

I AM MORE THAN...



...MY HIV+ STATUS

I am more than an infection risk

I am more than a medical statistic

I am more than a number

I AM MORE THAN...



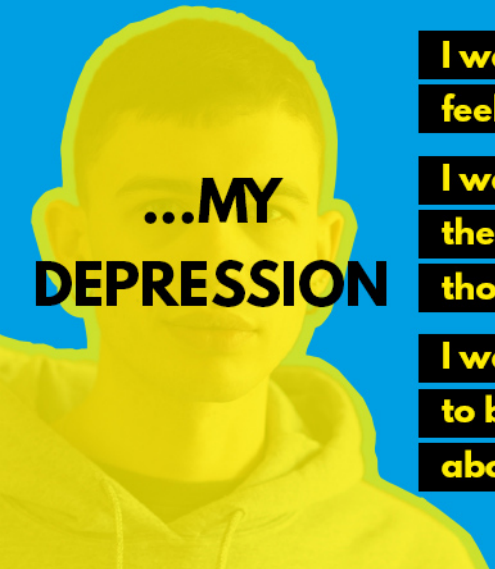
...MY LIFESTYLE

I am free spirited

I am energetic

I am present

I AM MORE THAN...



...MY DEPRESSION

I want to overcome feeling like this

I want to escape these negative thoughts

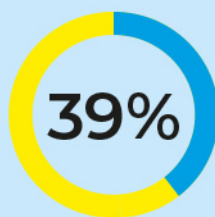
I want to be able to be positive about my future



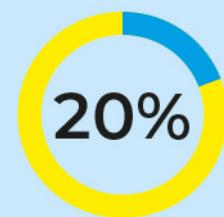
NOW THAT YOU KNOW ME WHAT NEXT?

Fictional patient

Psychological difficulties can result from an HIV diagnosis and the challenges of living with HIV¹



of PLHIV are reported to suffer from depression²




PLHIV experience suicidal feelings due to their status – particularly in those more-recently diagnosed³

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 2. Tran BX *et al.* Int J Environ Res Public Health 2019;16: 1772.
 3. British Psychological Society Stigma Survey UK, 2015.

ORIGINAL RESEARCH

Utility of CD4 count measurement in the era of universal antiretroviral therapy: an analysis of routine laboratory data in Botswana

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Objectives

National guidelines in Botswana recommend baseline CD4 count measurement and both CD4 and HIV viral load (VL) monitoring post-antiretroviral therapy (ART) initiation. We evaluated the utility of CD4 count measurement in Botswana in the era of universal ART.

Methods

CD4 and VL data were analysed for HIV-infected adults undergoing CD4 count measurement in 2015–2017 at the Botswana Harvard HIV-Reference Laboratory. We determined (1) the proportion of individuals with advanced HIV disease (CD4 count < 200 cells/ μ L) at initial CD4 assessment, (2) the proportion with an initial CD4 count \geq 200 cells/ μ L experiencing a subsequent decline in CD4 count to < 200 cells/ μ L, and (3) the proportion of these immunologically failing individuals who had virological failure. Logistic regression modelling examined factors associated with advanced HIV disease. CD4 count trajectories were assessed using locally weighted scatterplot smoothing (LOWESS) regression.

Results

Twenty-five per cent (3571/14 423) of individuals with an initial CD4 assessment during the study period had advanced HIV disease at baseline. Older age \geq 35 years; adjusted odds ratio (aOR) 1.9; 95% confidence interval (CI) 1.8–2.1] and male sex were associated with advanced HIV disease. Fifty per cent (7163/14 423) of individuals had at least two CD4 counts during the study period. Of those with an initial CD4 count \geq 200 cells/ μ L, 4% (180/5061) experienced a decline in CD4 count to < 200 cells/ μ L; the majority of CD4 count declines were in virologically suppressed individuals and transient.

Conclusions

One-quarter of HIV-positive individuals in Botswana still present with advanced HIV disease, highlighting the importance of baseline CD4 count measurement to identify this at-risk population. Few with a baseline CD4 count \geq 200 cells/ μ L experienced a drop below 200 cells/ μ L, suggesting limited utility for ongoing CD4 monitoring.

Keywords: HIV, AIDS, Botswana, laboratory monitoring

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Introduction

The role of CD4 T-cell count measurement in HIV care in the era of universal antiretroviral therapy (ART) is unclear [1,2]. Prior to universal ART, CD4 count measurement played a key role in determining eligibility for ART and was used to monitor patients' progress on ART [3],

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particularly in the absence of accessible HIV viral load (VL) measurement. In 2015, the World Health Organization recommended universal ART for all HIV-positive persons regardless of CD4 count on the basis of strong evidence for improved clinical outcomes and prevention of HIV transmission [4–7]. This removed much of the previous rationale for baseline CD4 count measurement as a prerequisite for ART initiation in most HIV-positive individuals [1,2]. Furthermore, widespread adoption of VL monitoring in HIV treatment programmes in many low- and middle-income countries (LMICs) has potentially removed the need for ongoing CD4 monitoring following ART initiation [1,2,4]. For these reasons, the need for CD4 count measurement in LMIC HIV treatment programmes has now been questioned [8–10]; some programmes and funders are withdrawing support for ongoing CD4 count measurement [11], and data show marked declines in CD4 measurement in LMICs following the introduction of universal ART [12,13].

However, CD4 count is a strong predictor of mortality in HIV-positive individuals [14,15], and baseline (i.e. pre-ART) CD4 count measurement remains the best way to determine the need for screening and prophylactic interventions against common opportunistic infections in those with advanced HIV disease, including cotrimoxazole chemoprophylaxis and cryptococcal antigen screening [16,17]. It also enables identification of individuals at high risk of opportunistic infections, HIV-related malignancies, and immune reconstitution inflammatory syndrome (IRIS) following ART initiation and needing close clinical monitoring. Additionally, many LMICs still have limited access to more expensive VL measurement and rely on CD4 monitoring after ART initiation to identify individuals failing ART [18,19]. Scaling back or removing CD4 measurement capacity in LMIC ART programmes may thus adversely impact clinicians' ability to identify individuals presenting to care with advanced HIV disease or those developing low CD4 counts following ART initiation, and hinder efforts to reduce the substantial morbidity and mortality in this patient group [13,16,20,21].

Botswana, a middle-income country in southern Africa with an estimated 310 000 people receiving ART through a national treatment programme [22], introduced universal ART in July 2016 [23]. Current national guidelines recommend baseline CD4 count measurement and both CD4 and VL monitoring for patients on ART [23]. Laboratory monitoring is widely accessible to HIV-positive patients in most parts of the country, with > 95% of patients on ART receiving VL measurement [24]. We performed an analysis of routine programmatic data from Botswana to assess the continued utility of CD4 count measurement in HIV programmes in LMICs following the

introduction of universal ART and widespread VL measurement, both at baseline for identifying patients with advanced disease at presentation, and during treatment monitoring for identifying patients at risk of advanced disease and virological failure.

Methods

Between January 2015 and December 2017, we collected anonymized data for all CD4 and VL measurements performed at the Botswana-Harvard HIV Reference Laboratory (BHHRL). The BHHRL performs nearly all CD4 measurements for patients attending clinics offering HIV care and support in greater Gaborone, with a total catchment population of approximately 300 000. Data obtained for the analysis included all CD4 count and HIV VL results, measurement dates, age and sex, as well as unique laboratory identification numbers used to identify measurements performed before 2015 as well as repeat CD4 and VL measurements during the study period. As all laboratory data for an individual are populated under their unique patient identifier, deterministic matching could be used to extract prior CD4 and VL data. We restricted analysis to adults (≥ 16 years old) undergoing baseline CD4 count measurement during the study period. Data were exported directly from the laboratory information system into STATA 14 (StataCorp, College Station, TX) for cleaning and analysis.

Botswana national HIV guidelines recommend CD4 count measurement at baseline, at 3 months post ART initiation, at 6 months if the CD4 count is < 200 cells/ μ L, and then annually. HIV VL is measured at 3 months post ART, and then 6-monthly [23]. A patient's first CD4 count measurement within the study period was defined as "baseline" if they had no previous CD4 count measurement in the national HIV database dating back to 2004; these individuals were assumed to be ART-naïve and first-time presenters for care. A CD4 count drop was defined as a decline to < 200 cells/ μ L at any subsequent measurement during the analysis period. Virological failure was defined as an HIV-1 RNA measurement exceeding 400 HIV-1 RNA copies/mL. All patients who had a VL measurement were assumed to be on ART, as VL measurement is not performed prior to ART initiation in Botswana, and VL is only measured for treatment monitoring. Data on ART initiation dates and ART regimen were not available; however, programme data show a median time from baseline visit to ART initiation of 30 days prior to universal ART, declining to 1 day post universal ART [25].

Analyses were performed to address three primary objectives: (1) to quantify the proportion of patients presenting to ART clinics with baseline CD4 counts < 200 cells/ μ L and

explore factors associated with low baseline CD4 cell count; (2) to determine the proportion of patients presenting with CD4 counts ≥ 200 cells/ μL who experienced a drop in CD4 count to < 200 cells/ μL during follow-up and the proportion of these patients with falling CD4 counts who were not virologically suppressed; and (3) to examine CD4 trajectories over time according to baseline CD4 strata. Firstly, the distribution of baseline CD4 counts was assessed to determine the proportion of patients presenting with advanced disease (CD4 count < 200 cells/ μL). A logistic regression model was fitted to determine factors associated with advanced HIV disease, and the proportion of individuals presenting with advanced disease was analysed by 6-month time periods to evaluate temporal trends. Secondly, descriptive statistics were used to identify the proportion of patients with a first CD4 count ≥ 200 cells/ μL experiencing a drop in CD4 count to < 200 cells/ μL during follow-up and ascertain VL results in these individuals. This analysis was restricted to individuals who had had at least two CD4 counts (inclusive of the baseline CD4 count) during the study period. Thirdly, trends of CD4 count over time were displayed using locally weighted scatterplot smoothing (LOWESS) regression to estimate the mean CD4 value as a function of the number of days post baseline count, stratified by baseline CD4 count (< 100 , 100 – < 200 , 200 – < 350 and ≥ 350 cells/ μL). As our data collection period was relatively short and the data set did not include multiple sequential CD4 counts for a large number of individuals, we did not model CD4 trajectory growth curve models. The nonparametric LOWESS models provide a flexible approach to representing data making few assumptions about the underlying data distribution; however, they have the disadvantage that they do not produce a regression function easily represented using a mathematical formula. The cumulative probability of achieving a CD4 count of ≥ 200 cells/ μL at 6, 12 and 18 months after baseline measurement was calculated in individuals with baseline CD4 counts < 200 cells/ μL using a Kaplan–Meier “failure” function, with “failure” defined as having a CD4 count ≥ 200 cells/ μL . All individuals were censored at the end of the study data collection period.

The study was conducted in partnership with the Botswana National Health Laboratory and received ethical approval from the Botswana Ministry of Health and Wellness Health Research and Development Committee (HRDC), the University of Botswana Biomedical Institutional Review Board, and the London School of Hygiene and Tropical Medicine Research Ethics Committee. No identifying data were used, and patient confidentiality was maintained during the analysis. Individual patient consent was not sought as the analysis was conducted using de-identified retrospective data.

Results

Between January 2015 and December 2017, the BHHRL performed 199 157 CD4 count measurements in 62 666 individual patients, 60 899 of whom were ≥ 16 years old; 23.7% (14 423/60 899) of these had no record of previous CD4 cell count measurements before 2015 and were included in our analysis. Among included participants, 64% (9159/14 423) were female, the median age was 34 years [interquartile range (IQR) 28–42 years], and the median baseline CD4 count was 372 cells/ μL (IQR 201–552 cells/ μL). The median duration of “follow-up” (i.e. time from baseline CD4 count measurement to the end of the study period) was 22 months (IQR 14–29 months). Thirty-one per cent of participants (4482/14 423) had three or more CD4 measurements during the 3-year study period, 19% (2681/14 423) had two measurements, and 50% (7260/14 423) had only one CD4 count result. Seventy-nine per cent (11 454/14 423) of participants had at least one HIV VL measurement confirming initiation on ART during follow-up (Table 1).

Advanced HIV disease at baseline

Twenty-five per cent (95% CI 24–26%) of patients had advanced HIV disease (CD4 count < 200 cells/ μL) at baseline; 12% (1774/14 423) with a baseline CD4 count < 100 cells/ μL and 13% (1797/14 423) with a baseline CD4 count of 100 – < 200 cells/ μL (Figure 1). Male sex and older age were associated with increased risk of baseline advanced HIV disease (Table 2). Thirty-five per cent

Table 1 Baseline characteristics of study participants and baseline CD4 count results

Variable	Result (overall $n = 14\ 423$)
Baseline characteristics	
Female sex [% (n)]	64 (9159)
Age (years) [median (IQR)]	34 (28–42)
Baseline CD4 count (cells/ μL) [median (IQR)]	372 (201–552)
Number of CD4 counts [% (n)]	
1	50 (7260)
2	19 (2681)
3	13 (1804)
4	9 (1345)
≥ 5	9 (1333)
Viral load measurement performed [% (n)]	79 (11 454)
Distribution of baseline CD4 counts [% (n)]	
0–99 cells/ μL	12 (1774)
100–199 cells/ μL	13 (1797)
200–349 cells/ μL	22 (3132)
≥ 350 cells/ μL	54 (7720)

IQR, interquartile range; n , number.

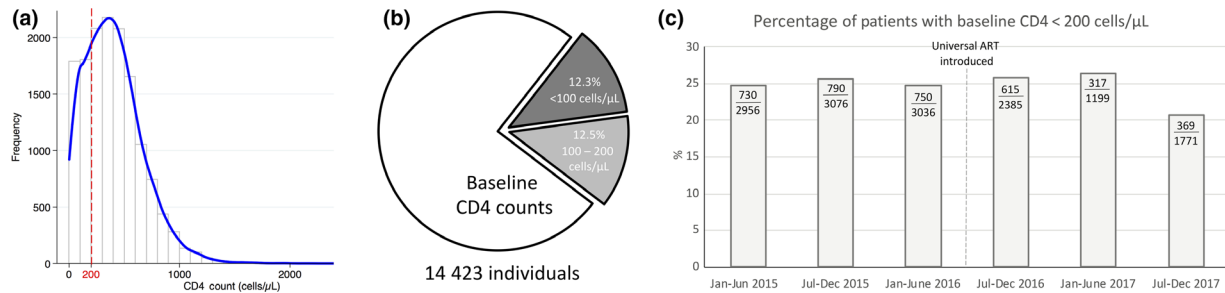


Fig. 1 Distribution of baseline CD4 counts in 14 423 individuals with an initial CD4 measurement in Gaborone, Botswana, 2015–2017. (a) A frequency polygon of all CD4 counts, with a dotted line indicating 200 cells/ μL . (b) A pie chart illustrating the percentage of baseline CD4 counts < 100 cells/ μL and 100–199 cells/ μL . (c) The proportion of individuals with a baseline CD4 count by 6-month calendar period. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2 Baseline associations with advanced HIV disease (CD4 count < 200 cells/ μL)

Variable	Category	CD4 count < 200 cells/ μL [% (n)]	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Sex	Female	19 (1733)	Base	Base
	Male	35 (1836)	2.3 (2.1–2.5)	2.1 (1.9–2.3)
Age	< 35 years	18 (1423)	Base	Base
	\geq 35 years	32 (2148)	2.1 (2.0–2.3)	1.9 (1.8–2.1)
Time period [†]	Pre universal ART	25 (2270)	Base	Base
	Post universal ART	24 (1301)	1.0 (0.9–1.0)	0.9 (0.9–1.0)

ART, antiretroviral therapy; CI, confidence interval; IQR, interquartile range; *n*, number.

*The adjusted model included age, sex and time period. When age was further broken down into those aged < 25, 25–34, 35–44 and \geq 45 years, the proportions with advanced HIV disease were 12.3% (291/2373), 20.9% (1132/5422), 33.1% (1346/4070) and 32.1% (777/2424), respectively. Adjusted odds of advanced HIV disease relative to the < 25 year age group were 1.7 (95% CI 1.5–2.0) in those aged 25–34 years, 3.0 (95% CI 2.6–3.4) in those aged 35–44 years, and 2.8 (95% CI 2.4–3.2) in those aged \geq 45 years.

[†]Split at end of June 2016 when universal ART was introduced into the Botswana National HIV Guidelines.

(1836/5264) of men had a baseline CD4 count < 200 cells/ μL compared to 19% (1733/9159) of women [odds ratio (OR) 2.1; 95% CI 1.9–2.3; $P < 0.001$ adjusted for age and calendar year]. Thirty-two per cent (2148/6629) of individuals \geq 35 years of age had a baseline CD4 count < 200 cells/ μL compared to 18% (1423/6371) of those < 35 years old (OR 1.9; 95% CI 1.8–2.1; $P < 0.001$ adjusted for sex and calendar year). The proportion of individuals presenting with advanced HIV disease broken down by 6-month period is shown in Figure 1. Between January 2015 and June 2017, the proportion remained stable at 25–26%, with a slight reduction to 21% (369/1771) in the 6-month period from July to December 2017 (χ^2 test for trend $P = 0.045$).

The utility of CD4 count monitoring to identify individuals with treatment failure

Seven thousand one hundred and sixty-three patients (50%) had at least two CD4 count measurements during the study period, 95% (6813/7163) of whom also had VL

results confirming ART initiation. Seventy-one per cent (5061/7163) had a baseline CD4 cell count \geq 200 cells/ μL . Of these, 4% (180/5061) had a subsequent drop in CD4 count to < 200 cells/ μL during the study period, occurring at a median of 236 days (IQR 57–489 days) after baseline CD4 count assessment. Men were at increased risk of CD4 decline; 6% (85/1507) of men and 3% (95/3554) of women had a drop in CD4 count to < 200 cells/ μL (OR 2.2; 95% CI 1.6–2.8; $P < 0.001$). The median baseline CD4 count in those experiencing a subsequent drop in CD4 count to < 200 cells/ μL was 262 cells/ μL (IQR 224–360 cells/ μL) (Figure 2). Restricting the analysis to those who had a repeat CD4 count measurement performed at 6 months after baseline or at 1 year after baseline yielded similar results. At the 6-month timepoint, 3% of men (40/1505) and 2% of women (58/3554) undergoing measurements had a drop to < 200 cells/ μL (OR 1.6; 95% CI 1.1–2.5); at the 1-year timepoint, 4% of men (28/727) and 1% of women (20/1743) undergoing measurements had a drop to < 200 cells/ μL (OR 3.5; 95% CI 1.9–6.2).

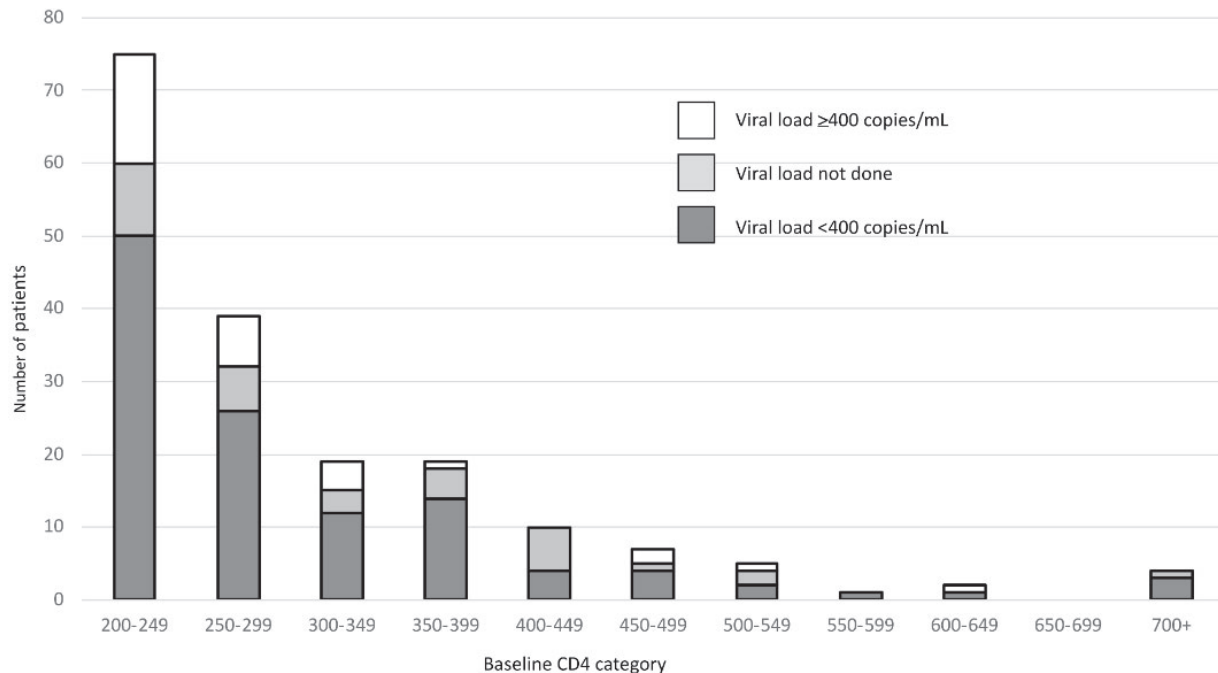


Fig. 2 Baseline CD4 count category and viral load status at the time of CD4 decline, in the 180 patients who experienced a drop in CD4 count to < 200 cells/ μ L. All individuals with a viral load result were assumed to have initiated antiretroviral therapy (ART). Data regarding ART adherence were not available; it was not possible to determine whether individuals without viral load measurement had initiated ART. The majority of individuals experiencing a decline in CD4 count to < 200 cells/ μ L during routine CD4 count monitoring had baseline CD4 counts of 200–249 or 250–299 cells/ μ L. Only 31 individuals identified with a decline in CD4 count to < 200 cells/ μ L had a detectable viral load at the time of measurement.

Ninety-one per cent (164/180) of those who had a drop in CD4 count to < 200 cells/ μ L had at least one VL measurement over the study period indicating that they had initiated ART; 82% (148/180) had the VL result within a 6-month period following the decline in CD4 count, with most VL measurements performed within several days of the CD4 measurement (median interval between the CD4 drop and VL measurement 4 days; IQR 2–9 days). Of those who had a VL result, 79% (117/148) were virologically suppressed (VL < 400 copies/mL). The majority of CD4 declines below 200 cells/ μ L in these virologically suppressed individuals were transient; 62% (73/117) had a subsequent CD4 count during the study period, 74% (54/73) of whom had a CD4 recovery to \geq 200 cells/ μ L.

CD4 count trajectories over time

CD4 trajectories following baseline counts were modelled using a LOWESS regression model stratified by baseline CD4 count (Figure 3). Overall, increases in CD4 counts over time were seen within all CD4 strata. In an analysis restricted to individuals with at least two CD4 counts during the study period and documented VL (i.e. those

known to have started ART), in those with a baseline CD4 count of < 100 cells/ μ L the probability of having a CD4 count \geq 200 cells/ μ L was 16% (95% CI 14–19%) within 6 months, 34% (95% CI 32–38%) within 1 year, and 49% (95% CI 46–52%) within 18 months. In those with a baseline CD4 count of 100–199 cells/ μ L, the probability of having a CD4 count \geq 200 cells/ μ L was 45% (95% CI 42–48%) within 6 months, 70% (95% CI 67–73%) within 1 year, and 79% (95% CI 76–81) within 18 months.

Discussion

Analysis of programmatic data for almost 15 000 patients undergoing baseline CD4 assessment in an urban setting in Botswana showed that a substantial proportion of HIV-positive individuals still present to care with advanced HIV disease despite a well-developed ART programme with high population ART coverage [24]. One-quarter of patients presented with a CD4 count < 200 cells/ μ L between 2015 and 2017, and this proportion did not substantially decline following the rollout of universal ART in mid-2016. These findings highlight the ongoing need for baseline CD4 measurement to identify the

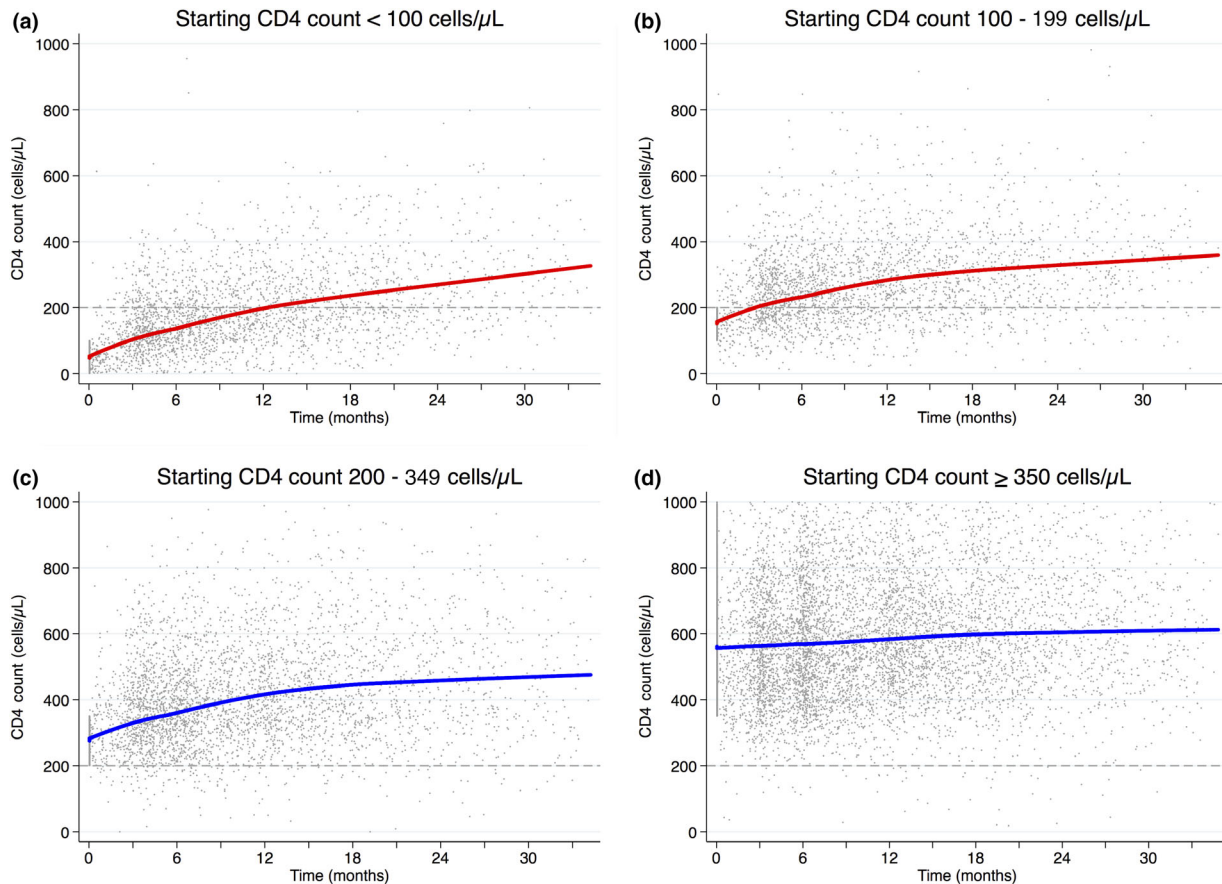


Fig. 3 CD4 cell count trajectories stratified by baseline CD4 category. Trends in CD4 counts over time were modelled using locally weighted scatterplot smoothing (LOWESS) regression to estimate the mean CD4 value as a function of the number of days post baseline count, stratified by baseline CD4 count. [Colour figure can be viewed at wileyonlinelibrary.com]

large number of HIV-positive individuals who continue to present with advanced HIV disease, in order to provide differentiated medical care for this population [16], guide prophylaxis against opportunistic infections, and reduce early mortality [26–29]. Our findings also emphasize the importance of maintaining CD4 measurement capacity and infrastructure if donor funding for CD4 measurement is reduced as global efforts prioritize scale-up of VL monitoring in LMICs [13,30,31].

A higher proportion of men than women presented to care with advanced disease. This has been shown in other HIV-infected cohorts in sub-Saharan Africa [32,33], and is probably attributable to comparatively poor health-seeking behavior by men, and more frequent opportunities for HIV testing and linkage to care for women during antenatal visits or when accessing family planning services [34]. Older age (defined in our study as ≥ 35 years) was also associated with advanced disease, as has been shown in previous cohorts [33]. Our data are consistent

with regional data from countries with lower population ART coverage showing that up to 33% of individuals still present for ART with CD4 counts < 200 cells/ μL [33,35], and indicate that ongoing efforts are still needed to encourage early testing, linkage and retention to care, especially in working-age men in urban and semi-urban areas, in order to improve outcomes in this key population.

In contrast to the evidence demonstrating the continued utility of baseline CD4 measurement, our data did not provide a strong justification for ongoing CD4 monitoring in individuals initiating ART with CD4 counts ≥ 200 cells/ μL in the context of routine VL monitoring. Only a small proportion (3.6%) of patients with a baseline CD4 count ≥ 200 cells/ μL experienced a drop to < 200 cells/ μL over follow-up, nearly three-quarters of whom had an initial CD4 count < 350 cells/ μL . Furthermore, we showed that the majority of individuals experiencing a decline in CD4 count had a suppressed VL, and the CD4

count declines were usually transient, with subsequent CD4 measurements showing that they were not on a downward trajectory, and therefore of little clinical relevance.

These findings suggest that routine CD4 monitoring is of very limited benefit in individuals entering ART treatment programmes with baseline CD4 counts ≥ 200 cells/ μL in LMIC settings with routine VL measurement, as is current practice in Botswana, and add further to the published data from both LMIC and high-income settings showing limited utility for routine CD4 monitoring [36–39]. A 2015 systematic review including 12 cohorts of individuals initiating ART [with 13 775 of 20 297 (68%) from African sites] reported that between 0 and 2.6% of virologically suppressed individuals experienced an unexplained drop in CD4 count to < 200 cells/ μL , with a pooled estimate of 0.4% [39]. Previously published data are also consistent with our finding that drops in CD4 count in virologically suppressed individuals are often transient [9,40,41]; most occur in individuals with starting CD4 counts just above 200 cells/ μL [42], and some may simply reflect variation in intra-laboratory measurements [41]. Further, it has been shown elsewhere that such CD4 declines are rarely unexplainable, usually occurring in patients with intercurrent illnesses [43].

It is thus likely that routine post-ART CD4 monitoring could be safely discontinued in the majority of individuals in HIV treatment programmes in LMIC settings such as Botswana when VL measurement is readily available, with CD4 measurement only performed in cases where there is a clinical indication. Observational studies from high-income settings suggest that reducing the frequency of CD4 count monitoring to annually is safe in individuals with a baseline CD4 count ≥ 200 cells/ μL [44], and prospective evidence from the AntiRetroviral Therapy with TMC114 ExaMined In naïve Subjects: a randomized, open-label phase-III trial (ARTEMIS) study did not show a benefit of continued CD4 measurement beyond 48 weeks in patients who achieved viral suppression and CD4 counts ≥ 200 cells/ μL [45]. Equivalent data from Africa are lacking; however, our findings along with those of other regional investigators [8,9,40] provide evidence that the vast majority of individuals starting ART with CD4 counts ≥ 200 cells/ μL in Africa and achieving viral suppression do not have significant or clinically relevant declines in CD4 counts, and VL monitoring alone is sufficient for monitoring treatment response. In addition to simplifying clinical care, the cost implications of reducing the frequency of CD4 measurement in our setting are considerable [10,46]; Botswana currently maintains approximately 15% of its entire population on lifelong ART, and each of these individuals should undergo at least one CD4 measurement a year according to current guidelines

[23]. Modelled data from South Africa estimate that stopping routine CD4 monitoring beyond the first year of ART reduced CD4 measurement costs by 51% and led to potential savings of ZAR 740 million (equivalent to approximately US\$70 million) [47].

As expected, CD4 counts increased over time in all baseline CD4 count strata [48,49]. The duration of CD4 count monitoring that is required in individuals initiating ART with advanced HIV disease depends on individual CD4 count trajectories, with most guidelines recommending 6-monthly monitoring until a CD4 count ≥ 200 cells/ μL is achieved [4]. In our study, a significant majority of the patients with a baseline CD4 cell count < 200 cells/ μL had attained a CD4 count ≥ 200 cells/ μL within 12 months on treatment, and we may have underestimated the proportion attaining CD4 counts of ≥ 200 cells/ μL given that not all individuals had repeat measurements at this timepoint, suggesting that a relatively short duration of CD4 monitoring is required in most cases.

Analyses of programmatic data such as ours have a number of limitations. We did not have any clinical data with which to further elucidate the reasons for a drop in CD4 counts in some of the patients. A small number of CD4 counts performed in the public sector laboratories may not have been captured in the central database if the electronic medical records (EMR) was not accessible because of network outages and manually reported results were not back-entered. We did not have ART data and had to make a number of assumptions based on CD4 and VL measurement results to determine likely ART status and timing. We were also unable to assess retention in care in individuals without laboratory measurements. Importantly, adherence data and details regarding treatment interruptions were lacking. Finally, analyses of laboratory-based data such as these can only report findings from those individuals engaging in care and undergoing laboratory measurement, precluding any overall assessments of programmatic outcomes. We may have underestimated the overall proportion of individuals with advanced HIV disease, as there are likely to be individuals with very low CD4 counts who either die prior to seeking care or do not survive long enough have CD4 measurement performed.

Conclusions

We report that a significant proportion of patients still present to care with advanced HIV disease in Botswana, a country with an established ART programme with excellent population level coverage. Our data highlight that baseline CD4 cell count measurement remains an

essential component of HIV care in the universal ART era and is critically important to identify individuals with low CD4 counts and enable differentiated care focused on reducing the high morbidity and mortality in this vulnerable patient group. However, for patients presenting with higher baseline CD4 counts, routine CD4 monitoring is of limited clinical utility, with very few patients on suppressive ART having a significant decline in CD4 counts. Reductions in CD4 monitoring in this patient population in LMICs, with CD4 monitoring restricted to unwell or virologically failing patients, would enable diversion of resources to scale up VL measurement capacity.

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Conflicts of interest: All authors declare no relevant conflicts of interest.

Authors' contributions

JNJ conceptualized the project with TBL and RH. BN and DR from the national ART programme and MM provided some input to the project and provided the data for analysis. KL, CM, TM, MT and FM under the leadership of MM and JN provided CD4 measurements at the Botswana Harvard HIV Reference Laboratory. TBL with input from RH and JNJ performed the statistical analysis. TBL, MWT and JNJ drafted the manuscript and finalized it for review by the co-authors. All authors read and contributed to the final manuscript.

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