinical stage & serial CD4 values, reasons for referrals) of patient to COE to get appointment dates |
| Step 2 | SACEP coordinator/COE reviews patient history and gives appointment date/time to the referring centre. |
| Step 3 | The referring ART center shall then communicate the date/time with patient by phone, and counsel the patient for suspect treatment failure and need for SACEP review. |
| Step 4 | Referring ART center sends photocopies of patient records together with Referral/Reply Form **(ANNEX VI)** – and confirms that SACEP coordinator has received it. |

## 2.4 Protocol for SACEP review

| | |
|---|---|
| Step 1 | SACEP coordinator/COE vets the emailed referral from ART center. |
| Step 2 | SACEP coordinator informs ART center of appointment date/time by email/phone |

| | |
|---|---|
| Step 3 | SACEP coordinator enter patient details into SACEP register (SL-1) |
| Step 4 | SACEP coordinator prepares weekly SACEP meeting formats |
| Step 5 | • The SACEP will review the case notes **only in presence of the patient.**<br>• The SACEP will meet every Tuesday afternoon(or the next day if Tuesday is a holiday) to review the results and decide on management of the case. There will be a maximum of 15-20 patients at each review meeting |
| Step 6 | • The SACEP will order a Viral load test according to **Protocol A 1.2** Blood sample and DBS to be taken to the linked Viral Load Lab will be processed according Laboratory guidelines section.<br>The SACEP will review the viral load results in next meeting and decide on management of the case.<br>• The SACEP will document its decision ie<br>○ Provide alternative 1st line ARV drug<br>○ Provide 2nd line ART<br>○ Not eligible for 2nd line ART<br>○ Re-evaluate / others |
| Step 7 | Once the decision is made by the SACEP to provide 2nd line ART to the patient reviewed, the clinical management of the patient will be done at the COE itself. |
| Step 8 | The SACEP coordinator shall inform the referring ART center for the following actions:<br>• 'Transfer-out' the patient in the M&E formats, to COE<br>• Send the completed reply form to the referring ART center **(Annex VI)** |
| Step 9 | The patient must undergo 3 counseling sessions (minimum) to ensure treatment preparedness at the COE. |
| Step 10 | The follow up visits shall be monthly at the COE. |
| Step 11 | After patient on 2nd line ART has the 6 month Viral load result and reviewed by COE to be stable, patient may be transferred back to the referring ART center on case to case basis depending on case to case basis. |
| Step 12 | SACEP coordinator to prepare SACEP formats SL-2 befroe each meeting and send SL-3 to NACO monthly: secondline2008@gmail.com |

Also Refer to M&E section for tools.

The COE Nodal officer will be the physician responsible; backed up by the COE ART center staff to ensure high quality of care for the patient on 2nd line. Prescription of the 2nd line shall be done only by the nodal officer of the COE

The patient who is confirmed treatment failure and is to be started 2nd line may be optionally admitted at the COE or the linked Community Care Center (CCC) for inpatient care, monitoring of toxicities and to reinforce adherence**.** The COE ART team shall ensure that the patient on 2nd line is linked to a NGO/CBO/ICTC for care and support as well as the positive network for other support. Condom use, nutrition advice and positive prevention is to be emphasized.

Details in the reporting and recording formats should be completed by the COE staff so that good documentation is present.

## 2.5 TOR of additional manpower: Counselor-cum-facilitator

For carrying out these activities, each COE shall be provided with an additional manpower in form of a "counselor –cum- facilitator". The TORs for **Counselor cum facilitator"** are:

1. Disclosure to the family of the HIV+ person about starting second line ART.
2. Address all issues related to preparedness for starting Second line ARV treatment and its follow up :
   - Treatment readiness exercises i.e. preparing the patient before starting second line ART; encourage and help in finding guardian support.
   - Explain the details of treatment and its importance, side effects of the Second line ARV drugs and limitations of Second line ART (e.g.no further option on failure of Second line)
   - Adherence counseling and monitoring, identification of barriers to adherence and suggestions (remedies) to remove these barriers.
   - Home visits for the patients defaulting on Second Line ART.
3. Provide emotional, social, and psychological support to patients and/or direct the patient to the concerned person or organization that can do so.
4. Direct patients to linked or referred centers and departments and assist in palliative and home-based care.
5. Promote positive living, prevention and condom use and dispense condoms.
6. Complete the required sections in the recording and reporting tools on second line at the ART center.
7. Prepare case summaries of patients to be reviewed by SACEP every week in SACEP format.
8. Give appointments to patients referred from other ART centers for second line.
9. Provide feedback to referral centers and carry out the procedure for transfer back of patients to referral centers after initiation of six months on second line ART, on case- to case basis.

**The Counselor-cum- facilitator is the SACEP Coordinator**

# Section III :

# Laboratory Guidelines

## 3.1 INTRODUCTION

HIV infection has become a pandemic in the last 20 years. The dynamics of the HIV/AIDS epidemic in India will have a major impact on the overall disease burden of HIV in the Asia-Pacific region and the world. National estimates indicate that India has 2.1 to 3.1 million people living with HIV infection (2006). The overall average adult prevalence in India is 0.36%.

The viral load assay, the estimation of copies of HIV-1 ribonucleic acid (RNA) in plasma of infected individuals, is critical in monitoring patients' response to ART (Antiretroviral therapy) and progression towards AIDS. Hence, HIV-1 viral load assay would be one of the key parameters for assessment of patients with clinical and immunological failure on first line ART (who may be requiring second line ART). HIV-1 viral load assay results will help to initiate second line ART at designated centers as per NACO guidelines.

Viral load assays quantify the amount of HIV-1 RNA circulating in the blood of an infected individual. Although total quantification includes cell-free virus, virus in infected cells in all compartments of the body as well as integrated provirus, the easiest measurement of viral load is of cell-free virus in an individual's plasma. Currently there is no clinical indication for viral load testing of tissues. HIV-1 plasma viral load (PVL) level is being successfully used to predict time to progression to AIDS and to assess efficacy of ART. During treatment, the decay of viral load in tissues typically corresponds with virologic responses in plasma, making blood plasma a useful sentinel for virologic response in general.

## 3.2 INTENDED USE OF HIV-1 PVL ASSAY IN NACO's SECOND LINE ART INITIATIVE

The HIV-1 PVL assay will be performed in HIV infected individuals that fail first line ART at NACO designated ART sites. The results of PVL assay will be used to decide the initiation of second line ART.

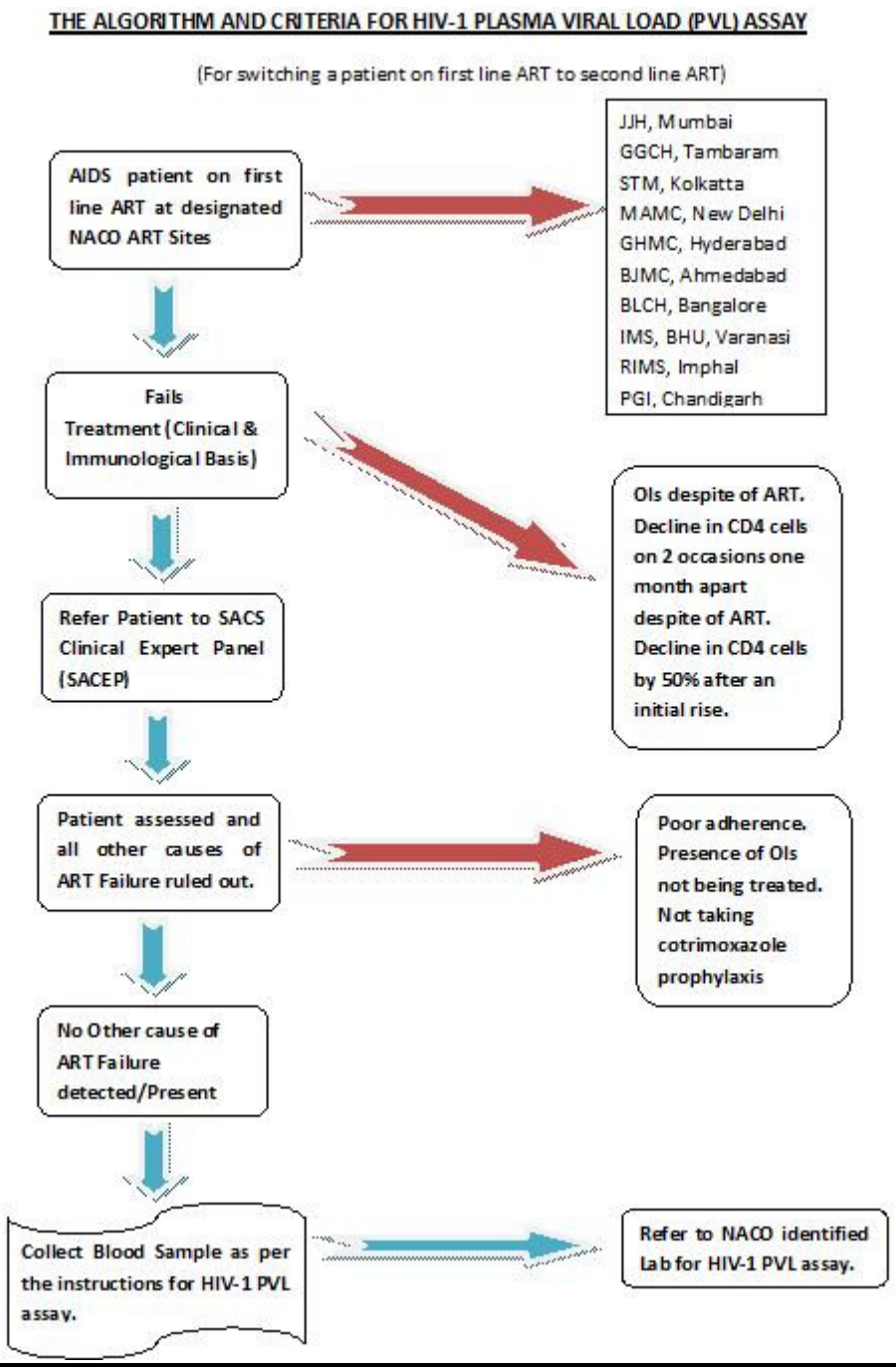
The PVL assay will be performed:

- Before starting second line ART to get the reference value to decide on further course of action. A PVL measurement will be performed on patients referred by SACEP. The decision on whether to switch ART or not will be made based on the viral load detected as detailed below:
    - PVL < 400copies/mL: No change in 1st line ART
    - PVL 400-10,000 copies /mL: Repeat PVL after 3 months with stringent monitoring of patient for adherence to first line ART regimen
    - PVL > 10,000 copies/mL: Start patient on second line ART. Repeat PVL after 6 months to assess suppression in viral load
    - Repeat PVL assay, only once, after 6 months of initiation of second line ART regimen

- **Repeat PVL on the same patient must be done at the same laboratory with the same technique/procedure, using the same platform**

  **** This must be especially noted for laboratories which are initially linked to other laboratories and likely to have their own viral load assay set ups in the near future***

# THE ALGORITHM AND CRITERIA FOR HIV-1 PLASMA VIRAL LOAD (PVL) ASSAY: FOR SWITCHING A PATIENT SHOWING CLINICAL AND/OR IMMUNOLOGICAL FAILURE FROM FIRST LINE ART TO SECOND LINE ART



If treatment failure is suspected based on immunological (second confirmation of CD4 T cell levels) and/or clinical criteria, the ART centre must follow the NACO protocol for management as detailed in pages 19 (protocol A1.1).

The ART center will suspect treatment failure in patients who are on first line ART for at least 6 months and have:

- A new OI (clinical failure)
- Slow rise of CD4 cells or failure of CD4 cells to rise after 6 -12 months of treatment
- Decline in CD4 cells by 50% after an initial rise, as per NACO/WHO guidelines

Perform CD4 cell estimation immediately in cases of suspected clinical failure and repeat after 4 weeks for confirmation of failure as per protocol A1.1

- Simultaneously undertake the following:

    - Evaluate patient for ART adherence
    - Rule out presence of OIs like tuberculosis, oesophageal candidiasis, etc.
    - Ensure patient has been on cotrimoxazole prophylaxis.
    - Treat and review OIs if present.
    - The ART center to send the request form with complete patient details along with the confirmed contact phone number to the nodal officer.

The nodal officer refers such a patient to SACS Clinical Expert Panel (SACEP) for decision on HIV-1 viral load testing.

**Eligibility**

All HIV positive patients registered with and receiving 1st line ART at the following hospitals and showing signs of failure on First line ART will be eligible for review by SACEP:

- JJ Hospital, Mumbai
- Government General Chest Hospital (GGCH), Tambaram
- School of Tropical Medicine (STM), Kolkata
- Mualana Azad Medical College (MAMC), New Delhi
- Gandhi Hospital and Medical College, Hyderabad
- Biramjee Jeejeebhoy Medical College (BJMC), Ahmedabad
- Bowring and Lady Curzon Hospital, Bangalore
- Institute of Medical Sciences (BHU), Varanasi
- Regional Institute of Medical Sciences (RIMS), Imphal
- Post Graduate Institute of Medical Education and Research (PGI), Chandigarh

In addition, all HIV positive patients registered with and receiving first line ART at centers linked to the above mentioned centers (as per NACO instructions on second line ART treatment) would also be eligible for review by SACEP in case of failure on first line ART*.

*NOTE: Blood is not to be drawn for a viral load test within four weeks of any infection or immunization.

**Protocol for the review panel**

The SACEP will review the case notes (preferably in presence of the patient), in case the patient is local or voluntarily willing to be present on the proposed day, the expert committee would also examine the patient clinically to confirm the findings.

The panel will then order a viral load test if required. Specimens (whole blood and DBS as per the Annexure) will be collected from the patient at the ART centre on Monday/Tuesday and sent to the identified viral load lab as detailed below in the section on specimen collection, storage and transport. The SACEP will meet on the following Monday/Tuesday (which if happens to be a holiday then on the next working day) to review the results of viral load assay and, based on the result of PVL, decide on further management of the case.

## 3.4 TECHNIQUES OF HIV-1 PVL ASSAY

Viral load assays measure the amount of HIV-1 RNA in the collected plasma specimen. HIV-1 RNA is responsible for HIV replication. The amount of HIV-1 RNA in plasma can be measured by the following different techniques for measurement of HIV-1 RNA.

- Quantitative PCR (polymerase chain reaction) is the most frequently used test. For PCR the viral RNA is extracted; an enzyme converts the extracted RNA to DNA (cDNA); this DNA is then multiplied many folds by the help of an enzyme polymerase; the product is detected through changes in the intensity/color of certain chemical markers. This process makes the detection of viral RNA easier. The original number of RNA copies would be then quantified based on the final numbers of cDNA obtained. Test results are reported as HIV-1 RNA copies/ml.
- The bDNA (branched DNA) is a fairly frequently used test. It makes use of signal amplification (light emitting material). This material binds with the HIV particles. The amount of light is measured and converted to a viral count.
- NASBA (Nucleic Acid Sequence Based Amplification Assay) is an *in vitro* nucleic acid amplification test for quantification of amplified HIV-1 RNA which is measured by means of electrochemiluminescence.

*The PCR test results are often different from the bDNA results for the same specimen. Because the tests are different, only one kind of test (PCR or bDNA) should be used to measure a person's viral load over time.*

Viral load assay results are reported as copies of HIV-1 RNA in one milliliter of blood. The best viral load assay result in patients on ART is "undetectable" viral load. This does not mean that there is no virus in the blood; it just means that the level is not enough to be detected through the test used. "Undetectable" level (No of copies/mL of plasma) will depend on the sensitivity of the assay system used.

**Some relevant terminologies**

- **Sensitivity:** Sensitivity is defined as the lowest viral load level that can be detected in the specimen 95 percent of the time. The statistical method of assessing sensitivity is generally considered to be the standard to determine the quantitative "limit of detection" (LoD) for quantitative HIV-1 RNA assays
- **Precision:** The precision or reproducibility of an assay is defined by its ability to obtain the same value when tested repeatedly. In viral loads, precision is measured by the ability to detect "fold changes" in the levels of the viral loads.
- **Dynamic Range:** The dynamic range of an assay is defined as the quantitative range over which the results are reliably reported.

## 3.5 PLASMA VIRAL LOAD ASSAYS CURRENTLY IN USE IN NACO'S SECOND LINE ROLL OUT

### 3.5.1 Amplicor HIV-1 Monitor Test, version 1.5

The Amplicor HIV-1 Monitor Test, version 1.5 (v1.5) is an *in vitro* nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus Type 1 (HIV-1) RNA in human plasma. The Amplicor HIV-1 Test, version 1.5 uses PCR technology to achieve maximum sensitivity and dynamic range for the quantitative detection of HIV-1 RNA in EDTA anticoagulated plasma.

The Amplicor HIV-1 Monitor version 1.5 (v1.5) is programmed on, and approved for use on Applied Biosystems Gene-Amp PCR system 9600/9700 thermal cycler. In Amplicor HIV-1 monitor the specimen preparation is manual, the amplification is automated on the ABI 9600/9700 and detection is by manual ELISA or automated ELISA reader.

The test can quantitate HIV-1 RNA over the range of 50-750,000 copies /mL by using a combination of two specimen preparation procedures, the Standard (dynamic range 400-750,000 copies /ml) and UltraSensitive (dynamic range 50-1,00,000 copies/ml) procedures. Test results less than 400 are below the lower limit of detection of the Standard test. If quantitative results are desired for such specimens, original plasma specimens should be retested using the Ultra sensitive specimen preparation procedure

This test is based on five major processes: specimen preparation, reverse transcription of target RNA to generate complementary DNA (cDNA); PCR amplification of target cDNA
using HIV-1 specific complementary primers; hybridization of the amplified products to oligonucleotide probes specific to the target(s); and detection of the probe bound amplified products by colorimetric determination.

The Amplicor HIV-1 Monitor Test, v1.5 can be used with either of two specimen preparation procedures, the Standard procedure or the Ultra Sensitive procedure. In the Standard specimen preparation procedure, HIV-1 RNA is isolated directly from plasma by lysis of virus particles with a chaotropic agent followed by precipitation of the RNA with alcohol. With the UltraSensitive specimen preparation procedure, HIV-1 viral particles in plasma are concentrated by high speed centrifugation, followed by lysis of the virus particles with a chaotropic agent and precipitation of the HIV-1 RNA with alcohol. A known number of quantitation standard RNA molecules are introduced into each specimen with the lysis reagent. The HIV-1 Quantitation Standard is carried through the specimen preparation, reverse transcription, amplification and detection steps and is used for the quantitation of HIV-1 RNA in the test specimen.

### 3.5.2 Cobas Amplicor HIV-1 Monitor™ Test, version 1.5

The Cobas Amplicor HIV-1 Monitor Test, version 1.5 (v1.5) is an *in vitro* nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus Type 1 (HIV-1) RNA in human plasma on the Cobas Amplicor ™ analyzer.

In Cobas Amplicor the specimen preparation is manual and the amplification and detection steps are automated.

The test can quantitate HIV-1 RNA over the range of 50-750,000 copies /mL by using a combination of two specimen preparation procedures, the Standard (dynamic range 400-7,50,000 copies /ml) and Ultra Sensitive (dynamic range 50-1,00,000 copies/ml) procedures. Test results less than 400 are below the lower limit of detection of the Standard test. If quantitative results are desired for such specimens, original plasma specimens should be retested using the Ultra sensitive specimen preparation procedure.

This test is based on five major processes: specimen preparation; reverse transcription of target RNA to generate complementary DNA cDNA; PCR amplification of target cDNA
using HIV-1 specific complementary primers; hybridization of the amplified products to oligonucleotide probes specific to the target(s); and detection of the probe bound amplified products by colorimetric determination.

The Cobas Amplicor HIV-1 Monitor Test, v1.5 can be used with either of two specimen preparation procedures, the Standard procedure or the Ultra Sensitive procedure. In the Standard specimen preparation procedure, HIV-1 RNA is

isolated directly from plasma by lysis of virus particles with a chaotropic agent followed by precipitation of the RNA with alcohol. With the UltraSensitive specimen preparation procedure, HIV-1 viral particles in plasma are concentrated by high speed centrifugation, followed by lysis of the virus particles with a chaotropic agent and precipitation of the HIV-1 RNA with alcohol. A known number of quantitation standard RNA molecules are introduced into each specimen with the lysis reagent. The HIV-1 Quantitation Standard is carried through the specimen preparation, reverse transcription, amplification and detection steps and is used for the quantitation of HIV-1 RNA in the test specimen.

### 3.5.3 COBAS TaqMan HIV-1 Test

The COBAS TaqMan HIV-1 Test is an *in vitro* nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus Type 1 (HIV-1) RNA in human plasma with EDTA, using the High Pure System Viral Nucleic Acid Kit for manual specimen preparation and the COBAS TaqMan analyzer for automated amplification and detection. The test can quantitate HIV-1 RNA over the range of 47 - 10,000,000 copies/ ml

The COBAS TaqMan HIV-1 Test utilizes real time PCR technology to achieve maximum sensitivity and dynamic range for the quantitative detection of HIV-1 RNA in EDTA anti-coagulated plasma. The use of dual-labeled fluorescent probes provides for real-time detection of PCR product accumulation by monitoring of the emission intensity of fluorescent reporter dyes released during the amplification process. The COBAS TaqMan HIV-1 Test accurately provides quantitative results over a very wide dynamic range since the monitoring of amplicon is performed during the exponential phase of amplification. The higher the HIV-1 titer of a specimen, the earlier the fluorescence of the reporter dye of the HIV-1 probe rises above the baseline fluorescence level.

The COBAS TaqMan HIV-1 Test is based on four processes: Specimen preparation to obtain HIV-1 RNA; Automated reverse transcription of the target RNA to generate complementary DNA (cDNA); Simultaneous PCR amplification of target cDNA using HIV-1 specific complementary primers; and detection of cleaved dual fluorescent dye-labeled oligonucleotide detection probes.

The COBAS TaqMan HIV-1 Test processes EDTA containing plasma specimens and isolates HIV-1 RNA through a generic manual specimen preparation (in case ampliprep is not available) based on nucleic acid binding to glass fibers. The HIV-1 virus particles are lysed by incubation at an elevated temperature with a protease and chaotropic lysis/binding buffer that releases nucleic acids and protects the released HIV-1 RNA from RNAs in plasma. A known number of HIV-1 ‘Quantitation Standard Armored’ RNA molecules are introduced into each specimen along with the lysis reagent. Subsequently, isopropanol is added to the lysis mixture which is then centrifuged through a column with a glass fiber insert. During centrifugation, the HIV-1 RNA and HIV-1 Quantitation Standard RNA are

bound to the surface of the glass fiber filter. Unbound substances, such as salts, proteins and other cellular impurities, are removed by centrifugation. The adsorbed nucleic acids are washed and eluted with an aqueous solution. The disposables allow for a parallel processing of 12 specimens or multiples thereof. The processed specimen, containing HIV-1 RNA and HIV-1 Quantitation Standard RNA, is added to the amplification/detection mixture. The HIV-1 target RNA and the HIV-1 Quantitation Standard RNA are then reverse transcribed, amplified and detected on the COBAS TaqMan - analyzer using the amplification and detection reagents provided in the test kit.

## 3.6 SPECIMEN COLLECTION, STORAGE AND TRANSPORTATION

### 3.6.1 Collection days and timings

- Specimen collection is to be done between 11.00 A.M to 1:00PM on SACEP day (Mondays/Tuesdays, as decided by the center).
- In case the specimen collection day is a holiday, specimen collection is to be posted on an alternate day with prior arrangement with the receiving laboratory.
- Do not collect specimen if next day to SACEP is a holiday (as specimens have to be processed for HIV-1 PVL by the receiving laboratory within 24 hours of collection)
- Previous arrangement with testing center to be made in case the specimen is to be collected on a day not scheduled for the purpose (Collection and transport of specimen)

### 3.6.2 Specimen collection

- Standard work precautions are to be followed stringently
- Page 1 of the VL-1 form (as per Appendix I) is to be filled mandatorily in **duplicate**/ photocopy. (Specimens accompanied with incomplete forms will be rejected)
- Confirm information on VL-1 form (patient's name, registration/accession number, test needed, date and time of collection, and physician's/clinic's name, etc) mandatorily before collection of specimens
- Sterile EDTA (lavender top) evacuated blood collection tubes are to be used.
- The blood collection tubes are to be **labeled** (cryolabel) with patient's name, registration/accession number, test needed, date and time of collection, and physician's/clinic's name. The information on the form should match the information on the specimen collection tube
- 4mL blood is to be collected and placed in prescribed sterile tubes using EDTA (lavender top) as the anticoagulant. *Do not collect blood in heparin vials. (*The choice of anticoagulant used in blood collection tubes can significantly alter viral load results, by affecting either the virion decay rate *ex vivo* or the detection by the assay type used.

Plasma treated with sodium heparin is not appropriate for PCR assays because heparin is a potent inhibitor of PCR)

***In case the linked HIV-1 PVL laboratory is in a different city, Dried Blood Spot (DBS) Preparation and Storage (as per Section 3.14) and then plasma separation (as per below) are to be performed by the ART Centre itself.***

***In case the linked laboratory is in the same city or same hospital, DBS Preparation and Storage (as per Section 3.14) and then plasma separation (as per below) are to be performed by the PVL laboratory within 6 hours of receipt of specimen.***

### 3.6.3 Packaging and transportation

- All specimens will be transported by hand by lab technicians of the centre of excellence
- The specimen is to be packaged carefully to protect from breakage, and leakage and insulated to protect from extreme temperature. Cool packs are to be used to maintain temperature of 2-8$^0$C. Ensure whole blood does not freeze during transportation.
- For packaging, the tube containing the specimen is placed in a leak proof container (e.g. a sealed plastic bag).
- The cool packs are to be placed around and the package is to be placed inside a puncture proof container with sufficient material to absorb all the contents in case the tube breaks or leaks.
- Cap the container tightly.
- Place the VL-1 form in an envelope and fasten securely to the outside of the container.
- A biohazard label should be pasted on the visible outer surface of the package containing the specimens.
- In case the laboratory is located in the same city: The Lab technician of the ART centre should transport the specimen with the VL-1 form in duplicate and ensure delivery to the testing lab of the whole blood specimen at 2-8$^o$C within 3 hours of collection (i.e. by 2.00 P.M. on Monday/Tuesday afternoon).
- In case the laboratory is located in a different the city: The Lab technician of the ART centre should transport the ***plasma*** specimen (First having prepared, packaged and stored DBS; and then separated the plasma at the ART centre) with the VL-1 form in duplicate and ensure delivery to the testing lab of the plasma specimen at 2-8$^o$C within 24 hours after collection (i.e. by 10AM. on Tuesday/Wednesday).
    - The technician from the centre of excellence carrying the specimens must participate with the technicians at the PVL laboratory in the processes of estimation of HIV-1 PVL in order to learn the techniques involved.

***The DBS samples will be collected and stored as per section 3.14.It is recommended that the DBS samples be stored at 2-8 deg C for 20 days and then be couriered to NARI, Pune along with the consent forms. It is important to note that the consent form must be sent to the lab making DBS in case of intercity linkages for sending to NARI, Pune. The details on the envelope may be as follows:***

**For Second Line roll out**

**Dr Srikanth Tripathy**

**National AIDS Research Institute**

**73 G Block, MIDC**

**Bhosari, Pune-411026**

**India**

### 3.6.4 Receiving specimen at the HIV-1 PVL testing laboratory

- Receiving lab to identify the specimen properly. If there is discrepancy in the test requisition form versus the labeled tube, *DO NOT PROCEED*. Take corrective action to ensure that the patient's name and number on the request form are correct. In case of any confusion check back with the collection site.
- Receiving lab to check and thereby ensure at the time of specimen receipt that the temperature of the specimen never exceeded $8^0$C and the whole blood specimen was not frozen, during storage at the collection site and transport to the testing site. Leakage is also checked for.
- In case, of any doubt send back the specimen and VL-1 form back to the COE, duly signed by lab in-charge, with the COE technician. Another specimen must be collected for PVL.
- The receipt of the specimens to be duly documented on both the copies of the VL-1.
- In case specimen is rejected, one copy of the VL-1form with signatures of lab in charge to be sent back with the center of excellence technician by hand on the same day.
- Receiving lab to record the time / date of specimen receipt.
- **Do not freeze whole blood.** Do not store whole blood for more than 6 hours after collection-even at temperature range of 2-25 $^0$ C. Plasma at the receiving lab has to be separated from the whole blood within 2

hours of specimen receipt, within 6 hours of specimen collection (i.e. by 4.00 P.M. on the same day Monday/Tuesday).

### 3.6.5 Processing of the whole blood specimen in the receiving lab:

- After preparation of DBS, the remaining whole blood specimen is be centrifuged for separation of plasma as detailed below and processed further for estimation of HIV-1 PVL as per the instructions of the manufacturer of the kit being used.
    - Separation of plasma from whole blood:
        - Centrifuge whole blood at 800 -1600 x g for 10 minutes at room temperature.
        - Remove the plasma and recentrifuge at 800 x g for another 10 minutes.
        - Aliquot and store 800-900µl of plasma in a sterile 2 ml polypropylene screw-capped tube.
        - In case of inadvertent delay, plasma specimen to be separated and stored at 2-8 $^{0}$C overnight and transported to the testing site next morning at 2-8 $^{0}$C for performance of the test on the same day (to be processed for PVL within 24 hours after collection).
        - Plasma specimen is to be kept at 2-8℃ till processed.
        - Receiving lab must process the specimen within 24 hours after specimen collection.
        - The plasma specimen must be brought to ambient temperature before performing the test as per the manufacturer's protocol.
    - Perform PVL assay as per manufacturers protocol on the available platform

| Current Linkage Plan | | | | | | |
|---|---|---|---|---|---|---|
| **SACEP Center of Excellence** | **Frequency of specimen collection and transportation** | **Preparation of DBS and separation of plasma from whole blood** | **Transportation by lab technician carrying the specimens** | **PVL testing lab** | **Specimens tested*** ** | **Results reported to ART Centre and NACO** |
| **BHU, Varanasi** | Day of SACEP, Tue every 15 days | At ART centres: BHU, Varanasi, PGI, Chandigarh | Rail/Road* at 2-8°C | IHBAS, New Delhi | Day of receipt of specimen (preferably within 24 hours after collection); Wed | By weekend of receipt of specimen |
| **PGI Chandigarh** | | | Rail/Road* at 2-8°C | | | |
| **BJMC Ahmedabad** | Day of SACEP, Tue every 15 days | At ART centre: BJMC, Ahmedabad | Rail/Road* at 2-8°C | Kasturba Hospital, Mumbai | Day of receipt of specimen (preferably within 24 hours after collection); Wed | By weekend of receipt of specimen |
| **RIMS Imphal** | Day of SACEP, Tue once a month | At ART centre: RIMS, Imphal | Air ** at 2-8°C | NICED, Kolkata | Day of receipt of specimen (preferably within 24 hours after collection); Wed | By weekend of receipt of specimen |
| **MAMC, Delhi** | Day of SACEP, Tue once every week | At IHBAS, New Delhi | Road at 2-8°C | IHBAS, New Delhi | Day of receipt of specimen (preferably within 24 hours after collection); Wed | By weekend of receipt of specimen |
| **STM, Kolkata** | Day of SACEP, Tue once every week | At NICED, Kolkata | Road at 2-8°C | NICED, Kolkata | Day of receipt of specimen (preferably within 24 hours after collection); Wed | By weekend of receipt of specimen |
| **Bowring & LC Hospital, Bangalore** | Day of SACEP, Wed, once every week | At St Jones, Bangalore | Road at 2-8°C | St Jones, Bangalore | Day of receipt of specimen (preferably within 24 hours after collection); Thursday | By weekend of receipt of specimen |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Gandhi Hospital & MC, Hyderabad** | Day of SACEP, Mon/Tue, once every week | GHMC Lab, Hyderabad | Road at 2-8$^{o}$C | GHMC Lab, Hyderabad | Day of receipt of specimen (preferably within 24 hours after collection); Tue/Wed | By weekend of receipt of specimen |
| **JJ Hospital, Mumbai** | Day of SACEP, Mon/Tue, once every week | Kasturba Hospital | Road at 2-8$^{o}$C | Kasturba Hospital | Day of receipt of specimen (preferably within 24 hours after collection); Tue/Wed | By weekend of receipt of specimen |
| **GHTM, Tambaram** | Day of SACEP, Mon/Tue, once every week | TRC, chennai | Road at 2-8$^{o}$C | TRC, chennai | Day of receipt of specimen (preferably within 24 hours after collection); Tue/Wed | By weekend of receipt of specimen |
| * Costs of TA/DA for COE technician carrying specimens will be paid from contingency grant of COE | | | | | | |
| ** Technician should book air ticket in advance by apex fares which will be paid from contingency grant | | | | | | |
| **COE technician carrying the specimens must participate in the processes and learn estimation of PVL at the PVL testing lab | | | | | | |

## 3.7 FACTORS TO BE CONSIDERED WHILE INTERPRETING THE VIRAL LOAD RESULTS

The HIV-1 PVL quantification assay is influenced by many factors. Thus the interpretation of absolute viral concentration measurement results is not straightforward. One important issue to consider is whether measured change in viral load actually reflects a biological event, or whether the change is within the variability limit of the assay. Repeat tests of the same blood specimen can give results that vary by a factor of 3. This means that a meaningful change would be a drop to **less than 1/3** or an increase to **more than 3 times** the previous viral load result. For example, a change from 200,000 to 600,000 is within the normal variability of the test. A drop from 50,000 to 10,000 would be significant. However, the most important change in a patient responding well/optimally to ART is reaching an undetectable viral load level.

There is a considerable variation in the results of various types of assays used in quantification of the same specimen but if performed proficiently, a commercial assay shows reproducibility within approximately 0.2-0.5 $\log_{10}$, (varying in different regions of the assays' dynamic range). Daily variation in viral loads among clinically stable patients is minimal at approximately 0.4 $\log_{10}$. Therefore a

change in viral load of greater than 0.5 $\log_{10}$ RNA copies/ml (approximately 3-fold) exceeds assay and diurnal variations, and may be considered to represent true biological events, while changes of less than 0.5 $\log_{10}$ cannot be distinguished whether these are from random variability or a biological event. It is important to note that in the low end of the dynamic range, assay variability has greater impact on interpretation of absolute viral load change.

**How are the changes in viral load measured?**

Viral load changes are often described as "log" changes. This refers to scientific notation, which uses powers of 10. For example, a 2-log drop is a drop of $10^2$ or 100 times. A drop from 60,000 to 600 would be a 2-log drop. Small changes of 10, 20, 30 copies are often not considered to be a significant change in viral load and can reflect normal viral “blips,” not a change in treatment response.

***What do the numbers mean?***

It is not known how long a HIV positive patient would stay healthy with any particular viral load. All that is known so far is that lower PVL is better and seems to mean a longer, healthier life. The viral load should drop to reach less than 50 copies within 6 months of ART. Even when the HIV-1 viral load in a HIV positive is undetectable, the HIV virus can be passed on to another person, although the risk is lower. There is no "safe" level of viral load**.**

## 3.8 LIMITATIONS OF VIRAL LOAD ASSAYS

RNA assays used to measure PVL are perhaps most heavily relied upon in the medical management of people diagnosed with AIDS and in people who test positive on the HIV-1 antibody tests. As many important clinical decisions are based on these tests, the highest standards of sensitivity and specificity are recommended. There are however some concerns with the viral load tests as given below:

- Intra-assay and biologic variability may affect the findings.
- The viral load test results can be unreliable if the body is fighting an infection, or if the patient has just received an immunization. Blood should not be taken for a viral load test within four weeks of any infection or immunization. Temporary increases in viral load have been seen in these instances. Also, the physician must review the patient’s adherence to the ART regimen and should postpone testing if recent doses of ART have been missed that may cause rapid replication of HIV, *in vivo*. Such patients may already be experiencing viral rebound and their ART therapy could be incorrectly judged to be failing.
- A drawback to PVL testing is the high cost of assays and requirement of technical expertise.

## 3.9 STANDARDIZATION OF HIV-1 PLASMA VIRAL LOAD REPORTING

Laboratory reports of viral load assays should be standardized, accurate and adequate for patient treatment and public health monitoring of the HIV infection and acquired immunodeficiency syndrome (AIDS) epidemic. To ensure test report comparability among laboratories, standard testing and reporting methods are needed; moreover, standardized results are needed for early detection of treatment failure and early access to patient care.

**Required items to report**

- The laboratory should completely fill out the report found in Annex I, as per testing platform.
- It should be duly signed in the VL-1 reporting format (See Annex 1)
- It should be sent from the lab to the ART centre by courier by Saturday to reach the ART center latest by Monday. The courier will be paid from the contingency grant.
- A copy of the report should be e-mailed to NACO by Saturday at drbbrewari@yahoo.com and sandhyakabra@gmail.com

## 3.10 QUALITY ASSURANCE FOR HIV-1 PLASMA VIRAL LOAD TESTING

Viral load testing is an integral part of the management of HIV disease. It is absolutely imperative to ensure the accuracy, precision and reproducibility of the test results by adhering to stringent Quality Assurance and Quality Control measures at all times.

Quality Assurance is defined as a set of planned and systematic activities to ensure adequate confidence that requirements for quality will be met.

Internal Quality Control refers to those measures that must be taken to ensure that the test is working, the technical aspects of the test procedure have been met/ followed and the results produced are valid within the limitation of the test system used. Laboratories performing HIV-1 Viral load quantification need to use external quality control specimens in addition to the controls contained in test kits for validation of the result.

It is recommended that a high positive control, low positive control and a negative control that come with the test kits be included with each run. The copy number per mL for each positive result should fall within the range of values indicated in the package insert. The negative control should give a less than the lower detection limit result. If controls are not as expected, the run is not valid and is to be repeated. These controls should meet the prescribed regulatory requirements for such controls. It is good to have traceability to international reference standards. Use of above test controls, that are used to validate a test run and to quantitate HIV-I RNA, would however not validate the analytic testing process

which may include testing problems related to pipetting, inadequate incubation or washing or variability in kit lot sensitivity.

### 3.10.1 Invalid test runs

When invalid positive or negative results are obtained on running internal controls, the run is declared invalid and the entire test procedure for all the specimens has to be repeated in another run by processing another aliquot of the original plasma specimens.

Flags and comments may be generated by the analyzer during the run. The operator must check the run printout(s) for flags and comments to verify that the run is valid.

With the exception of instrument failures subsequent to the denaturation of amplicons, an instrument failure during a test run as indicated by the system error messages also constitutes an invalid test run.

### 3.10 2 Internal quality control (Assay controls-part of the system)

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- Controls are supplied by the manufacturer and are to be processed like patient specimens. A low positive, high positive and a negative control are supplied with the kit. Run controls to check accuracy and reproducibility.
- All quality control failures must be logged and corrective action completed before specimen analysis takes place.
- All reagents used must be logged onto log sheets with the date opened, expiry date and signature. Reagents discarded due to contamination, spillage, etc. must be logged in the appropriate log sheets.
- Reagents must be stored as recommended by the manufacturer and daily temperature logs should be maintained.
- Results should be entered onto Levy-Jennings plots to monitor any trends, shifts or bias in results.

### 3.10.3 External quality assessment

Every testing facility must be able to demonstrate and document its competence in performing the tests. External quality assessment (EQA) is an evaluation by an outside agency of the performance of a laboratory on specially supplied small panels of well characterized specimens. The objective is to achieve between-laboratory and between-method comparability.

### 3.10.4 Objectives of EQAS

- The primary objective is to continually improve and maintain the high standard of the laboratory's performance.
- To continually institute a formal monitoring and evaluation programme.
- To continually promote the concept of quality assurance, quality control, and quality assessment in the laboratory.

- To assess the quality of service of the participating laboratory.
- To identify problems and take appropriate interventions for corrective actions.
- To encourage the implementation of good laboratory practices.
- To provide teaching and training programs.

Participation in external quality assessment (EQA) is not a substitute to day to day internal quality control practices. EQA is designed to assess the integrity of the entire lab testing process. Even when all precautions have been taken to achieve accuracy and precision in the laboratory, errors may arise which may be detected by objective external assessment. The principle is that the assessed material (values are known) is sent from an international, national or regional centre to a large number of participating laboratories at regular designated intervals. The results produced by the participating laboratories are assessed for accuracy, precision and reproducibility in a confidential manner by the lab conducting EQA. The labs producing inaccurate results are revamped through training and troubleshooting.

The EQAS essentially contains the following components:

- Filling up questionnaire to understand the laboratory capabilities and additional requirements
- Training for viral load estimation procedure and participation in EQAS
- Processing of the specimens received under EQAS following the routine procedure of viral load estimation
- Submission of report to the EQA conducting laboratory
- Doing analysis of results, assessment of performance and trouble shooting

### 3.10.5 EQA for HIV-1 Plasma Viral Load Testing

The NACO designated laboratories that will initiate/perform HIV-1 PVL testing for second line roll out are to participate in EQA being conducted by the centre listed below for the time being:

RCPA (Royal College of Pathologists Australasia) Quality Assurance Program

RCPA Quality Assurance Programs Pvt Ltd was established by the Royal College
of Pathologists of Australasia in 1988 and is providing the EQA services to over 40 countries and 4,000 programs around the world. RCPA Quality Assurance Program Pvt Limited is a NATA (National Associated Testing Authority, Australia) accredited Proficiency Testing provider for HIV-I RNA Viral load and complies with the requirements of ILAC G13.

## 3.11 OPERATIONAL PLAN FOR HIV-1 VIRAL LOAD TESTING AND EQAS

It is proposed that HIV-1 viral load testing facilities for the National HIV/AIDS care and treatment program would initially be set up at select centers. The NACO labs that have been identified to initiate and perform HIV-1 PVL testing for specimens being sent by the NACO identified second line centers are:

- Kasturba Hospital for Infectious Diseases, Mumbai
- Tuberculosis Research Center (TRC), Chennai
- Institute of Human Behavior and Allied Sciences (IHBAS), New Delhi
- National Institute of Cholera and Enteric Diseases (NICED), Kolkata
- Gandhi Hospital and Medical College, Hyderabad
- St John's Hospital, Bangalore
- Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh
- Institute of Medical Sciences (BHU), Varanasi
- Biramjee Jeejeebhoy Medical College (BJMC), Ahmedabad
- Regional Institute of Medical Sciences (RIMS), Imphal

NACO has created the following interim linkages until all the designated HIV-1 PVL testing centres become operational:

The above linked centres, both the COEs and the testing labs, should coordinate their collection days and times so that viral load specimens that are being sent from different centres to the same lab can be coordinated to be processed together on the same day, ensuring the efficient use of viral load reagents and laboratory time.

It is proposed to identify the eligible patients after a detailed examination by the SACEP. The SACEP meeting will be held on Monday/Tuesday morning between 9:00AM to 11:00AM depending on the convenience of the institution. Eligible candidates will be subjected to HIV-1 PVL testing before SACEP takes the decision to initiate second line ART.

Blood specimen (4ml) will be collected in an EDTA vacuum evacuated tube immediately after SACEP meeting and processed as given below:

- In case the PVL testing lab is in the same city as the COE: whole blood specimen is to be transported to the PVL testing lab at 2-8$^{o}$C within a maximum of 6 hours after collection
- In case the PVL testing lab is in a different city as the COE: the laboratory technician at the COE will prepare, package, and store the DBS (Section 3.14) and separate the plasma (as detailed above) within 2 hours after specimen collection. The plasma specimen will be stored at 2-8$^{o}$C until transported by the COE technician. The specimen will be hand carried by

the COE technician from COE to the PVL testing laboratory as detailed above. The COE must ensure that the lab technician carrying the specimens must leave the COE that same day.

- Frequency and processing of specimen and transport details will be as detailed in Table 1
- Once the specimens have been received at the PVL testing lab, estimation of HIV-1 PVL must be done within 24 hours after the specimen was collected.
- The PVL testing lab must courier back the test reports to the corresponding COE by the weekend. Cost of the same will be met from contingency grant.

To ensure the quality of the testing on a daily basis and to ensure that all labs meet international testing standards, these centers would participate in EQAS for HIV-1 viral load testing. An attempt is being made to provide EQAS specimens to all the NACO identified testing labs for HIV-1 PVL testing. All labs must participate and provide necessary cooperation for implementing the same.

*The details of the EQAS process flow have been annexed at the end of the laboratory guidelines for VL testing*

## 3.12 PRECAUTIONS AND SPECIFIC INSTRUCTIONS FOR REAGENTS & EQUIPMENT

### 3.12.1 General

- Viral load assay is for *in vitro measurement of plasma HIV-1 RNA copies and is not for* diagnostic use
- Treat all specimens as potentially infectious. Adhere to Standard Work Precautions when performing the assay.
- Only personnel trained in handling infectious material should perform this procedure
- Screw capped tubes must be used for processing specimens and controls to prevent splashing and potential cross-contamination of specimens or controls***. Do not use snap-cap tubes.*** Handle all specimens or controls in accordance with the Good Lab Practices in order to prevent cross-contamination
- Do not pipette by mouth.
- Do not eat, drink or smoke in laboratory work areas. Wear protective disposable gloves, laboratory coats and eye protection when handling specimens and kit reagents. Wash hands thoroughly after handling specimens and kit reagents
- Avoid contact of these materials with the skin, eyes or mucous membranes. If contact does occur, immediately wash with large amounts of water. Burns can occur if left untreated. If spills of these reagents occur, dilute with water before wiping dry.
- Avoid contaminating gloves while manipulating specimens
- Specimens and controls should always be prepared in the laminar flow - failure to do so may result in specimen contamination

- Handle and manipulate specimens in a Class II Biological Safety Cabinet
- Thoroughly clean and disinfect all work surfaces with a freshly prepared solution of 0.5% sodium hypochlorite and follow by wiping down the surface with 70% ethanol.
- Any deviations from the specified procedures and guidelines may affect optimal assay performance.
- This test is for use with human plasma collected in EDTA anticoagulants only. ***Heparin has been shown to inhibit PCR and must not be used with this procedure.***

### 3.12.2 Reagents storage and use

- Store reagents strictly as per manufacturers specific reagent storage recommendations
- Visually inspect each reagent bottle before use to ensure that there are no signs of leakage and or abnormal color.
- Do not use a kit after expiry date. DO NOT interchange, mix or combine reagents from kits with different master lot numbers. Ensure that all reagents used are of the same master lot of reagents.
- Add all reagents using a pipette capable of accurately delivering specified volumes.
- Regularly calibrate pipettes for accurate delivery and maintain logs
- Avoid microbial and ribonuclease contamination of reagents when removing aliquots from reagent bottles. The use of sterile disposable pipettes and RNase-free pipette tips is recommended.
- Do not freeze reagents or controls
- Do not pool reagents from different lots or from different bottles of the same lot.

### 3.12.3 Equipment

- Perform manufacturer recommended maintenance and calibration of all equipment, including pipettes to ensure proper functioning.

### 3.12.4 Work areas

To minimize the possibility of lab areas becoming contaminated with the amplicon, the lab area should be separated into several distinct areas organized around the pre-amplification (separate reagent and specimen preparation areas) and post-amplification (Amplification and Detection) areas. Personnel should use proper anti-contamination safeguards when moving between areas.

- Workflow in the laboratory must proceed in a uni-directional manner, beginning in the Pre-Amplification Area and moving to the Post-Amplification (Amplification and Detection) Area.
- Pipettes and other supplies should be dedicated to a specific area. Specimens, equipment and reagents should not be returned to the area where a previous step was being performed and should not be used for other activities or moved between areas

- Pre-amplification activities must begin with reagent preparation and proceed to specimen preparation.
- Supplies and equipment must be dedicated to each pre-amplification activity and not used for other activities or moved between areas. Equipment and supplies used for reagent preparation must not be used for specimen preparation activities or for pipetting or processing amplified DNA or other sources of target DNA
- Gloves must be worn separately in each area and must be changed before leaving that area.
- The pre-amplification area should have a template free area for preparation of reagents and an amplicon free area for specimen and control preparation
- Post-amplification supplies and equipment must remain in the Post-Amplification Area at all times
- The post-amplification area should have analyzer(s) and Data station(s) with additional area for preparing Working Amplification and Detection reagents.

## 3.13 TROUBLE SHOOTING

- While performing the viral loads in the lab, there will be occasions when things may go wrong. The problems could occur because of mechanical, chemical or human error. Staff should be trained to recognize when there is a problem and how to correct them so that the final patient results sent out are not affected. Please follow the manufacturer's instructions for troubleshooting

***Note: Adhere to standard work precautions and PEP as per NACO HIV testing. Keep eye splashers, body showers and supply of running tap water within vicinity of the working lab***

## 3.14 DBS collection for all patients undergoing Viral load testing

**The national programme will collect DBS samples from all patients who are sent for Viral load. The consent form is as annex V (integrated consent for 2nd line ART as well as for collection of blood for storage)**

The purpose of this collection and storage of blood on Dried Blood Spots (DBS) from patients undergoing evaluation for second-line ART in India, is to subsequently conduct HIV genotypic resistance testing on these specimens to evaluate the patterns of HIV drug resistance that have developed among patients who have developed treatment failure to the standard first-line ART regimen. Clinical and laboratory data will be abstracted from patient records to further analyze and correlate HIVDR findings with virologic, immunologic, and clinical

outcomes of patients receiving second-line treatment. Overall, the findings of these analyses can be used to guide the expansion of ART services, and specifically second-line ART services, in India.

The objective of the analysis will be:
1. Determine the patterns of HIVDR that are present among patients who have developed treatment failure to the standard first-line regimen
2. Among patients who receive second-line therapy, determine if HIVDR patterns at therapy switch have an impact on virologic suppression at 6 months and/or 12 months
3. Evaluate the clinical, immunologic, and survival outcomes of patients who developed failure to first-line ART at 12 and 24 months. This analysis can be stratified by HIV RNA at the time of initial second-line evaluation (<400 copies/mL, 401-10,000 copies/mL, >10,000 copies/mL)

### 3.14.1 Specimen Collection, Processing, and Storage

Blood is routinely collected from patients at the time of evaluation for second-line ART at the SACEP for HIV RNA, chemistry panel, liver function tests, and complete blood count. At this time, a dried blood specimen (DBS) will also be collected.

*Specimen collection:*
DBS should only be made from patient's blood tubes that have been specifically labelled or marked as eligible. Before the DBS is made, the DBS-ID and ART-ID for the participant should be written on the filter paper card. Anti-coagulated blood should be spotted onto filter paper within 24 hours of collection. The filter paper should be handled only at the edge; the areas that will be used to collect specimens should not be touched. A filter should only be spotted with the blood of a single patient.
For recently collected, fresh whole blood, invert the blood collection tube 2-3 times to mix the whole blood. Carefully open the blood collection tube. Use a pipette (with disposable tip) to aspirate 100 µl of whole blood and apply it to the centre of one pre-printed circle to fully saturate the circle. Repeat this procedure to fill each circle on the card with blood. For each specimen at least **four** saturated circles should be obtained. Opening of the tubes and pipetting should be performed following standard laboratory biosafety precautions.

***Specimen drying:***
Avoid touching the part of the card with the blood spot. Dry all specimen cards at least 4 hours at ambient temperature in a suspended horizontal position. Depending on the climate it might be necessary to allow spots to dry over night. Do not use oven to fasten the drying time of the cards. When dry, the spots should be a uniform dark brown. The appearance should be similar to that of a dried bloodstain and no areas of red coloration should be seen.

*Specimen packaging:*
Make sure the DBS or DPS are completely dry before packing. Packaging of each DBS card into a separate gas-impermeable zip-lock bag with 2-3 desiccant packs (to remove any residual moisture from the cards) per bag and a humidity indicator card (to indicate the relative humidity inside the bag) is recommended. When packing, make sure that the humidity indicator cards are faced outside. Place the front of the humidity indicator card facing outside so that the markings are clearly visible. Press the bag with both hands to squeeze out the air from the bag and then seal it. Place 5-10 of the above small bags into a large plastic bag. In the large plastic bag, also place a printed manifest with specimen information. Plastic or foil bags used for storage must be gas- impermeable to keep the contents of the bag humidity-free. Bags available from grocery stores or other outlets that do not sell scientific supplies are inadequate.

Humidity indicator cards and desiccant packs have a color indicator which changes from blue to pink as humidity increases. All humidity indicator and desiccants should be replaced with fresh material before they have all changed to a pink color. To ensure proper packaging of the DBS cards, the humidity indicator card should be examined once a week if the sample is kept at room temperature. Before placing desiccant packs into a zip-lock bag with DBS, make sure desiccant packs have remained dry during storage (indicator card should show blue color). When an indicator is beginning to change, it is time to change the humidity indicator and desiccant packs. Desiccant packs can become moist after use with DBS, but also after storage in a humid environment. Store desiccant packs with humidity indicator cards to evaluate whether their moisture level has become too high. Humidity cards and desiccant packs can be re-used. Moist humidity indicator cards and desiccant packs should be dried in a 65℃ oven over night until the color indicator returns to blue. Remove from the oven and store in a sealed bag with a humidity indicator card until reuse or until they once again need to be dried in the oven.

*Specimen storage:*
For short-term storage (preferably two weeks maximum, but no more than 30 days) at the collecting sites, DBS can be kept in the gas impermeable zip-lock bags with desiccants and stored at room temperature. DBS held at room temperature should be stored in a box or container so that direct light will not damage them. DBS should be examined frequently (e.g., weekly) to evaluate whether the 30% circle in the humidity indicator card has changed to a pink color; when it does, the desiccants must be changed immediately.

DBS can be kept at room temperature or at 4℃ *only* for short term storage (<30 days). DBS should not be frozen at the collection site unless definite arrangements can be guaranteed to maintain them in a frozen state until they reach the genotyping laboratory. In settings where constant refrigeration may not be possible because of frequent electricity outages, or where high humidity is likely within the available refrigerator/freezer, it is preferable to hold the DBS at room temperature. If possible, DBS should not remain at a collecting site with limited storage conditions for more than 7 days before being transported to a

laboratory with a constant electricity supply and a refrigerator or freezer in which the humidity has been evaluated and confirmed as suitable for long-term storage of DBS.
For long term storage (>30 days), DBS should be transported to a central facility where there is a constant electricity supply in a freezer at **-20°C or below** that has been evaluated and confirmed as suitable for long term storage of DBS. If frozen, DBS should only be taken out of cold storage when they are being transported to a reference laboratory or tested.

*Specimen Transport*
DBS should be transported to the regional or national genotyping laboratory using the quickest and reliable arrangements. Unless humidity at the blood draw site is substantially higher than in the processing laboratory, and provided suitable storage boxes are available at the site to keep DBS from light and contamination, no special arrangements need be made to transport DBS more often than weekly.

For specimens that have been stored at room temperature: The desiccants in the specimens bags should be changed before transport for DBS specimens that have been stored for longer than 7 days at the collection site. This should be done even if the indicator remains blue. Reseal the bag and transport specimens by the fastest means using courier service or through the postal system (preferably with expedited service and a guaranteed delivery) at room temperature.
For specimens that have been stored at 4 $^{o}$C: Remove the bagged specimens from the refrigerator and allow them to reach room temperature before opening the bag. Once the sealed bag has equilibrated, open it and remove the old desiccants. Add fresh desiccants and reseal the bag. Transport the bag by the fastest means. If a cooler is available for transport this will protect specimens from short periods of high temperature.
For specimens have been frozen at -20 $^{o}$C or -70 $^{o}$C: Specimens should be transported on dry ice or liquid nitrogen. Thawing of frozen DBS specimens should be avoided if possible.
A cooler is not sufficient to maintain them in a frozen state.

All DBS specimens should be logged into the survey system (whether it is a notebook or a computer software package). The log should include notes on specimen quality and packaging.
The logbook should include a record of eligible specimens for which there is no DBS material available to be sent to the genotyping laboratory, and the reason.
An acknowledgement or notification system should be set up involving the survey coordinator, the transport system, and the receiving genotyping laboratory, to ensure all DBS are delivered promptly to genotyping lab and arrive in good condition. Either email or fax notification using the shipping manifests may be used for this purpose. DBS should be re-examined for packaging and specimen quality on arrival in the genotyping laboratory and recorded in the genotyping laboratory.

**Every ART center shall be linked to a VL lab for which instructions will be given by NACO to send the DBS filter paper to the corresponding HIV drug resistance genotyping national reference labs.**

**Annex VII** – Viral Load Test Requisition Form

VL-1 | Page 1

# National AIDS Control Organization

## HIV-1 Plasma Viral Load Test Reauisition Form

Accession Number

*For Testing Lab Use Only*

***To be filled out by the MO/ Nurse / Lab technician***

| ART Centre Information | Patient Section |
|---|---|
| ART Centre Name: _____ | Patient ID #: _____ |
| Address: _____ | Patient Name: _____ |
| District: _____ State: _____ | Sex: M / F |
| Telephone #: _____ | Age: _____ |

**Previous HIV-1 Plasma Viral Load Test Results from ART Centre**

Baseline: 6 months: Other *(please explain)*:

**Relevant Clinical Details**

Latest CD4 Count, with date: _____

Earlier HIV-1 PVL Test Performed? **Y / N** Date of Earlier HIV-1 PVL: ____ ____ ___
dd mm yy

Result of Earlier HIV-1 PVL Testing (if performed): _____

Manufacturer of Previous HIV-1 PVL Test: _____ Assay/Kit Used: _____

Any infection or immunization in the past 4 weeks? Y / N

**HIV-1 PVL Specimen Collection**

Collection Date: _____ _____ _____ Collection Time: _____
day month year

Name of MO/ Nurse / Lab Technician: _____ Signature: _____

Signature of ART Nodal Officer: _____ Stamp: _____

***To be filled out by the ART lab technician carrying the specimens***

**For Lab Technician Couriering the Specimen**

Name of Lab Technician In-Charge: _____

Name of ART Centre: _____

Date of Specimen Transport to Lab: _____ _____ ___ Time of Departure: _____
day month year

**Signature:**

***To be filled out by laboratory - For Laboratory Use Only***

Date Specimen Received ( dd / mm / yy ): _____ Time Received: _____

Specimen received in the acceptable condition: Y / N (please circle)
If No, list the state of specimen received:
Unlabeled/Mislabeled/Insufficient/Inappropriate/Invalid/Other

Name of Lab In-Charge: _____ Stamp:

Signature: _____

**Annex VIII –** Cobas Amplicor Reporting Format

VL - 1 | **Lab Name**

Page 2 | ***Address (street, district, state)***

*lab phone number*

**HIV-1 Plasma Viral Load Result Form**

**Cobas Amplicor**

Accession Number/Lab Registration Number : _____

Patient ID Number: _____

Date Specimen Tested *(dd/mm/yy)*: _____ Date of Report *(dd/mm/yy)*: _____

Test Kit Name: Cobas Amplicor HIV-1 Monitor Test, version 1.! Manufacturer: _____

Version:_____

**Result**

| | |
|---|---|
| HIV-1 RNA Copies/mL | |
| $log_{10}$ transformation: | |

**NOTES**: HIV-1 Quantization by Cobas Amplicor

*Human immunodeficiency virus (HIV) is the etiologic agent of Acquired Immunodefiency Syndrome (AIDS). Quantitative measurements of HIV viremia in the peripheral blood have shown that higher virus levels may be correlated with increased risk of clinical progression of HIV disease.*

***Interpretation***: This procedure can detect virions associated HIV-1 RNA plasma at concentrations as low as 50 RNA copies/ml to 750,000 HIV-1 RNA copies/mL. Low viral load values may occur as "False Positives" and have been documented in the plasma of uninfected persons or persons infected with other RNA viruses that resemble HIV (e.g. HTLV). Therefore, caution must be exercised when such a result is obtained on a specimen of a patient not confirmed as being infected with HIV (through EIA, Western Blot, or HIV DNA assays).

- The minimum reliable and significant change in measurement (as compared to baseline value or previous test value) is a 3-fold (0.5 log) change.

***Recommendations***: A positive viral load result must always be correlated with clinical history and HIV status of the patient. The Cobas Amplicor HIV-1 Monitor test 1.5 is not intended to be used as a diagnostic test for HIV-1 infection. This test is not intended for HIV-2 patients. It is recommended that the follow up viral load tests be repeated at the same laboratory with the same technique/procedure in order to compare changes in subsequent

**Name of lab in-charge:** _____ **Stamp of lab in-charge:**

**Signature of lab in-charge:** _____

*Not valid for medical legal purposes*

**Annex IX –** Taqman Reporting Format

VL -1 | **Lab Name**

Page 2 | ***Address (street, district, state)***

*lab phone number*

**HIV-1 Plasma Viral Load Result Form**

**Cobas TaqMan**

Accession Number/Lab Registration Number : _____

Patient ID Number: _____

Date Specimen Tested *(dd/mm/yy)*: _____ Date of Report *(dd/mm/yy)*: _____

Test Kit Name: Cobas TaqMan HIV-1 Test Manufacturer: _____

Version: _____

**Result**

| | |
|---|---|
| HIV-1 RNA Copies/mL | |
| $log_{10}$ transformation: | |

**NOTES**: COBAS TaqMan HIV-1 Test

*Human immunodeficiency virus (HIV) is the etiologic agent of Acquired Immunodefiency Syndrome (AIDS). Quantitative measurements of HIV viremia in the peripheral blood have shown that higher virus levels may be correlated with increased risk of clinical progression of HIV disease.*

***Interpretation:*** This procedure can detect virions associated HIV-1 RNA plasma at concentrations as low as 47 RNA copies/ml to 10,000,000 HIV-1 RNA copies/mL. Low viral load values may occur as "False Positives" and have been documented in the plasma of uninfected persons or persons infected with other RNA viruses that resemble HIV (e.g. HTLV). Therefore, caution must be exercised when such a result is obtained on a specimen of a patient not confirmed as being infected with HIV (through EIA, Western Blot, or HIV DNA assays).

• The minimum reliable and significant change in measurement (as compared to baseline value/previous viral load test) is a 3-fold (0.5 log) change.

***Recommendations:*** A positive viral load result must always be correlated with clinical history and HIV status of the patient. The COBAS TaqMan HIV-1 Test is not intended to be used as a diagnostic test for HIV-1 infection. This test is not intended for HIV-2 patients. It is recommended that viral load tests be repeated at the same laboratory with the same technique/procedure in order to compare changes in subsequent viral load counts.

**Name of lab in-charge:** _____ **Stamp of lab in-charge:**

**Signature of lab in-charge:** _____

*Not valid for medical legal purposes*

## Annex X – Viral Load Result Form, Amplicor HIV Monitoring, v1.5

VL - 1 | **Lab Name**

Page 2 | ***Address (street, district, state)***

*lab phone number*

**HIV-1 Plasma Viral Load Result Form**

**Amplicor HIV Monitoring, version 1.5**

Accession Number/Lab Registration Number : _____

Patient ID Number: _____

Date Specimen Tested *(dd/mm/yy)*: _____ Date of Report *(dd/mm/yy)*: _____

Test Kit Name: Amplicor HIV-1 Monitor Test, version 1.5 Manufacturer: _____

Version:_____

**Result**

| | |
|---|---|
| HIV-1 RNA Copies/mL | |
| $\log_{10}$ transformation: | |

**NOTES**: HIV-1 Quantization by Amplicor HIV Monitor Test, version 1.5

*Human immunodeficiency virus (HIV) is the etiologic agent of Acquired Immunodefiency Syndrome (AIDS). Quantitative measurements of HIV viremia in the peripheral blood have shown that higher virus levels may be correlated with increased risk of clinical progression of HIV disease.*

***Interpretation*:** This procedure can detect virions associated HIV-1 RNA plasma at concentrations as low as 50 RNA copies/ml to 750,000 HIV-1 RNA copies/mL. Low viral load values may occur as "False Positives" and have been documented in the plasma of uninfected persons or persons infected with other RNA viruses that resemble HIV (e.g. HTLV). Therefore, caution must be exercised when such a result is obtained on a specimen of a patient not confirmed as being infected with HIV (through EIA, Western Blot, or HIV DNA assays).

• The minimum reliable and significant change in measurement (as compared to baseline value or previous test value) is a 3-fold (0.5 log) change.

***Recommendations*:** A positive viral load result must always be correlated with clinical history and HIV status of the patient. The Amplicor HIV-1 Monitor test 1.5 is not intended to be used as a diagnostic test for HIV-1 infection. This test is not intended for HIV-2 patients. It is recommended that the follow up viral load tests be repeated at the same laboratory with the same technique/procedure in order to compare changes in subsequent viral load

**Name of lab in-charge:** _____ **Stamp of lab in-charge:**

**Signature of lab in-charge:** _____

*Not valid for medical legal purposes*

**Annex XI**

## Process for External Quality Assessment for the laboratories performing HIV-1 Viral Load Testing

### Introduction

Process for External Quality Assessment for the laboratories performing HIV-1 Viral Load Testing will include 4 surveys in a calendar year to the NACO identified centres for performing HIV-1 Viral Load Testing for the second line initiative.

This will serve as an important tool in the process of continuous quality improvement in these laboratories.

### Confidentiality

Participants will be given a Participant Number to be used as a reference in all correspondence. At no time and under no circumstances is the identity of a participating laboratory revealed. Report reviewers who assess results and provide comments/discussions and an educational component for each report are unaware of the identity of participants.

### Participating Laboratories:

Name of Laboratory & Contact Person of each participating lab would be provided to RCPA

### EQAS coordinating laboratory in India

NACO has designated NARI to be the EQAS coordinating laboratory for VLEQAS in India.
NARI, Pune would take on the responsibility for ensuring that the EQAS program is successfully and regularly implemented with active participation of testing labs by coordinating, monitoring, supervising, training, and providing troubleshooting support for the VL EQAS runs held at regular quarterly intervals. Roche India would support NARI in this activity and coordinate with RCPA Australia and the participating centers for all related activities including but not limited to the delivery of the EQAS specimens to these labs for proficiency testing four times a year at predetermined schedules. Roche India would also provide coordination training and troubleshooting support to NARI as and when required for the NACO VL labs in this entire activity. NARI would submit formal quarterly reports to NACO on the performance of the NACO VL laboratories in the VLEQAS.

## Testing

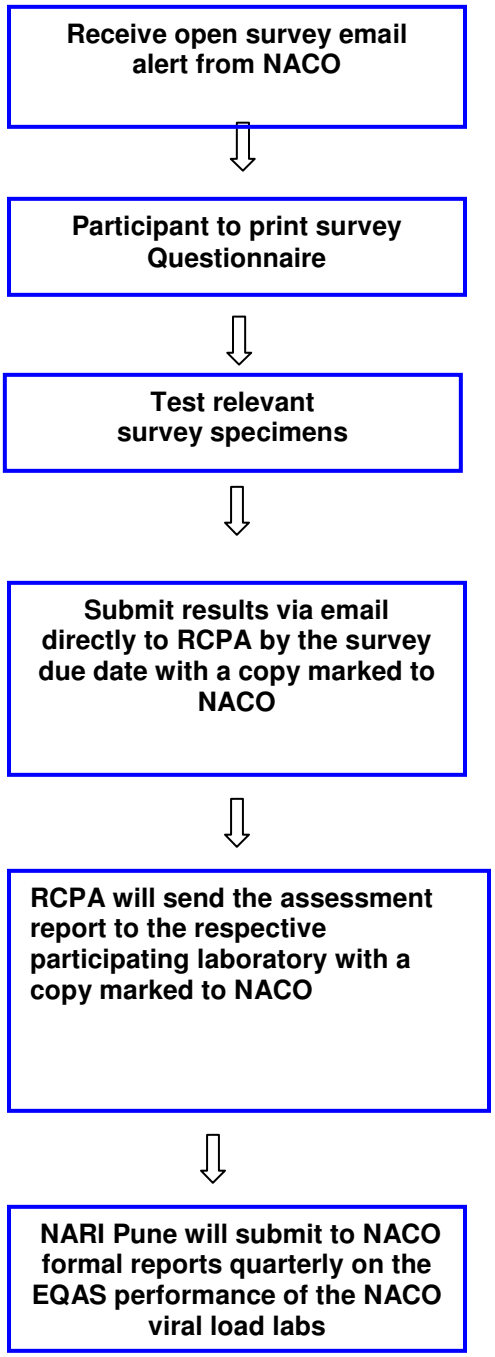
**Participants should test specimens in the same manner as patient specimens.**

(1) The specimens should be tested with the laboratory's regular patient workload by personnel who routinely perform the testing in the laboratory.
(2) The participant should test specimens the same number of times that it routinely tests patient specimens.
(3) The participant should maintain a copy of all records, including a copy of the completed questionnaire, to record proficiency testing results.
(4) The results sheet should be signed by the analyst and the laboratory manager, documenting that proficiency testing specimens were tested in the same manner as patient specimens, the report reviewed, results discussed and action taken (if appropriate). This documentation should be kept for a minimum of three years from the date of the proficiency testing event.

## Specimen Delivery

- The survey panels will be sent to Roche Diagnostics India from RCPA Quality Program Pvt. Limited, Australia in the frozen conditions
- Upon arrival these panels would checked for the shipping conditions by an Authorized person of Roche and supplemented with additional dry ice
- 4 surveys (1 survey per quarter) each consisting of 3 specimens will be sent out to each participating laboratory each cycle of surveys.
- The specimens will be sent out at the start of the survey and delivered by Roche Diagnostics personnel to the individual laboratories to ensure ease of logistics and that the specimen integrity is maintained.
- Upon delivery, the specimens are to be frozen at -70°C or -80°C until the appropriate questionnaire is received via email. It is essential that specimens are frozen immediately upon receipt and stored in a freezer which is *not a frost free instrument* or does not have a defrost cycle.
- Specimens may contain virulent pathogens and must be treated with the same degree of caution as routine diagnostic specimens. Specimens are issued to participants on the understanding that they will be used for quality assurance purposes and that they will be tested by staff trained to handle equivalent clinical specimens.

## Survey Process



## Survey Questionnaires

- Participants are given 18 days to perform testing and submit survey results.
- Instructions are on each questionnaire explaining what is required. Please contact the NARI if you do not understand any aspect of the questionnaire.
- Feedback from participants is encouraged and a 'Compliments, Concerns, Suggestions' section is in each survey questionnaire, so that participants can immediately provide feedback for specific surveys, as well as the overall Program.

## Disposal of Material

Any part of specimens which is not used by the participant shall be destroyed in the manner required by any law or regulatory agency for the disposal of potentially biohazardous waste.

## Late Return of Completed Questionnaires (Results)

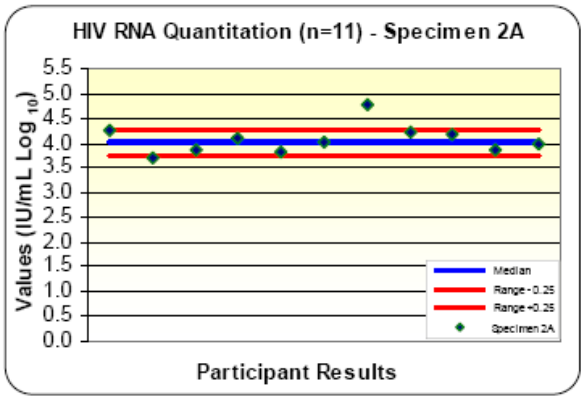
Late results will delay report preparation. If a completed questionnaire arrives **after** all data has been entered and collation of data has commenced, the received questionnaire will be marked **LATE** and the final report to NARI from RCPA will not be amended to include these late results.

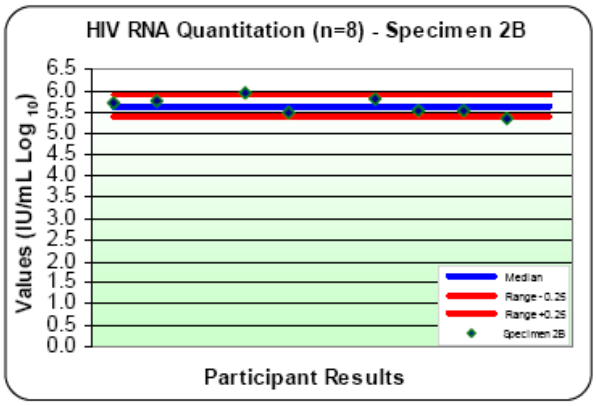
## Survey Reports

Survey reports are presented in the following format:-

• **Section One** will contain a Participant Performance Table. This table identifies participants returning results inconsistent with consensus of ≥80% of participating laboratories, omission of kit details, use of expired kits, occurrence of transcription errors, inconsistent or incomplete data, inappropriate interpretative comment selection and non identification of clerical errors.

• **Section Two** contains the collated report, which is a summary of participant results, and includes discussion/comment from a scientist/pathologist with HIV expertise.


HIV RNA Quantitation (n=11) - Specimen 2A
Values (IU/mL Log 10)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Median
Range - 0.25
Range +0.25
Specimen 2A
Participant Results


HIV RNA Quantitation (n=8) - Specimen 2B
Values (IU/mL Log 10)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Median
Range - 0.25
Range +0.25
Specimen 2B
Participant Results

# Section IV :

# M & E Tools

**This is only indicative**

**The revised formats have been sent to all COE and ART plus centres and only those are to be used**

**This section will be further updated**

The monitoring plan for second-line ART focuses on two main aspects of National ART Program namely – Clinical Monitoring of the Patients and Program Performance. The system developed tries to build on the existing monitoring systems existing at ART centers. Refinements are added in current tools to record details of secondline and additional tools are developed for critical areas of monitoring.

These tools would allow :

- Clinicians to effectively monitor the patient on 2nd line clinically, and
- The ART program to monitor the progress in implementation, identify problems, refine and adapt the implementation strategies; assess the effectiveness of the interventions.

## 4.1 Instructions for Monitoring / records Keeping for second line ART

1**. When the patient is referred from any ART center to COE for evaluation, the patient is NOT 'Transferred Out' and would continue to receive the first line drugs from referring ART Center till recommended otherwise.**
SACEP/COE will inform the referring center once decision is made if patient is to be transferred out or not.

2. The patient once recommended for 2nd line is transferred out to center of excellence. The normal procedure of T/o is followed. The records are thus transferred as per the usual procedure, if not already done.

3. The current ART enrollment register is used for recording the clinical details of the patient on second-line by filling the information on switch

4. In the same ART enrolment register **a post fix to the ART registration** – S (secondline) can be indicated in the first blank column before "ART date of start"

**5.** The **SACEP Register (SL-1)** would be maintained by centers treating patients for second line treatment. The SACEP register is a clinic administration tool which helps to track patients from referral to outcomes, provide information for weekly and monthly reporting to NACO. **(Annex-XII)**

- The SACEP coordinator is responsible for maintaining and updating the register
- To fill in the register, please note that:
    a. The register will not be printed by NACO as yet. Buy a book register of minimum size 32 cm x 19 cm
    b. Patient is to be entered only ONCE in SACEP register with details in same row. No multiple entries for same patient should exist (unique)

6. **SACEP Meeting format (SL-2)** records the details of every meeting and is to be maintained at COE/ ART plus **(Annex-XIII)**

7. A new white card is to be made for each patient starting 2nd line ART where the referring ART center have sent photocopies of patient records, as well as where original white cards are damaged/full. The new white card must mention the same ART Registration number as earlier. The old and new card must be kept together (tied) to ensure that they form single record for the patient and all previous as well as current information is available.

The patient card (white card) will be used with an **additional insert** for table 5 and 6 and pill consumption details to capture the 2nd line details. The Name of this insert is PATIENT TREATMENT RECORD FOR SECONDLINE ART. Rest of the details would continue to be fill in the existing card. **Remember that the base patient treatment card and the new insert should be attached together and are viewed as integrated Patient Treatment Card**. This would either be stapled or sticked on the front page of the existing card. (The Insert form is in **Annex-XV)**

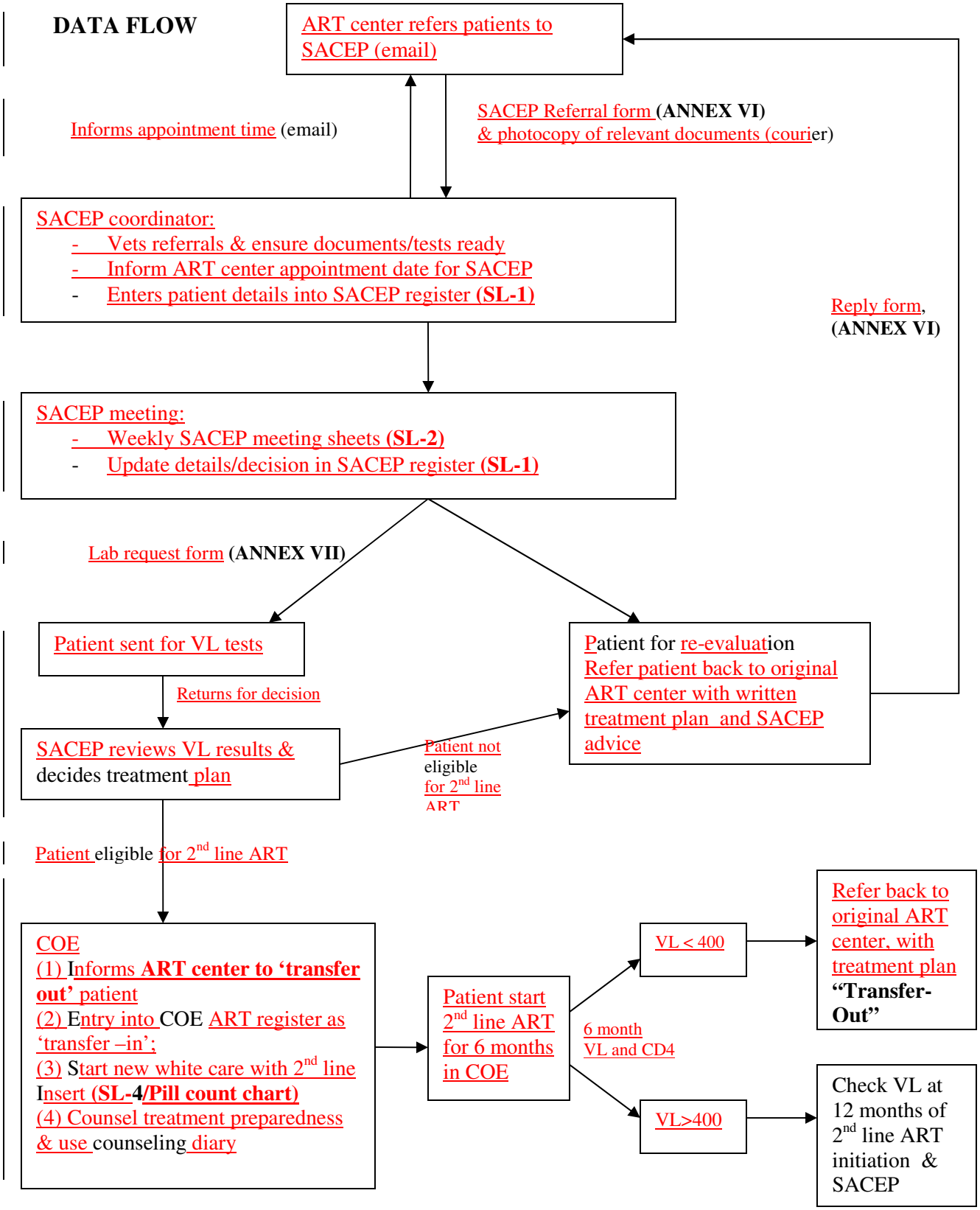
8. In the existing patient treatment card, side effects listing in table 13 (footnote) should be appended additionally with
a. LPD- Lipid abnormality
b. LAC – Lactic acidosis
This can be appended either as sticker or just by writing by pen

10. The COE need to send the current monthly input form with an attachment capturing the details of the secondline treatment. The **Secondline Monthly Input form (SL-3)** would be used by all COE's initially and once the patient is stabilized and transferred out to the original center, the ART center also need to send the Secondline Monthly Input Form **(Annex-XVI)**

Table: Reporting formats for 2nd line

| Sr No | Format | Reporting protocol |
|---|---|---|
| 1 SL + AL | SACEP register | to be maintaiend at COE |
| 2 AL | Format to be prepared before every SACEP meeting for children and adults to be reviewed in that particular meeting for initiation of Alternative first line ART | to be prepared before every SACEP meeting and maintained at COE |
| 2 SL | Format to be prepared before every SACEP meeting for children and adults to be reviewed in that particular meeting for initiation of 2nd line ART | to be prepared before every SACEP meeting and maintained at COE |
| 3 AL +SL | Combined monthly reporting format for 2nd line and Alternative first line for Adults and Children | to be submitted to NACO by 4th of every month |
| 4 SL +AL | List of patiets on 2nd line and Alternative first line ART | to be maintaiend at COE |

Note: Electronic copies (excel) are available for the above formats from NACO. Contact secondline2008@gmail.com


DATA FLOW
ART center refers patients to SACEP (email)
Informs appointment time (email)
SACEP Referral form (ANNEX VI)
& photocopy of relevant documents (courier)
SACEP coordinator:
- Vets referrals & ensure documents/tests ready
- Inform ART center appointment date for SACEP
- Enters patient details into SACEP register (SL-1)
Reply form, (ANNEX VI)
SACEP meeting:
- Weekly SACEP meeting sheets (SL-2)
- Update details/decision in SACEP register (SL-1)
Lab request form (ANNEX VII)
Patient sent for VL tests
Returns for decision
Patient for re-evaluation
Refer patient back to original ART center with written treatment plan and SACEP advice
SACEP reviews VL results & decides treatment plan
Patient not eligible for 2nd line ART
Patient eligible for 2nd line ART
COE
(1) Informs ART center to 'transfer out' patient
(2) Entry into COE ART register as 'transfer –in';
(3) Start new white care with 2nd line Insert (SL-4/Pill count chart)
(4) Counsel treatment preparedness & use counseling diary
Patient start 2nd line ART for 6 months in COE
6 month VL and CD4
VL < 400
Refer back to original ART center, with treatment plan "Transfer-Out"
VL>400
Check VL at 12 months of 2nd line ART initiation & SACEP

## Annex- XII (SL-1) SACEP Register

To be kept at COE

**SL-1 : SACEP Register for Alternative first line & Second line ART - Adults and Children**

**(SACEP Coordinator should maintain the register)**

**Month:**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sl. No. | ART Registration Number | SACEP registration Number | Patient Name | Age | Gender | Address | Contact Number | Contact Number of linked NGO | Referring ART Center | Contact No of ART Center | Date of Referral | Date of assessment by SACEP | Reason For Referral[1] | CD4 (with date) at the time of SACEP assessment | Clinical Staging at time of SACEP assessment | Functional Status at time of SACEP assessment | VL recommended by SACEP? (Y/N) | If Viral Load recommended, result (with date)/ Grade of toxicity | Recommendations of SACEP[2] | Regimen to start, Regimen Number as per NACO ART Guidelines | Date of initiation of 2nd line/ Alt first line ART | Patient referred back to the nodal ART centre |
| 1 | | | | | | | | | | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | | | | | | | | | | | |

[1] 1. Treatment Failure 2. Substitution with PI regimen 3. Substitution with other Regimen - Specify code 4. Management of complicated cases/Others

[2] 1. Start Secondline ART 2. Repeat VL testing 3. Substitution for toxiciy with PI 4. Substitution with other Regimen - Specify code 5. Others (Specify)_____

Note For Altaernate first line patients mention A after the serial no eg: 1A, 2 A

**ANNX XIII (SL-2) FORMAT FOR SACEP MEETING**

## Second Line SL2 : Format for SACEP Meeting - Adult & Children (to be kept at COE)- must be prepared before SACEP meeting

**Meeting date :**

| Second line line ART | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sl No. | Date | Refered from | ART Reg no | Name | Age/sex | ART start date (with in the program) | ART start date (outside the program if avail.) | Adherence to first line drugs | CD4 counts (with date) | | | | Recommended for Viral Load Test? (Y/N) | Viral Load | Clinical Status | Whether recommended for Second line? (Yes/ No) | Remarks |
| | | | | | | | | | | | | | | | | | |
| | | | | New cases | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | Old Cases | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | |

| Summary -Second Line ART | | |
|---|---|---|
| Sl. No | | No of patients |
| 1 | Total Number of patients reviewed by SACEP | |
| 2 | Total number of patients recommended for Viral Load | |
| 3 | Total number of patients recommended for Second Line | |
| 4 | Total number of patients actually initiated on Second Line ART | |

| Members Presents during the SACEP | |
|---|---|
| 1 | |
| 2 | |
| 3 | |
| 4 | |
| 5 | |
| 6 | |

**ANNEX XV ) : Insert for patients on Second-line ART**

ART Registration Number : --- __ __ /__ __ / __ __ __ / __ __ __ __ SND **SL SL-4**

ID No as per chield Health Card __ __ __ __ __ __ __ __ __ __ __ __ Date of Start of 2nd line ART : __ __ / __ __ / __ __ __ __

**PATIENT TREATMENT RECORD FOR SECONDLINE ART**

| Clinical and Laboratory Investigations ( Summary ) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Date (dd/mm/ yy) | Clinical staging/ T staging | Weight (kg ) | Height (cm) | Functional Status WAB ** | CD4 Count No. | % | Viral Load |
| At ART medical eligibility | | | | | | | | |
| At start of ART- 2nd Line | | | | | | | | |
| At 6 months ART- 2nd Line | | | | | | | | |
| At 12 months ART 2nd Line | | | | | | | | |
| At 24 months ART 2nd Line | | | | | | | | |
| At 36 months ART 2nd Line | | | | | | | | |
| AT 48 months ART 2nd Line | | | | | | | | |

T Stage: T1, T2, T3 & T4 > Once patient start on ART the clinical staging would be T1-T4.

| Antiretroviral Treatment ( Summary ) | | | | | | |
|---|---|---|---|---|---|---|
| | | SUBSTITUTION within 2nd line, STOP, RESTART | | | | |
| Regimen IV (_____) | Regimen (_____ | Date | Substitution, Switch or stop | Reason ( Code ) | Date Restart | New regimen |
| | | | | | | |
| | | | | | | |
| Regimen V | Regimen Va (_____) | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

# Annex- XVI (SL-3)

## Monthly Reporting Format for Second-Line ART: (To be filled in by COE)

SL-3 Combined Monthly Reporting Format for 2nd & Alternative first Line ART — vers.August 2010

1. Name of ART Centre — 2. Code Number (state (2#) / clinic (2#))
3. Name of the District
4. Name of the State
5. Name of the ART Centre incharge
6. Report for the period — month | year

| Second line ART | | | | | | |
|---|---|---|---|---|---|---|
| **7. Details of PLHA referred to SACEP review for treatment failure** | **Adult** | | | **Children** | | **total** |
| | **Male** | **Female** | **TS/TG** | **Male** | **Female** | |
| 7.1 Cumulative number of PLHA referred to SACEP for assessment at the beginning of this month | | | | | | 0 |
| 7.2 Number of new PLHA referred to SACEP for assessment during the month | | | | | | 0 |
| **7.3 Cumulative number of PLHA referred to SACEP for assessment at the end of this month = 7.1 + 7.2** | 0 | 0 | 0 | 0 | 0 | 0 |
| 7.4a Cumulative number of patients referred from COE (The reporting centre) (out of 7.3) | | | | | | 0 |
| 7.4b Cumulative number of patients referred from other ART centres (out of 7.3) | | | | | | 0 |
| 7.4c Cumulative number of PLHA referred for Viral Load (out of 7.3) | | | | | | 0 |
| 8.1 Cumulative number of PLHA found eligible for 2nd line at beginning of month | | | | | | 0 |
| 8.2 Number of PLHA found eligible for 2nd line during the month | | | | | | 0 |
| **8.3 Total number of PLHA found eligible for 2nd line at the end of the month** | 0 | 0 | 0 | 0 | 0 | 0 |
| 8.4 Cumulative number of patients ever started on 2nd line ART (Number at the beginning of this month) (8.7 of previous month) | | | | | | 0 |
| 8.5 Number of new patients started on 2nd line ART during this month | | | | | | 0 |
| 8.6 Number of patients "restarted "on 2nd line ART | | | | | | 0 |
| **8.7 Cumulative number of patients ever started on 2nd line ART (Number at the end of this month) = 8.4+8.5** | 0 | 0 | 0 | 0 | 0 | 0 |
| 9.1 Cumulative number of patients on 2nd line who died since the beginning of the programme | | | | | | 0 |
| 9.2a Cumulative number of patients on 2nd line who are "transferred out" ( to other COE) | | | | | | 0 |
| 9.2b Cumulative number of patients on 2nd line who are "transferred in" ( from other COE) | | | | | | 0 |
| 9.3 The number of all patients on 2nd line treatment whose treatment status in this month is "stopped treatment" | | | | | | 0 |
| 9.4 Cumulative Number of patients receiving 2nd line who are lost to follow-up (LFU) | | | | | | 0 |
| 9.5 The number of patients on 2nd line treatment who did not return to the ART center (Defaulter) / whose treatment status is "MIS" in this month | | | | | | 0 |
| **9.6 Total number of patients alive and on 2nd line ART (OT) at the end of this month = 8.7+9.2b - (9.1+9.2a+9.3+9.4+9.5)** | 0 | 0 | 0 | 0 | 0 | 0 |
| 9.7a Out of 9.6, the number of patients on 2nd line ART initiated on DOTS this month | | | | | | 0 |
| 9.7b Out of 9.6, the number of patients on 2nd line ART initiated on non-DOTS anti-tuberculosis treatment this month | | | | | | 0 |
| 9.7c Out of 9.6, the total number of pregnant women on 2nd line ART this month | | | | | | 0 |
| **Alternative first line ART** | | | | | | |
| 10.1 Cumulative number of PLHA referred to SACEP for assessment at the beginning of this month | | | | | | 0 |
| 10.2 Number of new PLHA referred to SACEP for assessment during the month | | | | | | 0 |
| **10.3 Cumulative number of PLHA referred to SACEP for assessment at the end of this month** | 0 | 0 | 0 | 0 | 0 | 0 |
| 10.4 Referred from COE (The reporting center) | | | | | | 0 |
| 10.5 Referred from other ART centers | | | | | | 0 |
| 11.1 Cumulative number of PLHA found eligible for Alternative first line ART at beginning of month | | | | | | 0 |
| 11.2 Number of PLHA found eligible for Alternative first line ART during the month | | | | | | 0 |
| 11.3 Total number of PLHA found eligible for Alternative first line ART till the end of the month | 0 | 0 | 0 | 0 | 0 | 0 |
| 12.1 Cumulative number of patients ever put on Alt first line (Number at the beginning of this month) | | | | | | 0 |
| 12.2 Number of new patients started on alternative first line ART during this month | | | | | | 0 |
| **12.3Cumulative number of patients ever on Alt first line ART (Number at the end of this month) =12.1+12.2** | 0 | 0 | 0 | 0 | 0 | 0 |
| 13.1 Cumulative number of patients on alternate first line who died since the beginning of the programme | | | | | | 0 |
| 13.2a Cumulative number of patients on Alt first line who are "transferred out" to nodal ART centre/ other COE | | | | | | 0 |
| 13.2b Cumulative number of patients on Alt first line who are "transferred in" from other centres | | | | | | 0 |
| 13.3 The number of all patients on Alt first line treatment whose treatment status in this month is "stopped treatment" | | | | | | 0 |
| 13.4 Cumulative Number of patients receiving Alt first line who are lost to follow-up (LFU) | | | | | | 0 |
| 13.5 The number of patients on Alt first line treatment who did not return to the ART center (Defaulter) / whose treatment status is "MIS" in this month | | | | | | 0 |
| **13.6 Total number of patients alive and on Alt first line ART= 12.3+13.2b-(13.1+13.2a+13.3+13.4+13.5)** | 0 | 0 | 0 | 0 | 0 | 0 |
| 13.7 Out of 13.6, the number of patients on Alt. first line ART initiated on DOTS this month | | | | | | 0 |
| 13.8 the number of patients on Alt first line ART initiated on non-DOTS anti-tuberculosis treatment this month | | | | | | 0 |
| 13.9 the total number of pregnant women on Alt first line ART this month | | | | | | 0 |

| **14. Treatment Adherence ( Only for patients on 2nd line ART)** | **Number** |
|---|---|
| 14.1a Of all patients who are on treatment this month (9.6) the number who have NOT been assessed for adherence (refer guideline) | |
| 14.1b Of all patients who are on treatment this month (13.5 a, b) the number who have NOT been assessed for adherence (refer guideline) | |
| 14.2 aOf all patients on ART (9.6) this month and who have been assessed for adherence, how many had 95% adherence or better (refer guideline) | |
| 14.2b Of all patients on ART (13.5 a, b) this month and who have been assessed for adherence, how many had 95% adherence or better (refer guideline) | |

**15 a. Primary Rgimens of PLHA started with 2 line/ Alt first line ART at the end of the month**

| **Adults** | **a) Number of clients alive and on ART** |
|---|---|
| Regimen III Tenofovir+ Lamivudine + Nevirapine | |
| Regimen III a Tenofovir + Lamivudine + Efavirenz | |
| Regimen IV Zidovudine + Lamivudine + Lopinavir/Ritonavir | |
| Regimen IVa Stavudine + Lamivudine + Lopinavir/Ritonavir | |
| Regimen V Tenofovir + Lamivudine + Lopinavir/Ritonavir + Zidovudine | |
| Regimen Va Tenofovir + Lamivudine+ Lopinavir/Ritonavir | |
| Others | |
| **Total Number of Adults** | |
| **Children** | |
| Regimen P III Abacavir + Lamivudine + Nevirapine | |
| Regimen P III (a) Abacavir + Lamivudine + Efavirenz | |
| Regimen P III (b) Abacavir + Lamivudine + Lopinavir/ Ritonavir | |
| Regimen P IV Zidovudine + Lamivudine + Lopinavir/ Ritonavir | |
| Regimen P IV (a) Stavudine + Lamivudine + Lopinavir/ Ritonavir | |
| Regimen P V Abacavir + Lamivudine + Didanosine + Lopinavir/ Ritonavir | |
| Others | |
| **Total Number of Children** | |

**15.b. Total Number of Patients on CTZ Prophylaxis**

| **Regimen** | **a) Number of ADULTS on CPT** | **b) Number of CHILDREN on CPT** |
|---|---|---|
| Contrimoxazole (DS) | | |
| Contrimoxazole (SS) | | |
| Contrimoxazole Susp | | |
| **Total number of patients** | | |

**16.1 second line/ Alt first line ARV Drug Stock Status** (use separate sheet if required)

| Generic Drug Name | a) Opening stock | b) Stock received during month | | Consumption during the month | | e) Expiry during the month | f) stock on last day of the month | g) Amt. reqst for 3 mo. based | h) Date of earliest expiry | i) Quantity of stock expiring |
|---|---|---|---|---|---|---|---|---|---|---|
| | | b1.From Supplier | b2.FromOther Center | For 2nd line | For Alt. first line | | | | | |
| TDF/3TC | | | | | | | 0 | | | |
| LPV/r | | | | | | | 0 | | | |
| AZT | | | | | | | 0 | | | |
| TDF/3TC | | | | | | | 0 | | | |
| LPV/r | | | | | | | 0 | | | |
| Nevirapine | | | | | | | 0 | | | |
| Didanosine 200 | | | | | | | 0 | | | |
| Didanosine125 | | | | | | | 0 | | | |
| LPV/ r 125 | | | | | | | 0 | | | |
| LPV/ r syrup | | | | | | | 0 | | | |
| ABC60+3TC30 | | | | | | | 0 | | | |

**16.2 Was there a stock-out of antiretroviral drugs this month?** Yes 0

**16.3.Were there any specific side effects noted for 2 line/ Alt first line ART during the month**

| **Particulars** | **Male** | **Female** | **Particulars** | **Male** | **Female** |
|---|---|---|---|---|---|
| 1. AZT Induced Anaemia | | | 8. IRIS | | |
| 2. Preipheral Neuropathy | | | 9. Lipid abnormalities | | |
| 3. Hepatitis | | | 10 Lactic Acidosis | | |
| 4. Lipo Dystrophy | | | 11. Nephrotoxicity | | |
| 5.Pancreatitis | | | 12. GI related side effects | | |
| 6. Skin Reaction | | | | | |
| 7. CNS Side Effects | | | | | |

**SL-4 : List of patients on Second line ART** (to be maintained at COE)

| Sr. No. | Reg. No. | Name | Age | Sex | Address | Telephone | 1st line date | CD4 | Viral load | 2nd lne date | SACEP | ON Second Rx | REMARKS | Patient referred back to the nodal ART centre (yes/ no?) | Date of referral back to the nodal ART centre |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | | | | |
| 6 | | | | | | | | | | | | | | | |
| 7 | | | | | | | | | | | | | | | |
| 8 | | | | | | | | | | | | | | | |
| 9 | | | | | | | | | | | | | | | |
| 10 | | | | | | | | | | | | | | | |
| 11 | | | | | | | | | | | | | | | |
| 12 | | | | | | | | | | | | | | | |
| 13 | | | | | | | | | | | | | | | |
| 14 | | | | | | | | | | | | | | | |
| 15 | | | | | | | | | | | | | | | |
| 16 | | | | | | | | | | | | | | | |

**ANNEX XVII : Details of Pill Consumption (PILL COUNT)**

**ART Registration Number……..**
**Patient name……Gender/age ……**

| Rx( Details of Regimen) | #Pills Prescribed/day | Total Pills for month | Pills Consumed per month by the patient | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Dates of visits | | | | | | | | | | | | | | | | | | | | | | | |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
| | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | | | | | | |

**Rough guide:**
TDF/3TC combined pill load per month: 30
LPV/r combined pill load per month : 120
AZT total pill load per month : 60