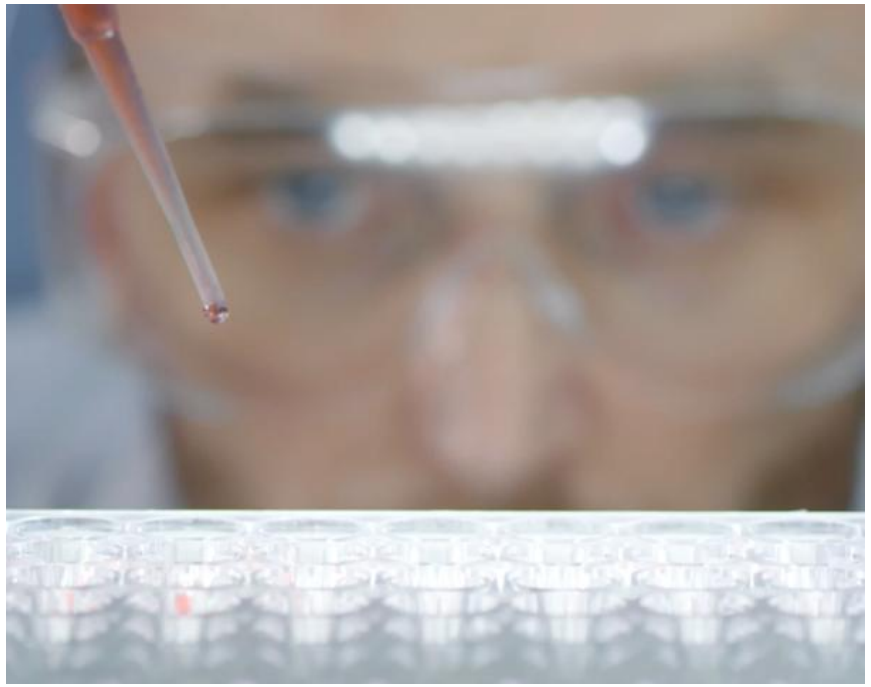
Advanced Hiv Disease: Re-establishing CD4 Testing as a Clinical Priority



- Akanmu AS
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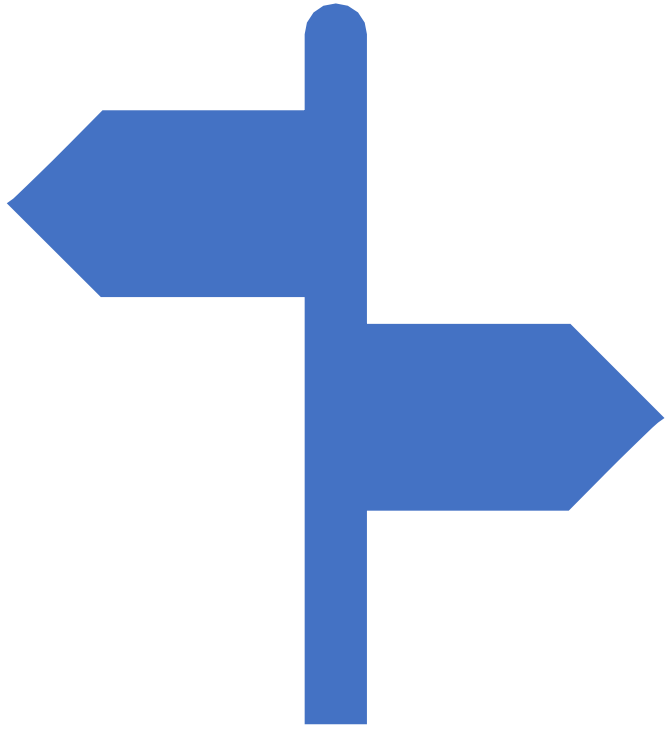
- College of Medicine University of Lagos
- Chairman: National Task Team on ART

Summary of Presentation

- CD4 molecule and the Aetiopathogenesis of HIV Infection
- The CD4+ T- cell Count and the Evolution of the Criteria for Initiation of antiretroviral Therapy then
- The Use of VL assays as prefered method for assessment of ART efficacy
- The coming of Advanced HIV disease resulting in re-establishment of CD4+ Cell count as absolute lab test to distinguish between:
  - Persons at risk of death at initiation of ART and those
  - Persons that will survive after initiation of ARV.



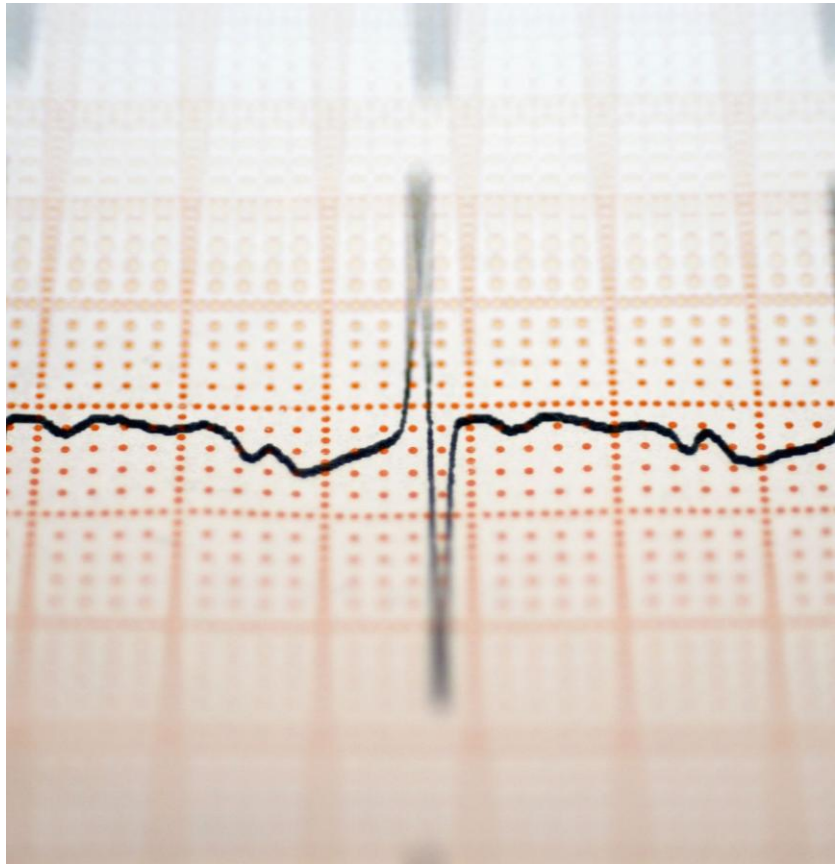
Understanding immunopathogenesis of HIV infection

The cytokine storm

Lymphocytopaenia

The Acute Phase Reactants and Cytokine Storm

- The reaction is to the initial viraemia about 5 days after infection
  - alpha1-antitrypsin and serum amyloid A,
- Burst of inflammatory cytokines correspond to the time of steep rise in VL (Viral ramp-up)
  - interferon-α
  - interleukin-15 and a
  - shower of plasma microparticles with surface phosphatidylserine, derived apoptotic cells.
  - IL-1, IL-6, TNF-a
- These cytokines are believed to mediate symptoms of clinical symptoms of acute HIV infection.



Cytokine storm leads to:

1

Flu-like or mononucleosis-like symptoms-

2

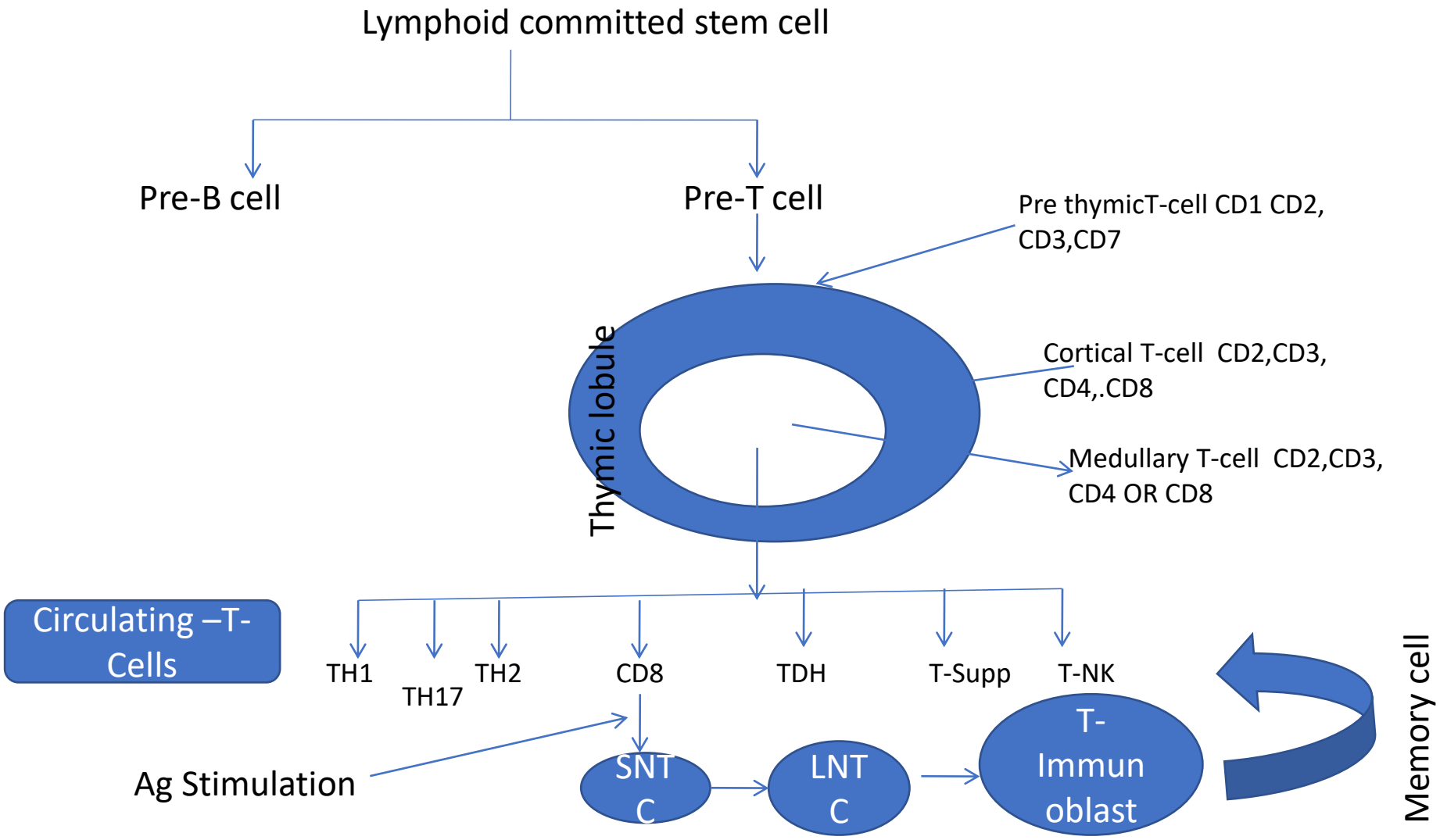
Reset of Hypothallamic Temperature Regulatory centre

3

: Fever

- Fatigue
- Myalgia
- Night sweats

Locating the T-helper cells In lymphopoiesis



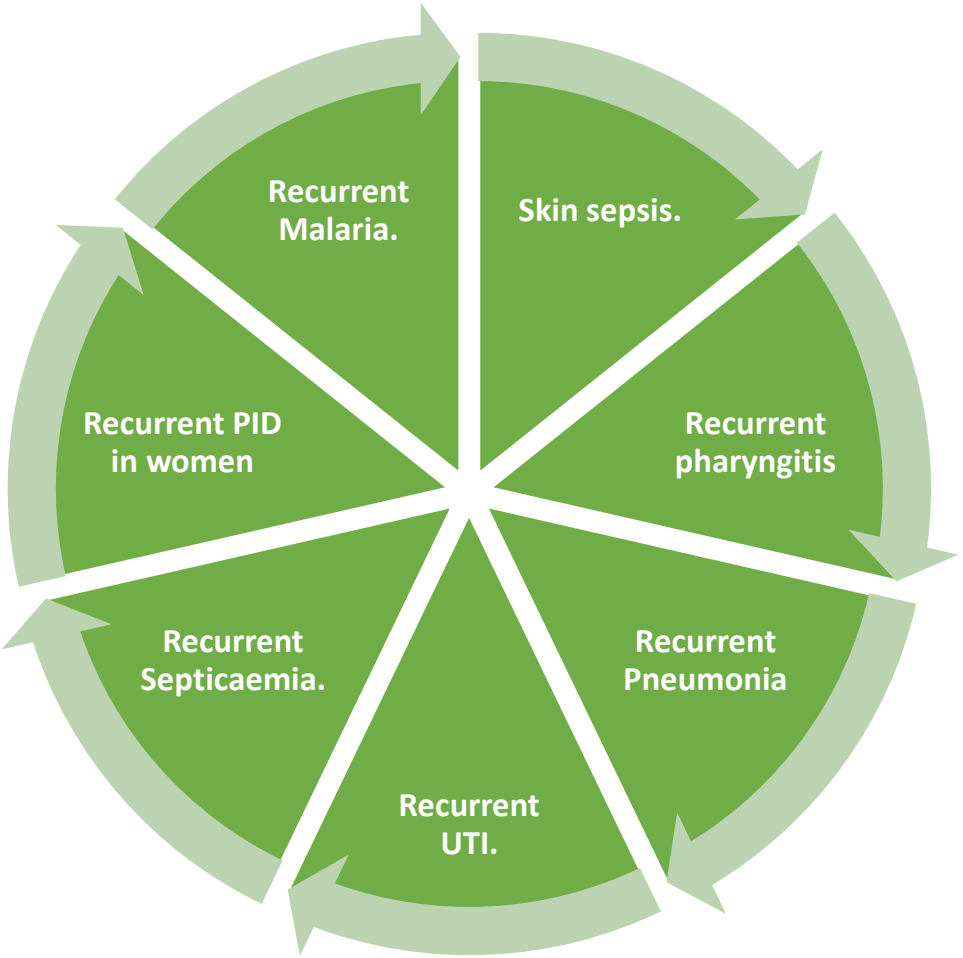
Diseases of Immunosuppression

Mainly As a Result of Loss of CD4+ T-lymphocytes

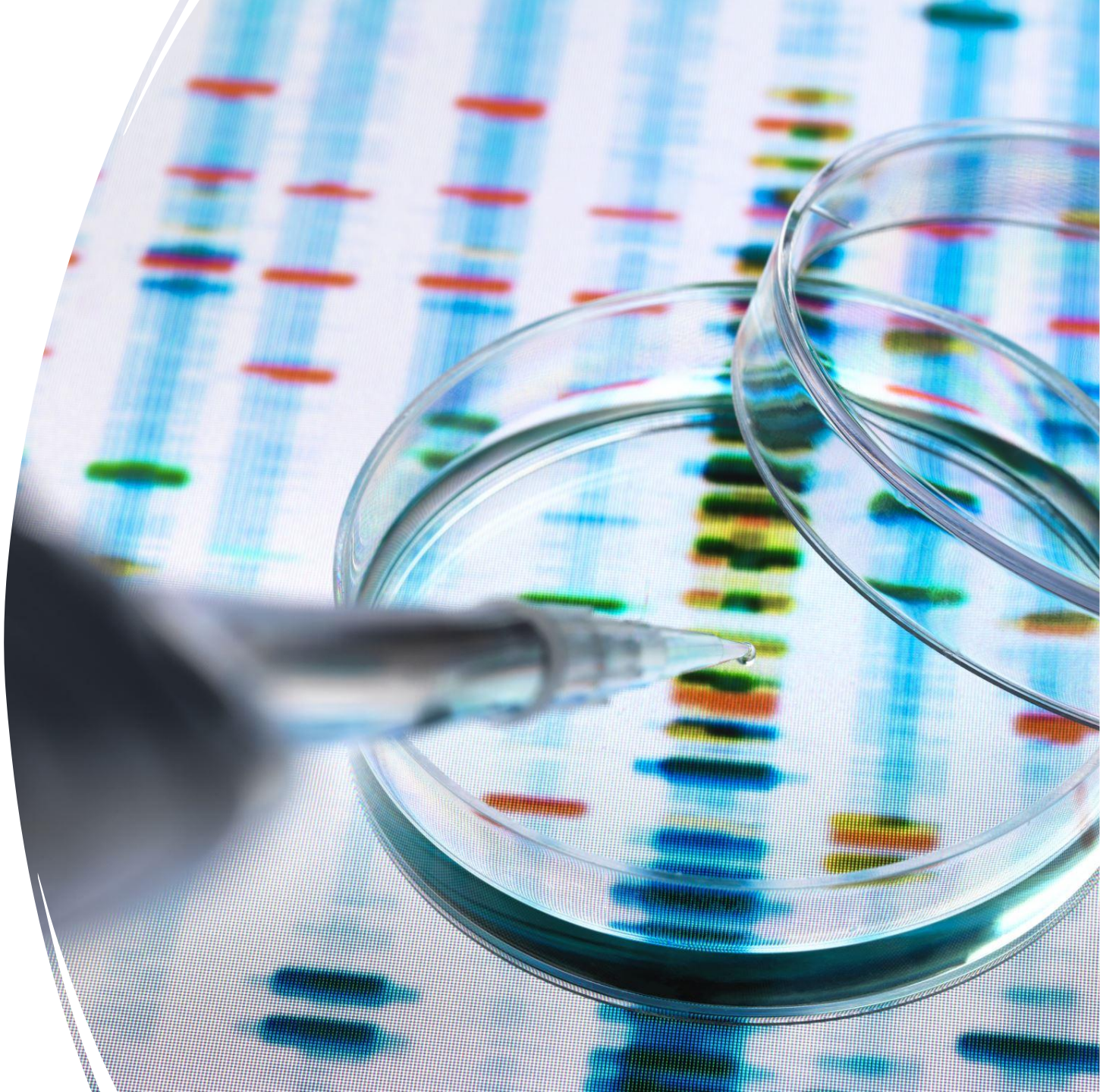
Mechanisms of CD4+ T-cell lymphocytopaenia

- Syncitium Cell formation due to syncitium forming variant.
- Cytotoxic T-cell killing of infected cells.
- Cytotoxic T-cell killing of uninfected cell expressing Gp^{120} shed from infected cells.
- Antibody Dependent cytotoxity.
- Killing caused by domination of host cell protein synthesis by viral RNA and protein synthesis.
- Damage to CD4 cell membrane as a result of massive budding of newly formed virions.

Dysfunction of B-Cells

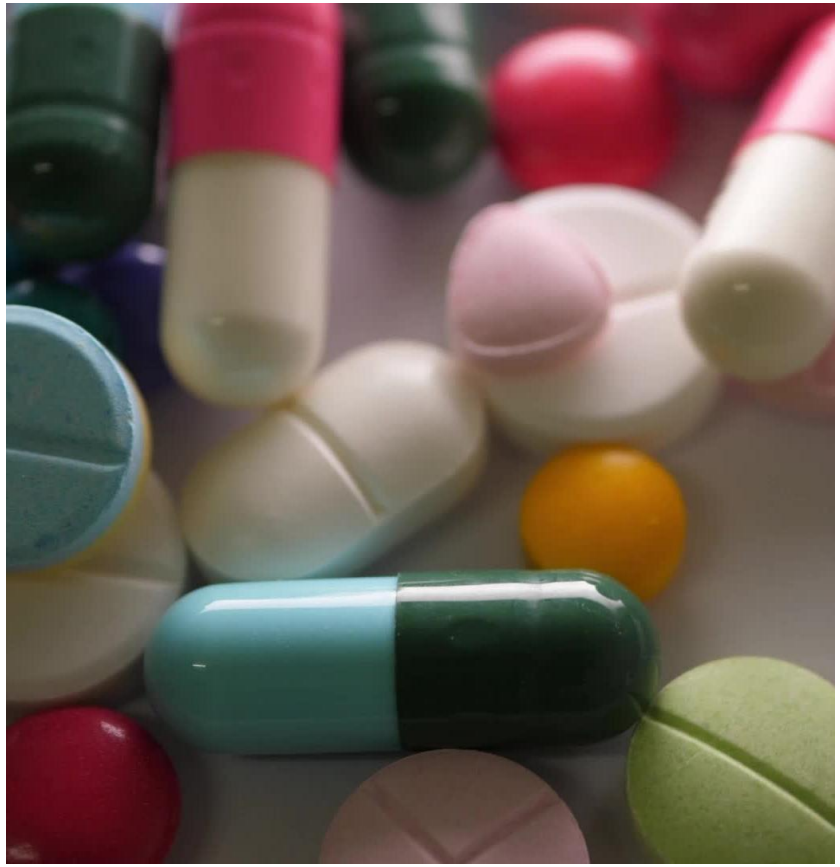


CD4+ T-cell and decision to initiate ARV



When to start treatment-The 1990s

- Over the last 35 years, CD4 cell count was the major decision-making assessment
- The decision level during 1990s was a value 200/mm3 and below
  - treatment was expensive and
  - associated with significant drug toxicity.
  - there were fewer treatment options and
  - the decision about when to start treatment needed to balance
    benefits against the significant risks.



When to start treatment: 2002 to 2010 events

- Treatment became more affordable and
- Less toxic
- Evidence became more abundant that early initiation is more beneficial and safer.
- Thus, most treatment guidelines reflected this by increasing CD4+ cell count threshold from
  - 200 cells/mm3 to 350 cells/mm3 in 2010

Guidelines continued to evolve

WHO 2010 Consolidated Guideline

SUMMARY OF MAJOR RECOMMENDATIONS

(2009 WHO ART Guidelines for Adults and Adolescents)

When to start

Recommendations

1. It is recommended to treat all patients with CD4 count <350 cells/mm^3, irrespective of WHO clinical stage. (Strong recommendation, moderate quality of evidence)

2. It is recommended that all patients with WHO Clinical Stage 1 and 2 should have access to CD4 testing to decide when to initiate treatment (Strong recommendation, low quality of evidence)

3. It is recommended to treat all patients with WHO HIV clinical stage 3 and 4, irrespective of CD4 count. (Strong recommendation, moderate quality of evidence)

WHO 2013 Consolidated Guideline

When to start ART in adults and adolescents	
Target population	**Recommendation**
Severe/advanced HIV infection (WHO clinical stage 3 or 4)	Initiate ART in all individuals regardless of CD4 cell count
HIV infection (WHO clinical stage 1 or 2)	Initiate ART if CD4 ≤500 cells/mm^3 (CD4 ≤350 cells/mm^3 as a priority)
TB disease	Initiate ART in all individuals with active TB disease regardless of CD4 cell count[a] *(Unchanged from 2010 recommendations (2))*
Hepatitis B coinfection	Initiate in all individuals with CD4 ≤500 cells/mm^3 and regardless of CD4 cell count in the presence of severe chronic liver disease[b]
HIV-serodiscordant couples	Provide ART to all partners infected with HIV regardless of CD4 cell count (to reduce the risk of HIV transmission to the negative partner) *(Existing 2012 recommendation (49))*

THE 2015 events: two major trials confirming that ARV be initiated at CD4 levels > 500/mm^3

THE INSIGHT STUDY 2015

Published in final edited form as:
N Engl J Med. 2015 August 27; 373(9): 795–807. doi:10.1056/NEJMoa1506816.

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

Abstract

BACKGROUND—Data from randomized trials are lacking on the benefits and risks of initiating antiretroviral therapy in patients with asymptomatic human immunodeficiency virus (HIV) infection who have a CD4+ count of more than 350 cells per cubic millimeter.

METHODS—We randomly assigned HIV-positive adults who had a CD4+ count of more than 500 cells per cubic millimeter to start antiretroviral therapy immediately (immediate-initiation group) or to defer it until the CD4+ count decreased to 350 cells per cubic millimeter or until the development of the acquired immunodeficiency syndrome (AIDS) or another condition that dictated the use of antiretroviral therapy (deferred-initiation group). The primary composite end point was any serious AIDS-related event, serious non–AIDS-related event, or death from any cause.

RESULTS—A total of 4685 patients were followed for a mean of 3.0 years. At study entry, the median HIV viral load was 12,759 copies per milliliter, and the median CD4+ count was 651 cells per cubic millimeter. On May 15, 2015, on the basis of an interim analysis, the data and safety monitoring board determined that the study question had been answered and recommended that patients in the deferred-initiation group be offered antiretroviral therapy. The primary end point occurred in 42 patients in the immediate-initiation group (1.8%; 0.60 events per 100 person-years), as compared with 96 patients in the deferred-initiation group (4.1%; 1.38 events per 100 person-years), for a hazard ratio of 0.43 (95% confidence interval [CI], 0.30 to 0.62; P<0.001). Hazard ratios for serious AIDS-related and serious non–AIDS-related events were 0.28 (95% CI, 0.15 to 0.50; P<0.001) and 0.61 (95% CI, 0.38 to 0.97; P = 0.04), respectively. More than two thirds of the primary end points (68%) occurred in patients with a CD4+ count of more than 500 cells per cubic millimeter. The risks of a grade 4 event were similar in the two groups, as were the risks of unscheduled hospital admissions.

CONCLUSIONS—The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells per cubic millimeter provided net benefits over starting such therapy

THE TEMPRANO STUDY 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

The members of the writing group, who are listed in the Appendix, assume responsibility for the content and integrity of this article. Address reprint requests to Dr. Anglaret at INSERM Unité 897, Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux, France, or at xavier.anglaret@isped.u-bordeaux2.fr.

*A list of additional members of the TEMPRANO ANRS 12136 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 20, 2015, at NEJM.org.

N Engl J Med 2015;373:808-22.
DOI: 10.1056/NEJMoa1507198

ABSTRACT

BACKGROUND
In sub-Saharan Africa, the burden of human immunodeficiency virus (HIV)–associated tuberculosis is high. We conducted a trial with a 2-by-2 factorial design to assess the benefits of early antiretroviral therapy (ART), 6-month isoniazid preventive therapy (IPT), or both among HIV-infected adults with high CD4+ cell counts in Ivory Coast.

METHODS
We included participants who had HIV type 1 infection and a CD4+ count of less than 800 cells per cubic millimeter and who met no criteria for starting ART according to World Health Organization (WHO) guidelines. Participants were randomly assigned to one of four treatment groups: deferred ART (ART initiation according to WHO criteria), deferred ART plus IPT, early ART (immediate ART initiation), or early ART plus IPT. The primary end point was a composite of diseases included in the case definition of the acquired immunodeficiency syndrome (AIDS), non–AIDS-defining cancer, non–AIDS-defining invasive bacterial disease, or death from any cause at 30 months. We used Cox proportional models to compare outcomes between the deferred-ART and early-ART strategies and between the IPT and no-IPT strategies.

RESULTS
A total of 2056 patients (41% with a baseline CD4+ count of ≥500 cells per cubic millimeter) were followed for 4757 patient-years. A total of 204 primary end-point events were observed (3.8 events per 100 person-years; 95% confidence interval [CI], 3.3 to 4.4), including 68 in patients with a baseline CD4+ count of at least 500 cells per cubic millimeter (3.2 events per 100 person-years; 95% CI, 2.4 to 4.0). Tuberculosis and invasive bacterial diseases accounted for 42% and 27% of primary end-point events, respectively. The risk of death or severe HIV-related illness was lower with early ART than with deferred ART (adjusted hazard ratio, 0.56; 95% CI, 0.41 to 0.76; adjusted hazard ratio among patients with a baseline CD4+ count of ≥500 cells per cubic millimeter, 0.56; 95% CI, 0.33 to 0.94) and lower with IPT than with no IPT (adjusted hazard ratio, 0.65; 95% CI, 0.48 to 0.88; adjusted hazard ratio among patients with a baseline CD4+ count of ≥500 cells per cubic millimeter, 0.61; 95% CI, 0.36 to 1.01). The 30-month probability of grade 3 or 4 adverse events did not differ significantly among the strategies.

CONCLUSIONS
In this African country, immediate ART and 6 months of IPT independently led to lower rates of severe illness than did deferred ART and no IPT, both overall and among patients with CD4+ counts of at least 500 cells per cubic millimeter. (Funded by the French National Agency for Research on AIDS and Viral Hepatitis;

The Sept 2015 Start Guideline

Recommendation 1: When to start ART among people living with HIV			
Target population	**Specific recommendation**	**Strength of the recommendation**	**Quality of the evidence**
Adults[a] (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	*Strong*	*Moderate* NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong	*Strong*	*Moderate* UPDATED
Adolescents (10–19 years old)	ART should be initiated in all adolescents living with HIV at any CD4 cell count	*Conditional*	*Low* NEW
	As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Children (1 to <10 years old)	ART should be initiated in all children 1 to <10 years old living with HIV at any CD4 cell count	*Conditional*	*Low* NEW
	As a priority, ART should be initiated among all children <2 years old and those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4% <25% (if <5 years old) or CD4 count ≤350 cells/mm^3 (if ≥5 years old)	*Strong*	*Moderate*
Children (<1 year old)	ART should be initiated in all children living with HIV younger than 1 year old	*Strong*	*Moderate*

Viral load assay as a preferred method of assessment of ART efficacy

A Robust Systematic review has proven the superiority Viral load assay as a better predictor of treatment Failure as compared with CD4+ cell count

A number of other reviews show that in patients stable on ART (undetectable viral load), CD4+ cell count do not change significantly over a period of 24 months

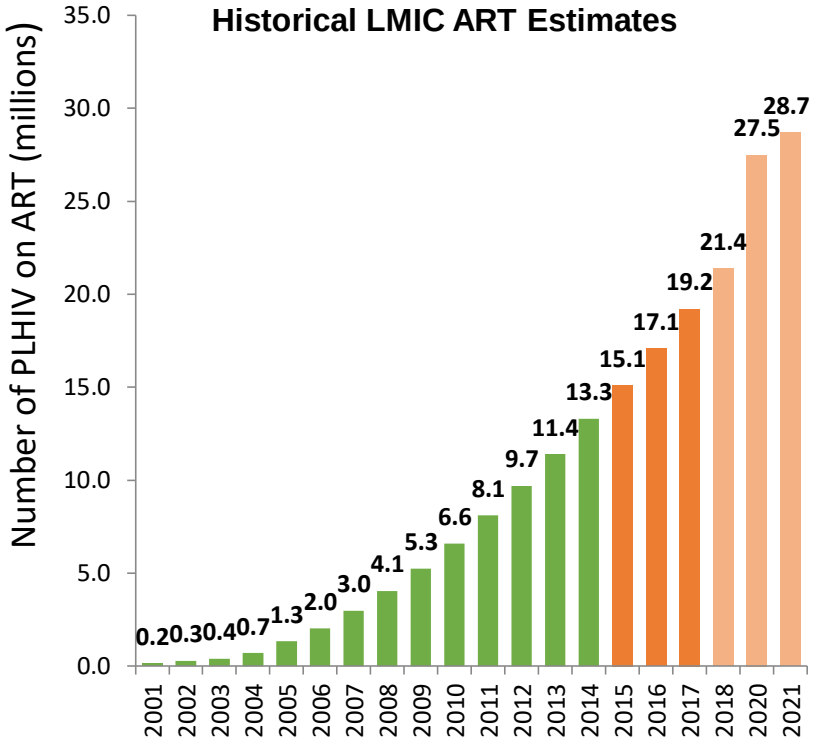
De Luca A, Marazzi MC, Mancinelli S, et al. Prognostic value of virological and immunological responses after 6 months of antiretroviral treatment in adults with HIV-1 infection in sub-Saharan Africa. J Acquir Immune Defic Syndr 2012; 59:236–244.

Ford N, Stinson K, Gale H, et al. CD4 changes among virologically suppressed patients on antiretroviral therapy: a systematic review and metaanalysis. J Int AIDS Soc 2015; 18:20061

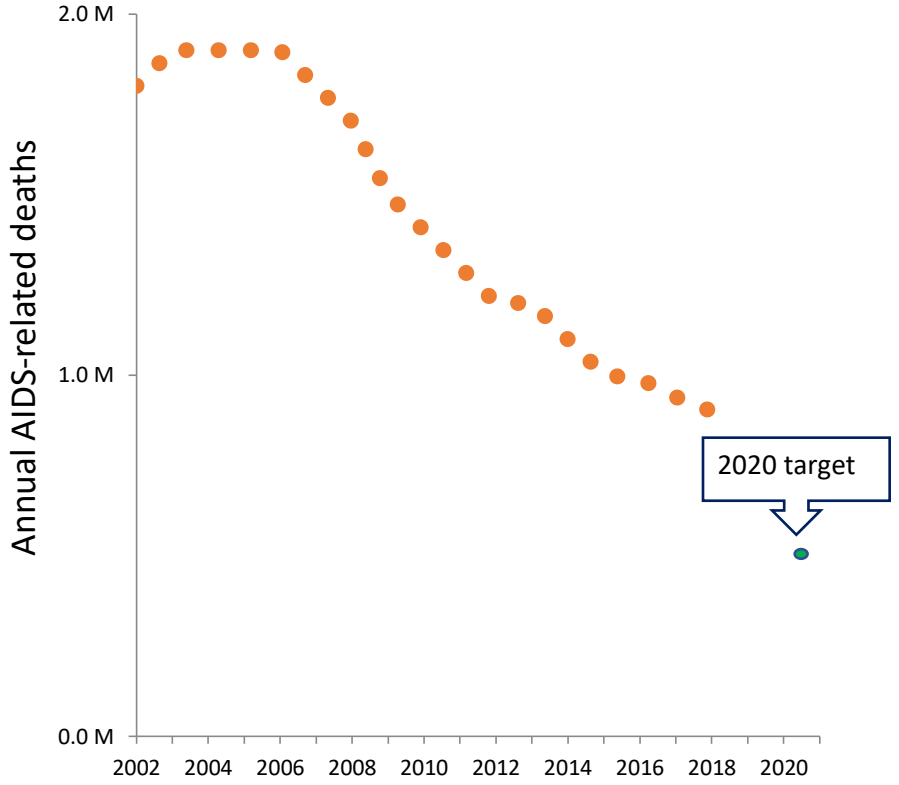
What role is left for CD4+ cell enumeration in HIV/AIDS care and programming

ART has scaled up dramatically since 2000, reaching over 28M people living with HIV (PLHIV) in 2021

Historical scale up of PLHIV on ART in low- and middle-income countries (LMICs)



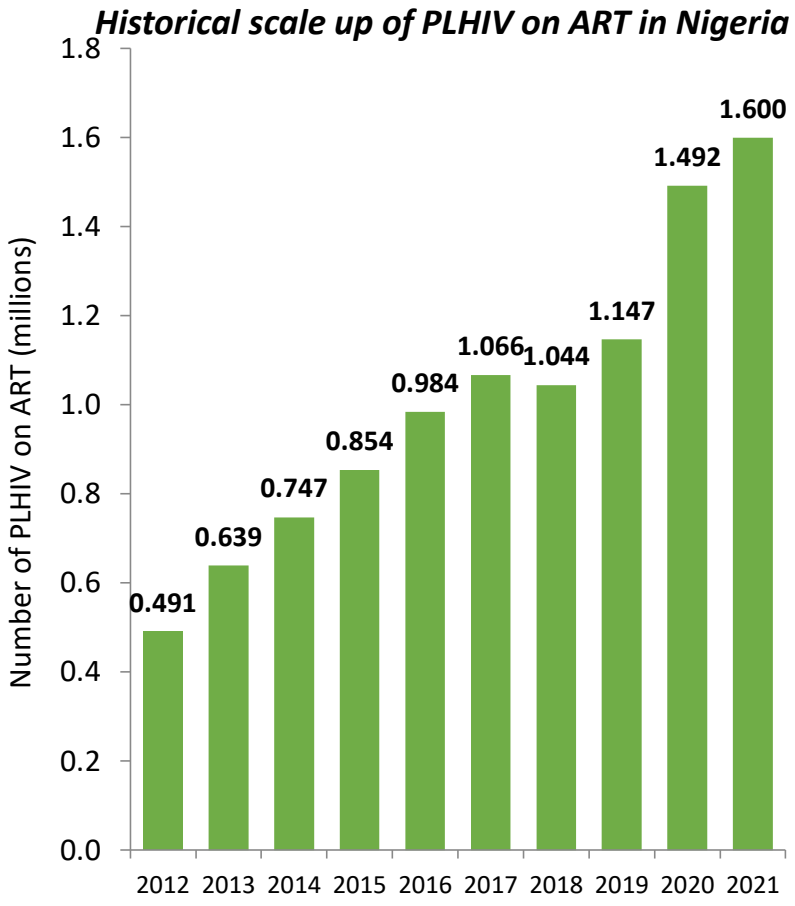
Number of AIDS-related deaths, global, 1990–2017 and 2020 target

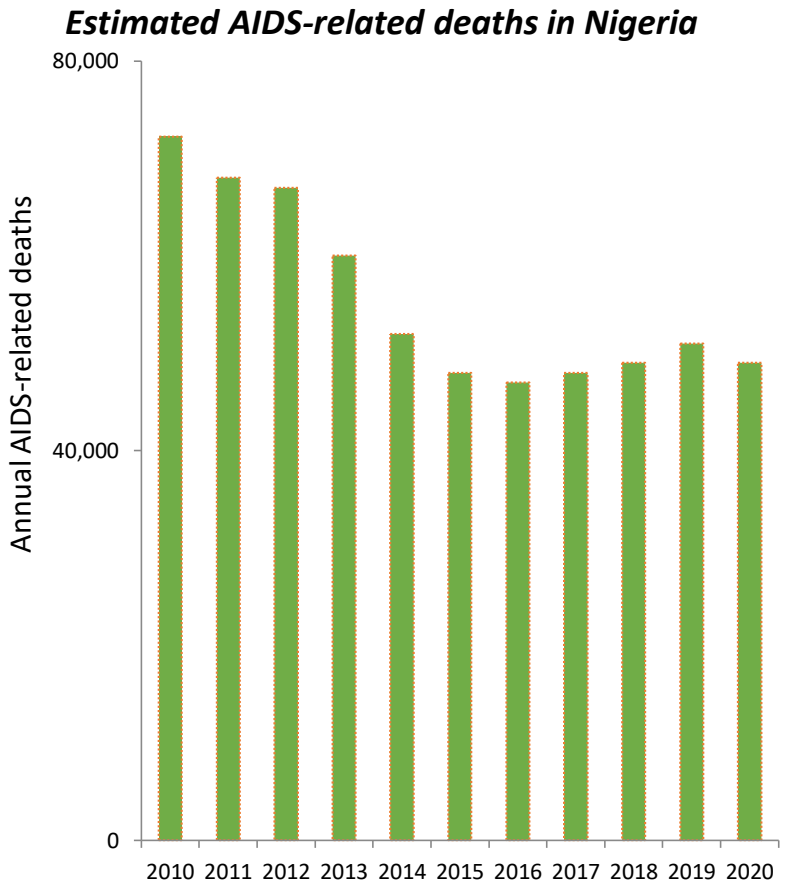


Source: WHO/UNAIDS for historical estimates

Note: 2010-2018 ART coverage figures calculated for LMICs using 2019 World Bank Income Classifications and UNAIDS AIDSinfo database, accessed August 29, 2019 (only includes countries with both ART and PLHIV numbers reported)

Nigeria ART coverage and AIDS-related deaths





Source: NASCP

Despite the increased access to treatment

The number of people with advanced HIV at the time of diagnosis remains high 30-40% and

It Is not declining very fast, especially among men

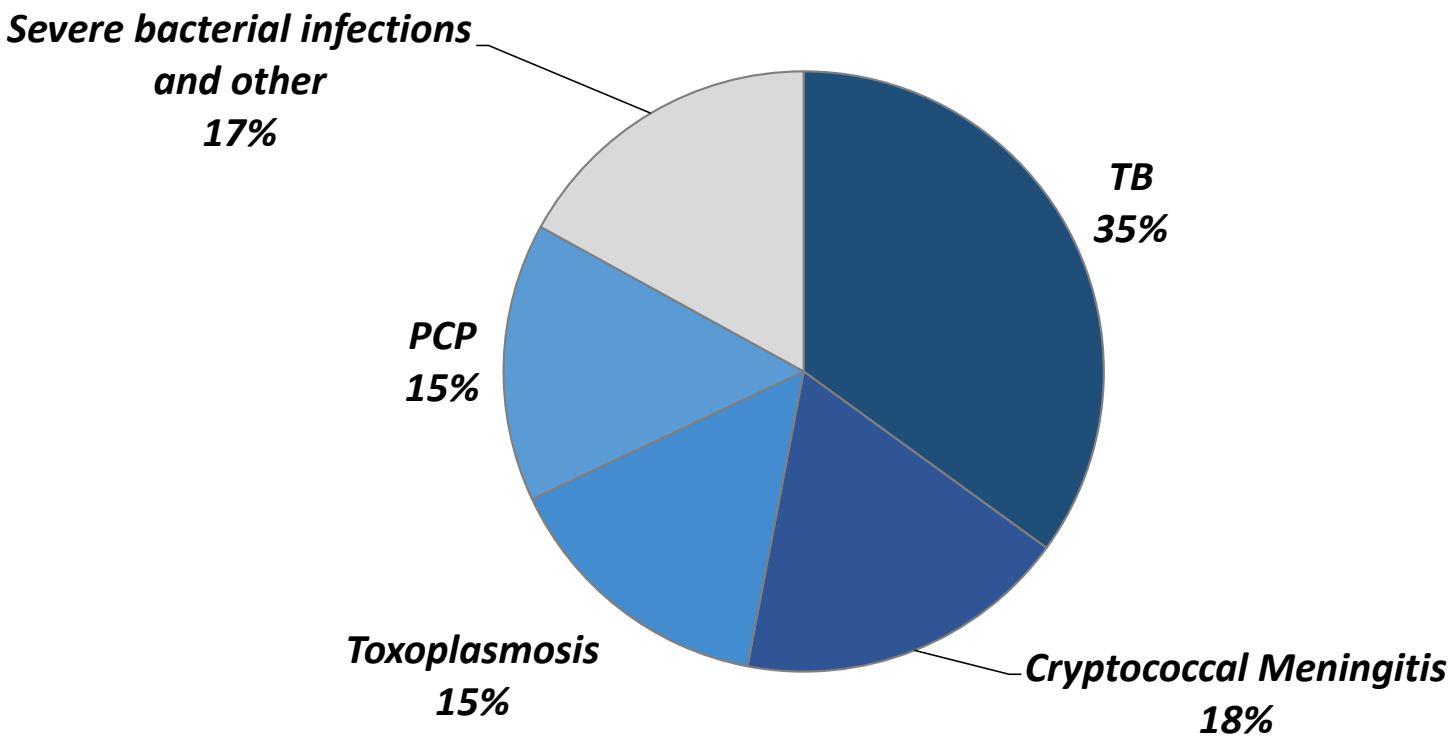
Also,

The mortality rate among people with advanced HIV disease is high even with access to ART.

The risk of death is higher with CD4+ lymphocyte count <100 cells/mm^3

AIDS-related mortality is driven by a small number of OIs, including TB and fungal infections like Cryptococcus

Source: WHO AHD Guidelines, 2017.



DTG and the Advanced HIV Disease: call for caution when initiating ARV

Dolutegravir avidly and nearly irreversibly complex the integrase

It sinks Viral load in days and usually less than 4 weeks

The Immune recovery is dramatic and

The RISK of IRIS is nearly 100% in patients initiating anew on DTG

For this reason, there is need to exclude advanced HIV disease in any person initiating DTG containing first line regimen

Summary of WHO Package of care for AHD

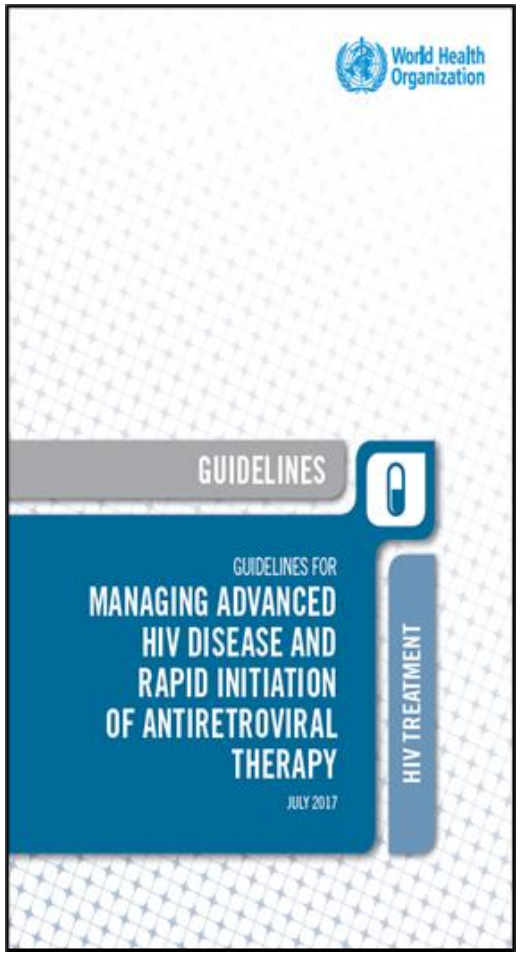


Table 1 Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adolescents	Children
Diagnosis	Sputum Xpert® MTB/RIF as the first test for TB diagnosis among symptomatic people	Any	Yes	Yes	Yes
	LF-LAM for TB diagnosis among people with symptoms and signs of TB	≤100 cells/mm³ Or at any CD4 count if seriously ill	Yes	Yes	Yes[a]
	Cryptococcal antigen screening	≤100 cells/mm³	Yes	Yes	No
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis[b]	≤350 cells/mm³ or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections	Yes	Yes	Yes For criteria, see Annex 1
	TB preventive treatment[b]	Any	Yes	Yes	Yes[c]
	Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis	<100 cells/mm³	Yes	Yes	Not applicable (screening not advised)
ART initiation	Rapid ART initiation (as recommended in Chapter 3)	Any	Yes	Yes	Yes
	Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3)	Any	Yes	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible	<200 cells/mm³	Yes	Yes	Yes

**Tailored counselling: considerations to be made e.g. for involvement of family support, community and/or home based care*

CD4+ T cell count and HIV/AIDS research

- Death Outcomes
- Attrition outcomes
- Susceptibility to OIs and
- Differences in cell surface receptors and susceptibility to infection
- Adaptive immunity cellular and humoral and the match towards CURE research

Use of CD4+ cell count in the current dispensation

- Although it is no longer a requirement of treatment initiation
- It is the cell principally infected and killed by HIV therefore remains the cell to be counted for
  - Quantitative immune recovery
  - Pathogen specific immune recovery
- From WHO 2017 Treatment Guideline
  - HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter).
  - CD4 cell count every 6 months until patients are stable on ART

Use of CD4+ cell count in the current dispensation

- Decisions to initiate and stop prophylaxis for OIs.
- To manage advanced HIV disease
- Monitor patient returning to care after initial default and
- Those Failing Therapy
- The Role in the era of DTG based first line regimen
- HIV/AIDS Research

Thank you