12 Steps to CD4 Testing

2018 Technical Overview

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2016-17 WHO Guidelines

The 2016 and 2017 WHO guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the care of people living with HIV and the use of antiretroviral (ARV) drugs for treating and preventing HIV infection.

While these guidelines recommend lifelong antiretroviral therapy (ART) regardless of CD4 cell count ("treat all policy") and analysis of viral load (VL) as the preferred monitoring approach, they also provide clear guidance on the indispensable role of CD4 in assessing baseline risk of disease progression, particularly for individuals presenting with advanced disease, decisions regarding starting and stopping prophylaxis for opportunistic infections (OIs), and prioritization decisions regarding ART initiation in settings where universal treatment is not possible. CD4 cell count measurement may also be important for people who are failing ART.

World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed.

World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy.

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1 CD4 Baseline Testing

CD4 cell count testing at baseline for all people living with HIV

The 2017 WHO guidelines point out that **CD4 cell count testing at baseline for all people living with HIV remains important,** because relying on clinical staging alone risks missing substantial numbers of people living with HIV with severe immune suppression.[1]

In a study from Kenya, Malawi, Uganda and Zimbabwe, almost half the people with **CD4 count <100 cells/µL** were classified as having WHO clinical stage 1 or 2 disease[1]. Hence, identifying people with advanced HIV disease who are eligible for elements of a package of care requires CD4 cell count testing[1].

All patients entering or re-entering care should receive a CD4 test at treatment baseline and as clinically indicated for patients who are unstable or with advanced HIV disease.[2]

1.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, page 6.

2.) World Health Organization (2017): What's new in treatment monitoring: Viral load and VCD4 testing. Information Note WHO/HIV/2017.22, page 1.

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Definition of Advanced HIV Disease

People presenting with advanced HIV disease are at high risk of death. The 2017 WHO guidelines define advanced HIV disease as follows:[3]

- For adults and adolescents, and children older than five years, advanced HIV disease is defined as **CD4 cell count <200cells/µL or WHO stage 3 or 4 event.**
- All children younger than five years old with HIV are considered as having advanced HIV disease.
- A **severely immunosuppressed** adult is defined as having a CD4 cell count **<50cells/µL**
- People presenting with advanced HIV disease are at high risk of death, even after starting ART, with the risk increasing with decreasing CD4 cell count, especially with **CD4 cell count <100 cells/µL.**[4]

Relying on clinical staging alone risks missing substantial numbers of people living with HIV with severe immune suppression.[1]

Advanced HIV Disease Package of Care

People with advanced disease are defined as those presenting to care with a **CD4 count below 200 cells/µL** or WHO disease stages 3 and 4. The package of care for these people should include the following:[5]

- Rapid initiation of ART (once the risk of immune reconstitution inflammatory syndrome [IRIS] is ruled out);
- Systematic screening for Cryptococcus antigen;
- Screening and treatment for tuberculosis (TB) or isoniazid preventive treatment (IPT) as indicated;
- Screening for toxoplasmosis and Co-trimoxazole (CTX) prophylaxis; and
- Intensive follow-up.

1.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of anti retroviral therapy, page 6.

3.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of anti retroviral therapy, page v.

4.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of anti retroviral therapy, page 2.

5.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 241

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Priorization of antiretroviral therapy (ART) initiation

CD4 provides guidance on when to start ART[6]:	
When to start ART in adults (>19 years old)	ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count.
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a **CD4 count ≤350 cells/µL**
When to start ART in adolescents (10–19 years of age)	ART should be initiated in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count.
	As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a **CD4 count ≤350 cells/µL**
When to start ART in children younger than 10 years of age	ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count: • Infants diagnosed in the first year of life • Children living with HIV 1 year old to less than 10 years old
	As a priority, ART should be initiated in all children <2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or **CD4 count ≤750 cells/µL** or **CD4 percentage <25%** and children 5 years of age and older with WHO clinical stage 3 or 4 or **CD4 count ≤350 cells/µL**
Timing of ART for adults and children with TB	ART should be started in all TB patients living with HIV regardless of CD4 count. TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment.
	HIV-positive TB patients with profound immunosuppression (e.g. **CD4 counts less than 50 cells/µL)** should receive ART within the first two weeks of initiating TB treatment.
	ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of antituberculosis treatment regardless of the CD4 cell count and clinical stage.

6.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page xxxi.

Recommendation for rapid initiation of ART

People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation, including the option of same-day initiation[7].

Rapid ART start is especially important for people with very low CD4 cell count, for whom the risk of death is high[7].

Although no longer a requirement for ART initiation, **baseline CD4 cell count testing should be performed** to determine whether the patient has advanced HIV disease[7].

7.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, page 20

Monitoring the response to ART and diagnosing treatment failure in the absence of viral load testing and in individuals who are not stable on ART

Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure.[8]

If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm viral failure where possible[8].

In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed.[8]

A patient is considered stable on ART based on the following criteria[8]: on ART for at least 1 year, no current illnesses, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measurements below 1,000 copies/ml).

8.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page xxxiv.

The role of CD4 in identifying immunological failure

The 2016 WHO guidelines point out the role of CD4 in the identification of immunological failure for the decision to switch ART regimens[9]:

Adults and adolescents:
CD4 count at or below 250 cells/µL following clinical failure
or
Persistent CD4 levels below 100 cells/µL

Children younger than 5 years
Persistent CD4 levels below 200 cells/µL

Children older than 5 years
Persistent CD4 levels below 100 cells/µL

9.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 131.

Prophylaxis interventions for people with advanced HIV disease

Co-trimoxazole (CTX) prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a **CD4 count ≤350 cells/µL**[10;11]

Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage, and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with a **CD4 count ≤350 cells/µL**[10;11.]

Pre-emptive antifungal therapy: In adults and adolescents, if blood cryptococcal antigen screening positive among people with **CD4 counts <100 cells/µL** (where lumbar puncture is negative or not feasible or if lumbar puncture excludes cryptococcal meningitis)[12].

10.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 193.

11.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, pages 35-37.

12.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 197.

Recommendations for the package of prophylaxis interventions for people with advanced HIV disease[11]

Intervention: Co-trimoxazole prophylaxis		
INDICATIONS TO START	**Adults**	Severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or with a CD4 cell count <350 cells/ mm3. *Strong recommendation, moderate-quality evidence* Malaria and/or severe bacterial infections highly prevalent: co-trimoxazole, prophylaxis should be initiated regardless of CD4 cell count or WHO stage. *Conditional recommendation, moderate-quality evidence.*
	Adolescents	Same as children
	Children	Regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage, those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 count ≤350 cells/mm3. *Strong recommendation, high-quality evidence*
INDICATIONS TO STOP	**Adults**	Clinically stable on ART, with evidence of immune recovery and viral suppression. *Conditional recommendation, low-quality evidence* Malaria and /or severe bacterial infections are highly prevalent: co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage. *Conditional recommendation, moderate-quality evidence.*
	Adolescents	Same as children
	Children	High prevalence of malaria and/ or severe bacterial infections: continued regardless of whether ART is provided. *Conditional recommendation, moderate-quality evidence* Low prevalence of malaria and/ or severe bacterial infections: discontinued for children who are clinically stable and/or virally suppressed on ART for at least 6 months and with a CD4 cell count >350 cells/mm3. *Strong recommendation, very-low-quality evidence*

11.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, pages 35-37.

Intervention:

Pre-emptive anti-fungal therapy: fluconazole 800 mg/ day for two weeks, then 400 mg/day for eight weeks and continued maintenance with fluconazole 200 mg/day

INDICATIONS TO START	**Adults**	Blood cryptococcal antigen screening positive among people with CD4 counts <100 cells/mm3 (where lumbar puncture is negative or not feasible or if lumbar puncture excludes crypto-coccal meningitis) a *Conditional recommendation, low-quality evidence*
	Adolescents	Same as adults
	Children	Not applicable since screening is not recommended
INDICATIONS TO STOP	**Adults**	If HIV viral load monitoring is not available: When people are stable and adherent to ART and receiving antifungal maintenance therapy for at least one year and have a CD4 cell count ≥200 cells/mm3 (two measurements six months apart). *Strong recommendation, low-quality evidence* If viral load monitoring is available: When people are stable and adherent to ART and antifungal maintenance treatment for at least one year and with a CD4 cell count ≥100 cell/mm3 (two measurements six months apart) and a suppressed viral load. *Conditional recommendation, low-quality evidence*
	Adolescents	Same as adults b
	Children	Not applicable since screening is not recommended

11.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, pages 35-37.

Identification of opportunistic infections: Tuberculosis (TB)

Except as specifically described below for people with HIV infection with low CD4 counts or who are seriously ill, **urine lateral flow (LF)-LAM** should **not** be used for the diagnosis of TB[12].

LF-LAM may be used to assist in the diagnosis of active TB in adult inpatients living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary), who have a **CD4 count less than or equal to 100 cells/µL**, or people living with HIV who are seriously ill, regardless of CD4 cell count or with unknown CD4 cell count[12].

LF-LAM should not be used as a screening test for active TB[12].

12.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 197.

Identification of opportunistic infections: Cryptococcus spec.

The use of routine serum or plasma Cryptococcus antigen (CrAg) screening in ART-naive adults, followed by pre-emptive antifungal therapy if CrAg positive to reduce the development of cryptococcal disease, may be considered prior to ART initiation in:[13]

a. patients with a **CD4 count less than 100 cells/µL;** and
b. where this population also has a high prevalence (>3%) of cryptococcal antigenaemia.

13.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 205.

Identification of opportunistic infections: Skin and oral conditions

HIV infection increases the prevalence and severity of skin and oral diseases, especially when the person's **CD4 count declines below 200 cells/µL**. As a result, skin and oral conditions affect up to 90% of adults and children with HIV in resource-limited settings.[14]

Certain systemic diseases, such as Kaposi sarcoma, may initially be noted on the skin and may require urgent ART to reduce mortality. Others, while not always a major cause of mortality, can be a source of severe morbidity through, for example, itching that provokes scratching, secondary infections, disfigurement, sleep disturbance and psychological stress. In the case of candidiasis, it can cause pain on swallowing, limiting a person's ability to take ARV drugs.[14]

14.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 214/215.

Vaccination Scheme: Measles

Vaccines usually have better safety and efficacy among people with HIV who are receiving ART and those without significant immunosuppression, **notably when the CD4 count is above 200 cells/µL**.[14] People with more severe immunosuppression may be at higher risk of complications from some live attenuated vaccines.[14]

Measles:
Vaccination should be routinely administered to potentially susceptible, asymptomatic children and adults living with HIV and should be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to WHO definitions **(CD4 cell counts <50 cells/µL).**[15]

14.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 214/215.

15.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, page 16-17.

Vaccination Scheme: Yellow Fever

Yellow fever:
Yellow fever vaccine may be offered to asymptomatic people living with HIV with **CD4 cell counts ≥200 cells/µL**; it is therefore contra-indicated in people with advanced HIV disease until they achieve a CD4 cell count ≥200 cells/µL. Although the data on the safety and immunogenicity of yellow fever vaccine when used among children living with HIV are limited, yellow fever vaccine may be administered to all clinically well children. HIV testing is not a prerequisite for vaccination.[15]

15.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, page 16-17.

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Adherence Support Interventions

The 2016 WHO Guidelines strongly recommend to provide adherence support interventions to people on ART.[16]

The following interventions have demonstrated benefit in improving adherence and viral suppression:[16]

- Peer counsellors
- Mobile phone text messages
- Reminder devices
- Cognitive-behavioural therapy
- Behavioural skills training/medication adherence training
- Fixed-dose combinations and once-daily regimens

16.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page xlii

Effective laboratory and diagnostic services

Effective laboratory and diagnostic services require sound leadership and governance to enable the following activities:[17]

- Strengthening and expanding laboratory and diagnostic services;
- Supporting a dedicated specimen referral system;
- **Appropriate availability of CD4 count testing;**
- Increased access to HIV viral load testing for all people on ART, for monitoring purposes;
- Supporting the expansion of diagnostic services to include testing at the point of care;
- Training and certifying health-care workers who perform testing;
- Ensuring high-quality diagnostics and plans for implementing these, including quality assurance (QA); and
- Ensuring appropriate deployment of diagnostic technologies to increase their efficient and optimal use.

17.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 295-297

Effective laboratory and diagnostic services

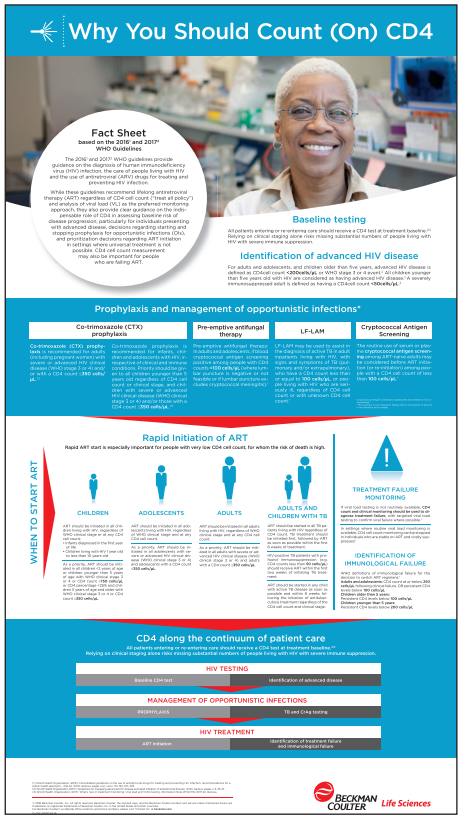
Even in settings with full access to viral load testing, **CD4 cell count testing capability will continue to be needed as part of HIV programmes for baseline risk and other clinical assessments**. Depending on the context, as the transition to viral load monitoring from CD4 count testing for initiation and monitoring progresses, programmes may wish to consider centralizing the continued use of CD4 count testing.[17]

17.) World Health Organization (2016): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed., page 295-297

CD4 Decision Levels

A summary of the Continuum of Care is available on an educational wall chart for your lab.

Educate your lab and download your Continuum of Care poster from:
http://www.globalcause.co.uk/infectious-diseases/why-more-of-us-should-be-counting-on-the-cd4-test



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