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Advanced HIV Disease During the 'Treat All' Era in Botswana

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HIV-1 infection is a potentially manageable chronic disease through early diagnosis, engagement in a model of chronic care, and sustained use of antiretroviral therapy (ART). In sub-Saharan Africa (SSA), where HIV prevalence is highest, effective models of care have been established for ART delivery and HIV testing has become a ubiquitous intervention at health facilities, in the community, and even at home. HIV-related mortality and HIV incidence have been cut drastically over the past 15 years. In recent years, most countries have adopted 'Treat all,' which is expected to accelerate control the HIV epidemic. Unfortunately, advanced HIV disease, the phase of infection that is characterized by severe immunodeficiency and high incidence of life-threatening opportunistic infections, appears to an enduring problem in SSA. Lebelonyane and colleagues analyzed the prevalence, predictors, and outcomes advanced HIV disease in Botswana, which has been among the most ambitious in adopting evidence-based HIV treatment and prevention interventions, including 'Treat all', and was the first country in SSA to announce it had achieved the 90–90-90 targets [1].

Investigators performed a secondary analysis of the Botswana Combination Prevention Project, an intervention that was implemented from October 2013 to March 2018, among adults (16–64 year-olds) across 15 communities [2]. The intervention package included HIV testing campaigns, scale-up of medical male circumcision, universal ART regardless of CD4 count, and enhanced linkage and retention in HIV care. People living with HIV (PLHIV) who were identified as not taking ART, because they were either newly diagnosed or previously diagnosed but not currently on therapy, were linked to clinical care at the facility. Among those who linked to care, investigators described the proportion of adults with advanced HIV disease, defined as CD4 count ≤200 cells/mm^3, identified demographic and treatment-related risk factors, and described subsequent ART outcomes, in comparison to those with higher CD4 counts. Data from children and younger adolescents were unfortunately not reported.

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Among eligible PLHIV who participated in the intervention, linked to care, and had available CD4 results, 17.2% had advanced disease. Strikingly, advanced disease become *more common* after 'Treat all' was adopted in Botswana compared to beforehand (24.7% versus 15.5%; P<0.001). Men had twice the odds advanced disease compared to women. The majority of individuals (82%) with advanced disease were asymptomatic (WHO clinical stage 1). Half reported previous HIV care (i.e., had disengaged from the HIV care continuum), including 22% who initiated and later stopped ART. PLHIV who started/re-started ART in the setting of advanced disease had significantly lower levels of retention and viral suppression at 1 year, and as expected, experienced nearly 3-fold increased mortality at the end of follow-up (4.9% versus 1.7%), compared to those with higher CD4 counts.

Building on other reports [3, 4], this paper demonstrates the persistent nature of advanced HIV disease during the 'Treat all' era in SSA. Whether advanced HIV disease is increasing in frequency must be confirmed in diverse settings. Addressing advanced disease should remain a major priority within the HIV response because it is strongly linked with HIV-related mortality and many individuals with advanced disease have non-suppressed HIV RNA that puts others at risk of transmission. Interventions to address advanced HIV disease should have a strong focus on men, as well as other populations lagging behind in testing and sustained viral suppression.

These data provide further evidence that advanced HIV disease has shifted from a late diagnosis problem to a retention in care problem. Half of PLHIV with advanced disease in Botswana self-reported prior disengagement; however, the real figure may be even higher as patients face stigma and other psychosocial barriers to openly reporting having disengaged. In analyses of hospitalized PLHIV with advanced disease in Zambia, Malawi, Kenya, and the Democratic Republic of Congo, up to 90% reported prior knowledge of HIV status and 65–86% had prior ART use, suggesting that relatively few were 'late presenters' [5–7]. Losses to follow-up have also presumably shifted from the pre- to the post-ART parts of the cascade [8] under 'Treat all.' Recognizing this, many programs patients that are late for scheduled appointments more aggressively than before, and are working to improve clinic factors, and the patient experience, which may contribute to disengagement from care [9]. Also of note, evidence in SSA on interventions to treat or prevent common coinfections in advanced HIV disease were mainly derived from trials with ART-naïve individuals [10, 11]. Additional data are needed to assess the effectiveness of these interventions among ART-experienced, disengaged, and hospitalized individuals with advanced disease.

To effectively and efficiently address advanced HIV disease, CD4 count testing must be maintained, ideally as close to the clinic as possible, because many of these patients are asymptomatic until they become critically ill. The scale-up of routine HIV viral load monitoring in SSA has reduced the attention on and resources for CD4 testing [12], with potentially negative consequences for patient care. A report from Zambia found that ART initiators without a baseline CD4 test had 50% higher risk of death at 1 year compared to those with known CD4 count [13], presumably because they were less likely to be screened and treated for major coinfections. When 'Treat all' began in July 2016 the Botswana program analyzed, CD4 testing shifted from the point-of-care (POC) to a centralized approach. It would have been informative to know whether this change was associated with

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reduced implementation of advanced HIV disease interventions, which strongly rely on knowledge of CD4 count [14]. A recently developed qualitative lateral flow assay to detect a CD4 count ≤200 cells/mm^3 could help to more efficiently implement advanced HIV disease care [15].

In conclusion, Lebelonyane and colleagues paper showed that advanced HIV disease has persisted as public health problem in SSA, despite progress in achieving targets for HIV testing, ART use, and viral load suppression. Most cases of advanced disease now come from the population of PLHIV with suboptimal engagement in care after HIV diagnosis, with male predominance. Implementation of best practices for advanced disease management will depend on strong access to CD4 testing.

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References:

1. Essex M, Makhema J, Lockman S. Reaching 90–90-90 in Botswana. Current Opinion in HIV and AIDS. 2019;14(6):442–8. [PubMed: 31449090]
2. Lebelonyane R, Mills LA, Mogorosi C, Ussery F, Marukutira T, Theu J, et al. Advanced HIV Disease in the Botswana Combination Prevention Project: Prevalence, Risk Factors, and Outcomes. AIDS. 2020.
3. Ford N, Doherty M. The enduring challenge of advanced HIV infection. Mass Medical Soc; 2017.
4. 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. Clinical Infectious Diseases. 2018;66(suppl_2):S118–S25. [PubMed: 29514233]
5. Hachaambwa L, Kandiwo N, Zulu P, Rutagwera D, Geng E, Holmes CB, et al. Care continuum and post-discharge outcomes among HIV-infected adults admitted to the hospital in Zambia. Open Forum ID. 2019;In Press.
6. Ousley J, Niyibizi AA, Wanjala S, Vandenbulcke A, Kirubi B, Omwoyo W, et al. High Proportions of Patients With Advanced HIV Are Antiretroviral Therapy Experienced: Hospitalization Outcomes From 2 Sub-Saharan African Sites. Clinical Infectious Diseases. 2018;66(suppl_2):S126–S31. [PubMed: 29514239]
7. Matoga MM, Rosenberg NE, Stanley CC, LaCourse S, Munthali CK, Nsona DP, et al. Inpatient mortality rates during an era of increased access to HIV testing and ART: a prospective observational study in Lilongwe, Malawi. PloS one. 2018;13(2).
8. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS medicine. 2011;8(7):e1001056.
9. Mwamba C, Sharma A, Mukamba N, Beres L, Geng E, Holmes CB, et al. 'They care rudely!': resourcing and relational health system factors that influence retention in care for people living with HIV in Zambia. BMJ global health. 2018;3(5):e001007.
10. 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. The Lancet. 2015;385(9983):2173–82.
11. Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C, et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. New England Journal of Medicine. 2017;377(3):233–45.

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12. Ehrenkranz PD, Baptiste SL, Bygrave H, Ellman T, Doi N, Grimsrud A, et al. The missed potential of CD4 and viral load testing to improve clinical outcomes for people living with HIV in lower-resource settings. PLoS medicine. 2019;16(5).

13. Sikombe K, Eshun-Wilson I, Koyuncu A, Simbeza S, Mody A, Czaicki N, et al. Early mortality in HIV-infected patients initiating ART without a pretherapy CD4. Conference on Retroviruses and Opportunistic Infections; Seattle, USA2019. p. Abstract 148.

14. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, 7 2017. 2017.

15. Luchters S, Technau K, Mohamed Y, Chersich MF, Agius PA, Pham MD, et al. Field performance and diagnostic accuracy of a low-cost instrument-free point-of-care CD4 test (Visitect CD4) performed by different health worker cadres among pregnant women. Journal of clinical microbiology. 2019;57(2):e01277–18.