Same-day ART initiation as a predictor of loss to follow-up and viral suppression among people living with HIV in sub-Saharan Africa

Jonathan Ross*[1], Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA and Montefiore Health System, Bronx, NY, USA;
Ellen Brazier*, Institute for Implementation Science in Population Health, City University of New York, New York, NY, USA and Graduate School of Public Health and Health Policy, City University of New York, New York, NY, USA;
Geoffrey Fatti, Kheth'Impilo AIDS Free Living, Cape Town, South Africa and Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa;
Antoine Jaquet, University of Bordeaux, National Institute for Health and Medical Research (INSERM) UMR 1219, Research Institute for Sustainable Development (IRD) EMR 271, Bordeaux Population Health Centre, Bordeaux, France;
Aristophane Tanon, Service de Maladies Infectieuses et Tropicales (SMIT), Treichville Teaching Hospital, Abidjan, Côte d'Ivoire;
Andreas D. Haas, Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland;
Lameck Diero, Department of Medicine, Moi University School of Medicine and Moi Teaching and Referral Hospital, Eldoret, Kenya;
Barbara Castelnuovo, Department of Medicine, Moi University School of Medicine and Moi Teaching and Referral Hospital, Eldoret, Kenya;
Constantin T Yiannoutsos, Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA;
Denis Nash, Institute for Implementation Science in Population Health, City University of New York, New York, NY, USA and Graduate School of Public Health and Health Policy, City University of New York, New York, NY, USA;
Kathryn M. Anastos, Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA and Montefiore Health System, Bronx, NY, USA;
Marcel Yotebieng, Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA and Montefiore Health System, Bronx, NY, USA;
On behalf of International epidemiology Databases to Evaluate AIDS (IeDEA)^

***** contributed equally to this manuscript

[1] Corresponding author: 3300 Kossuth Avenue, Bronx, NY 10467 USA; 718-920-7064 (p); 718-561-5165 (f); joross@montefiore.org

^ IeDEA study group members are listed in Acknowledgments

Running title: Same-day ART initiation and loss to follow-up

ABSTRACT

Background

Treat-All guidelines recommend initiation of antiretroviral therapy (ART) for all people living with HIV (PLHIV) on the day of diagnosis when possible, yet uncertainty exists about the impact of same-day ART initiation on subsequent care engagement. We examined the association of same-day ART initiation with loss to follow-up and viral suppression among patients in 11 sub-Saharan African countries.

Methods

We included ART-naïve adult PLHIV from sites participating in the International epidemiology Databases to Evaluate AIDS consortium (IeDEA) who enrolled in care after Treat-All implementation and prior to January 2019. We used multivariable Cox regression to estimate the association between same-day ART initiation and loss to follow-up, and Poisson regression to estimate the association between same-day ART initiation and 6-month viral suppression.

Results

Among 29,017 patients from 63 sites, 18,584 (64.0%) initiated ART on the day of enrollment. Same-day ART initiation was less likely among those with advanced HIV disease versus early-stage disease. Loss to follow-up was significantly lower among those initiating ART ≥1 day of enrollment, compared with same-day ART initiators (20.6% vs 27.7%; adjusted hazard ratio 0.66, 95% CI 0.57-0.76). No difference in viral suppression was observed by time to ART initiation (adjusted rate ratio 1.00, 95% CI 0.98-1.02).

Conclusions

Patients initiating ART on the day of enrollment were more frequently lost to follow-up than those initiating later but were equally likely to be virally suppressed. Our findings support recent

WHO recommendations for providing tailored counseling and support to patients who accept an offer of same-day ART.

Keywords: antiretroviral therapy, Treat-All, sub-Saharan Africa, loss to follow-up

INTRODUCTION

Initiation of antiretroviral therapy (ART) soon after HIV diagnosis improves clinical outcomes for people living with HIV (PLHIV) and reduces HIV transmission [1–3]. Accordingly, the World Health Organization (WHO) 2015 "Treat-All" guidelines recommend rapid ART initiation ART for all PLHIV as soon as possible after diagnosis, ideally within 7 days, and on the same day when possible [4].

While nearly all countries have adopted Treat-All guidelines [5], uncertainty exists about the impact of same-day ART (SDA) initiation on subsequent engagement in care including care retention and viral suppression. Randomized controlled trials of SDA have demonstrated outcomes that are as good as, or better than, later ART initiation among PLHIV [6–8], findings replicated in a recent, large regression discontinuity analysis of routine clinical data in Zambia [9]. However, several observational studies examining outcomes after Treat-All implementation have found that SDA is associated with higher rates of loss to care [10–12]. Accordingly, recently updated WHO guidelines now emphasize that an offer of SDA should include approaches to improve uptake, treatment adherence and retention [13].

Sub-Saharan Africa (SSA), where Treat-All implementation occurred later than other global regions, continues to be disproportionately impacted by HIV [14]. While virtually all countries in SSA have adopted Treat-All policies, investigations of SDA in this region have been limited to single-country studies, with most studying relatively small cohorts [10–12,15–18], and few reporting on viral suppression [8,17,18]. A more generalizable understanding of whether SDA has impacted clinical outcomes for patients in SSA is critical for reaching regional goals for

epidemic control. We therefore examined the association between SDA and both loss to follow-up (LTFU) and viral suppression among patients enrolled in HIV care at clinics participating in the global International epidemiologic Databases to Evaluate AIDS (IeDEA) consortium in 11 African countries.

METHODS

Data sources and management

We used data from HIV programs in SSA that participate in the global IeDEA consortium. IeDEA pools clinical data on approximately 2.2 million PLWH enrolling in HIV care since 2004 in 44 countries globally, including 240 care and treatment sites in 23 countries in SSA [19,20]. Comprising public and private primary, secondary and tertiary-level health facilities, IeDEA is a purely observational cohort reflecting real-world service delivery across diverse settings.

Prior to analysis, data from IeDEA regions were standardized in accordance with IeDEA data definitions and formatting standards [21]. Data were de-identified before extraction into regional databases and approved for use by local research ethics committees in each IeDEA region as well as the institutional review boards of regional data management centers.

Inclusion and exclusion criteria

All patients who enrolled in HIV care at an IeDEA site after the Treat-All adoption date in each country and before January 2019 were eligible for inclusion (N=241,723). We excluded patients who: 1) were in care at sites that did not provide pre-ART care (i.e., only served patients already

initiated on ART) or that did not consistently report data on pre-ART care (N=107,245); 2) enrolled in care before national adoption of Treat-All (N=97,801); 3) were ART experienced at enrollment (3,324); 4) had <12 months of potential follow-up time between enrollment and database close (N=2,030); 5) were <15 years of age at enrollment (N=1,286); or 6) never initiated ART (N=946) (**Supplemental Figure 1**). We excluded 74 patients with missing or illogical data related to sex or dates of birth or death (e.g., recorded date of death that preceded the date of HIV care enrollment).

Countries where WHO's Treat-All recommendation was not officially reflected in national guidelines by December 2018 were excluded. As noted above, HIV programs were excluded if they did not provide any pre-ART care to patients or did not consistently report pre-ART data. To identify such clinics, we examined the proportion of patients whose date of ART initiation matched their date of enrollment in the two years prior to national Treat-All adoption, when CD4-based or other clinical criteria were used to determine ART eligibility. Clinics in which ≥75% of patients had matching enrollment and ART initiation dates in the pre-Treat-All period were considered not to report data on patients' pre-ART care and therefore excluded.

Measures

The primary exposure was time from care enrollment to initiation of a combined ART regimen. Because the large majority (84%) of patients initiating ART within 1 week did so on the day of enrollment, we classified timing of ART initiation as *same-day ART* (i.e., initiation of ART on the same day as enrollment) versus ≥1 day after enrollment. The primary outcome of interest was *loss to follow-up*, defined as no contact with the health center for >180 days among patients not

known to have died or transferred to another facility [22]. We also examined *viral suppression* at 6 months after ART initiation, defined as <1000 copies/mL, among patients with available viral load (VL) test data from assays performed between 4 and 8 months after ART initiation.

Additional enrollment characteristics included age, sex, body mass index (BMI; classified as <18.5 kg/m2, ≥18.5, unknown/missing), WHO stage (I or II, III or IV, unknown/missing), AIDS diagnosis at enrollment, and CD4 count in cells/mm^3 (<200, 200-349, 350-499, ≥500, unknown/missing). Data were used if recorded within 90 days of enrollment; for patients with more than one measure within 90 days, the observation closest to enrollment date was used. We restricted CD4 measures to those within 30 days after ART initiation, given that CD4 counts rebound rapidly after ART initiation [23]. Because of high levels of missingness in CD4 and WHO staging data, we created a composite measure of advanced HIV disease at enrollment, based on either CD4 cell counts <200 cells/μL or WHO stage 3 or 4.

Site characteristics (e.g., urban vs. rural location, facility type) were extracted from IeDEA databases. Information on HIV spending per prevalent case in 2017 was compiled from the Institute for Health Metrics and Evaluation's Global Burden of Disease databases [24].

Statistical analysis

All analyses were performed using SAS v9.4 (Cary, NC). We used descriptive statistics to summarize patient characteristics; chi-squared tests were used to assess differences in categorical variables, with Kruskal-Wallis tests used to assess differences in medians.

For time-to-event analyses, follow-up time was calculated in days from ART initiation to the last clinic contact (among those who were known to have died or transferred or were lost to clinic), or was censored at 365 days after ART initiation if none of those outcomes occurred. For all patients, one day of follow-up time was added to avoid the occurrence of zero follow-up time among patients who did not return to the clinic after the date of enrolling in care.

We used bivariate and multivariable Poisson regression models to estimate crude and adjusted relative risks of SDA and viral suppression. We used bivariate and multivariable Cox proportional hazards regression models with sandwich variance estimators to estimate hazards of LTFU within 12 months of enrollment. Because over half of the sample was missing VL data, we also used Poisson regression models to examine unadjusted and adjusted associations between predictor variables and VL missingness. Multivariable models adjusted for sex, age group, BMI, disease stage, facility location, health facility level, HIV spending per prevalent case in 2017; we did not include pregnancy status in models because of concern that pregnancy was substantially underreported. All models accounted for site-level clustering using generalized estimating equations (GEE).

Sensitivity analyses

We conducted several sensitivity analyses to test the robustness of our findings on the association of SDA with LTFU and viral suppression. First, to assess heterogeneity among those initiating ART after the day of enrollment, we used a four-level variable for the timing of ART initiation: same-day, 1-7, 8-30 and >30 days. Second, to better understand the impact of missing clinical data (disease stage, BMI) at enrollment, we restricted models to patients with complete

data for these variables. Third, a substantial number of patients had no follow-up data after the enrollment visit (i.e. single contact with the site), with no way to determine whether this was secondary to true LTFU, data error (e.g. undocumented transfer), or sites that operate on a hub-and-spoke model, transferring patients to peripheral clinics after ART initiation [25]. Therefore, we calculated the proportion of patients with a single contact at each site and excluded sites where >10% of patients never returned after the enrollment visit. Fourth, to address potential selection bias created by excluding patients who never initiated ART, we examined LTFU using models that included this group. For this sensitivity analysis, we categorized non-initiators together with those initiating ART ≥1 day after enrollment, with follow-up time starting at enrollment rather than ART initiation for patients never initiating treatment. Finally, given updated WHO guidelines defining viral suppression as <50 copies/mL [13], we repeated analyses for this outcome using this lower threshold

RESULTS

In total 29,017 patients were included (**Supplemental Figure 1**); among them, 17,610 (60.7%) were female and median age was 35 years (interquartile range 28-43) (**Table 1**). Most patients (90%) were from IeDEA cohorts in East Africa (Kenya, Tanzania, Uganda) and Central Africa (Burundi, Cameroon, Democratic Republic of Congo, Republic of Congo, Rwanda); the remainder were from West Africa (Cote d'Ivoire, Senegal) and South Africa. At enrollment, 21,458 (74.0%) were missing CD4 count and 11,742 (40.5%) were missing WHO stage. Among 18,836 (64.9%) with available data on either CD4 count or WHO stage, 6,195 (32.9%) were classified as having advanced disease at enrollment. The majority received care from district

hospitals (7,983, 27.5%) or regional, provincial or university hospitals (12,355, 42.6%), located in urban or mostly urban areas (21,586, 74.4%).

Time to ART initiation

Among all ART patients, median time to ART initiation was 0 days (95% CI 0,0). Overall, 18,584 (64.0%) initiated ART on the same day, 3,432 (11.8%) between 1-7 days, 4,409 (15.2%) between 8 and 30 days, and 2,592 (8.9%) >30 days after enrollment. SDA was less likely among those with advanced versus early-stage disease (adjusted risk ratio [aRR] 0.83, 95% CI 0.72-0.95) (**Table 2**). SDA was more likely at rural/mostly rural sites (vs. urban/mostly urban: aRR 1.40, 95% CI 1.11-1.75).

Loss to follow-up

During the 12 months after enrollment, 1,941 patients (6.7%) had documented transfers and 1,111 (3.8%) died. A total of 7,293 (25.1%) were LTFU, with a median time to LTFU of 29 days (95% CI 28, 31). Among SDA initiators, 27.7% were lost to clinic (including 11.5% who never returned after the enrollment visit) compared with 20.6% of those initiating ≥1 day after enrollment. In the adjusted model, hazard of LTFU within 12 months was 34% lower among those initiating ART ≥1 day of enrollment, compared with SDA initiators (aRR 0.66, 95% CI 0.57-0.76) (**Table 3, Supplemental Figure 2**). Hazard of LTFU was higher among men versus women, younger (15-19, 20-24 and 25-34 years) versus older (>34 years) patients, patients at district hospitals versus health centers, and in countries in the 1st (vs 2nd and 3rd) tertile of per-capita HIV spending.

In a sensitivity analysis using a four-level variable for time to ART initiation, compared with SDA initiators, hazard of LTFU decreased monotonically with increased time to initiation, from 0.77 (95% CI: 0.65-0.92) among those initiating ART at 1 to 7 days after enrollment to 0.59 (95% CI: 0.49-0.70) among those initiating ART >30 days after enrollment (**Supplemental Table 2, Supplemental Figure 2**). We observed results similar to our main analysis in additional sensitivity analyses examining LTFU (**Supplemental Table 1**).

Viral suppression

Among 28,894 patients with ≥8 months (244 days) of potential follow-up time after ART initiation or any VL testing between 4-8 months after ART initiation, 11,898 (41.2%) had a VL measured between 4-8 months after ART initiation. VL was more likely to be missing among SDA initiators, men, younger patients, and those with advanced disease at enrollment (**Supplemental Table 3**). Among those with VL data, 10,487 (88.1%) were virally suppressed. Among patients with a measured VL, no difference in rate of suppression was observed among SDA initiators versus those initiating ≥1 day after enrollment (aRR 1.00, 95% CI 0.98-1.02) (**Table 4**). Suppression was less likely among patients with BMI <18.5 (vs ≥18.5) kg/m^2 and those with advanced disease at enrollment compared with patients without advanced disease. Results from sensitivity analyses were similar (**Supplemental Tables 2 and 4**).

DISCUSSION

In this analysis of routine clinical data from diverse HIV service delivery settings in 11 African countries, most patients initiated ART quickly after enrollment, with nearly two-thirds initiating on the same day. A substantially higher proportion of these patients were lost to follow-up

compared with those who initiated ART later—results that were similar in sensitivity analyses. Notably, LTFU was not associated with advanced disease at care enrollment (including in analyses stratified by time to ART initiation, not shown), suggesting that this factor is not a primary driver of care engagement. Our results are consistent with findings from observational studies in eSwatini, Ethiopia, and South Africa [10–12,17] reporting that SDA initiators were more likely to be lost to follow-up. While SDA may reduce logistical and structural challenges to delivering care, prior research under Treat-All has identified patient-level barriers to rapid ART initiation, including feeling overwhelmed by the diagnosis, fear of lifelong medication, and feeling insufficiently engaged in care [26–28]. In this context, our findings support recent WHO recommendations for providing tailored counseling and support to patients who accept an offer of SDA [13].

It is possible that the higher LTFU among SDA initiators reflects undocumented transfers or deaths immediately after initiation, as has been documented in prior tracing studies in SSA [29–31]. However, in sensitivity analyses excluding sites where high proportions of patients had only one contact with the health center, the association between SDA and LTFU was not substantively attenuated. Furthermore, it is unlikely that many SDA initiators died prior to follow-up, given that this group was less likely to have advanced HIV at enrollment than patients who initiated ART later. Our findings suggest a need for supplementary investigations such as tracing studies and sampling-based approaches that augment routinely collected data to better ascertain outcomes and to understand reasons for disengaging from care.

We observed high rates of viral suppression among patients with available VL, with no differences by timing of ART initiation—results consistent with the very limited literature published to date [8,17]. These results provide some reassurance that the timing of ART initiation (same-day versus later) likely does not negatively impact subsequent viral suppression among those with a VL test. Our findings suggest that later initiation of ART is a reasonable approach when patient or provider concerns arise, consistent with guidance from WHO [13]. Notably, only 41% of patients had available VL data between 4 to 8 months after ART initiation, despite longstanding WHO guidance recommending monitoring at 6 months [13, 32], suggesting that gaps remain in reaching VL monitoring goals. Furthermore, observed differences in VL availability by time to ART, age and disease stage, suggest that patterns of viral suppression may differ among the entire cohort compared with those with available VL, and that patients less likely to be engaged in care (e.g. SDA initiators) are potentially less likely to be virally suppressed.

Several additional findings from this analysis are worth noting. The rapid time to LTFU (median 29 days) highlights the need for adequate support systems immediately after enrollment, a particularly vulnerable time for newly-diagnosed PLHIV. Younger patients were as likely as patients >24 years to initiate ART on the day of enrollment, but more likely to be lost to clinic. HIV incidence is higher among adolescents and young adults than every other age group in SSA [33]; they remain at high risk of poor outcomes, including potential for onward transmission of HIV given relatively higher rates of sexual activity [34, 35]. Our findings suggest that particular care should be taken to ensure support systems are in place prior to offering SDA to younger

PLHIV. We also observed that patients with more advanced HIV were less likely to initiate ART immediately and less likely to be virally suppressed but did not experience higher rates of LTFU.

A key strength of this observational study is the use of data from a large number of patients enrolled in HIV care across a diverse group of 63 sites in 11 African countries. Results from this large, diverse sample are reflective of real-world implementation of WHO's recommendations for ART initiation [4]. This study also has several limitations. Despite the size and diversity of the sample, certain groups (e.g., pregnant women and patients at sites with limited data on pre-ART care) were likely underrepresented in the study, and our findings may not be fully generalizable to these subgroups. Because of incomplete data on the date of HIV diagnoses, we were not able to directly measure the impact of ART initiation on the day of diagnosis and could only assess the timing of ART initiation relative to care enrollment. Additional studies are needed to understand trajectories of linkage to care and very early care engagement in the Treat-All era, including prevalence and predictors of early transfers. We were not able to ascertain definitively what proportion of those LTFU were truly lost from care. We were also unable to measure other important factors that may influence decision-making on when to initiate ART (e.g., type of ART counseling received, presence of medical conditions that may impact ART timing, or patient or clinician assessments of readiness for ART. Finally, the substantial amount of missing VL data may have introduced bias into the analysis of viral suppression.

In sum, we observed high levels of same-day ART initiation among patients across diverse HIV care programs in various countries in SSA, suggesting that WHO's recommendations for rapid ART initiation for patients newly enrolling in HIV care have been widely adopted and scaled up.

Nonetheless, patients initiating ART on the day of enrollment were more likely to be LTFU than those initiating later. Our findings suggest that careful consideration of patient and programmatic factors is necessary to optimize timing of ART as programs increasingly move towards rapid initiation of treatment for all PLHIV.

NOTES

Funding

The International Epidemiology Databases to Evaluate AIDS (IeDEA) is supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, the Fogarty International Center, and the National Library of Medicine: ***AsiaPacific***, U01AI069907; ***CCASAnet***, U01AI069923; ***Central Africa***, U01AI096299; ***East Africa***, U01AI069911; ***NA-ACCORD***, U01AI069918; ***Southern Africa***, U01AI069924; ***WestAfrica***, U01AI069919. Informatics resources are supported by the Harmonist project, R24AI24872. JR is supported by the U.S. National Institute of Mental Health (K23 MH114752). AH was supported by a grant from the Swiss National Science Foundation under award number 193381. KA, DN, EB and CTY reports support from U.S. National Institutes of Health. GF reports support from International Epidemiologic Databases to Evaluate AIDS-Southern Africa, using funding

provided by the US National Institutes of Health (Funding provided to Kheth'Impilo AIDS Free Living (Nonprofit)). BC reports support from NIH-NIAID (5 UO1 AI 069911-16: Name of PD/PI: Kare Wools-Kaloustian, Yiannoutsos Constantin, Aggrey Semwendero Semeere). This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

Acknowledgments. The authors acknowledge the patients and staff at all facilities who contributed data to this study, as well as the site investigators and data managers across the IeDEA collaboration (see Supplementary File 2).

Potential conflicts of interest: DN received research support from Pfizer, Inc., payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Various academic lectures at Universities (paid to author), and consulting fees from Epidemic Intelligence, LLC and Medscape. JR reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events for Grand Rounds speaker in 2019 (paid to author). EB reports support from U.S. National Institutes of Health. GF reports support from International Epidemiologic Databases to Evaluate AIDS-Southern Africa, using funding provided by the US National Institutes of Health (Funding provided to Kheth'Impilo AIDS Free Living (Nonprofit)). BC reports support from NIH (D43 TW 009771: Name of PD/PI: Castelnuovo/Kambugu/Manabe) and EDCTP (TWA 2017GSF-1936: Castelnuovo). CTY and KA reports grants or contracts and support for attending meetings and/or travel from NIH (paid to institution). MY reports grants or contracts from NIH: U01AI096299, R01HD087993, R01HD105526, and U54CA254568. No other authors report potential conflicts of interest.

REFERENCES

1. Insight Start Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015;373(9):795–807.

2. Temprano Anrs Study Group, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015;373(9):808–22.

3. 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 Aug 11;365(6):493–505.

4. World Health Organization, Department of HIV/AIDS. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015 Sep.

5. Ford N, Vitoria M, Doherty M. Providing antiretroviral therapy to all who are HIV positive: the clinical, public health and programmatic benefits of Treat All. J Int AIDS Soc [Internet]. 2018 Feb;21(2). Available from: https://www.ncbi.nlm.nih.gov/pubmed/29436776

6. Koenig SP, Dorvil N, Devieux JG, Hedt-Gauthier BL, Riviere C, Faustin M, et al. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial. PLoS Med. 2017 Jul;14(7):e1002357.

7. Amanyire G, Semitala FC, Namusobya J, Katuramu R, Kampiire L, Wallenta J, et al. Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in

Africa: a stepped-wedge cluster-randomised trial. Lancet HIV. 2016 Nov;3(11):e539–48.

8. Rosen S, Maskew M, Fox MP, Nyoni C, Mongwenyana C, Malete G, et al. Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. PLoS Med. 2016 May;13(5):e1002015.

9. Mody A, Sikazwe I, Namwase AS, et al. Effects of implementing universal and rapid HIV treatment on initiation of antiretroviral therapy and retention in care in Zambia: a natural experiment using regression discontinuity. Lancet HIV 2021; 8: e755–65.

10. Lilian RR, Rees K, McIntyre JA, Struthers HE, Peters RPH. Same-day antiretroviral therapy initiation for HIV-infected adults in South Africa: Analysis of routine data. PLoS One. 2020 Jan 14;15(1):e0227572.

11. Joseph Davey D, Kehoe K, Serrao C, Prins M, Mkhize N, Hlophe K, et al. Same-day antiretroviral therapy is associated with increased loss to follow-up in South African public health facilities: a prospective cohort study of patients diagnosed with HIV. J Int AIDS Soc. 2020 Jun;23(6):e25529.

12. Kerschberger B, Boulle A, Kuwengwa R, Ciglenecki I, Schomaker M. The Impact of Same-Day Antiretroviral Therapy Initiation Under the World Health Organization Treat-All Policy [Internet]. American Journal of Epidemiology. 2021. Available from: http://dx.doi.org/10.1093/aje/kwab032

13. Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring. Geneva: World Health Organization; 2021.

14. UNAIDS Data 2021. Geneva: Joint United Nations Programme on HIV/AIDS; 2021. Available from: https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf. Accessed 22 August 2022.

15. Lebelonyane R, Bachanas P, Block L, Ussery F, Abrams W, Roland M, et al. Rapid antiretroviral therapy initiation in the Botswana Combination Prevention Project: a quasi-experimental before and after study. Lancet HIV. 2020 Aug;7(8):e545–53.

16. Mshweshwe-Pakela N, Hansoti B, Mabuto T, Kerrigan D, Kubeka G, Hahn E, et al. Feasibility of implementing same-day antiretroviral therapy initiation during routine care in Ekurhuleni District, South Africa: Retention and viral load suppression. South Afr J HIV Med. 2020;21(1):1–6.

17. Ahmed I, Demissie M, Worku A, Gugsa S, Berhane Y. Effectiveness of same-day antiretroviral therapy initiation in retention outcomes among people living with human immunodeficiency virus in Ethiopia: empirical evidence. BMC Public Health. 2020 Nov 26;20(1):1802.

18. Labhardt ND, Ringera I, Lejone TI, Klimkait T, Muhairwe J, Amstutz A, et al. Effect of Offering Same-Day ART vs Usual Health Facility Referral During Home-Based HIV Testing on Linkage to Care and Viral Suppression Among Adults With HIV in Lesotho: The CASCADE Randomized Clinical Trial. JAMA. 2018 Mar 20;319(11):1103–12.

19. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P, et al. Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-

Saharan Africa. Int J Epidemiol. 2012 Oct;41(5):1256–64.

20. IeDEA International epidemiology Databases to Evaluate AIDS [Internet]. [cited 2021 Jul 14]. Available from: https://www.iedea.org/. Accessed 24 May 2022.

21. Duda SN, Musick BS, Davies M-A, Sohn AH, Ledergerber B, Wools-Kaloustian K, et al. The IeDEA Data Exchange Standard: a common data model for global HIV cohort collaboration. medRxiv [Internet]. 2020; Available from: https://www.medrxiv.org/content/10.1101/2020.07.22.20159921v1.abstract

22. Chi BH, Yiannoutsos CT, Westfall AO, *et al.* Universal definition of loss to follow-up in HIV treatment programs: a statistical analysis of 111 facilities in Africa, Asia, and Latin America. *PLoS Med* 2011; **8**: e1001111

23. Lok JJ, Bosch RJ, Benson CA, Collier AC, Robbins GK, Shafer RW, et al. Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. AIDS. 2010 Jul 31;24(12):1867–76.

24. Global HIV/AIDS Spending 2000-2017 [Internet]. [cited 2021 Jul 15]. Available from: http://ghdx.healthdata.org/record/global-hivaids-spending-2000-2017

25. Agaba PA, Genberg BL, Sagay AS, Agbaji OO, Meloni ST, Dadem NY, et al. Retention in Differentiated Care: Multiple Measures Analysis for a Decentralized HIV Care and Treatment Program in North Central Nigeria. J AIDS Clin Res [Internet]. 2018 Feb 13;9(2). Available from: http://dx.doi.org/10.4172/2155-6113.1000756

26. Ross J, Ingabire C, Umwiza F, Gasana J, Munyaneza A, Murenzi G, et al. How early is too

early? Challenges in ART initiation and engaging in HIV care under Treat-All in Rwanda-A qualitative study. PLoS One. 2021 May 13;16(5):e0251645.

27. Horter S, Bernays S, Thabede Z, Dlamini V, Kerschberger B, Pasipamire M, et al. "I don't want them to know": how stigma creates dilemmas for engagement with Treat-all HIV care for people living with HIV in Eswatini. Afr J AIDS Res. 2019 Mar;18(1):27–37.

28. Onoya D, Sineke T, Mokhele I, Bor J, Fox MP, Miot J. Understanding the Reasons for Deferring ART Among Patients Diagnosed Under the Same-Day-ART Policy in Johannesburg, South Africa. AIDS Behav. 2021 Sep;25(9):2779–92.

29. Edwards JK, Lesko CR, Herce ME, Murenzi G, Twizere C, Lelo P, et al. Gone But Not Lost: Implications for Estimating HIV Care Outcomes When LTFU Is Not Loss to Care. Epidemiology. 2020 Jul;31(4):570–7.

30. Etoori D, Wringe A, Kabudula CW, Renju J, Rice B, Gomez-Olive FX, et al. Misreporting of Patient Outcomes in the South African National HIV Treatment Database: Consequences for Programme Planning, Monitoring, and Evaluation. Front Public Health. 2020 Apr 7;8:100.

31. Chammartin F, Zürcher K, Keiser O, Weigel R, Chu K, Kiragga AN, et al. Outcomes of Patients Lost to Follow-up in African Antiretroviral Therapy Programs: Individual Patient Data Meta-analysis. Clin Infect Dis. 2018 Nov 13;67(11):1643–52.

32. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. Geneva, 2013.

33. Karim SSA, Baxter C. HIV incidence trends in Africa: young women at highest risk. Lancet HIV. 2021 Jul;8(7):e389–90.

34. Enane LA, Vreeman RC, Foster C. Retention and adherence: global challenges for the long-term care of adolescents and young adults living with HIV. Curr Opin HIV AIDS. 2018 May;13(3):212–9.

35. Melesse DY, Mutua MK, Choudhury A, et alAdolescent sexual and reproductive health in sub-Saharan Africa: who is left behind? BMJ Global Health 2020;5:e002231.

TABLE 1. Baseline characteristics and clinical outcomes among ART-naïve patients who enrolled in care and initiated ART at an IeDEA site in sub-Saharan Africa after Treat-All implementation.

Variables	N	Median time to ART initiation in days (IQR)	Time to ART initiation: Same day n (%)	Time to ART initiation: Not same day n (%)	P value
Total	**29017**	0 (0-7)	18584 (64.0)	10433 (36)	
CHARACTERISTICS					
Patient-level					
Sex					<0.0001
Female	17610 (60.7)	0 (0-7)	11492 (61.8)	6118 (58.6)	
Male	11407 (39.3)	0 (0-8)	7092 (38.2)	4315 (41.4)	
Age					
Median age in years (IQR)	35 (28, 43)	-	35 (28, 43)	36 (29, 44)	<0.0001
15-19	723 (2.5)	0 (0-12)	451 (2.4)	272 (2.6)	<0.0001
20-24	3331 (11.5)	0 (0-6)	2253 (12.1)	1078 (10.3)	
25-34	9442 (32.5)	0 (0-7)	6178 (33.2)	3264 (31.3)	
>34	15521 (53.5)	0 (0-7)	9702 (52.2)	5819 (55.8)	
Pregnant at enrollment (among females)					<0.0001
Not pregnant	7823 (44.4)	0 (0-2)	5653 (49.2)	2170 (35.5)	
Pregnant	942 (5.4)	0 (0-15)	619 (5.4)	323 (5.3)	
Unknown status	8845 (50.2)	0 (0-9)	5220 (45.4)	3625 (59.3)	
BMI at enrollment (kg/m^2)					<0.0001
<18.5	4769 (16.4)	0 (0-7)	3076 (16.6)	1693 (16.2)	
≥18.5	18804 (64.8)	0 (0-5)	12633 (68.0)	6171 (59.1)	
Missing	5444 (18.8)	0 (0-21)	2875 (15.5)	2569 (24.6)	
WHO Stage at enrollment					<0.0001
I	8581 (29.6)	0 (0-4)	5713 (30.7)	2868 (27.5)	
II	4513 (15.6)	0 (0-1)	3307 (17.8)	1206 (11.6)	
III	3144 (10.8)	0 (0-8)	1838 (9.9)	1306 (12.5)	
IV	1037 (3.6)	2 (0-14)	471 (2.5)	566 (5.4)	
Missing	11742 (40.5)	0 (0-13)	7255 (39.0)	4487 (43)	
CD4 count at enrollment (cells/mm^3)					<0.0001
<200	2491 (8.6)	0 (0-9)	1289 (6.9)	1202 (11.5)	
200-349	1632 (5.6)	0 (0-7)	906 (4.9)	726 (7.0)	
350-499	1372 (4.7)	0 (0-7)	796 (4.3)	576 (5.5)	
≥500	2064 (7.1)	0 (0-7)	1225 (6.6)	839 (8.0)	
Missing	21458 (74.0)	0 (0-7)	14368 (77.3)	7090 (68)	
AIDS diagnosis at enrollment					<0.0001
No AIDS diagnosis	13249 (45.7)	0 (0-3)	9058 (48.7)	4191 (40.2)	
AIDS diagnosis	4695 (16.2)	0 (0-14)	2543 (13.7)	2152 (20.6)	
Missing/unknown	11073 (38.2)	0 (0-12)	6983 (37.6)	4090 (39.2)	
Disease stage at enrollment*					<0.0001
Non-advanced disease	12641 (43.6)	0 (0-4)	8668 (46.6)	3973 (38.1)	
Advanced disease	6195 (21.4)	0 (0-12)	3330 (17.9)	2865 (27.5)	
Missing/unknown	10181 (35.1)	0 (0-11)	6586 (35.4)	3595 (34.5)	
Clinic- and country-level					
Urban/rural					<0.0001
Urban/Mostly urban	21586 (74.4)	0 (0-10)	12643 (68.0)	8943 (85.7)	
Rural/Mostly rural	7431 (25.6)	0 (0-0)	5941 (32.0)	1490 (14.3)	
Level of facility					<0.0001
Health center	8679 (29.9)	0 (0-6)	5467 (29.4)	3212 (30.8)	
District hospital	7983 (27.5)	0 (0-1)	5932 (31.9)	2051 (19.7)	
Regional, provincial or university hospital	12355 (42.6)	0 (0-9)	7185 (38.7)	5170 (49.6)	
HIV spending per prevalent case in 2017					<0.0001
1st tertile ($218 - $284)	3550 (12.2)	0 (0-3)	2146 (11.5)	1404 (13.5)	

Variables	N	Median time to ART initiation in days (IQR)	Time to ART initiation		P value
			Same day n (%)	Not same day n (%)	
2nd tertile ($285 - $362)	6875 (23.7)	0 (0-14)	3603 (19.4)	3272 (31.4)	
3rd tertile ($363 - $611)	18592 (64.1)	0 (0-5)	12835 (69.1)	5757 (55.2)	

Variables	N	Median time to ART initiation in days (IQR)	Time to ART initiation: Same day n (%)	Time to ART initiation: Not same day n (%)	P value
OUTCOMES AFTER ART INITIATION					
Transfer within 12 months of					0.0003
Did not transfer	27076 (93.3)	0 (0-7)	17414 (93.7)	9662 (92.6)	
Transferred out	1941 (6.7)	0 (0-8)	1170 (6.3)	771 (7.4)	
Death within 12 months					0.505
Did not die	27906 (96.2)	0 (0-7)	17862 (96.1)	10044 (96.3)	
Died	1111 (3.8)	0 (0-8)	722 (3.9)	389 (3.7)	
Lost to follow-up within 12 months					<0.0001
Not lost	21724 (74.9)	0 (0-8)	13437 (72.3)	8287 (79.4)	
Lost	7293 (25.1)	0 (0-2)	5147 (27.7)	2146 (20.6)	
Viral suppression at 6 months					<0.0001
Not suppressed (≥1000 copies)	1802 (6.2)	0 (0-8)	1094 (5.9)	708 (6.8)	
Suppressed (<1000 copies)	12575 (43.3)	0 (0-8)	7768 (41.8)	4807 (46.1)	
No measured VL	14640 (50.5)	0 (0-7)	9722 (52.3)	4918 (47.1)	

ART: antiretroviral therapy; IQR: interquartile range; BMI: body mass index

*Advanced disease at care entry: WHO stage 3 or 4 or CD4 at enrollment < 200, or AIDS diagnosis at enrollment

TABLE 2. Factors associated with same-day ART initiation among all included patients.

Variables	N	n (%)	RR (95% CI)*	aRR (95% CI)*^
Total	**29017**	18584 (64.0)		
Patient-level				
Sex				
M	11407	7092 (62.2)	0.95 (0.91-1.00)	0.97 (0.92-1.02)
F (ref)	17610	11492 (65.3)	1	1
Age				
15-19 (ref)	723	451 (62.4)	1.00 (0.91 - 1.09)	1.00 (0.90 - 1.10)
20-24	3331	2253 (67.6)	1.08 (1.00 - 1.17)	1.05 (0.98 - 1.13)
25-34	9442	6178 (65.4)	1.05 (0.99 - 1.11)	1.03 (0.98 - 1.08)
>34	15521	9702 (62.5)	1	1
BMI at enrollment				
<18.5 (ref)	4769	3076 (64.5)	1	1
≥18.5	18804	12633 (67.2)	1.04 (0.97-1.12)	1.05 (1.02-1.09)
Unknown/missing	5444	2875 (52.8)	0.82 (0.73-0.91)	0.88 (0.79-0.99)
Disease at enrollment				
Non-advanced disease (ref)	12641	8668 (68.6)	1	1
Advanced disease	6195	3330 (53.8)	**0.78 (0.68-0.90)**	**0.83 (0.72-0.95)**
Unknown/missing	10181	6586 (64.7)	0.94 (0.75-1.18)	0.95 (0.79-1.13)
Clinic- and country-level				
Urban/rural				
Urban/mostly urban (ref)	21586	12643 (58.6)	1	1
Rural/Mostly rural	7431	5941 (79.9)	**1.37 (1.14-1.64)**	**1.40 (1.11-1.75)**
Level of facility				
Health center (ref)	8679	5467 (63.0)	1	1
District hospital	7983	5932 (74.3)	1.18 (0.96-1.45)	1.12 (0.92-1.36)
Regional, provincial or university hospital	12355	7185 (58.2)	0.92 (0.66-1.29)	1.09 (0.82-1.45)
HIV spending per prevalent case in 2017				
1st tertile ($218 - $284) (ref)	3550	2146 (60.5)	1	1
2nd tertile ($285 - $362)	6875	3603 (52.4)	0.87 (0.50-1.51)	0.76 (0.46-1.28)
3rd tertile ($363 - $611)	18592	12835 (69.0)	1.14 (0.94-1.38)	1.03 (0.77-1.37)

ART: antiretroviral therapy; IQR: interquartile range; BMI: body mass index; RR: rate ratio; CI: confidence interval

* Rate ratios estimated via Poisson regression, accounting for clustering within health center. Models include patients with missing data related to BMI and HIV disease stage at time of enrollment in HIV care.

^ Adjusted for sex, age group, BMI at enrollment, disease stage at enrollment, urban vs. rural facility location, health facility level, HIV spending per prevalent case in 2017.

TABLE 3. Factors associated with loss to follow-up (LTFU) within 12 months after ART initiation.

Variables	N	LTFU within 12 months n (%)	Median time to LTFU Days (IQR)	HR (95% CI)*	aHR (95% CI)*^
Total	**29017**	7293 (25.1)	29 (1-153)		
Patient-level					
Same-day ART initiation					
Initiated ≥1 day after enrollment	10433	2146 (20.6)	56 (1-183)	**0.71 (0.59-0.84)**	**0.66 (0.57-0.76)**
Initiated on same day as enrollment (ref)	18584	5147 (27.7)	19 (1-136)	1	1
Sex					
M	11407	2830 (24.8)	29 (1-148)	0.98 (0.91-1.07)	**1.09 (1.03-1.15)**
F (ref)	17610	4463 (25.3)	30 (1-155)	1	1
Age					
15-19	723	244 (33.7)	16 (1-122)	**1.67 (1.37-2.04)**	**1.80 (1.49-2.17)**
20-24	3331	1098 (33.0)	43 (1-161)	**1.58 (1.40-1.79)**	**1.73 (1.58-1.89)**
25-34	9442	2546 (27.0)	30 (1-155)	**1.26 (1.16-1.36)**	**1.32 (1.23-1.42)**
>34 (ref)	15521	3405 (21.9)	26 (1-151)	1	1
BMI at enrollment					
<18.5 (ref)	4769	1092 (22.9)	40 (1-149)	1	1
≥18.5	18804	4326 (23.0)	34 (1-165)	0.97 (0.87-1.09)	0.93 (0.84-1.03)
Unknown/missing	5444	1875 (34.4)	9 (1-125)	**1.61 (1.21-2.14)**	**1.68 (1.31-2.17)**
Disease at enrollment					
Non-advanced disease (ref)	12641	3027 (23.9)	33 (1-159)	1	1
Advanced disease	6195	1529 (24.7)	22 (1-139)	1.06 (0.90-1.26)	1.10 (0.94-1.27)
Unknown/missing	10181	2737 (26.9)	29 (1-149)	1.16 (0.90-1.50)	1.09 (0.90-1.31)
Clinic- and country-level					
Urban/rural					
Urban/mostly urban (ref)	21586	5612 (26.0)	24 (1-147.5)	1	1
Rural/Mostly rural	7431	1681 (22.6)	44 (1-165)	0.86 (0.63-1.16)	0.86 (0.67-1.12)
Level of facility					
Health center (ref)	8679	1925 (22.2)	73 (1-186)	1	1
District hospital	7983	2258 (28.3)	37 (1-144)	**1.32 (0.93-1.88)**	**1.45 (1.11-1.91)**
Regional, provincial or university hospital	12355	3110 (25.2)	3 (1-120)	1.17 (0.78-1.77)	1.01 (0.59-1.72)
HIV spending per prevalent case in 2017					
1st tertile ($218 - $284) (ref)	3550	1312 (37.0)	1 (1-57)	1	1
2nd tertile ($285 - $362)	6875	1468 (21.4)	58 (1-166)	**0.55 (0.35-0.85)**	**0.53 (0.38-0.73)**
3rd tertile ($363 - $611)	18592	4513 (24.3)	40 (1-162)	**0.62 (0.51-0.75)**	**0.50 (0.30-0.84)**

ART: antiretroviral therapy; IQR: interquartile range; BMI: body mass index; HR: hazard ratio; CI: confidence interval

* Hazard ratios estimated via Cox proportional hazards regression, accounting for clustering within site/center. Models include patients unknown BMI and HIV disease stage at time of enrollment in HIV care.

^ Adjusted for sex, age group, BMI at enrollment, disease stage at enrollment, urban vs. rural facility location, health facility level, HIV spending per prevalent case in 2017.

TABLE 4. Viral load monitoring among patients initiating ART, and factors associated with viral suppression among patients with a viral load measured between 4 to 8 months after ART initiation.[#]

Variables	N	Viral load measured n (%)	Viral load suppressed (among those measured) n (%)	RR (95% CI)*	aRR (95% CI)*^
Total	**28894**	11898 (41.2)	10487 (88.1)		
Patient-level					
Same-day ART initiation					
Initiated ≥1 day after enrollment	10310	4322 (41.9)	3809 (88.1)	1.00 (0.97-1.03)	1.00 (0.98-1.02)
Initiated on same day as enrollment	18584	7576 (40.8)	6678 (88.1)	1	1
Sex					
M	11363	4563 (40.2)	3993 (87.5)	0.99 (0.97-1.01)	0.99 (0.98-1.01)
F (ref)	17531	7335 (41.8)	6494 (88.5)	1	1
Age					
15-19 (ref)	718	227 (31.6)	194 (85.5)	0.98 (0.94 - 1.02)	0.96 (0.92 - 1.01)
20-24	3321	1199 (36.1)	1079 (90.0)	**1.03 (1.01 - 1.05)**	1.01 (0.99 - 1.03)
25-34	9401	3792 (40.3)	3377 (89.1)	1.02 (1.00 - 1.04)	1.01 (0.99 - 1.03)
>34	15454	6680 (43.2)	5837 (87.4)	1	1
BMI at enrollment					
<18.5 (ref)	4761	2000 (42.0)	1679 (84)	1	1
≥18.5	18773	8484 (45.2)	7570 (89.2)	**1.06 (1.04-1.08)**	**1.05 (1.03-1.07)**
Unknown/missing	5360	1414 (26.4)	1238 (87.6)	1.04 (1.00-1.08)	1.03 (0.99-1.07)
Disease at enrollment					
Non-advanced disease (ref)	12613	5503 (43.6)	5023 (91.3)	1	1
Advanced disease	6179	2225 (36)	1941 (87.2)	**0.96 (0.94-0.98)**	**0.96 (0.94-0.97)**
Unknown/missing	10102	4170 (41.3)	3523 (84.5)	**0.93 (0.90-0.95)**	**0.94 (0.91-0.96)**
Clinic- and country-level					
Urban/rural					
Urban/mostly urban (ref)	21479	8532 (39.7)	7482 (87.7)	1	1
Rural/Mostly rural	7415	3366 (45.4)	3005 (89.3)	1.02 (0.97-1.07)	1.02 (1.00-1.04)
Level of facility					
Health center (ref)	8632	3673 (42.6)	3258 (88.7)	1	1
District hospital	7958	3678 (46.2)	3115 (84.7)	0.95 (0.92-0.99)	0.97 (0.94-1.00)
Regional, provincial or university hospital	12304	4547 (37.0)	4114 (90.5)	1.02 (0.98-1.06)	1.00 (0.96-1.05)
HIV spending per prevalent case in 2017					
1st tertile ($218 - $284) (ref)	3536	827 (23.4)	756 (91.4)	1	1
2nd tertile ($285 - $362)	6817	2881 (42.3)	2635 (91.5)	1.00 (0.95-1.05)	1.00 (0.96-1.03)
3rd tertile ($363 - $611)	18541	8190 (44.2)	7096 (86.6)	0.95 (0.92-0.97)	0.96 (0.92-1.01)

ART: antiretroviral therapy; BMI: body mass index; RR: rate ratio; CI: confidence interval

Analyses restricted to patients with at least 244 days' potential follow-up time between ART initiation and database close or <244 days potential follow-up time and a viral load test between 120 and 244 days after ART initiation)

*Rate ratios estimated via Poisson regression, accounting for clustering within site/center.

^ Adjusted for sex, age group, BMI at enrollment, disease stage at enrollment, urban vs. rural facility location, health facility level, HIV spending per prevalent case in 2017.