HHS Public Access

Author manuscript

HIV Med. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

HIV Med. 2021 January ; 22(1): 1–10. doi:10.1111/hiv.12951.

Utility of CD4 Count Testing in the Era of Universal ART: An Analysis of Routine Laboratory Data in Botswana

Tshepo B. Leeme[1,2,*], **Madisa Mine**[3], **Kwana Lechiile**[1], **Fredah Mulenga**[3], **Mosepele Mosepele**[4], **Thongbotho Mphoyakgosi**[3], **Charles Muthoga**[1,5], **Julia Ngidi**[3], **Bornapate Nkomo**[6], **Dinah Ramaabya**[6], **Modiri Tau**[6], **Mark W. Tenforde**[5], **Richard Hayes**[7], **Joseph N. Jarvis**[1,2]

[1]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana

[2]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

[3]National Health Laboratory, Gaborone, Botswana

[4]Faculty of Medicine, University of Botswana, Gaborone, Botswana

[5]Botswana–UPenn Partnership, Gaborone, Botswana

[6]Ministry of Health and Wellness, Gaborone, Botswana

[7]Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

Abstract

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

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

Results—25% (3,571/14,423) of individuals with initial CD4 assessment during the study period had advanced HIV at baseline. Older age (≥35 years, adjusted odds ratio [aOR] 1.9, 95%

*Corresponding author: Dr Tshepo B Leeme, Botswana Harvard AIDS Institute Partnership, Private Bag BO320, Gaborone, Botswana. tbleeme@yahoo.com /tleeme@bhp.org.bw.

Authors' contributions

JNJ conceptualised the project with TBL and RH. BN and DR from the national ART programme and MM made some input on the project and provided the data for analysis. KL, CM, TM, MT and FM under the leadership of MM and JN provided CD4 testing 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 finalised it for review by the co-authors. All authors have read and contributed to the final manuscript.

confidence interval [CI]:1.8–2.1) and male sex were associated with advanced HIV. 50% (7,163/14,423) of individuals had ≥2 CD4 counts during the study period. Of those with an initial CD4 ≥200 cells/μL, 4% (180/5,061) experienced a decline in CD4 count to <200 cell/μL; 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 testing to identify this at-risk population. Few with a baseline CD4 ≥200 cells/μL experienced a drop below 200 cells/μL, suggesting limited utility for ongoing CD4 monitoring.

Keywords

HIV; AIDS; CD4; Botswana; laboratory monitoring

Introduction

The role of CD4 T-cell count (CD4) testing in HIV care in the era of universal antiretroviral therapy (ART) is unclear (1, 2). Prior to universal ART, CD4 testing played a key role in determining eligibility for antiretroviral therapy and was used to monitor patients' progress on ART (3), particularly in the absence of accessible HIV viral load (VL) testing. 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 testing as a prerequisite for ART initiation in most HIV-positive individuals (1, 2). Furthermore, widespread adoption of VL monitoring in HIV-treatment programs 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 testing in LMIC HIV-treatment programs has now been questioned (8–10); some programs and funders are withdrawing support for ongoing CD4 testing (11), and data show marked declines in CD4 testing 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 testing remains the best way to determine the need for screening and prophylactic interventions against common opportunistic infections in those with advanced HIV, 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 testing and rely on CD4 monitoring after ART initiation to identify individuals failing ART (18, 19). Scaling back or removing CD4 testing capacity in LMIC ART programs 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 program (22), introduced universal ART in July

2016 (23). Current national guidelines recommend baseline CD4 testing and both CD4 and viral load monitoring for patients on ART (23). Laboratory monitoring is widely accessible to HIV-positive patients in most parts of the country, with over 95% of patients on ART receiving viral load testing (24). We performed an analysis of routine programmatic data from Botswana to assess the continued utility of CD4 testing in HIV-programs in LMICs following the introduction of universal ART and widespread VL testing; both at baseline for identifying patients with advanced disease at presentation, and during treatment monitoring for identifying patients at risk for advanced disease and viral failure.

Methods

Between January 2015 and December 2017, we collected anonymized data on all CD4 and VL tests performed at the Botswana-Harvard HIV Reference Laboratory (BHHRL). The Botswana-Harvard HIV Reference Laboratory performs nearly all CD4 testing 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 and HIV VL test results, testing dates, age and sex, as well as unique laboratory identification numbers used to identify testing performed before 2015 as well as repeat CD4 and VL testing 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) undergoing baseline CD4 testing 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 testing at baseline, three months post-ART initiation, at six months if CD4 is <200 cells/μL, then annually. HIV VL is measured at three months post-ART, then 6-monthly (23). A patient's first CD4 cell 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 cell count drop was defined as a decline to <200 cells/μL at any subsequent measurement during the analysis period. Virological failure was defined as HIV-1 RNA measurement exceeding 400 copies/mL. All patients who had a VL measurement were assumed to be on ART, as VL testing is not performed prior to ART initiation in Botswana, and only measured for treatment monitoring. Data on ART initiation dates and ART regimen were not available; however, program 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/μL 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 experience 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

<200 cells/μL). A Logistic regression model was fitted to determine factors associated with advanced HIV, 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 ≥200 cells/mL experiencing a drop in CD4 cell count to <200 cells/μL during follow-up and ascertain viral load 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 cell 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 cells/μL, 100-<200 cells/μL, 200-<350 cells/μL, and ≥350 cells/μL). As our data collection period was relatively short and the dataset did not include multiple sequential CD4 counts on a large number of individuals we did not model CD4 trajectories growth curve models. The non-parametric LOWESS models provide a flexible approach to representing data making few assumptions about the underlying data distribution, however, have the disadvantage that they do not produce a regression function easily represented using a mathematical formula. The cumulative probability of reaching a CD4 count of >200 cells/μL at 6, months, 12 months, and 18 months after baseline testing 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’s 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 tests on 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% (9,159/14,423) were females, the median age was 34-years (IQR 28–42), and median baseline CD4 cell count was 372 cells/μL (IQR 201–552). Median duration of “follow-up” (i.e. time from baseline CD4 testing to end of the study period) was 22 months (IQR 14–29). Thirty-one percent of participants (4,482/14,423) had three or more CD4 tests during the 3-year study period, 19% (2,681/14,423) had two tests, and 50% (7,260/14,423) had only one CD4 cell count result. Seventy-nine percent (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 percent (95%CI: 24–26) of patients had advanced HIV-disease (CD4 <200 cells/μL) at baseline; 12% (1,774/14,423) with a baseline CD4 <100 cells/μL and 13% (1,797/14,423) with a baseline CD4 100-<200 cells/μL (Figure 1). Male sex and older age were associated with increased risk of baseline advanced HIV (Table 2). Thirty-five percent (1,836/5,264) of men had a baseline CD4 <200 cells/μL compared to 19% (1,733/9,159) of women (OR 2.1, 95% confidence interval [CI]:1.9–2.3, p<0.001 adjusted for age and calendar year). Thirty-two percent (2,148/6,629) of individuals ≥35-years of age had baseline CD4 <200 cells/μL compared to 18% (1,423/6,371) of those <35-years (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 six-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% (369/1,771) in the six-month period from July to December 2017 (chi-square 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 tests during the study period, 95% (6,813/7,163) of whom also had VL results confirming ART initiation. Seventy-one percent (5,061/7,163) had a baseline CD4 cell count ≥200 cells/μL. Of these, 4% (180/5,061) had a subsequent drop in CD4 to <200 cells/μL during the study period, occurring at a median of 236 days (IQR 57–489) after baseline CD4 count assessment. Men were at increased risk of CD4 decline; 6% (85/1,507) of men and 3% (95/3,554) of women had a drop in CD4 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 to below 200 cells/μL was 262 cells/μL (IQR 224–360) (Figure 2). Restricting analysis to those who had a repeat CD4 count testing performed at six months after baseline or at one year after baseline yielded similar results. At the six month time point 3% of men (40/1,505) tested and 2% of women (58/3,554) tested had a drop to below 200 cells/μL (OR 1.6, 95%CI 1.1–2.5); at the one year timepoint 4% of men (28/727) and 1% of women (20/1,743) tested had a drop to below 200 cells/μL (OR 3.5, 95%CI 1.9–6.2).

Ninety-one percent (164/180) of those who had a drop in CD4 to <200 cells/μL had at least one viral load measurement over the study period indicating that they had initiated ART; 82% (148/180) had the viral load test result within a 6-month period following decline in CD4 count, with most viral load tests performed within several days of CD4 testing (median interval between the CD4 drop and viral load testing 4 days [IQR 2–9 days]). Of those who had a VL result, 79% (117/148) were virally suppressed (VL <400 copies/mL). The majority of CD4 declines below 200 cells/μL in these virally 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 ≥200 cell/μL.

CD4 count trajectories over time

CD4 trajectories following baseline counts were modelled using a locally weighted scatterplot smoothing (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 viral load (i.e. those known to have started ART), in those with a baseline CD4 count of <100 cells/μL the probability of having a CD4 count ≥200 cells/μL within 6 months was 16% (95%CI 14–19%), 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/μL the probability of having a CD4 count ≥200 cells/μL 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 from 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 program with high population ART coverage (24). One-quarter of patients presented with a CD4 cell count <200 cells/μL between 2015–2017, 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 testing to identify the large number of HIV-positive individuals who continue to present with advanced HIV 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 emphasise the importance of maintaining CD4 testing capacity and infrastructure if donor funding for CD4 testing is reduced as global efforts prioritize scale-up of viral load 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 cohorts in SSA (32, 33), and is likely 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 and older) 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 cell counts below 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 testing, our data did not provide a strong justification for ongoing CD4 monitoring in individuals initiating ART with CD4 cell counts over 200 cells/μL in the context of routine VL monitoring. Only a small proportion (3.6%) of patients with a baseline CD4 cell 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 viral load, and the CD4 count declines were usually transient with subsequent CD4 tests showing that they were not on a downward trajectory, therefore of little clinical relevance.

These findings suggest that routine CD4 monitoring is of very limited benefit in individuals entering ART treatment programs with baseline CD4 cell counts over 200 cells/μL in LMIC settings with routine VL testing, 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 virally suppressed individuals experienced an unexplained drop in CD4 cell count to below 200 cells/μL, with a pooled estimate of 0.4% (39). Previously published data are also consistent with our finding that drops in CD4 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 programs in LMIC settings such as Botswana when VL testing is readily available, with CD4 testing only performed in cases where there is a clinical indication. Observational studies from high-income setting 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 ARTEMIS trial did not show a benefit of continued CD4 testing beyond 48 weeks in patients who achieved viral suppression and CD4 counts over 200 cell/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 above 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 frequency of CD4 testing in our setting are considerable (10, 46); Botswana currently maintains approximately 15% of its entire population on lifelong ART, each of whom should undergo at least one CD4 test 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 testing 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 ≥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 testing 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 to further understand 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 EMR was not accessible due to 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 test results to determine likely ART status and timing. We were also unable to assess retention in care in individuals without laboratory testing. Importantly, adherence data and details regarding treatment interruptions were lacking. Finally, analyses of laboratory-based data such as this can only report findings from those individuals engaging in care and undergoing laboratory testing, 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 testing performed.

Conclusion

We report that a significant proportion of patients still present to care with advanced HIV-disease in Botswana, a country with an established ART program with excellent population level coverage. Our data highlight that baseline CD4 cell count testing remains an essential component of HIV-care in the universal ART era and is critically important to identify individuals with low CD4 cell 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 cell 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, restricted to unwell or virologically failing patients, would enable diversion of resources to scale up viral load testing capacity.

Acknowledgements

TBL is funded through a Wellcome Trust / UK Medical Research Council / Department for International Development Joint Global Health Trials and European and Developing Countries Clinical Trials partnership co-funded grant (TRIA2015-1092; MR/P006922/1). JNJ has received support from the U.K. National Institute for Health Research using Official Development Assistance (ODA) funding through a Global Health Professorship (RP-2017-08-ST2-012). The views expressed are those of JNJ and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. RH receives funding from the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and also part of the EDCTP2 programme supported by the European Union. Grant Reference MR/K012126/1. Outside of this submitted work, MWT received support from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number F32AI140511. The content is solely the responsibility of MWT and does not necessarily represent the official views of the National Institutes of Health. All authors declare no relevant conflicts of interest.

References

1. Ford N, Meintjes G, Pozniak A, Bygrave H, Hill A, Peter T, et al. The future role of CD4 cell count for monitoring antiretroviral therapy. Lancet Infect Dis. 2015 2; 15(2):241–7. [PubMed: 25467647]
2. Ford N, Meintjes G, Vitoria M, Greene G, Chiller T. The evolving role of CD4 cell counts in HIV care. Curr Opin HIV AIDS. 2017 03; 12(2):123–8. [PubMed: 28059957]
3. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach: 2010 revision. World Health Organization, Geneva, 2010 Available at: https://www.who.int/hiv/pub/arv/adult2010/en/ Accessed 31 July 2019.

4. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach - Second edition. World Health Organization, Geneva, 2016 Available at: https://www.who.int/hiv/pub/arv/arv-2016/en/ Accessed 31 July 2019.
5. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 8; 373(9):795–807. [PubMed: 26192873]
6. Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, Ouassa T, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 8; 373(9):808–22. [PubMed: 26193126]
7. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 8 11; 365(6):493–505. [PubMed: 21767103]
8. Ford N, Stinson K, Davies MA, Cox V, Patten G, Cragg C, et al. Is it safe to drop CD4+ monitoring among virologically suppressed patients: a cohort evaluation from Khayelitsha, South Africa. AIDS. 2014 9; 28(14):2003–5. [PubMed: 25102088]
9. Reynolds SJ, Sempa JB, Kiragga AN, Newell K, Nakigozi G, Galiwango R, et al. Is CD4 monitoring needed among ugandan clients achieving a virologic and immunologic response to treatment? AIDS Patient Care STDS. 2014 11; 28(11):575–8. [PubMed: 25290988]
10. Hamers RL, Sawyer AW, Tuohy M, Stevens WS, Rinke de Wit TF, Hill AM, et al. Cost-effectiveness of laboratory monitoring for management of HIV treatment in sub-Saharan Africa: a model-based analysis. AIDS. 2012 8; 26(13):1663–72. [PubMed: 22695297]
11. PEPFAR. PEPFAR 2018 Country Operational Plan Guidance for Standard Process Countries. 2018 Available at: https://www.pepfar.gov/documents/organization/276459.pdf Accessed 31 July 2019.
12. Nasuuna E, Tenforde MW, Muganzi A, Katunguuka E, Jarvis JN, Manabe YC, et al. Reduction in Baseline CD4 count testing following HIV “Treat All” adoption in Uganda clinics. Clin Infect Dis. 2020; Epub ahead of print.
13. Rice B, Boulle A, Schwarcz S, Shroufi A, Rutherford G, Hargreaves J. The Continuing Value of CD4 Cell Count Monitoring for Differential HIV Care and Surveillance. JMIR Public Health Surveill. 2019 3; 5(1):e11136. [PubMed: 30892272]
14. Egger M, May M, Chêne G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002 7; 360(9327):119–29. [PubMed: 12126821]
15. Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O’Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. JAMA. 2001 11; 286(20):2568–77. [PubMed: 11722271]
16. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. World Health Organization, Geneva, 2017 Available at: https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/ Accessed 31 July 2019.
17. World Health Organization. Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children. World Health Organization, Geneva, 2018 Available at: https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/ Accessed 31 July 2019.
18. Zaniewski E, Ostinelli CHD, Maxwell N, et al. Trends in cd4 and viral load testing in southern africa: analysis of 6 countries. Conference on Retroviruses and Opportunistic Infections; March 4–7, 2019; Seattle, WA.
19. Lecher S, Williams J, Fonjungo PN, Kim AA, Ellenberger D, Zhang G, et al. Progress with Scale-Up of HIV Viral Load Monitoring - Seven Sub-Saharan African Countries, January 2015-June 2016. MMWR Morb Mortal Wkly Rep. 2016 12; 65(47):1332–5. [PubMed: 27906910]
20. Calmy A, Ford N, Meintjes G. The Persistent Challenge of Advanced HIV Disease and AIDS in the Era of Antiretroviral Therapy. Clin Infect Dis. 2018 3; 66(suppl_2):S103–SS5. [PubMed: 29514231]
21. Peeling RW, Ford N. Reprising the role of CD4 cell count in HIV programmes. Lancet HIV 2017 09; 4(9):e377–e8. [PubMed: 28579226]

22. UNAIDS. Botswana 2018 Country Factsheet. 2018 Available at: https://www.unaids.org/en/regionscountries/countries/botswana Accessed 31 July 2019.
23. Botswana Ministry of Health. Handbook of the Botswana 2016 Integrated HIV Clinical Care Guidelines. 2016 Available at: www.moh.gov.bw/Publications/Handbook_HIV_treatment_guidelines.pdf Accessed 31 July 2019.
24. Gaolathe T, Wirth KE, Holme MP, Makhema J, Moyo S, Chakalisa U, et al. Botswana's progress toward achieving the 2020 UNAIDS 90–90-90 antiretroviral therapy and virological suppression goals: a population-based survey. Lancet HIV. 2016 5; 3(5):e221–30. [PubMed: 27126489]
25. Lebelonyane R, Bachanas P, Block L, Ussery F, Abrams W, Roland M, Theu J, Kapanda M, Matambo S, Lockman S, Gaolathe T, Makhema J, Moore J, Jarvis JN. Rapid Antiretroviral therapy Initiation in the Botswana Combination Prevention Project. A quasi-experimental before-and-after study. Lancet HIV. 2020 IN PRESS.
26. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS. 2008 10; 22(15):1897–908. [PubMed: 18784453]
27. Gupta A, Nadkarni G, Yang WT, Chandrasekhar A, Gupte N, Bisson GP, et al. Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): a systematic review and meta-analysis. PLoS One. 2011; 6(12):e28691. [PubMed: 22220193]
28. Mfinanga S, Chanda D, Kivuyo SL, Guinness L, Bottomley C, Simms V, et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. Lancet. 2015 3 9.
29. Walker AS, Ford D, Gilks CF, Munderi P, Ssali F, Reid A, et al. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. Lancet. 2010 4; 375(9722):1278–86. [PubMed: 20347483]
30. Tenforde MW, Walker AS, Gibb DM, Manabe YC. Rapid antiretroviral therapy initiation in low- and middle-income countries: A resource-based approach. PLoS Med. 2019 01; 16(1):e1002723. [PubMed: 30645592]
31. Clinton Health Access Initiative. Breakthrough agreement will reduce costs and increase access to diagnostic technology for millions in low- and middle-income countries. Available at: https://clintonhealthaccess.org/breakthrough-agreement-diagnostic-testing/ Accessed 31 July.
32. Maman D, Ben-Farhat J, Chilima B, Masiku C, Salumu L, Ford N, et al. Factors associated with HIV status awareness and Linkage to Care following home based testing in rural Malawi. Trop Med Int Health. 2016 11; 21(11):1442–51. [PubMed: 27714902]
33. Carmona S, Bor J, Nattey C, Maughan-Brown B, Maskew M, Fox MP, et al. Persistent High Burden of Advanced HIV Disease Among Patients Seeking Care in South Africa's National HIV Program: Data From a Nationwide Laboratory Cohort. Clin Infect Dis. 2018 3; 66(suppl_2):S111–S7. [PubMed: 29514238]
34. Huerga H, Van Cutsem G, Ben Farhat J, Reid M, Bouhenia M, Maman D, et al. Who Needs to Be Targeted for HIV Testing and Treatment in KwaZulu-Natal? Results From a Population-Based Survey. J Acquir Immune Defic Syndr. 2016 12; 73(4):411–8. [PubMed: 27243903]
35. Osler M, Hilderbrand K, Goemaere E, Ford N, Smith M, Meintjes G, et al. The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa. Clin Infect Dis. 2018 3; 66(suppl_2):S118–S25. [PubMed: 29514233]
36. Gale HB, Gitterman SR, Hoffman HJ, Gordin FM, Benator DA, Labriola AM, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts >=300 cells/μL and HIV-1 suppression? Clin Infect Dis. 2013 5; 56(9):1340–3. [PubMed: 23315315]
37. Chow EP, Read TR, Chen MY, Fehler G, Bradshaw CS, Fairley CK. Routine CD4 cell count monitoring seldom contributes to clinical decision-making on antiretroviral therapy in virologically suppressed HIV-infected patients. HIV Med. 2015 3; 16(3):196–200. [PubMed: 25236189]

38. Hughes RA, Sterne JA, Walsh J, Bansi L, Gilson R, Orkin C, et al. Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. HIV Med. 2011 11; 12(10):583–93. [PubMed: 21569188]
39. Ford N, Stinson K, Gale H, Mills EJ, Stevens W, Pérez González M, et al. CD4 changes among virologically suppressed patients on antiretroviral therapy: a systematic review and meta-analysis. J Int AIDS Soc. 2015; 18:20061. [PubMed: 26257204]
40. Davies MA, Ford N, Rabie H, Fatti G, Stinson K, Giddy J, et al. Reducing CD4 Monitoring in Children on Antiretroviral Therapy With Virologic Suppression. Pediatr Infect Dis J. 2015 12; 34(12):1361–4. [PubMed: 26379169]
41. Raboud JM, Haley L, Montaner JS, Murphy C, Januszewska M, Schechter MT. Quantification of the variation due to laboratory and physiologic sources in CD4 lymphocyte counts of clinically stable HIV-infected individuals. J Acquir Immune Defic Syndr Hum Retrovirol. 1995; 10 Suppl 2:S67–73. [PubMed: 7552516]
42. Phillips AN, Youle M, Lampe F, Sabin CA, Hill A, Ransom D, et al. CD4 cell count changes in individuals with counts above 500 cells/mm and viral loads below 50 copies/ml on antiretroviral therapy. AIDS. 2002 5; 16(7):1073–5. [PubMed: 11953476]
43. Duro R, Rocha-Pereira N, Figueiredo C, Piñeiro C, Caldas C, Serrão R, et al. Routine CD4 monitoring in HIV patients with viral suppression: Is it really necessary? A Portuguese cohort. J Microbiol Immunol Infect. 2018 10; 51(5):593–7. [PubMed: 28712820]
44. Caniglia EC, Cain LE, Sabin CA, Robins JM, Logan R, Abgrall S, et al. Comparison of dynamic monitoring strategies based on CD4 cell counts in virally suppressed, HIV-positive individuals on combination antiretroviral therapy in high-income countries: a prospective, observational study. Lancet HIV. 2017 06; 4(6):e251–e9. [PubMed: 28411091]
45. Girard PM, Nelson M, Mohammed P, Hill A, van Delft Y, Moecklinghoff C. Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? AIDS. 2013 11; 27(17):2759–63. [PubMed: 23842127]
46. Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. JAMA Intern Med. 2013 10; 173(18):1746–8. [PubMed: 23978894]
47. Stevens WS, Ford N. Time to reduce CD4+ monitoring for the management of antiretroviral therapy in HIV-infected individuals. S Afr Med J. 2014 6; 104(8):559–60. [PubMed: 25213847]
48. Battegay M, Nüesch R, Hirschel B, Kaufmann GR. Immunological recovery and antiretroviral therapy in HIV-1 infection. Lancet Infect Dis. 2006 5; 6(5):280–7. [PubMed: 16631548]
49. Kaufmann GR, Perrin L, Pantaleo G, Opravil M, Furrer H, Telenti A, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med. 2003 10; 163(18):2187–95. [PubMed: 14557216]

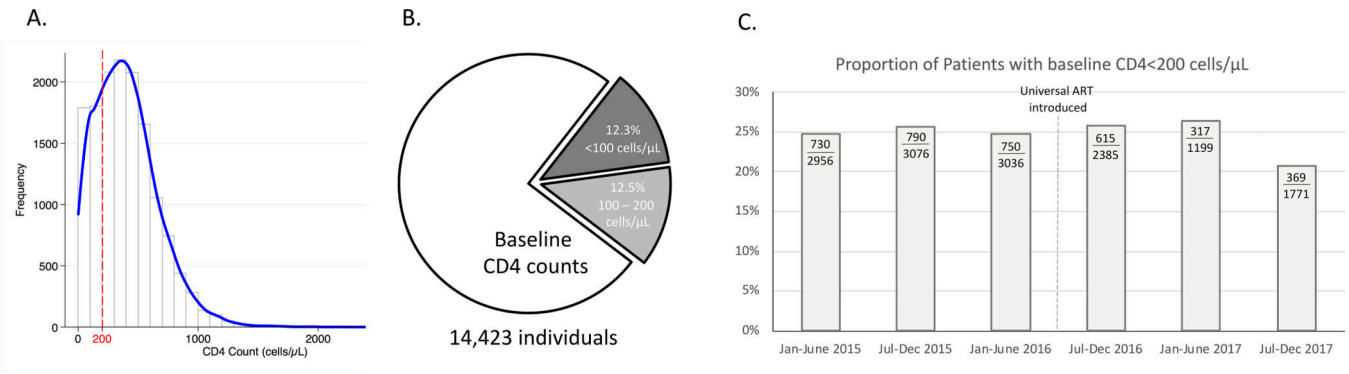

Figure 1: Distribution of baseline CD4 counts in 14,423 individuals with an initial CD4 test in Gaborone, Botswana, 2015–2017.

Panel (A) shows a frequency polygon of all CD4 counts, with a dotted line indicating 200 cells/μL. The pie-chart in panel (B) illustrates the percentage of baseline CD4 counts < 100 cells/μL, and 100–199 cells/μL. Panel (C) shows the proportion of individuals with a baseline CD4 by 6-month calendar period.

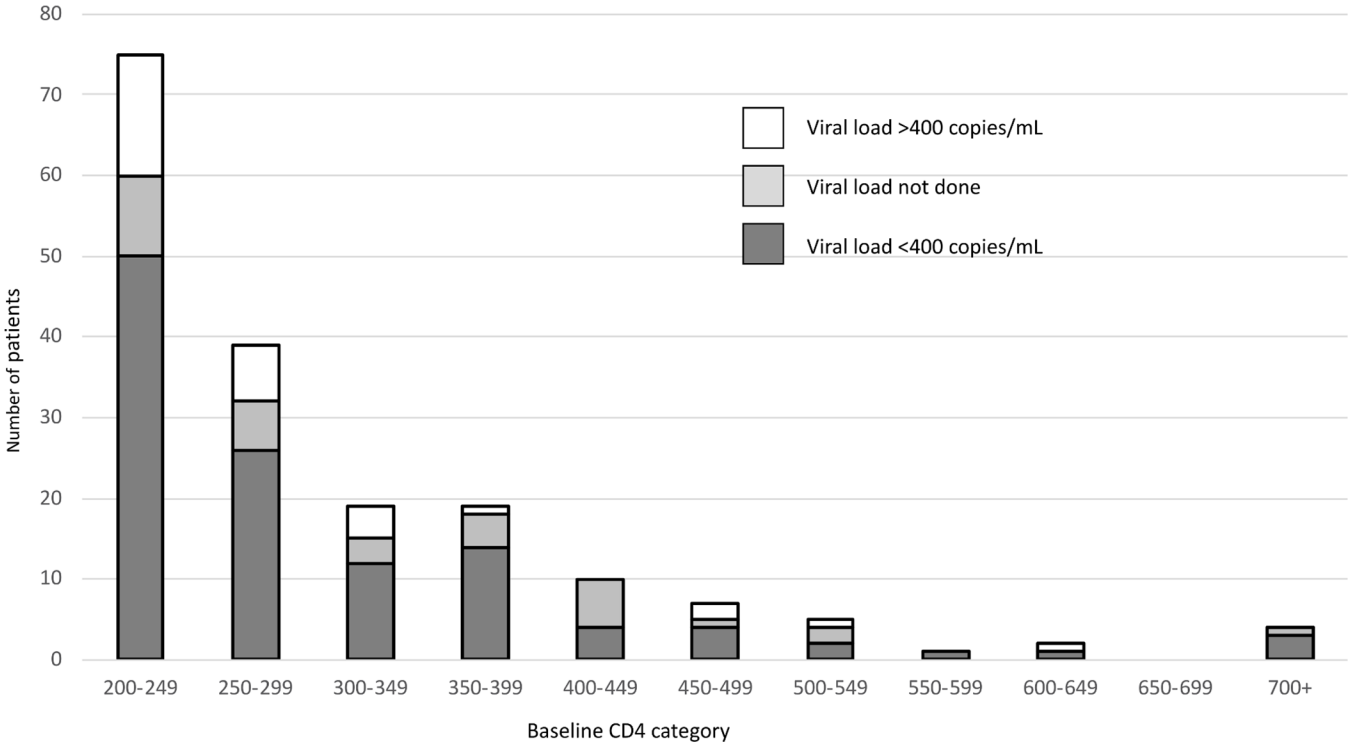

Figure 2. Baseline CD4 category and viral load status at the time of CD4 decline, of the 180 patients who experienced a drop in CD4 count to <200 cells/μL.

All individuals with a viral load result are assumed to have initiated ART. Data regarding ART adherence were not available; it was not possible to determine whether individuals without viral load testing had initiated ART. Than majority of individuals experiencing a decline in CD4 count to below 200 cells/μL during routine CD4 count monitoring had baseline CD4 counts of 200–249 (n, %) or 240–299 cells/μL (n %). Only 31 (%) individuals identified with a decline in CD4 count to below 200 cells/μL had a detectable viral load at the time of testing.

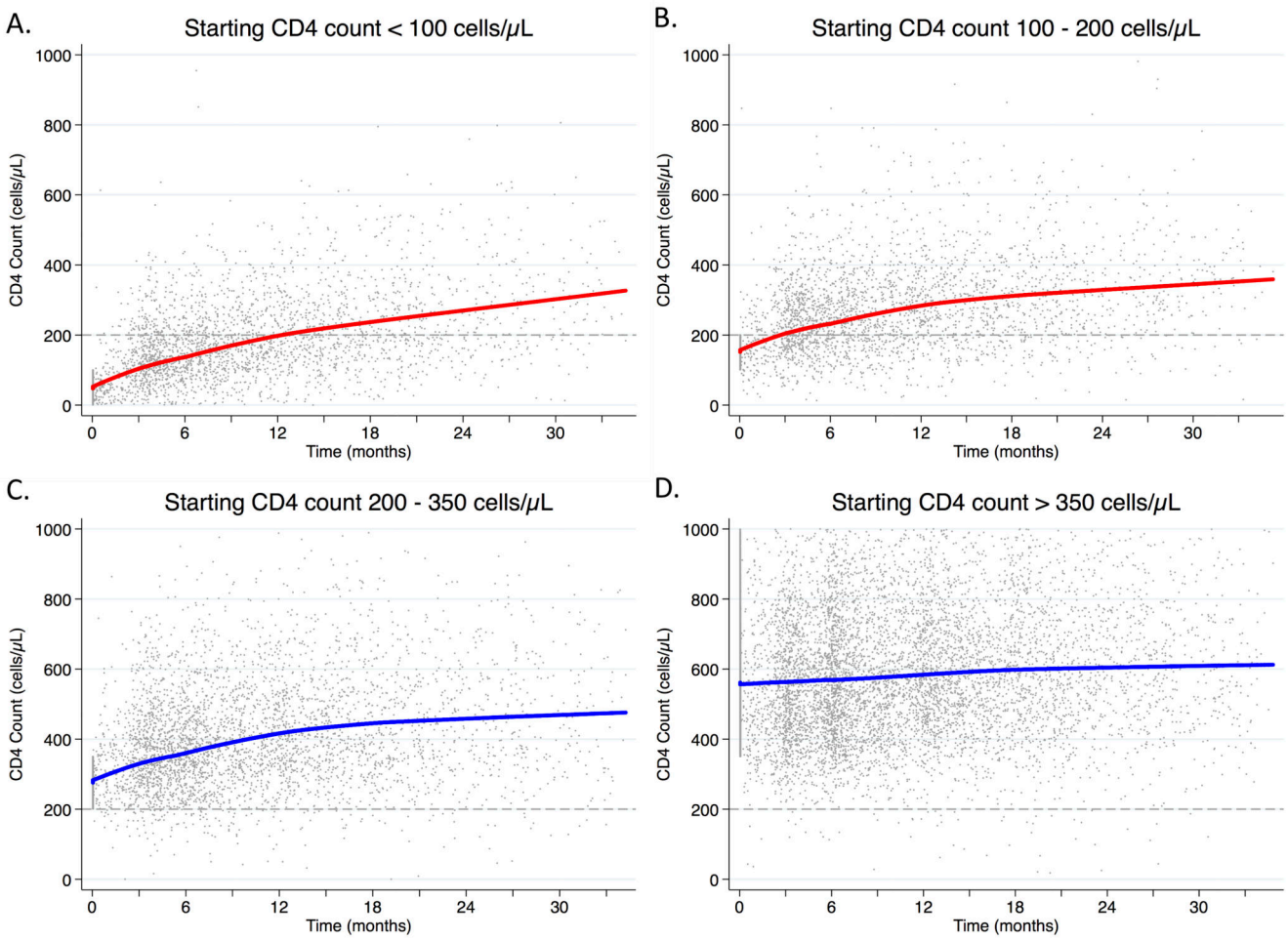

Figure 3. CD4 cell count trajectories stratified by baseline CD4 category.

Trends in CD4 cell 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 (<100 cells/μL, 100–200 cells/μL, 200–350 cells/μL, and ≥350 cells/μL).

Table 1.

Baseline characteristics of study participants and baseline CD4 cell count results

(A) Baseline characteristics of participants		
Variable		*Result (overall n=14,423)*
Sex (% female, n)		64% (9,159)
Age (median, IQR)		34 years (28–42 years)
Baseline CD4 count (median, IQR)		372 cells/μL (201–552 cells/μL)
Number of CD4 cell counts	1	50% (7,260)
	2	19% (2,681)
	3	13% (1,804)
	4	9% (1,345)
	5+	9% (1,333)
Viral load testing performed		79% (11,454)
(B) Distribution of baseline CD4 cell counts		
0–99 cells/μL		12% (1,774)
100–199 cells/μL		13% (1,797)
200–349 cells/μL		22% (3,132)
≥350 cells/μL		54% (7,720)

Footnotes: n = number; IQR = interquartile range

Table 2.

Baseline associations with advanced HIV-disease

Associations with advanced HIV disease (CD4 <200 cells/μL)

Variable	*Category*	*CD4 <200 cells/μL (%, n)*	*Crude odds ratio (OR)*	*Adjusted odds ratio (aOR)**
Sex	Female	19% (1,733)	base	base
	Male	35% (1,836)	2.3 (2.1–2.5)	2.1 (1.9–2.3)
Age	< 35 years	18% (1,423)	base	base
	≥ 35 years	32% (2,148)	2.1 (2.0–2.3)	1.9 (1.8–2.1)
Time period†	Pre-Universal ART	25% (2,270)	base	base
	Post-Universal ART	24% (1,301)	1.0 (0.9–1.0)	0.9 (0.9–1.0)

Footnotes: n = number; IQR = interquartile range

*Adjusted model included age, sex, and time period. Odds ratios are presented with 95% confidence intervals (95% CI). If age was further broken down into those <25 years, 25–34 years, 35–44 years, and >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 25–34 years; 3.0 (95% CI 2.6–3.4) in those 35–44 years; and 2.8 (95% CI 2.4–3.2) in those >45 years.

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