

CD4 monitoring needs to be improved to enhance quality of care in the ART programme



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Policy Brief Prepared by Melanie Bisnauth.

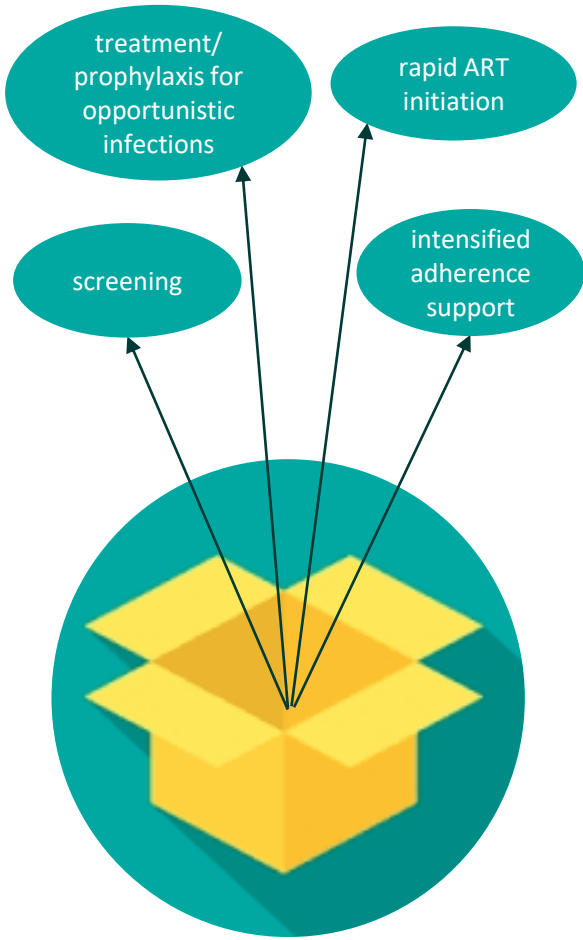
Background

Adult patients are considered to have **advanced HIV disease** if their CD4 count is below 200 cells/mm³. These patients are at risk of opportunistic infections and are more likely to die.

Advanced clinical care (ACC) should be provided to patients with advanced HIV disease. According to the [World Health Organization](#), ACC is a package of screening, treatment and/or prophylaxis for opportunistic infections, rapid initiation of antiretroviral therapy (ART) and intensified adherence support (1). This encompasses screening for cryptococcal antigen (CrAg) in patients with CD4 counts below 100 to enable early diagnosis and treatment of cryptococcal meningitis, as well as diagnosis of tuberculosis (TB) in symptomatic patients. Interventions to protect against infections include cotrimoxazole prophylaxis (CPT) for patients with CD4 below 200 and TB preventive therapy (TPT).

CD4 testing to identify patients with advanced HIV disease should be performed for everyone before starting ART (baseline CD4 testing) and 12 months after ART initiation. CD4 testing should also be repeated 6-monthly in patients with virological failure, as these patients may require ACC interventions if their CD4 count falls below 200 cells/mm³ while receiving ART.

Some patients who are virally suppressed on ART may still have low CD4 counts. These patients are known as **immunological non-responders** because ART does not improve their immune function even though it does suppress the HIV virus. It is important to repeat CD4 testing after ART initiation so that these patients can be identified to receive appropriate ACC care and clinical management.



Advanced Clinical Care

The Objective: Why did we want to look at this?

CD4 counts are a critical marker of immune function and an important tool to guide clinical care.

This analysis describes CD4 testing at baseline and subsequent to ART initiation in order to identify possible areas for intervention to improve implementation of CD4 monitoring and subsequent patient management. It is essential that CD4 results are reviewed and appropriate action taken in order to improve patient outcomes.

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What was our approach?

We analysed routine TIER.Net data exported in February 2020 for the following 5 districts: Johannesburg, Sedibeng, Capricorn, Mopani and Cape Town. The Cape Town dataset only included 15% of facilities in the district, as the remaining facilities do not use TIER.Net.

TIER.Net records were included in the analysis for HIV-infected adults who were 15-80 years of age and who had initiated ART from 2004 onwards. Records with data quality concerns were excluded from the analysis.

We investigated trends in baseline CD4 counts and described CD4 testing subsequent to ART start. Although CD4 monitoring guidelines have changed over time, we assessed current guidelines regarding CD4 testing after ART start. We also described immunological non-responders, defined as patients who had been on ART for more than 4 years who had a suppressed viral load (VL) and a CD4 count ≤ 350 .

What did we find out?

Baseline CD4 Testing

Baseline CD4 testing in patients newly starting ART has decreased markedly in recent years across all districts (Figure 1). This is likely due to the implementation of Universal Test and Treat from September 2016, which specifies that CD4 test results are no longer needed to assess ART eligibility. In 2019, one-third to two-thirds of patients did not have a baseline CD4 test – patients starting ART with CD4 counts below 200 who should have received ACC would therefore have been missed.

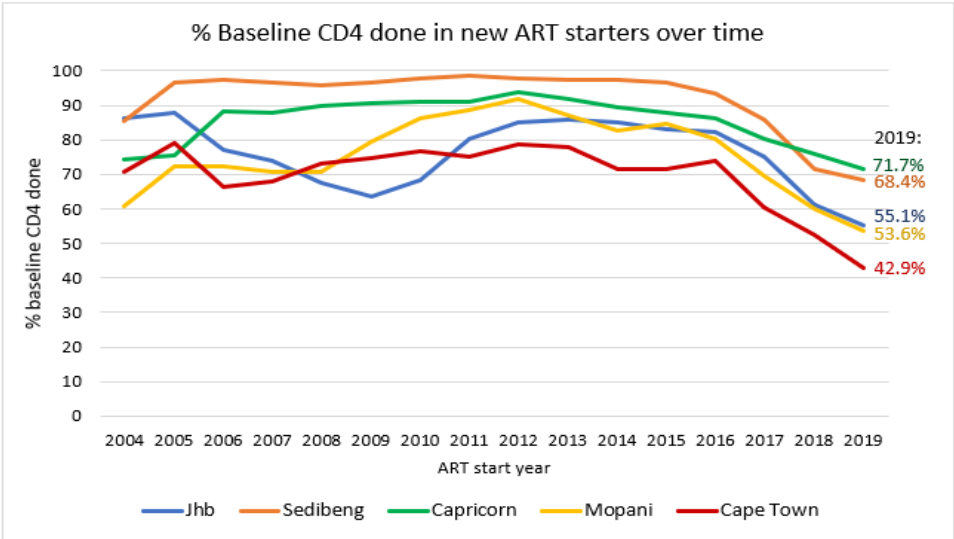


Figure 1: The proportion of new ART starters receiving baseline CD4 testing over time.

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What did we find out?

Baseline CD4 Testing

In 2019, a large number of patients were still initiating ART with CD4 counts ≤ 200 , ranging from 1 502 patients in Cape Town to 15 950 patients in Johannesburg (Figure 2a). This represent 30%-40% of patients with a baseline CD4 count on record (Figure 2b). Around 60% of patients initiated ART with CD4 ≤ 350 in 2019, ranging from 58.4% in Sedibeng to 62.1% in Mopani. Although this is an improvement compared to earlier years, this represents a large proportion of patients who are still starting ART with low CD4 counts i.e. people infected with HIV are not initiating treatment early enough, before the development of advanced disease.

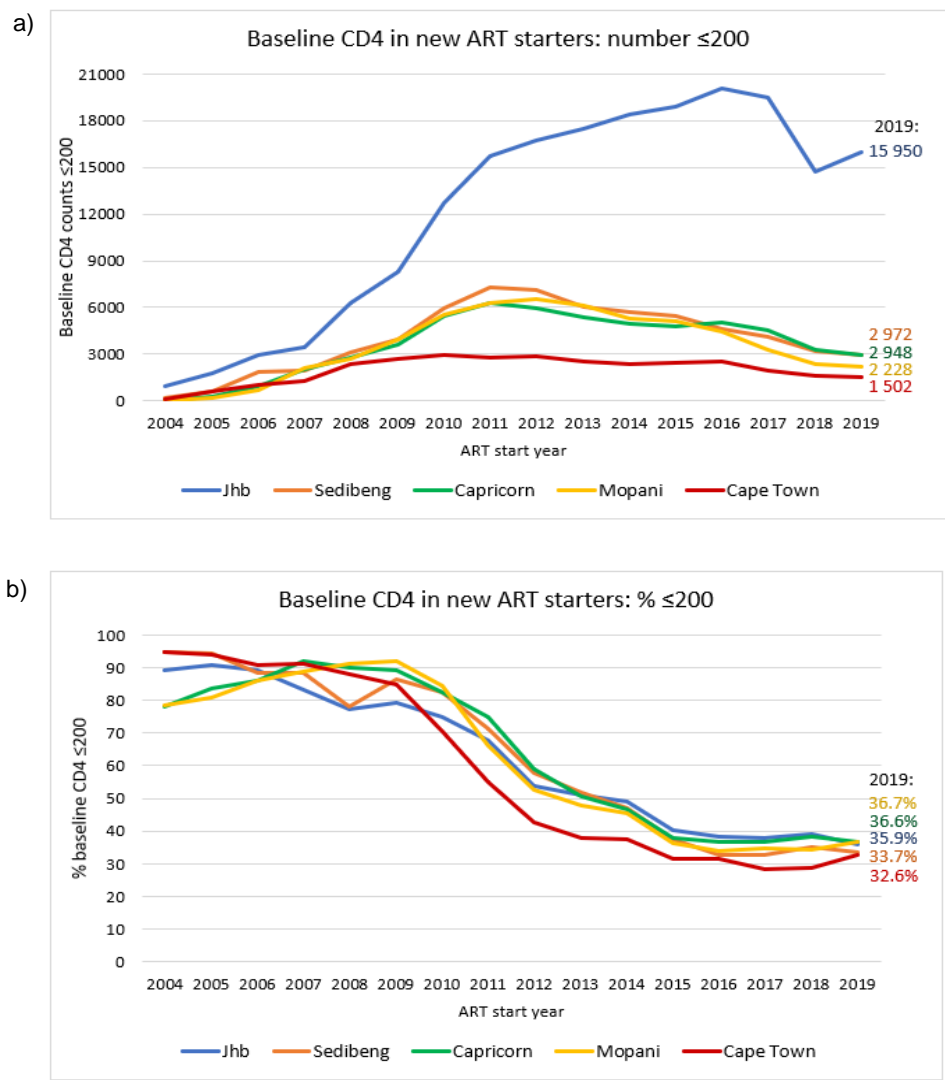


Figure 2. a) Absolute number and b) proportion of baseline CD4 counts in new ART starters with CD4 ≤ 200 cells/mm³.

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What did we find out?

Baseline CD4 Testing

CPT is very poorly implemented, with less than half of the patients with baseline CD4 ≤ 200 receiving CPT across all districts in 2019 (Table 1).

Table 1. Implementation of guidelines and CD4 outcomes by district.

	Johannesburg	Sedibeng	Capricorn	Mopani	Cape Town subset (15% of facilities in the district)
Number of patients included in the analysis	760 103	173 538	173 807	193 740	138 933
CPT at ART start					
Proportion of new ART starters with baseline CD4 ≤ 200 who received CPT in 2019	9.4%	27.6%	41.4%	26.1%	8.2%
CD4 testing subsequent to ART start					
Proportion of patients with a CD4 test subsequent to baseline on record	39.4%	49.8%	57.1%	34.2%	47.4%
Proportion of patients with a subsequent CD4 test on record whose count was ≤ 200	13.6%	13.5%	15.2%	18.1%	14.4%
Proportion of patients with a subsequent CD4 test on record whose count was ≤ 350	35.5%	33.2%	34.5%	40.6%	35.4%
Guideline regarding 12-month retesting: Proportion of patients on ART for 12-18 months with a subsequent CD4 test on record	21.3%	23.7%	37.9%	8.0%	10.2%
Guideline regarding testing after unsuppressed VL: Proportion of non-suppressed patients on ART for >12 months with a CD4 test on record any time subsequent to baseline	50.3%	63.3%	70.7%	49.8%	70.1%
Immunological non-responders (suppressed VL but CD4 ≤ 350)					
Proportion of immunological non-responders out of those with a suppressed VL	20.9%	21.1%	16.4%	26.7%	29.1%
Proportion of immunological non-responders whose CD4 count was ≤ 200	28.6%	32.7%	26.4%	40.9%	39.0%

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CD4 testing subsequent to ART start

Between 30%-60% of patients had a subsequent CD4 test on record (Table 1) i.e. 40%-70% of patients never had their CD4 repeated.

This means that patients who needed CPT or extra clinical management **would not have been identified**

Guidelines regarding CD4 testing are **poorly implemented**

Guidelines regarding CD4 testing subsequent to ART start –

- Routine re-testing 12 months after ART start in all patients: This guideline was very poorly implemented, with less than 40% of patients who had been on ART for 12-18 months having a repeat CD4 test on record.
- CD4 testing in patients with unsuppressed VL: Only 50%-70% of patients with an unsuppressed VL had a repeat CD4 test. This is likely an overestimation, as it is not limited to CD4 tests performed *after* the unsuppressed VL. Patients who are not virally suppressed are more likely to have a low CD4 count and would therefore need ACC – these patients would be missed if their CD4 tests are not done.

Overall, 13%-20% of patients who had a CD4 test repeated after starting ART had a CD4 count ≤ 200 and 30%-40% had a CD4 count ≤ 350 (Table 1).

If we initiate 100 000 patients on ART in a year, & for every 100 patients who start ART 13-20 have a most recent CD4 ≤ 200 , then **13 000-20 000 patients** would have a CD4 ≤ 200 and require ACC

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What did we find out?

CD4 testing subsequent to ART start

Characteristics of patients with low CD4 counts are presented in Figure 3. We need to target these patients, including males and older clients, so that appropriate clinical management and CD4 monitoring can be provided.

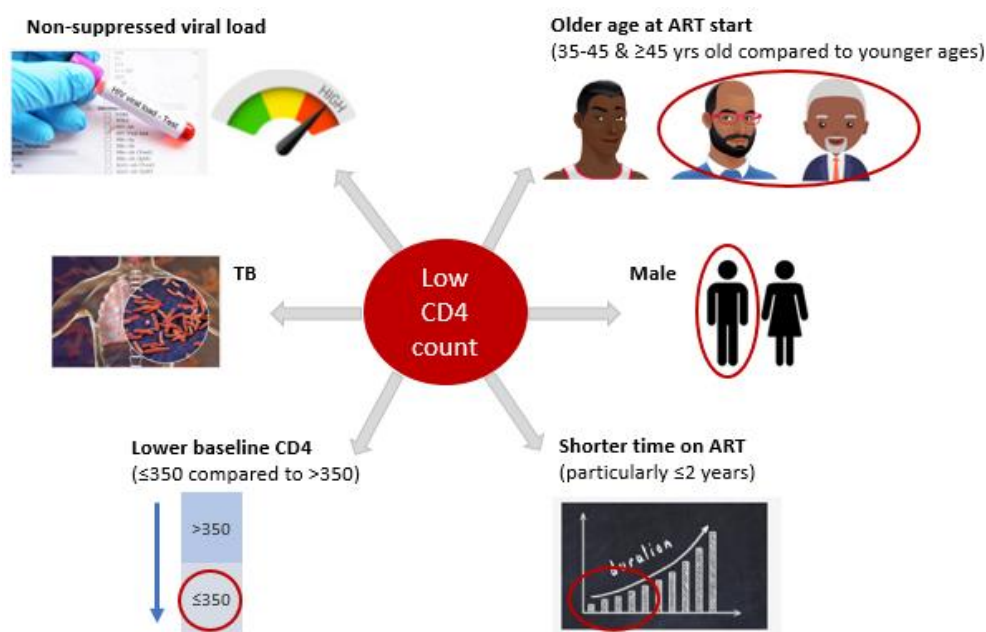


Figure 3. Characteristics of patients with low (≤ 200 & ≤ 350) CD4 counts subsequent to starting ART.

Immunological non-responders

Up to one-third of patients who were virally suppressed were immunological non-responders i.e. their CD4 counts remained ≤ 350 (Figure 4). Among these immunological non-responders, 25%-40% had a CD4 count ≤ 200 (Table 1). These patients were already well established on ART but still needed ACC interventions including CPT, continued CD4 monitoring and close clinical management.

Immunological non-response is more likely in patients starting ART with low CD4 counts. Since a noteworthy proportion of patients still start ART with low baseline CD4 (Figure 2), these patients are at risk of long-term immunological non-response and are therefore more likely to get sick and die. Immunological non-response is also more likely in patients on second-line ART, older patients, males and those with TB. These patients should be identified for CD4 monitoring and ACC interventions where needed.

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What did we find out?

Immunological non-responders

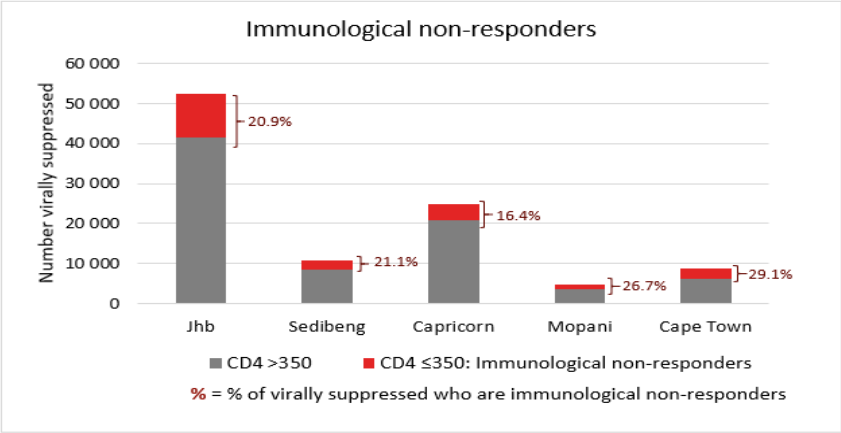


Figure 4. Proportion of immunological non-responders among virally suppressed patients on ART >4 years.

So what?



It is concerning that guidelines regarding CD4 monitoring are being poorly implemented across all districts. This has multiple implications for patient care and outcomes (Table 2).

Table 2. Implications of poor implementation of guidelines.

Guideline	Implications of poor implementation
Baseline CD4 testing	If baseline CD4 testing is not done, patients with low CD4 counts who need CPT, CrAg testing, TPT and ACC are not identified.
Early ART initiation	Patients who do not start ART early enough have low CD4 counts at baseline. These patients are more likely to have continued low CD4 counts and to be immunological non-responders, increasing their risk of illness and death.
Repeat CD4 testing	If repeat CD4 testing is not done, patients with low CD4 counts who need ACC are missed, increasing the risk of poor outcomes.

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What Can We Do?

There are several areas for intervention that can support improvements in the quality of patient care:

1

Healthcare workers need to be educated regarding the importance of CD4 testing as a tool to guide clinical care. The importance of implementing guidelines for CD4 testing at baseline, routinely 12 months after ART initiation and when patients have an unsuppressed VL needs to be emphasised.

2

A package of ACC interventions for patients with advanced disease needs to be standardised and linked to regular measurements of CD4 counts. Patients with CD4 ≤ 200 need to be enrolled into ACC to prevent morbidity and mortality. Ongoing file audits should be conducted to assess whether this is being implemented

3

Men are at higher risk of low CD4 counts and immunological non-response than women, emphasising the need for male friendly and male focused comprehensive services.

4

South Africa's HIV population is aging and older age is associated with poorer immunological response. There is a need to focus on elderly patients, including performing CD4 monitoring to identify those who need ACC.

5

TB is also associated with lower CD4 counts and poor immunological response. Efforts to identify and treat TB are essential.

6

We need to continue to engage with communities to emphasise the importance of starting ART early through increased uptake of different HIV testing modalities and improved linkage to care.

References

1. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization; 2017.