Module 1 – Background

Learning objectives:

By the end of this module, participants will be able to:

- State the differences between CD4 and viral load monitoring
- Define the 3 different types of ART treatment failure: clinical, immunological, and virological (WHO 2013)
- State the advantages of moving to routine viral load monitoring

Target audiences: all cadres: Clinicians, Counsellors, and Laboratorians

Pre-requisites: None

Participant materials required: Handouts 1-1, 1-2

Special preparations before facilitating: None

Icon	Meaning
	Refer to Handout
	Customize the slide for local context

Module-at-a-glance

Segment		What you do	Time	Handouts
Module opening			**0:02**	
	Slides 1-2	State the module objective.		
1. CD4 vs. Viral Load Monitoring			**0:15**	
	Slides 3-9	Explain the slides according to the content notes.		
	Slides 10-13	Knowledge checks - Ask participants to answer each question before showing the correct answers.		
2. Three Types of Treatment Failure Defined			**0:20**	
	Slides 14-16	Conduct activity 1A: How is treatment failure currently defined according to content notes.		**1-1, 1-2**
3. Benefits of Routine Viral Load Monitoring			**0:20**	
	Slides 17-19	Explain the slides according to the content notes.		
	Slide 20	Conduct a group discussion • Solicit participants' responses to the two questions on the slide. • Debrief each question after the group discussion. • Refer to the content notes for suggested answers.		
	Slides 21-22	Explain the slides according to the content notes.		
Module closing			**0:03**	
	Slides 23-24	Invite participants to supply words to complete each key message.		
		TOTAL MODULE DURATION:	**1:00**	

Slide Number	Content Notes for PowerPoint Slides
4	**Heading – What is CD4?** • CD4 cells are one of the white blood cells in our immune system that helps fight infection. It is these cells that the HIV virus targets to destroy and in so doing weakens the immune system and making it unable to fight multiple infections. • In a healthy individual the normal range can vary from 500 – 1,500 cells/mm3. The CD4 count is reported as the number of cells per cubic millimeter of blood. Measuring the CD4 count gives us an indication of how strong the immune system is with people infected with HIV. • When HIV is untreated it attacks the CD4 cells causing a decline in CD4 cells. When the CD4 count is low the patient is at risk of developing opportunistic infections.
5	**Heading – What is viral load?** • Viral load is the amount of virus circulating in the blood of an individual infected with HIV. When your viral load is high, it means you have more HIV virus in your body. • The Viral load test is a quantitative virological method used for measuring the amount of HIV present in the blood. o The genetic material measured by the test is the HIV RNA. o Viral load is described as the number of 'copies' of HIV's genetic material (RNA) per milliliter (copies/ml) • The higher the viral load the faster the CD4+ T-cells are destroyed and the faster the progress toward AIDS.
6	**Heading - Interaction between CD4 and Viral Load** There is a relationship between CD4 and viral load and taken together can determine how fast a patient progresses to AIDS. • During acute infection there is a peak in viral load, which is associated with a dip in the CD4 count. • Following acute infection, the viral load reaches peak levels followed by a drop to a lower more stable level, known as the "viral set point". This is explained by the virulence of the virus and the host immune response, which is capable of controlling the infection. • If left untreated, over a number of years the viral set point increases while the CD4 count gradually declines until it reaches a critical threshold, usually around CD4 200, where specific AIDS defining illnesses start to occur.
7	**Heading - Effect of ARVs on CD4 and VL** • When a patient is on effective antiretroviral therapy, the amount of HIV virus in the blood is suppressed and the CD4 cells are able to increase. Hence the patient is able to fight off infections. • If antiretroviral therapy is stopped, then the virus in the blood multiples, CD4 cells are reduced, and the patient becomes susceptible to infections again. WHO has defined a viral load of <u>< 1000 copies/ml</u> to indicate successful treatment.
8	**Heading - Converting Viral Load Copies/ml into Log** Viral load range can be so wide that results can be expressed in logarithmic (log) scale. The log value expresses the viral load value to the power 10, which is written as $\log_{10}$. The table shows examples of copies numbers converted into $\log_{10}$ values. This scale ($\log_{10}$) enables large copies/ml numbers to a manageable number. For example, 10,000,000 copies/ml will be expressed as 7.0 $\log_{10}$.

Slide Number	Content Notes for PowerPoint Slides
	Ask participants to supply the answers for the questions below. 1. 10,000 copies/ml can also be expressed as _4__Log_{10} 2. 5,000 copies/ml is between __3_Log_{10} and __4_Log_{10} 3. Why are log values used? Log values are an easier way to manage large viral load numbers
9	**Heading – Handout – What is "Undetectable" Viral Load?** • Besides a number (in terms of copies/ml or log), there is another possible viral load result – undetectable, or "below the limit of quantification." • This does not imply that HIV is not present; it just means that the level of HIV is too low to be detected or measured. • WHO has defined a viral load of < 1000 copies/ml to indicate successful treatment
10-13	**Heading - Knowledge Check** Gauge participants' knowledge with the Knowledge Check questions.
15 & 16  **Handouts 1-1, 1-2**	**Heading - Activity 1A: How is treatment failure currently defined?** 1. Explain the activity using slide 15 2. Refer participants to handout 1-1 and 1-2 3. Divide participants into small groups of 4-6 4. Monitor group activity (10 minutes) 5. Assign groups to report back their answers for a specified question. 6. Each group has one minute to report back (one minute per group) 7. Debrief – See below for suggested answers. • Treatment failure is defined only after at least 6 months on ART. • Clinical failure is defined as: _____ o Clinical failure in adults is defined as a new stage 4 condition (certain stage 3 conditions may also indicate failure). o In children a new or recurrent stage 3 or 4 (with the exception of TB) defines clinical failure. • Immunological failure is defined as: _____ o In adults immunological failure is defined as a CD4 count that has fallen below baseline or is persistently below 100. o In children younger than 5 years a persistent CD4 below 200 or < 10%. o For children older than 5 years failure is indicated by a CD4 < 100 cells/mm. • Virological failure is defined as: _____ Virological failure is currently defined as a plasma viral load above 1000 copies/ml based on two consecutive viral load measurements 3 months apart and after an adherence counselling intervention.
18	**Heading - What type of treatment failure comes first?** Ask participants to answer the question on the slide. Use this slide as a springboard to the next slide.
19	**Heading - Viral Load is the Best Measure of Treatment Response** • In resource limited settings, clinical and immunological monitoring is used to measure a patient's response to ART. However, both perform poorly and may lead to misclassification resulting in a lack switching or unnecessary switch to 2nd line ART.

Slide Number	Content Notes for PowerPoint Slides
	• If patients are not taking their medication correctly and/or the virus has developed some resistance to the medication, the first change that we can measure in the blood is an increase in the HIV viral load (virological failure). • Only after the viral load has been elevated for some time does this lead to a drop in the CD4 cell count (immunological failure). • Finally as the CD4 cell count declines, the patient is not able to fight off infections and clinical failure can occur.
20	**Heading - WHO 2013 recommendations: Use Viral Load to Monitor ART Response** WHO 2013 guidelines provide recommendations for monitoring patients on ART: • Viral load is recommended as the preferred monitoring approach to diagnose and confirm ART failure. • If the viral load testing is not routinely available, CD4 cell count and clinical monitoring, although suboptimal, could be used to diagnose treatment failure. See below for suggested answers. **1. What are the benefits of moving to routine viral load monitoring?** • *Provides better patient care* - Delayed detection of a high viral load will lead to a drop in CD4 , weakened immune response and eventually new infections with the risk of increased morbidity and mortality for the patient. • *Prevents development of drug resistance* - Identifying a patient with a high viral load and trying to intervene early if there are adherence problems may avoid future development of resistance. • *Prevents unnecessary switch to 2nd line ART* – An important reason for using viral load and always if possible confirming immunological or clinical failure with a targeted viral load is that the positive predictive value of the clinical and immunological criteria is very low – in fact they only get it correct 1 in every 3 cases (*Rutherford et al*). • *Reduces transmission* - If a high viral load is acted upon with an adherence intervention or a switch to 2nd line ART, transmission both to sexual partners and from mother to child can be reduced. • *Reduces frequency of clinic visits* - Knowing someone is suppressed and doing fine on ART provides reassurance and the potential for the patient to receive extended refills of ART or enter into alternative refill strategies such as fast track or community based refill groups. **2. If routine viral load monitoring is available, do we need routine CD4 testing?** • Emerging evidence suggests that where routine viral load testing is available, there is no added value to continue routine CD4 monitoring after obtaining a baseline CD4 cell count (see WHO 2014 supplement to the WHO guidelines). • Some countries have already stopped routine CD4 monitoring and introduced routine VL (South Africa, Kenya). • This has potential cost savings and may allow resources previously used for CD4 monitoring to be re-directed to viral load. • Viral load is the gold standard for detecting ART failure.
21	**Heading - UNAIDS Treatment Target**

Slide Number	Content Notes for PowerPoint Slides
	UNAIDS has set ambitious targets aimed at ending the AIDS epidemic by 2030. The three 90's is defined as by 2020. • 90% of all people living with HIV will know their HIV status. • 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy and • 90% of all people receiving antiretroviral therapy will have viral suppression.
22	**Heading - HIV Prevention Care and Treatment Continuum** • In summary the ultimate goal of any ART programme is to retain people on ART and for those people to remain virologically suppressed • These concepts have been embraced within the 90-90-90 targets set by UNAIDS the last 90 of which "90% of those on ART should be virologcally suppressed" will rely on the successful roll out of viral load monitoring and uptake of viral load results. • The following modules aim to provide information and practical tools to help achieve this target.
23-24	**Heading – Module 6: Key messages** Invite participants to supply words to complete each key message.

References

WHO 2013 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection (http://www.who.int/hiv/pub/guidelines/arv2013/download/en/)

Handout 1-1

Table 7.14 WHO definitions of clinical, immunological and virological failure for the decision to switch ARV regimens

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodefiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome[b] occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure[a]
Immunological failure	**Adults and adolescents** CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm³ **Children** Younger than 5 years Persistent CD4 levels below 200 cells/mm³ or <10% Older than 5 years Persistent CD4 levels below 100 cells/mm³	Without concomitant or recent infection to cause a transient decline in the CD4 cell count A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure *(182)*. The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
Virological failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support	The optimal threshold for defining virological failure and the need for switching ARV regimen has not been determined An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed Assessment of viral load using DBS and point-of-care technologies should use a higher threshold

[a] See the list of clinical conditions associated with advanced or severe HIV disease in Annex 1.
[b] Section 6.1 discusses immune reconstitution inflammatory syndrome.

Handout 1-2

12. ANNEXES

Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children

Source: Adapted from *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.* Geneva, World Health Organization, 2007 (www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf).

Adults and adolescents[a]	Children
Clinical stage 1	
Asymptomatic Persistent generalized lymphadenopathy	Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrhoeic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement
Clinical stage 3	
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 longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9/l) and/or chronic thrombocytopaenia (<50 x 10^9/l)	Unexplained moderate malnutrition[a] 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 one 1 month) Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Lymph node tuberculosis Pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotizing ulcerative gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9/l) or chronic thrombocytopaenia (<50 x 10^9/l)

Handout 1-2

Adults and adolescents[a]	Children
Clinical stage 3	
	Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4[c]	
HIV wasting syndrome *Pneumocystis (jirovecii)* 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 sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) Lymphoma (cerebral or B-cell non-Hodgkin) Symptomatic HIV-associated nephropathy or cardiomyopathy Recurrent septicaemia (including nontyphoidal *Salmonella*) Invasive cervical carcinoma Atypical disseminated leishmaniasis	Unexplained severe wasting, stunting or severe malnutrition[d] not responding to standard therapy *Pneumocystis (jirovecii)* 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 tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous 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 nephropathy or cardiomyopathy

[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.