



STANDARD OPERATING PROCEDURES ON VIRAL LOAD MONITORING FOR ICAP CLINICAL STAFF AND HEALTH CARE WORKERS

Version 1.1 July 2016

A Template Document for Country Adaptation



ACKNOWLEDGMENTS

This document was created by ICAP's Clinical and Training Unit with valuable input from our teams in Swaziland, Mozambique, Kenya, and Cote d'Ivoire.

It was developed as a template document to be adapted for use in various contexts and is one component of a viral load monitoring tool-kit, to be used in conjunction with ICAP's Viral Load Monitoring Flipchart and Enhanced Adherence Treatment Plan.

This area is evolving rapidly therefore it is expected that this document will require frequent updating over time, as recommendations change, and needs to be adapted according to local guidelines and context. This document reflects guidance provided by WHO contained in *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach - Second edition* (<http://www.who.int/hiv/pub/arv/arv-2016/en/>)

Organizations adapting this document for their own use, should credit ICAP at Columbia University and note that their work is an adaptation of: "*Standard Operating Procedures on Viral Load Monitoring for ICAP Clinical Staff and Health Care Workers: A Template Document for Country Adaptation; version 1.1*"

July 2016

About ICAP

ICAP was founded in 2003 at Columbia University's Mailman School of Public Health. Now a global leader in HIV and health systems strengthening, ICAP provides technical assistance and implementation support to governments and non-governmental organizations in more than 21 countries. ICAP has supported work at more than 5,250 health facilities around the world. More than 2.5 million people have received HIV care through ICAP-supported programs and over 1.7 million have begun antiretroviral therapy. [For more information: icap.columbia.edu](http://icap.columbia.edu)

Cover Photos Jake Price

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I. INTRODUCTION

The concentration of HIV RNA in the blood, referred to as “viral load”, is a valuable indicator of a patient’s response to antiretroviral therapy (ART) and risk for clinical progression.^{1,2} Viral load is a more sensitive and reliable means of determining treatment failure compared to clinical and/or immunological criteria.³⁻⁵ As a result, the 2013 World Health Organization (WHO) guidelines recommend viral load testing as part of routine therapeutic monitoring for all HIV-infected children and adults on ART in order to assess treatment response and detect treatment failure and the need to switch to second-line regimens in a timely manner.⁶ Viral load testing is not, however, recommended by WHO as part of the baseline assessment for people living with HIV (PLHIV) or for determining ART eligibility.

The purpose of this document is to describe standard operating procedures (SOP) for viral load monitoring, including the schedule for viral load testing when used for routine monitoring of children, adolescents and adults on ART; interpretation of results; patient management; and specimen collection, preparation and transport. The target audience is health care workers at HIV care and treatment facilities and other points of care such as PMTCT settings, as well as ICAP clinical staff supporting implementation of viral load monitoring. This area is evolving rapidly therefore it is expected that this document will require frequent updating over time as recommendations change and needs to be adapted according to local guidelines and context.

II. VIRAL LOAD PRINCIPLES

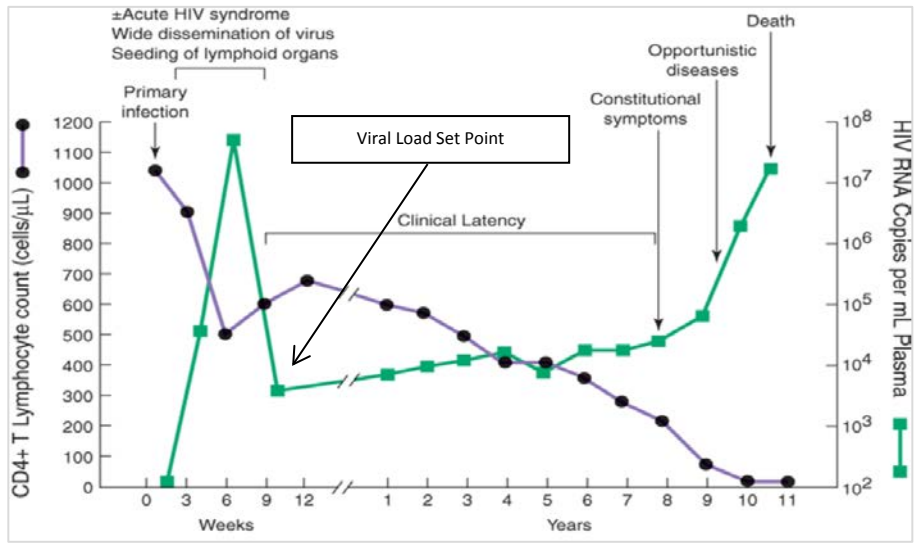
1. Viral Load Measurement

HIV viral load quantifies the amount of circulating HIV and is usually measured as HIV RNA copies per milliliter (copies/ml) of plasma. The HIV viral load test can be performed on whole blood, plasma, or dried blood spot (DBS) specimen types. Viral load can also be measured on a log₁₀ scale (see Appendix 1) where a 1-log change is equivalent to a 10-fold change in the number of copies/ml. When using this log scale, because of test and biologic variability, anything less than a 1.0 log change (e.g. change from 10,000 copies/ml [4 log] to 1,000 [3.0 log]) is not considered clinically meaningful.

2. Viral Load over the Course of HIV Infection

During acute infection, viral load reaches very high levels, often greater than 1 million copies/ml. Within the first 6 months to 1 year after infection, the host immune response brings the viral load down to a steady level which is sometimes called the **viral load set point**. In the absence of ART, the viral load will increase over the course of several years, and then rises more rapidly when the patient develops symptoms (Figure 1). The viral load set point can be used to predict HIV disease progression; the higher the set point, the more quickly the patient will progress to AIDS.

Figure 1. Viral Load Dynamics during Course of Untreated HIV Infection

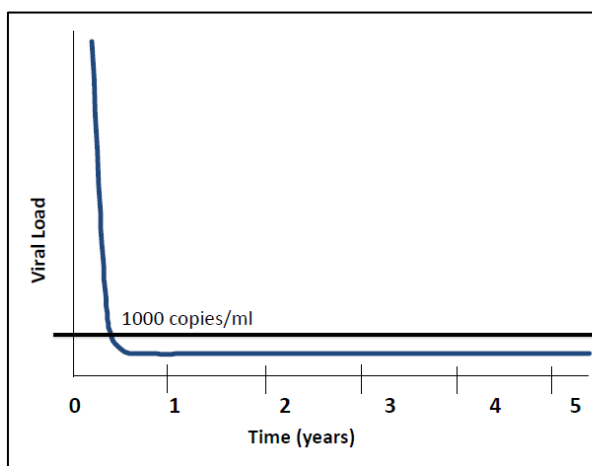


Adapted from Longo DL et al. Harrison's Principles of Internal Medicine and Pantaleo G et al. NEJM 1993;328:327-335.

3. Virologic Response to ART

Viral load is an excellent means of monitoring treatment response because ART prevents HIV replication by inhibiting viral enzymes causing the viral load to decline. The goal of treatment is to achieve an undetectable viral load which is associated with better clinical outcomes and a lower risk of HIV transmission. In addition, persistent viral replication while taking ART can lead to resistance to one or more antiretrovirals (ARVs). While it is desirable to have an undetectable viral load, for an initial public health and programmatic approach ≤ 1000 copies/ml is acceptable per WHO recommendations given the low risk of transmission and disease progression at this level. In most patients taking ART, the viral load should be ≤ 1000 copies/ml after 6 months of treatment (Figure 2).

Figure 2. Viral Load Decline After ART Initiation



4. Virologic Treatment Failure

Virologic treatment failure is defined by WHO as a persistent, detectable viral load exceeding 1000 copies/ml when measured using plasma after at least 6 months of using ART.⁶ “Persistent” is defined as two consecutive viral load measurements within a 3-6 month interval, with adherence support between measurements.

Viral Load Threshold When Using Dried Blood Spot (DBS) Technologies

Although there are differences between plasma and DBS testing methodology, at the present time it is recommended that the same threshold, ≥ 1000 copies/ml) should be operationalized for defining virologic treatment failure for viral load assessment results whether determined by plasma or DBS technology (WHO 2015).

III. VIRAL LOAD MONITORING

1. Routine versus Targeted Monitoring

Ideally, viral load testing should be performed at regular intervals for *all* individuals receiving ART to monitor treatment response (**routine viral load monitoring**). The recommended schedule for routine viral load monitoring is summarized below.

In settings where routine viral load monitoring is not feasible, viral load testing may be reserved for individuals on ART in whom treatment failure is suspected (**targeted viral load monitoring**). In targeted viral load monitoring, all individuals on ART are assessed for treatment failure using CD4 and clinical criteria. For those meeting criteria for immunological and/or clinical failure (Table 1 and Appendix 2), a viral load is measured to assess whether the patient meets criteria for virologic treatment failure. If virologic failure is confirmed, follow the algorithm in Figure 3. If there is no virologic failure, the current regimen should be maintained (viral load is a better measure of treatment failure than CD4 or clinical staging), and the patient should be referred for management of any new clinical conditions.

- **Routine viral load monitoring** allows early detection of virologic failure (preferred approach)
- **Targeted viral load monitoring** is used when routine viral load testing is not available, to confirm suspected immunological or clinical treatment failure.

**Table 1. Definitions of Clinical, Immunological, and Virologic Failure (WHO 2013)
After ≥ 6 Months of ART**

Populations	Clinical Failure	Immunologic Failure	Virologic Failure
Adults and adolescents	New or recurrent WHO stage 4 (and some stage 3)* conditions	CD4 at or below pre-ART baseline or persistently <100 cells/μl	2 consecutive viral load measurements >1000 copies/ml within a 3-6 month interval, with adherence support between measurements
Children 5-9 years of age	New or recurrent WHO stage 3 or 4 conditions, except TB	Persistently <100 cells/μl	
Children <5 years of age		Persistently <200 cells/μl or <10%	

*For adults certain stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure (WHO 2013)

2. Role of CD4 Testing When Routine Viral Load Monitoring is Available

In general when individuals are virologically suppressed on ART, meaningful CD4 decline is uncommon. As viral load testing is now the preferred monitoring approach for children and adults on ART, the role of CD4 testing is being reassessed when routine viral load monitoring is available. **Although CD4 results are no longer used to determine ART eligibility in countries that have moved to treating all PLHIV, baseline CD4 measurements may still be important in order to guide clinical decisions about screening and starting prophylaxis for opportunistic infections (OIs). CD4 may also be helpful in management of ill patients in order to determine if they are at risk for an OI.**

The changing role of CD4 cell counts in the context of viral load monitoring is summarized in the box below.

IV. SCHEDULE FOR ROUTINE VIRAL LOAD MONITORING

1. Children, Adolescents and Adults (not pregnant or breastfeeding) on ART

For non-pregnant adults, adolescents and children on ART in settings where routine viral load monitoring is available, viral load testing should routinely be performed at 6 months after ART initiation.

For patients who **transfer into care** from another facility and have been on ART for at least 6 months, viral load testing should be performed at the **first visit**, unless there is a documented viral load result ≤1000 copies/ml within the past 6 months.

When routine viral load monitoring first becomes available at a HIV care and treatment facility, viral load testing should be performed for all patients on ART for 6 months or longer at their next clinic visit, or according to the country's viral load monitoring phase-in plan when available.

If the viral load result is ≤ 1000 copies/ml, indicating successful HIV treatment, then the viral load should be repeated on an **annual basis** provided that the patient is clinically stable and adherent to ART.

If, however, an individual develops a new or recurrent WHO stage 3 or 4 condition or has a CD4 count meeting criteria for immunological failure, a viral load should be obtained at that time in order to assess for virologic treatment failure.

Role of CD4 Cell Counts When Routine Viral Load Monitoring Is Available†

- In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virologically suppressed.
- Routine viral load monitoring can be carried out at 6 months, at 12 months, and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting (conditional recommendation, very low quality evidence)

†November 2015 WHO HIV Treatment and Care: What's New In Monitoring Recommendations for a public health approach.

*Check national recommendations on CD4 measurement when adapting this SOP as some countries advise continued CD4 monitoring until VL ≤ 1000 is confirmed and minimum CD4 threshold (e.g. > 200 or > 350) is achieved.

If at any point in time the viral load is found to be > 1000 copies/ml, a detailed adherence assessment should be conducted and interventions to improve adherence should be provided, and the viral load repeated as per algorithm in Figure 3.

2. Pregnant or Breastfeeding Women on ART

For pregnant and breastfeeding women newly initiating ART, viral load testing should be performed at **6 months after ART initiation**. For pregnant or breastfeeding women **already on ART** for at least 6 months at the time of presentation for antenatal or postnatal care, a viral load should be performed at the **first visit**. If there is a documented viral load result ≤ 1000 copies/ml within the past 3 months, and adherence remains good, this viral load at first visit may be deferred until 6 months has elapsed from the prior result.

When viral load monitoring first becomes available at an antenatal or postnatal care facility, viral load should be performed for all pregnant and breastfeeding women on ART at their next clinic visit.

If the viral load result is ≤ 1000 copies/ml, then the viral load should be repeated **every 6 months** while the patient is either pregnant or breastfeeding. When the patient is no longer pregnant or breastfeeding, the viral load can be repeated on an annual basis, as per the schedule described above for non-pregnant or breastfeeding adults.

If however a pregnant or breastfeeding woman develops a new or recurrent WHO stage 3 or 4 condition or has a CD4 count meeting criteria for immunological failure, a viral load should be obtained at that time in order to assess for virologic treatment failure.

If at any point in time the viral load is found to be >1000 copies/ml, a detailed adherence assessment should be conducted and interventions to improve adherence should be provided. The viral load should be repeated as per algorithm below (Figure 3), and expert consultation is advised. In addition, enhanced prophylaxis for the infant should be considered.

Table 2. Schedule for Routine Viral Load Monitoring after ART Initiation and Subsequent Testing in Clinically Stable Patients with Viral Load ≤1000 copies/ml

Population	Time since ART initiation	Subsequent testing
Children, adolescents and adults [†]	6 months	6 months after 1 st test then annually
Pregnant/Breastfeeding women*	6 months	Every 6 months

[†]For patients who transfer into care and have been on ART for at least 6 months, viral load testing should be performed at the first visit, unless there is a documented viral load result <1000 copies/ml within the past 6 months.

*If already on ART for at least 6 months, a viral load should be performed at the first ANC or PNC visit. If there is a documented viral load result ≤1000 copies/ml within the past 3 months, and adherence remains good, a viral load at first visit may be deferred until 6 months has elapsed from the prior result.

Further Considerations for Population-specific Viral Load Monitoring

Groups at higher risk of non-adherence and treatment failure (such as young children, adolescents, persons with poorly controlled psychiatric disorders, migrant workers, homeless individuals, and those with prior viral load >1000 copies/ml) might benefit from more frequent viral load monitoring, such as every 6 months. Therefore national guidelines may differ in this regard.

Check national recommendations about population-specific viral load monitoring when adapting this SOP.

V. INTERPRETATION OF VIRAL LOAD TEST RESULTS AND SUBSEQUENT MANAGEMENT

Interpretation of viral load results and subsequent steps are outlined in the algorithm in Figure 3.

1. Viral Load Results ≤1000 copies/ml

A viral load ≤1000 copies/ml indicates that viral replication is sufficiently controlled, and therefore the patient is on an appropriate ART regimen and adherence is good. The actual value and meaning of the viral load test result should be explained to the patient at the next clinic visit. Using the *Viral Load Monitoring Flipchart*, the following points should be addressed:

- ART is working to stop HIV from reproducing
- No change in medication is recommended
- The patient should continue to take ART as prescribed

- The viral load will be repeated in 12 months (6 months if the patient is pregnant or breastfeeding).

Patients with viral load ≤ 1000 copies/ml should continue to receive routine HIV care and adherence support.

2. Viral Load Results >1000 copies/ml

A viral load >1000 copies/ml indicates that viral replication is not well controlled. This may be due to sub-optimal adherence and/or may indicate that the patient's HIV is resistant to one or more drugs in the patient's ART regimen.

It is important to bear in mind, however, that a concomitant or recent infection may result in a **transient** increase in viral load (as well as a transient decrease in CD4 cell count). Therefore the interpretation of viral load results should take into account whether the patient had an intercurrent infection at the time the specimen was collected and should follow the algorithm below.

Upon reviewing this viral load result, the clinician must ensure that the patient is contacted to come to the clinic as soon as possible, ideally within 1 week. At this visit, using the *Viral Load Monitoring Flipchart*, the actual value and meaning of the viral load test result should be explained to the patient, including the following points:

- The viral load is elevated (the goal is to have a viral load ≤ 1000 copies/ml)
- A viral load >1000 copies/ml indicates that HIV is replicating in the body. This could be happening because the patient is, or was, not taking ART properly (e.g. missing doses, etc.), or that the medications are no longer able to stop the virus (i.e., the HIV has developed resistance)
- Resistance to medications usually develops from missing doses
- Over time ongoing HIV replication can result in reduced CD4 cells (the body's defenses against infections and cancers) and the patient could become sick

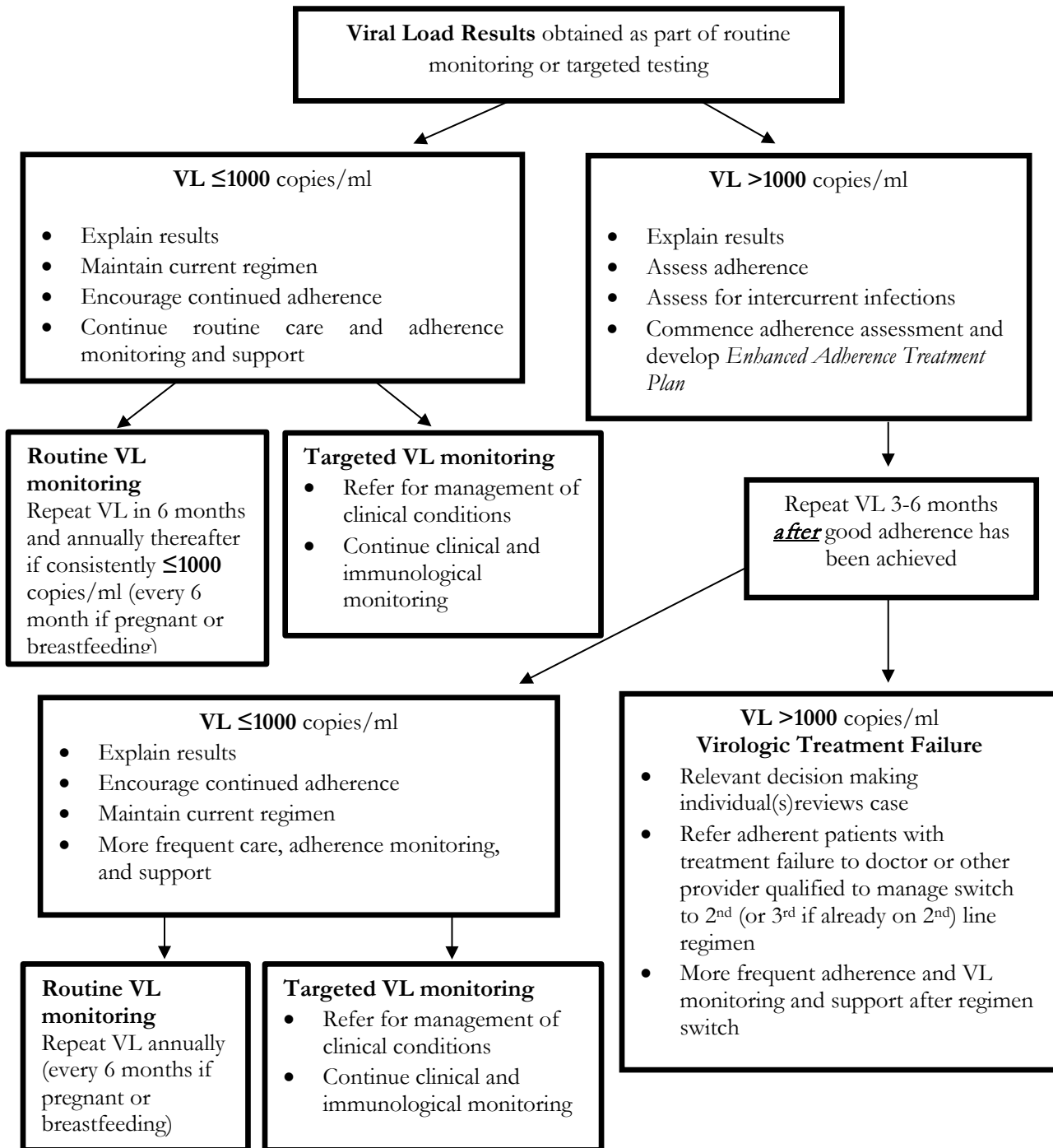
Patients with viral load >1000 copies/ml should undergo the adherence assessment found in the *Viral Load Monitoring Flipchart*. Based on identified barriers, an *Enhanced Adherence Treatment Plan* including specific interventions should be developed with the patient (see *Viral Load Monitoring Flipchart*, and *Enhanced Adherence Treatment Plan*). The patient should be seen monthly for at least two additional sessions. At each session an adherence assessment should be conducted and the treatment plan should be updated as needed to address barriers. After 3 or more sessions **and** once good adherence has been achieved, a repeat viral load test should be sent and the algorithm in Figure 3 should be followed depending on the results.

VI. MANAGEMENT OF PATIENTS WITH VIROLOGICALLY CONFIRMED TREATMENT FAILURE

Elevated viral load in the face of good ART adherence strongly suggests resistance to one or more of the drugs in the patient's ART regimen resulting in virologic treatment failure. Patients with confirmed viral load >1000 copies/ml (that is two consecutive viral load measurements within a 3-6 month interval, with adherence support between measurements) after at least 6 months of ART, likely need a change in regimen. Those with virologic treatment failure should be referred to the relevant decision making individual(s) (e.g.

consultant, multidisciplinary team, treatment failure committee, etc.) for further management, monitoring, and switch to a second-line regimen according to local guidelines.

Figure 3. Viral Load Monitoring Algorithm



VII. SPECIMEN COLLECTION AND PREPARATION

Specimen collection, processing and shipment to the testing laboratory must be performed in a manner which ensures sample integrity, accuracy in documentation and biosafety.

1. Specimen Collection

The HIV viral load test can be performed on whole blood, plasma or dried blood spot (DBS) specimen types. However, viral load testing has been traditionally performed using plasma-based specimens (see box on DBS above in section II. 4).

Specimen collection by venipuncture in a sterile 4ml EDTA tube is preferred. *Heparin containing tubes must not be used when collecting specimens for viral load testing because heparin has been shown to inhibit PCR.* In programs where viral load testing is performed on DBS specimens, DBS can be prepared from finger prick or venipuncture.

Each specimen should be labeled with a unique identifier. A Test Request Form and a Sample Tracking Form should be completed to accompany the specimen throughout the handling, storage and transport processes.

Clinicians collecting specimens and/or preparing DBS for viral load testing should follow appropriate standard operating procedures for the process. Care should be taken that storage of dried blood spot cards at room temperature does not exceed one week as this will affect results.

2. Specimen Handling and Storage

Whole blood specimens collected in EDTA tubes can be kept between 2°C and 25°C for up to 24 hours before testing. If testing cannot be done within 24 hours of collection, the whole blood must be centrifuged at 800-1600 RPM for 20 minutes at room temperature to extract and separate the plasma.

It is recommended that plasma be stored in 1.1 - 1.2 ml aliquots in sterile, 2.0 mL polypropylene screw-cap tubes. Plasma specimens may be stored at room temperature (25°C to 30°C) for up to 1 day, at 2°C to 8° C for 6 days, or frozen at -20°C to -80°C for up to 6 weeks.

Clinicians handling and storing specimens should follow appropriate standard operating procedures for the process.

3. Specimen Transport

During transport, specimen tubes must be protected from mechanical damage, thermal shock and tampering. Blood specimens in transit must never be left unattended.

Plasma may be transported at 2-8°C, however, once it has been frozen it is preferable to ship it frozen (the temperature it was frozen at should be maintained) as multiple freeze-thaw cycles can compromise specimen quality. If it is not feasible to transport frozen samples, the specimens should ALWAYS be packaged in cooler boxes with ice packs to maintain their integrity.

In the event of an accidental spill, the sample transporter should manage the spill using standard protocols for biohazard management. For spills and any transportation delay, an incident report must be completed on the Specimen Tracking Form for quality assurance purposes.

Clinicians facilitating specimen transport should follow appropriate standard operating procedures for the process.

4. Bio-Safety

All individuals handling blood specimens in any of the collection, processing and transportation steps must follow standard safety practices for dealing with potentially infectious biological material. The reduction of biohazard exposure is achieved through the combination of safe practices and procedures, safe facilities, and safety equipment that allows the containment of biohazards. Standard operating procedures outlined by National Laboratory Services for use of personal protective equipment, decontamination of reusable accessories such as cooler boxes, and decontamination and disposal of biohazard spills and wastes should be followed.

Samples will be rejected if:

- Insufficient sample volume
- Poorly labeled specimen tube
- Not labeled
- Collected in non EDTA anticoagulant (blood)
- Sample is clotted (blood)
- Possible contamination
- Poor separation of plasma
- Missing sample or lab request form

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VIII. APPENDIX

1. Interpretation of Viral Load Results on the Log Scale

It may on occasion be useful to consider the extent of reduction in viral load using log scale in some patients who have repeat viral load >1000. A reduction of ≥ 1 log per month with improved adherence may suggest that viral suppression is achievable on the current regimen with continued good adherence and additional time. If this is thought to be the case, the patient should be encouraged to continue the current regimen and the viral load repeated after 3 months to check if it has gone ≤ 1000 copies.

Viral load can also be measured on a log scale where a 1-log change is equivalent to a 10-fold change in the copies per ml.

Log ₁₀ scale	Copies/ml
1.0	10
1.5	32
2.0	100
2.5	316
3.0	1,000
3.5	3,162
4.0	10,000
4.5	31,623
5.0	100,000
5.5	316,228

2. WHO Clinical Staging of HIV Disease in Adults, Adolescents, and Children

Adults and adolescents ^a	Children
Clinical stage 1	
<ul style="list-style-type: none"> • Asymptomatic • Persistent generalized lymphadenopathy 	<ul style="list-style-type: none"> • Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2	
<ul style="list-style-type: none"> • Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Fungal nail infections • Seborrhoeic dermatitis 	<ul style="list-style-type: none"> • Unexplained persistent hepatosplenomegaly • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) • Herpes zoster • Lineal gingival erythema • Recurrent oral ulcerations • Papular pruritic eruptions • Fungal nail infections • Extensive wart virus infection • Extensive molluscum contagiosum • Unexplained persistent parotid enlargement
Clinical stage 3	
<ul style="list-style-type: none"> • Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhoea for longer than 1 month • Unexplained persistent fever (intermittent or constant, for >1 month) • Persistent oral candidiasis • Oral hairy leukoplakia • Pulmonary tuberculosis (current) • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anemia (<8 g/dl), neutropaenia (<0.5×10⁹/l) or chronic thrombocytopenia (<50×10⁹/l) 	<ul style="list-style-type: none"> • Unexplained moderate malnutrition ^b not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than 1 month) • Persistent oral candidiasis (after first 6 weeks of life) • Oral hairy leukoplakia • Lymph node TB • Pulmonary TB • Severe recurrent bacterial pneumonia • Acute necrotizing ulcerative gingivitis or periodontitis • Unexplained anaemia (<8.0 g/dl), neutropaenia (<0.5 x 10⁹/l) or chronic thrombocytopenia (<50 x 10⁹/l) • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4 ^c	

<ul style="list-style-type: none"> • HIV wasting syndrome • <i>Pneumocystis (jiroveci)</i> pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Extrapulmonary cryptococcosis including meningitis • Disseminated non-tuberculous mycobacterial infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis • Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis) • Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours • Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy • Recurrent septicaemia (including non-typhoidal <i>Salmonella</i>) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis 	<ul style="list-style-type: none"> • Unexplained severe wasting, stunting or severe malnutrition^d not responding to standard therapy • <i>Pneumocystis (jiroveci)</i> pneumonia • Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) • Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary TB • Kaposi sarcoma • Cytomegalovirus infection (retinitis or cytomegalovirus infection affecting another organ, with onset at age more than 1 month) • Central nervous system toxoplasmosis (after the neonatal period) • HIV encephalopathy • Extrapulmonary cryptococcosis, including meningitis • Disseminated non-tuberculous mycobacterial infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) • Lymphoma (cerebral or B-cell non-Hodgkin) • HIV-associated cardiomyopathy or nephropathy
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^a In the development of this table, adolescents were defined as 15 years or older. For those aged less than 15 years, the clinical staging for children should be used.

^b For children younger than 5 years, moderate malnutrition is defined as weight-for-height <-2 z-score or mid-upper arm circumference ≥115 mm to <125 mm.

^c Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.

^d For children younger than 5 years of age, severe wasting is defined as weight-for-height <-3 z-score; stunting is defined as length-for-age/height-for-age <-2 z-score; and severe acute malnutrition is defined as either weight for height <-3 z-score or mid-upper arm circumference <115 mm or the presence of oedema.

Ref: Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach, WHO 2013