HHS Public Access

Author manuscript

J Clin Epidemiol. Author manuscript; available in PMC 2021 December 28.

Published in final edited form as:

J Clin Epidemiol. 2021 December ; 140: 101–110. doi:10.1016/j.jclinepi.2021.09.001.

Regression discontinuity analysis demonstrated varied effect of Treat-All on CD4 testing among Southern African countries

Elizabeth Zaniewski[a], **Ellen Brazier**[b], **Cam Ha Dao Ostinelli**[a], **Robin Wood**[c], **Meg Osler**[d], **Karl-Günter Technau**[e], **Joep J van Oosterhout**[f,g], **Nicola Maxwell**[d], **Janneke van Dijk**[h], **Hans Prozesky**[i], **Matthew P Fox**[j,k,l], **Jacob Bor**[j,k,l], **Denis Nash**[b], **Matthias Egger**[a,d,m]

[a]Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland.

[b]Institute for Implementation Science in Population Health (ISPH), Graduate School of Public Health and Health Policy, City University of New York, New York, NY, USA.

[c]Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa.

[d]Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa.

[e]Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, University of the Witwatersrand, Johannesburg, South Africa.

[f]Partners in Hope, PO Box 302, Lilongwe, Malawi.

[g]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, USA.

[h]Solidarmed Zimbabwe, Masvingo, Zimbabwe.

[i]Division of Infectious Diseases, Department of Medicine, Stellenbosch University, Cape Town, South Africa.

[j]Department of Global Health, Boston University School of Public Health, Boston, MA, USA.

Correspondence to: Elizabeth Zaniewski, Institute of Social and Preventive Medicine (ISPM), University of Bern, Mittelstrasse 43, Bern 3012, Switzerland, elizabeth.zaniewski@ispm.unibe.ch, Tel +41 31 631 33 82.

CRediT authorship contribution statement

Elizabeth Zaniewski: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing.
Ellen Brazier: Conceptualization, Methodology, Writing – review & editing.
Cam Ha Dao Ostinelli: Data curation, Resources, Writing – review & editing.
Robin Wood: Resources, Writing – review & editing.
Meg Osler: Resources, Writing – review & editing.
Karl-Günter Technau: Resources, Writing – review & editing.
Joep J van Oosterhout: Resources, Writing – review & editing.
Nicola Maxwell: Data curation, Resources, Writing – review & editing.
Janneke van Dijk: Resources, Writing – review & editing.
Hans Prozesky: Resources, Writing – review & editing.
Matthew P Fox: Resources, Writing – review & editing.
Jacob Bor: Methodology, Writing – review & editing.
Denis Nash: Conceptualization, Methodology, Writing – review & editing.
Matthias Egger: Conceptualization, Supervision, Funding acquisition, Methodology, Writing – review & editing.

Conflicts of Interest

K.-G.T. reports grants from the NIH, during the conduct of this study. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and report no potential conflicts.

Declaration of interest: None

[k]Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa.

[l]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA.

[m]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.

Abstract

Objective: To determine whether Treat-All policy impacted laboratory testing practices of antiretroviral therapy (ART) programs in Southern Africa.

Study Design and Setting: We used HIV cohort data from Lesotho, Malawi, Mozambique, South Africa, Zambia and Zimbabwe in a regression discontinuity design to estimate changes in pre-ART CD4 testing and viral load monitoring following national Treat-all adoption that occurred during 2016–2017. This study included more than 230,000 ART-naïve people living with HIV (PLHIV) aged five years or older who started ART within two years of national Treat-All adoption.

Results: We found pre-ART CD4 testing decreased following adoption of Treat-All recommendations in Malawi (−21.4 percentage points (pp), 95% CI: −26.8, −16.0) and in Mozambique (−8.8pp, 95% CI: −14.9, −2.8), but increased in Zambia (+2.7pp, 95% CI: +0.4, +5.1). Treat-All policy had no effect on viral load monitoring, except among females in South Africa (+7.1pp, 95% CI: +1.1, +13.0).

Conclusion: Treat-All policy expanded ART eligibility, but led to reductions in pre-ART CD4 testing in some countries that may weaken advanced HIV disease management. Continued and expanded support of CD4 and viral load laboratory capacity is needed to further improve treatment successes and allow for uniform evaluation of ART implementation across Southern Africa.

Keywords

CD4 lymphocyte count; viral load; antiretroviral therapy; Southern Africa; HIV infection; regression discontinuity design

1. Introduction

In 2015 the World Health Organization (WHO) released “Treat-All” guidelines recommending immediate antiretroviral therapy (ART) for all people living with HIV (PLHIV) regardless of CD4 cell count [1]. The guidelines, progressively adopted by countries, removed CD4 eligibilitiy thresholds for initiating ART, but still recommend CD4 testing to identify PLHIV with advanced HIV disease who could benefit from prophylactic and diagnostic interventions prior to starting or restarting ART [2–4]. Guidelines also recommend viral load testing six months after initiating or switching ART to assess HIV-1 viral suppression [2]. An unsuppressed viral load may indicate treatment failure and prompts interventions to improve treatment outcome [2,5,6]. CD4 and viral load testing are also crucial population-level indicators of progress towards public health goals [4,7–9].

Despite the importance of CD4 and viral load testing, recent studies show declining pre-ART CD4 testing with HIV treatment expansion in several Southern African countries and no increases in viral load testing [10,11]. Additionally, a global study found that Treat-All adoption led to decreased pre-ART CD4 testing in low and lower-middle income countries while remaining high in upper-middle and high income countries [12]. Given the high HIV burden in many low and lower-middle income countries in Southern Africa and the increase in rapid ART initiation after Treat-All adoption [13,14], examining the effect of Treat-All on pre-ART CD4 testing and viral load monitoring within countries is critical for understanding its impact on patient care. The effect of Treat-All on pre-ART CD4 testing and viral load monitoring in Southern African countries is unknown.

Randomized trials guided the WHO Treat-All recommendations, but cannot provide insight into “real-world” policy implications [15–17]. Observational data may identify policy implementation ramifications, but only with limited strength of evidence [12,13,15,17]. Regression discontinuity design, a quasi-experimental approach, mimics randomized experimental designs, allowing for causal interpretation of observed effects within observational data [17–21].

We analyzed HIV cohort data from ART programs in six Southern African countries using regression discontinuity to estimate the effect of national Treat-All adoption on pre-ART CD4 testing and viral load monitoring practices.

2. Methods

2.1 Data sources

The International epidemiology Databases to Evaluate AIDS (IeDEA) is an international research consortium that collects deidentified patient-level data from approximately two million people across 46 countries [22,23]. IeDEA Southern Africa, one of four African IeDEA regions, comprises 16 ART programs that collect data on over one million PLHIV from facilities across Lesotho, Malawi, Mozambique, South Africa, Zambia and Zimbabwe [24]. Local review boards and ethics committies approved the use of IeDEA data for research within the IeDEA collaboration. The Ethics Committee of the Canton of Bern (150/14, PB 2016–00273), Switzerland, approved data merging and collaborative analyses. Informed consent for the use of IeDEA routinely collected data has been obtained or waived according to local requirements.

2.2 Exposure and outcomes

The exposure of interest was ART initiation before versus on or after national adoption of WHO’s Treat-All recommendations (Supplemental Table S1) [1,2]. We identified national Treat-All adoption dates from policy documents, literature and personal correspondence, as described elsewhere [13,25,26]. If the exact adoption date was unknown, we used the first day of the adoption month. The two outcomes were the percentage of PLHIV with pre-ART CD4 testing and the percentage with viral load monitoring. We defined pre-ART CD4 testing as any CD4 count taken within six months before and up to seven days after ART start. We defined viral load monitoring as any viral load measurement taken within

three to nine months after ART start to ensure we captured the first recommended viral load after ART start.

2.3 Eligibility criteria

We included ART-naïve PLHIV aged five years or older who initiated ART within two years of national Treat-All adoption, had complete age and sex information, and had sufficient follow-up time between ART initiation and the earliest of database closure, documented transfer out or death. We excluded facilities that provided less than 12 months of outcome data before and after Treat-All and excluded PLHIV who started ART within 90 days of the previously adopted national ART guideline and pregnant women for whom immediate ART was already recommended prior to Treat-All. To increase generalizability to national programs, we only included public programs using government CD4 and viral load laboratory services.

To ensure adequate time to capture the outcome, we excluded PLHIV in pre-ART CD4 analyses who started ART at facilities that provided less than six months of CD4 data before ART start and PLHIV who had less than seven days of follow-up time. In viral load monitoring analyses, we excluded PLHIV who started ART at facilities that provided less than nine months of viral load data after ART start and PLHIV who had less than nine months of follow-up time. Loss to follow-up, treatment interruption and death are common within the first year of initiating ART [27,28]; to reduce bias from attrition in these analyses, we only included PLHIV classified as in care. PLHIV who had a recorded encounter (e.g. clinic visit, change in treatment, or laboratory test) within three to nine months after ART start were considered in care.

2.4 Statistical methods

We used descriptive statistics to summarize patient characteristics at ART initiation, and a sharp regression discontinuity design to estimate the effect of Treat-All policy on pre-ART CD4 testing and viral load monitoring by country [21]. We used date of ART initiation as a continuous eligibility assignment variable, considering those starting ART before Treat-All adoption as unexposed and those starting on or after adoption as exposed. The regression discontinuity design assumes that unexposed and exposed populations have similar measurable and unmeasurable characteristics, thus mimicking a randomized experimental study design [17]. To verify this assumption, we used a sharp regression discontinuity approach to assess age and sex distributions of patients intiating ART before and after Treat-All adoption.

To estimate risk differences associated with Treat-All and predict outcomes at the Treat-All threshold, we compared local linear regression models calculated just before and after Treat-All adoption using Imbens-Kalyanaraman (IK) data-driven bandwidths [29,30] for a first-order polynomial with a rectangular (uniform) kernel:

$$E[Y_i|Z_i] = \beta_0 + \beta_1 Z_i + \beta_2 \times 1[Z_i \geq 0] + \beta_3 Z_i \times 1[Z_i \geq 0]$$

([12,17])

where Y_i is the patient's probability of receiving laboratory monitoring, Z_i is the number of days between a patients' ART start date and Treat-All adoption (negative for PLHIV starting ART before Treat-All adoption), and $1[Z_i \geq 0)]$ indicates ART initiation on or after the Treat-All adoption date.

In sensitivity analyses, we assessed the robustness of estimated risk differences at various bandwidths (365 days and IK bandwidths +/−90 days), with a triangular kernel and a second-order polynomial term. Since the date of Treat-All adoption may have slightly varied among facilities within a country, we assessed the stability of the local average treatment effect to such variations by calculating the treatment effect derivative, which is equivalent to the marginal threshold treatment effect under the local policy invariance assumption, with near-zero results suggesting stability [31,32].

To assess trends in pre-ART CD4 testing and viral load monitoring before versus after Treat-All adoption, we compared slopes from linear regression models that incorporated all data available within two years of policy adoption. These models assessed differences in the percentage point change per month before and after Treat-All adoption.

All statistical analyses were performed using Stata version 15.1 (Stata Corp., College Station, TX, USA).

3. Results

3.1 Pre-ART CD4 testing

The analysis included 235,828 PLHIV from 10 programs across six countries that adopted Treat-All between 2016 and 2017 (Table 1). Five of the ten programs were from South Africa; other countries each had one program, and Zambia contributed 75% of PLHIV. Fewer than 3% of PLHIV were excluded because they had insufficient follow-up time after ART start. The median age (IQR) at ART initiation was 33 (27 to 40) years, 64% were female, and 39% had pre-ART CD4 testing, ranging from 17% in Malawi to 83% in South Africa. Regression discontinuity analysis confirmed that population age and sex characteristics at the Treat-All adoption threshold were similar, except for Lesotho and Mozambique, where median age increased and decreased, respectively (Supplemental Table S2).

3.1.1 Effect of Treat-All—Pre-ART CD4 testing after Treat-All adoption decreased in Malawi by 21.4 percentage points (pp) (95% CI: −26.8, −16.0) and in Mozambique by 8.8pp (95% CI: −14.9, −2.8), but increased in Zambia by 2.7pp (95% CI: +0.4, +5.1); there was no evidence of an effect in other countries (Table 2, Fig. 1). Malawi had the lowest percentage of PLHIV with testing before Treat-All adoption (29.0%; 95% CI: 24.0, 33.9) and the largest relative reduction in testing following adoption (−73.8%). South Africa had the highest percentage with testing (86.5%; 95% CI: 84.8, 88.2) after policy adoption. All countries had treatment effect derivative estimates close to zero and sensitivity analyses yielded consistent results (Table 2, Supplemental Table S3).

In Malawi and Mozambique, testing decreased more among males than females, whereas it decreased only among females in Lesotho (Table 3). In Zambia, testing increased among males, with no change among females.

3.1.2 Trends before and after Treat-All—During the two years before Treat-All, testing was increasing over time in Lesotho, Mozambique and South Africa, and declining in Malawi, Zambia and Zimbabwe (Table 2, Supplemental Fig. S1). During the two years following Treat-All adoption, testing declined in all countries.

3.2 Viral load monitoring

The analysis included 149,646 PLHIV from nine programs across six countries in Southern Africa (Table 1). One program in South Africa included in the CD4 analysis did not have 365 days of viral load data available after Treat-All adoption and was excluded. About 37% of PLHIV were excluded because they had insufficient follow-up time after ART start or they were not classified as in care. Patient characteristics were similar to the CD4 analysis. Overall, 18% had viral load monitoring, ranging from 2% in Lesotho to 79% in South Africa. Regression discontinuity analysis confirmed that PLHIV intiating ART before and after national Treat-All adoption were similar with respect to age and sex (Supplemental Table S4).

3.2.1 Effect of Treat-All—Viral load monitoring increased by 7.1pp (95% CI: +1.1, +13.0) among women in South Africa, but there was no evidence of an effect in other countries (Table 4, Table 5, Fig. 1). Mozambique had the lowest percentage of PLHIV with monitoring just prior to Treat-All adoption (1.5%; 95% CI: 0.2, 2.8) and South Africa had the highest just following policy adoption (79.6%; 95% CI: 76.4, 82.7). The treatment effect derivative estimates for all countries were close to zero and sensitivity analyses indicated the robustness of results (Table 4, Supplemental Table S5).

3.2.2 Trends before and after Treat-All—Before Treat-All, viral load monitoring was increasing in Malawi, Mozambique, South Africa and Zambia (Table 4, Supplemental Fig. S1). Following Treat-All the slope decreased in South Africa, but increased more steeply in the other three countries. No significant changes were observed in Lesotho and Zimbabwe.

4. Discussion

4.1 Main findings

The effect of Treat-All on pre-ART CD4 testing varied in Southern Africa. Although a recent global IeDEA study found Treat-All adoption in low or lower-middle income countries led to an immediate decline in pre-ART CD4 testing among adults who enrolled in HIV care after Treat-All adoption [12], we found considerable heterogeneity in the direction and magnitude of the immediate effect in such countries [33], which also varied by sex. We found testing slightly increased in Zambia, but decreased substantially in Malawi and moderately in Mozambique, with no effect in Lesotho or Zimbabwe. In South Africa, the only upper-middle income country in our study [33], there was no effect on testing. Despite

initial heterogeneity, over subsequent years pre-ART CD4 testing declined throughout the region.

4.2 Interpretation

Our study and the recent global IeDEA study used IeDEA data and regression discontinuity design, however the latter study pooled data within broad income-group classifications that likely obscured heterogeneity among countries [12]. Further, the absence in the global study of Zambia, which comprised nearly 85% of low and lower-middle income data in our study and had the most divergent results, may further explain dissimilar findings.

The heterogeneity may reflect a combination of factors in each country, including the relative increase in ART initiation following removal of CD4 eligibility requirements, the population groups whose access to treatment had been most restricted by previous ART guidelines, and the capacity and resources available for CD4 testing. For example, prior research reported rapid ART initiation among adults increased 30 times more in Malawi than in Zambia following Treat-All adoption [13]; while modest increases in CD4 testing observed in Zambia may reflect the ability of testing capacity and resources to meet the increased numbers of patients initiating treatment, the sharp decrease in CD4 testing observed in Malawi may reflect the limits in local testing capacity to keep pace with the influx of ART initiators. Similarly, the larger effect of Treat-All among males than females in both Malawi and Mozambique may indicate that a larger proportion of pre-Treat-All testing among males was for determining ART eligibility, which was no longer required after Treat-All adoption.

Although we found Treat-All led to heterogeneous changes in pre-ART CD4 testing, there was no evidence of an immediate effect on viral load monitoring, aside from a moderate increase among women in South Africa, suggesting viral load testing volume increased proportional to the number newly starting treatment. Despite an increasing trend in viral load monitoring across the region during the two years before Treat-All adoption, in South Africa it subsequently declined. In contrast, in Malawi, Mozambique and Zambia, it increased more steeply. We found more than 75% of PLHIV in South Africa had viral load monitoring just after policy adoption, whereas coverage was less than 13% elsewhere. These findings are consistent with several recent studies, which reported disparities in viral load monitoring among income groups and countries in Southern Africa [10–12].

Delays in scale-up of routine viral load monitoring and rapidly growing demand under Treat-All [13] may explain some of the low viral load monitoring levels observed. Although fewer than 13% of PLHIV in Zambia had viral load monitoring just following Treat-All adoption in 2016, this is in line with their phased plans for expanding viral load testing coverage from 10% in 2016 to 70% by 2018 [34]. However, recent monthly mean percentages appear to plateau suggesting the 2018 goal is unlikely to be reached soon. In Zimbabwe, fewer than 9% of PLHIV had viral load monitoring at the Treat-All threshold, far below the 50% target for that year [35], and levels in Mozambique and Malawi were also low despite planned scale-up just before or alongside adoption of Treat-All recommendations [36,37], however the subsequent rising trend alongside increasing demand, suggests a strong scale-up effort. Some studies reported higher levels of viral load

monitoring than we observed, but they used broader definitions that encompassed any viral load measurement taken six or 12 months after ART start, whereas we aimed to emulate the recommended 6-month timeframe outlined in Treat-All policies [11,38,39]. A recent study in South Africa found the risk for treatment failure on ART increased by 9% for each month viral load testing was delayed highlighting the importance of timely viral load monitoring to enhance treatment success [40].

The President's Emergency Plan for AIDS Relief (PEPFAR) provides substantial support to countries in this study. Since 2018, PEPFAR has used results from pre-ART CD4 testing to determine the balance of support between continued CD4 testing and scale-up of viral load testing [9]. However, changes in pre-ART CD4 testing following Treat-All adoption could lead to a scenario where without adequate CD4 testing, PLHIV with advanced HIV disease may be missed, obscuring the need for continued CD4 testing. Further, varying levels of CD4 and viral load testing may affect studies and modelling efforts that rely on these data to inform policy recommendations and may also hinder measurement and assessment of progress towards global public health goals of earlier treatment initiation and the UNAIDS 95–95-95 targets, which rely on such data [8].

4.3 Strengths and limitations

The sharp regression discontinuity design to analyze country-level observational data is a strength of this study, allowing us to uncover important heterogeneity between countries despite similarities in HIV burden and country income. The use of data-driven bandwidths and sensitivity analyses permit causal interpretation akin to experimental studies. Previous studies found substantial loss to follow-up of PLHIV on ART in Southern Africa [27,28], but other studies found immediate ART may improve retention [41,42]. We only included PLHIV classified as in care to reduce associated biases. Finally, we included public ART treatment programs in six countries in the region and large study populations.

Study limitations include the fact that ART programs and clinics participating in IeDEA Southern Africa may not be nationally representative, thus potentially reducing generalizability. Further, a previous study of clinics in IeDEA found clinic-level introduction of national Treat-All policies vary within countries [26]. However, treatment effect derivative estimates suggest these variations were unlikely to influence estimated effects. We compared age and sex of populations before and after Treat-All adoption to confirm key assumptions for regression discontinuity, but lack of more detailed data on patient characteristics limited comparisons on other potential confounding factors. In the CD4 analysis, we identified age distribution differences in two countries, however these were relatively small and unlikely to affect results markedly. We did not account for differences in level of care, facility type, or location, nor did we attempt to correct for missing pregancy data, which may have affected results.

5. Conclusion

Regression discontinuity analyses of cohort data from ART programs in six Southern African countries revealed "real-world" unintended and varied effects of Treat-All policy on pre-ART CD4 testing, which may affect identification of PLHIV with advanced HIV

disease and worsen the quality of HIV care in some countries. Prior to adopting new policy, possible negative effects should be investigated and anticipated in order to mitigate or avoid them. Although Treat-All expanded ART eligibility to increase ART coverage, support for continued and expanded CD4 and viral load laboratory capacity is crucial for ensuring continued improvement of treatment success, appropriate resource allocation and uniform evaluation of ART implementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank all PLHIV, care providers and data managers in the IeDEA Southern Africa region for contributing data for this project. We would also like to thank Félix Cuneo for the initial statistical support.

Funding

This work was supported by the National Institute of Allergy and Infectious Diseases of the U.S. National Institutes of Health, as part of the International epidemiology Databases to Evaluate AIDS Southern Africa collaboration (award number U01AI069924). M.E. was supported by special project funding (grant 189498) from the Swiss National Science Foundation. This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

References

[1]. World Health Organization (WHO). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. WHO; 2015 http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1. Accessed August 23, 2021.

[2]. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Second edition. WHO; 2016. https://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed August 23, 2021.

[3]. World Health Organization (WHO). Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy. 2017. WHO; 2017. https://www.who.int/publications/i/item/9789241550062. Accessed August 23, 2021.

[4]. 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;12(2):123–128. doi: 10.1097/COH.0000000000000348. [PubMed: 28059957]

[5]. World Health Organization. HIV treatment and care. What's new in HIV treatment monitoring: Viral load and CD4 testing. Information note. Geneva: World Health Organization; 2017. Available from: https://www.who.int/hiv/pub/arv/treatment-monitoring-info-2017/en/. Accessed August 23, 2021.

[6]. Joint United Nations Programme on HIV/AIDS. The need for routine viral load testing. Questions and answers. Geneva: Joint United Nations Programme on HIV/AIDS; 2016. Available from: https://www.unaids.org/en/resources/documents/2016/JC2845. Accessed August 23, 2021.

[7]. Nash D, Robertson M. How to Evolve the Response to the Global HIV Epidemic With New Metrics and Targets Based on Pre-Treatment CD4 Counts. Curr HIV/AIDS Rep. 2019 8 5;16(4):304–13. 10.1007/s11904-019-00452-7 [PubMed: 31278620]

[8]. UNAIDS. 90–90-90 An ambitious treatment target to help end the AIDS epidemic. 2014. Available from: https://www.unaids.org/en/resources/documents/2017/90-90-90. Accessed August 23, 2021.

[9]. U.S. President's Emergency Plan for AIDS Relief. PEPFAR 2018 Country Operational Plan Guidance for Standard Process Countries. 2018. Available from: https://www.state.gov/pepfar/. Accessed August 23, 2021.

[10]. Zaniewski E, Dao Ostinelli CH, Chammartin F, Maxwell N, Davies M-A, Euvrard J, et al. Trends in CD4 and viral load testing 2005 to 2018: multi-cohort study of people living with HIV in Southern Africa. J Int AIDS Soc. 2020 7 8;23(7):2020.03.09.. 10.1002/jia2.25546 [PubMed: 20033423]

[11]. 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;65(47):1332–5. 10.15585/mmwr.mm6547a2 [PubMed: 27906910]

[12]. Brazier E, Tymejczyk O, Zaniewski E, Egger M, Wools-Kaloustian K, Yiannoutsos CT, et al. Effects of National Adoption of Treat-All Guidelines on Pre-Antiretroviral Therapy (ART) CD4 Testing and Viral Load Monitoring After ART initiation: A Regression Discontinuity Analysis. Clin Infect Dis. 2021 3 9; 10.1093/cid/ciab222

[13]. Tymejczyk O, Brazier E, Yiannoutsos CT, Vinikoor M, van Lettow M, Nalugoda F, et al. Changes in rapid HIV treatment initiation after national “treat all” policy adoption in 6 sub-Saharan African countries: Regression discontinuity analysis. PLOS Med. 2019;16(6):e1002822. 10.1371/journal.pmed.1002822 [PubMed: 31181056]

[14]. Tymejczyk O, Brazier E, Wools-Kaloustian K, Davies M-A, Dilorenzo M, Edmonds A, et al. Impact of Universal Antiretroviral Treatment Eligibility on Rapid Treatment Initiation Among Young Adolescents with Human Immunodeficiency Virus in Sub-Saharan Africa. J Infect Dis. 2020 8 4;222(5):755–64. 10.1093/infdis/jiz547 [PubMed: 31682261]

[15]. Ford N, Penazzato M, Vitoria M, Doherty M, Davies M-A, Zaniewski E, et al. The contribution of observational studies in supporting the WHO “treat all” recommendation for HIV/AIDS. J Virus Erad. 2018;4(Supplement 2):5–8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6248853/. Accessed August 23, 2021. [PubMed: 30515308]

[16]. 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: The. J Int AIDS Soc. 2018;21(2):17–9. 10.1002/jia2.25078

[17]. Bor J, Moscoe E, Mutevedzi P, Newell ML, Bärnighausen T. Regression discontinuity designs in epidemiology: Causal inference without randomized trials. Epidemiology. 2014;25(5):729–37. 10.1097/ede.0000000000000138 [PubMed: 25061922]

[18]. Jacob RT, Zhu P, Somers M-A, Bloom HS. A practical guide to regression discontinuity. 2012. Available from: http://www.mdrc.org/publications/644/full.pdf. Accessed August 23, 2021.

[19]. Moscoe E, Bor J, Bärnighausen T. Regression discontinuity designs are underutilized in medicine, epidemiology, and public health: A review of current and best practice. J Clin Epidemiol. 2015;68(2):132–43. 10.1016/j.jclinepi.2014.06.021

[20]. Bärnighausen T, Tugwell P, Røttingen J-A, Shemilt I, Rockers P, Geldsetzer P, et al. Quasi-experimental study designs series—paper 4: uses and value. J Clin Epidemiol. 2017 9;89:21–9. 10.1016/j.jclinepi.2017.03.012 [PubMed: 28365303]

[21]. Bärnighausen T, Oldenburg C, Tugwell P, Bommer C, Ebert C, Barreto M, et al. Quasi-experimental study designs series—paper 7: assessing the assumptions. J Clin Epidemiol. 2017 9;89:53–66. 10.1016/j.jclinepi.2017.02.017 [PubMed: 28365306]

[22]. International epidemiology Databases to Evaluate AIDS (IeDEA). Available from: https://www.iedea.org/. Accessed August 23, 2021.

[23]. Zaniewski E, Tymejczyk O, Kariminia A, Desmonde S, Leroy V, Ford N, et al. IeDEA – WHO Research-Policy Collaboration: contributing real-world evidence to HIV progress reporting and guideline development. J Virus Erad. 2018;4(Suppl 2):9–15. PMCID: PMC6248847. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6248847/. Accessed August 23, 2021. [PubMed: 30515309]

[24]. Chammartin F, Dao Ostinelli CH, Anastos K, Jaquet A, Brazier E, Brown S, et al. International epidemiology databases to evaluate AIDS (IeDEA) in sub-Saharan Africa, 2012–2019. BMJ Open. 2020 5 15;10(5):e035246. 10.1136/bmjopen-2019-035246

[25]. Tymejczyk O, Brazier E, Yiannoutsos C, Wools-Kaloustian K, Althoff K, Crabtree-Ramírez B, et al. HIV treatment eligibility expansion and timely antiretroviral treatment initiation following enrollment in HIV care: A metaregression analysis of programmatic data from 22 countries. PLOS Med. 2018;15(3): e10. 10.1371/journal.pmed.1002534

[26]. Brazier E, Maruri F, Duda SN, Tymejczyk O, Wester CW, Somi G, et al. Implementation of “Treat-all” at adult HIV care and treatment sites in the Global IeDEA Consortium: results from the Site Assessment Survey. J Int AIDS Soc. 2019 7 12;22(7):e25331. 10.1002/jia2.25331 [PubMed: 31623428]

[27]. Haas AD, Zaniewski E, Anderegg N, Ford N, Fox MP, Vinikoor M, et al. Retention and mortality on antiretroviral therapy in sub-Saharan Africa: collaborative analyses of HIV treatment programmes. J Int AIDS Soc. 2018 2;21(2):e25084. 10.1002/jia2.25084

[28]. Anderegg N, Hector J, Jefferys LF, Burgos-Soto J, Hobbins MA, Ehmer J, et al. Loss to follow-up correction increased mortality estimates in HIV–positive people on antiretroviral therapy in Mozambique. J Clin Epidemiol. 2020;128:83–92. 10.1016/j.jclinepi.2020.08.012 [PubMed: 32828836]

[29]. Imbens G, Kalyanaraman K. Optimal bandwidth choice for the regression discontinuity estimator. Rev Econ Stud. 2012;79(3):933–59. 10.1093/restud/rdr043

[30]. Hahn J, Todd P, Van Der Klaauw W, Econometrica S, Jan N. Identification and Estimation of Treatment Effects with a Regression-Discontinuity Design Author(s): Jinyong Hahn, Petra Todd and Wilbert Van der Klaauw Source: Econometrica. 2001;69(1):201–9. Available from: https://www.jstor.org/stable/2692190. Accessed August 23, 2021.

[31]. Dong Y, Lewbel A. Identifying the effect of changing the policy threshold in regression discontinuity models. Rev Econ Stat. 2015;97(5):1081–92.: 10.1162/REST_a_00510

[32]. Cerulli G, Dong Y, Lewbel A, Poulsen A. Testing stability of regression discontinuity models. Adv Econom. 2017;38:317–39. 10.1108/S0731-905320170000038013

[33]. The World Bank. New country classifications by income level 2016–2017. Available from: https://blogs.worldbank.org/opendata/new-country-classifications-2016. Accessed August 23, 2021.

[34]. Republic of Zambia Ministry of Health. Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection. 2016.

[35]. Zimbabwe M of H and CC. ZIMBABWE HIV Viral Load Scale-up Plan 2015–2018. 2015.

[36]. Republica de Mocambique Minsterio da Saude. Guião de implementação da abordagem do testar e iniciar. 2016.

[37]. Government of Malawi Ministry of Health. Integrated HIV Program Report July-September 2016. 2016.

[38]. Nicholas S, Poulet E, Wolters L, Wapling J, Rakesh A, Amoros I, et al. Point-of-care viral load monitoring: outcomes from a decentralized HIV programme in Malawi. J Int AIDS Soc. 2019;22(8):1–9. https://dx.doi.org/10.1002%2Fjia2.25387

[39]. Swannet S, Decroo T, de Castro SMTL, Rose C, Giuliani R, Molfino L, et al. Journey towards universal viral load monitoring in Maputo, Mozambique: Many gaps, but encouraging signs. Int Health. 2017;9(4):206–14.: 10.1093/inthealth/ihx021 [PubMed: 28810670]

[40]. Kerschberger B, Boulle AM, Kranzer K, Hilderbrand K, Schomaker M, Coetzee D, et al. Superior virologic and treatment outcomes when viral load is measured at 3 months compared to 6 months on antiretroviral therapy. J Int AIDS Soc. 2015;18(1):1–7. 10.7448/ias.18.1.20092

[41]. Bor J, Fox MP, Rosen S, Venkataramani A, Tanser F, Pillay D, et al. Treatment eligibility and retention in clinical HIV care: A regression discontinuity study in South Africa. PLOS Med. 2017;14(11):e1002463. 10.1371/journal.pmed.1002463 [PubMed: 29182641]

[42]. Mody A, Sikazwe I, Czaicki NL, Mwanza MW, Savory T, Sikombe K, et al. Estimating the real-world effects of expanding antiretroviral treatment eligibility : Evidence from a regression discontinuity analysis in Zambia. PLoS Med. 2018;1–19. 10.1371/journal.pmed.1002574

What is new?

Key findings

- Regression discontinuity analyses of antiretroviral therapy (ART) program data from six countries in Southern Africa found national Treat-All adoption led to heterogeneous changes in pre-ART CD4 testing among patients starting ART; except among females in South Africa, Treat-All had no effect on viral load monitoring.

What this adds to what is known?

- This study provides a new understanding of the "real-world" effects of Treat-All on ART-related laboratory testing within countries in Southern Africa.
- Although Treat-All expanded ART eligibility, its effect on pre-ART CD4 testing varied in magnitude and direction, even among countries with similar HIV-burden and income classification.

What is the implication and what should change now?

- Countries should anticipate, investigate and mitigate possible unintended effects of new national HIV treatment policies that may worsen the quality of HIV care.
- Adequate resource allocation for expanded CD4 and viral load laboratory capacity across Southern Africa is needed for uniform evaluation of ART implementation and continuing improvement of treatment outcomes.

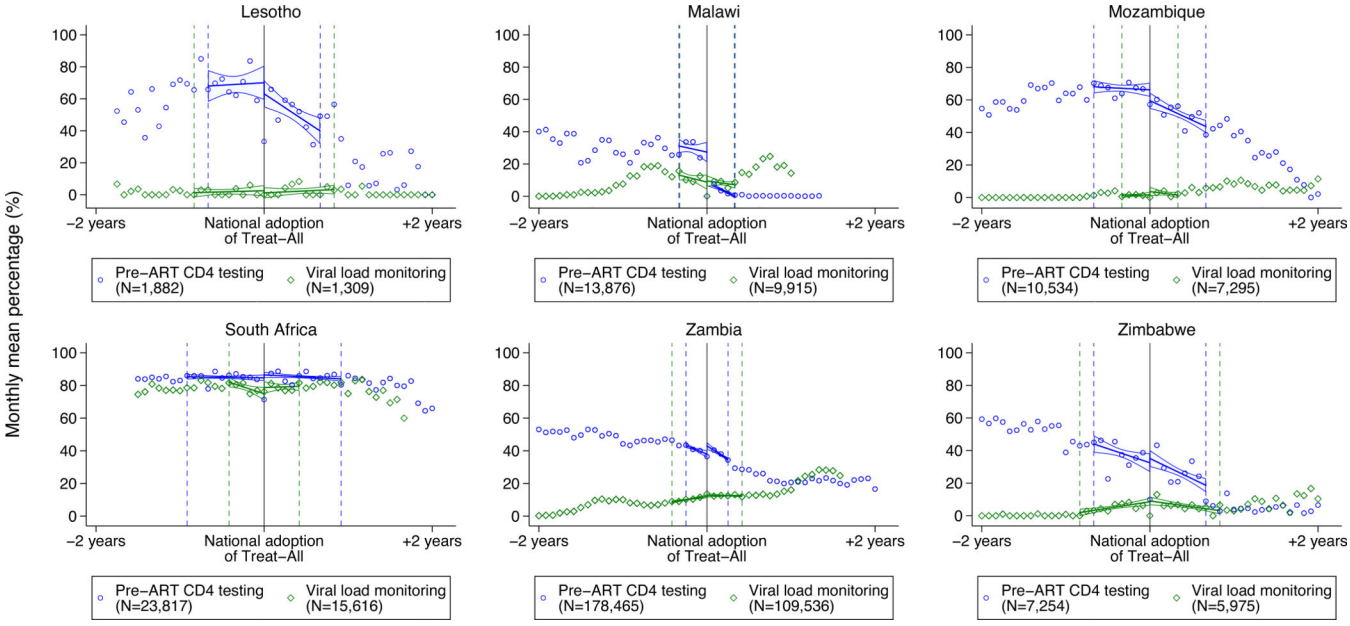

Fig. 1: Laboratory testing of patients (≥5 years of age) who initiated antiretroviral therapy (ART) before and after national Treat-All adoption by country.

These plots illustrate the monthly mean percentage with pre-ART CD4 testing or viral load monitoring, the linear prediction produced by the regression discontinuity models using Imbens-Kalyanaraman (IK) data-driven bandwidths to estimate effect size, the 95% confidence intervals, and the number of patients included in each analysis. Dotted vertical lines on either side of the Treat-All threshold represent the IK bandwidths used in each regression discontinuity analysis.

Table 1:

Baseline characteristics of patients (≥5 years) in pre-ART CD4 testing and viral load (VL) monitoring analyses by country.

	Lesotho	Malawi	Mozambique	South Africa	Zambia	Zimbabwe	Total
Pre-ART CD4 testing							
Total patients	1,882 (100%)	13,876 (100%)	10,534 (100%)	23,817 (100%)	178,465 (100%)	7,254 (100%)	235,828 (100%)
Female	1,249 (66%)	8,921 (64%)	6,907 (66%)	16,540 (69%)	112,876 (63%)	4,710 (65%)	151,203 (64%)
Age in years							
median (IQR)	35 (28–46)	33 (26–41)	31 (25–40)	33 (27–41)	33 (27–40)	34 (26–42)	33 (27–40)
≤15	67 (4%)	688 (5%)	235 (2%)	337 (1%)	6,085 (3%)	484 (7%)	7,896 (3%)
16–24	231 (12%)	2,401 (17%)	2,486 (24%)	3,248 (14%)	29,018 (16%)	1,191 (16%)	38,575 (17%)
≥25	1,584 (84%)	10,787 (78%)	7,813 (74%)	20,232 (85%)	143,362 (81%)	5,579 (77%)	189,357 (80%)
With pre-ART CD4 testing	896 (48%)	2,334 (17%)	5,211 (50%)	19,857 (83%)	61,852 (35%)	2,300 (32%)	92,450 (39%)
VL monitoring							
Total patients	1,309 (100%)	9,915 (100%)	7,295 (100%)	15,616 (100%)	109,536 (100%)	5,975 (100%)	149,646 (100%)
Female	861 (66%)	6,493 (66%)	4,921 (68%)	10,743 (69%)	69,687 (64%)	3,865 (65%)	96,570 (65%)
Age in years							
median (IQR)	36 (28–46)	33 (26–41)	31 (25–41)	34 (28–42)	33 (27–40)	35 (27–43)	33 (27–41)
≤15	47 (4%)	514 (5%)	179 (2%)	141 (1%)	4,097 (4%)	423 (7%)	5,401 (4%)
16–24	157 (12%)	1,582 (16%)	1,608 (22%)	1,887 (12%)	16,193 (15%)	843 (14%)	22,270 (15%)
≥25	1,105 (84%)	7,819 (79%)	5,508 (76%)	13,588 (87%)	89,246 (81%)	4,709 (79%)	121,975 (81%)
With VL monitoring	20 (2%)	1,010 (10%)	254 (4%)	12,323 (79%)	12,746 (12%)	260 (4%)	26,613 (18%)

Abbreviation: IQR, interquartile range.

Number of patients (%) are shown unless otherwise indicated.

Table 2:

Percentage with pre-ART CD4 testing before and after national Treat-All policy adoption by country.

	Lesotho	Malawi	Mozambique	South Africa	Zambia	Zimbabwe
Patients	1,882 (100%)	13,876 (100%)	10,534 (100%)	23,817 (100%)	178,465 (100%)	7,254 (100%)
before Treat-All	816 (43%)	7,260 (52%)	4,958 (47%)	10,777 (45%)	76,349 (43%)	3,868 (53%)
after Treat-All	1,066 (57%)	6,616 (48%)	5,576 (53%)	13,040 (55%)	102,116 (57%)	3,386 (47%)
Risk difference at threshold*	−8.6	**−21.4**	**−8.8**	1.2	**2.7**	0.2
(95% CI)	(−20.9, 3.7)	(−26.8, −16.0)	(−14.9, −2.8)	(−1.3, 3.7)	(0.4, 5.1)	(−7.0, 7.5)
p-value	0.171	**<0.001**	**0.004**	0.345	**0.024**	0.949
IK bandwidth (days)	238	123	238	347	105	241
patients within bandwidth	751	3,189	3,790	12,923	27,298	2,771
Treatment Effect Derivative	−0.101	−0.056	−0.048	−0.010	−0.066	−0.025
(95% CI)	(−0.198, −0.004)	(−0.130, 0.019)	(−0.091, −0.004)	(−0.021, 0.003)	(−0.104, −0.028)	(−0.078, 0.029)
p-value	0.041	0.145	0.004	0.128	0.001	0.368
Predicted outcomes at threshold						
just before Treat-All	70.5	29.0	66.5	85.3	39.5	34.0
(95% CI)	(60.5, 80.4)	(24.0, 33.9)	(62.6, 70.5)	(83.5, 87.1)	(37.8, 41.2)	(28.6, 39.3)
just after Treat-All	61.9	7.6	57.7	86.5	42.2	34.2
(95% CI)	(61.1, 69.7)	(5.3, 9.8)	(53.2, 62.2)	(84.8, 88.2)	(40.6, 43.9)	(29.3, 39.1)
relative change	−12.2%	−73.8%	−13.3%	1.4%	6.8%	0.6%
Slopes before and after Treat-All †						
before Treat-All (95% CI)	1.1 (0.6, 1.7)	**−0.4** (−0.5, −0.2)	**0.5** (0.3, 0.7)	**0.1** (−0.1, 0.2)	**−0.5** (−0.5, −0.4)	**−1.1** (−1.3,-0.9)
after Treat-All (95% CI)	−2.6 (−2.9, −2.2)	**−0.3** (−0.3, −0.2)	**−2.3** (−2.4, −2.1)	**−0.6** (−0.7, −0.5)	**−0.7** (−0.7, −0.6)	**−1.4** (−1.6,-1.3)
p-value	0.055	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Abbreviation: CI, confidence interval.

*Risk differences at the national Treat-All adoption threshold are from regression discontinuity analyses using Imbens-Kalyanaraman (IK) bandwidths derived from all data available within two years before and after the threshold to estimate the difference in local linear predictions. The bandwidth defines the area on each side of the threshold where the relationship between antiretroviral therapy (ART) start and pre-ART CD4 testing is assumed to be linear in local linear regression models.

† Slope comparison is from separate linear regression models comparing the percentage point change per month before and after Treat-All using all data available within two years before and after national Treat-All adoption.

Table 3:

Percentage with pre-ART CD4 testing before and after national Treat-All policy adoption by country and sex.

	Lesotho	Malawi	Mozambique	South Africa	Zambia	Zimbabwe
Female patients	1,249 (100%)	8,921 (100%)	6,907 (100%)	16,540 (100%)	112,876 (100%)	4,710 (100%)
before Treat-All	547 (44%)	4,883 (55%)	3,400 (49%)	7,586 (46%)	49,242 (44%)	2,621 (56%)
after Treat-All	702 (56%)	4,038 (45%)	3,507 (51%)	8,954 (54%)	63,634 (56%)	2,089 (44%)
Risk difference at threshold*	**−15.6**	**−14.7**	−4.5	0.8	1.6	−3.0
(95% CI)	(−29.4, −1.8)	(−20.8, −8.7)	(−12.0, 2.9)	(−2.6, 4.3)	(−1.0, 4.1)	(−11.7, 5.8)
p-value	**0.027**	**<0.001**	0.235	0.636	0.235	0.511
IK bandwidth (days)	302	129	257	274	134	248
patients within bandwidth	618	2,060	2,584	7,042	22,186	1,794
Male patients	633 (100%)	4,955 (100%)	3,627 (100%)	7,277 (100%)	65,589 (100%)	2,544 (100%)
before Treat-All	269 (42%)	2,377 (48%)	1,558 (43%)	3,191 (44%)	27,107 (41%)	1,247 (49%)
after Treat-All	364 (58%)	2,578 (52%)	2,069 (57%)	4,086 (56%)	38,482 (59%)	1,297 (51%)
Risk difference at threshold*	4.7	**−36.7**	**−14.5**	−1.7	**6.8**	6.2
(95% CI)*	(−16.8, 26.1)	−(−46.6, −26.8)	(−23.7, −5.4)	(−7.2, 3.8)	(2.8, 10.8)	(−5.6, 17.9)
p-value	0.669	**<0.001**	**0.002**	0.544	**0.001**	0.303
IK bandwidth (days)	278	128	260	188	110	272
patients within bandwidth	298	1,203	1,489	2,131	10,210	1,101

Abbreviation: CI, confidence interval.

*Risk differences at the national Treat-All policy adoption threshold are from regression discontinuity analyses using Imbens-Kalyanaraman (IK) bandwidths derived from all data available within two years before and after the threshold to estimate the difference in local linear predictions. The bandwidth defines the area on each side of the threshold where the relationship between antiretroviral therapy (ART) start and pre-ART CD4 testing is assumed to be linear in local linear regression models.

Table 4:

Percentage with viral load monitoring before and after national Treat-All policy adoption by country.

	Lesotho	Malawi	Mozambique	South Africa	Zambia	Zimbabwe
Patients	1,309 (100%)	9,915 (100%)	7,295 (100%)	15,616 (100%)	109,536 (100%)	5,975 (100%)
before Treat-All	626 (48%)	6,071 (61%)	3,421 (47%)	8,316 (53%)	56,951 (52%)	3,349 (56%)
after Treat-All	683 (52%)	3,844 (39%)	3,874 (53%)	7,300 (47%)	52,585 (48%)	2,626 (44%)
Risk difference at threshold*	−1.2	0.6	2.6	4.0	0.7	0.4
(95% CI)	(−5.4, 3.1)	(−4.7, 6.0)	(−0.5, 5.7)	(−0.9, 8.8)	(−0.9, 2.2)	(−3.2, 4.0)
p-value	0.589	0.815	0.094	0.108	0.400	0.809
IK bandwidth (days)	316	113	123	153	149	310
patients within bandwidth	576	2,519	1,365	4,225	28,068	2,981
Treatment Effect Derivative	0.001	0.024	−0.036	0.041	−0.031	−0.041
(95% CI)	(−0.021, 0.024)	(−0.061, 0.110)	(−0.077, 0.0048)	(−0.012, 0.095)	(−0.048, −0.013)	(−0.060, −0.024)
p-value	0.893	0.581	0.083	0.130	0.001	<0.001
Predicted outcomes at threshold						
just before Treat-All	2.5	8.9	1.5	75.6	12.0	8.4
(95% CI)	(−1.0, 6.0)	(4.6, 13.2)	(0.2, 2.8)	(72.0, 79.2)	(11.0, 13.1)	(6.1, 10.7)
just after Treat-All	1.3	9.5	4.1	79.6	12.7	8.8
(95% CI)	(−1.1, 3.8)	(6.4, 12.7)	(1.3, 7.0)	(76.4, 82.7)	(11.6, 13.8)	(6.0, 11.6)
relative change	−48.0%	6.7%	173.3%	5.2%	5.8%	4.8%
Slopes before and after Treat-All †						
before Treat-All (95% CI)	0.0 (−0.2, 0.2)	**0.8** (0.7, 0.8)	**0.1** (0.1, 0.2)	**0.2** (−0.0, 0.3)	**0.4** (0.4, 0.4)	0.4 (0.3, 0.4)
after Treat-All (95% CI)	−0.1 (−0.2, 0.0)	**1.4** (1.1, 1.7)	**0.2** (0.1, 0.3)	**−0.1** (−0.3, 0.1)	**1.0** (0.9, 1.1)	0.2 (0.0, 0.4)
p-value	1.000	**0.030**	**0.034**	**<0.001**	**0.012**	0.069

Abbreviation: CI, confidence interval.

*Risk differences at the national Treat-All policy adoption threshold are from regression discontinuity analyses using Imbens-Kalyanaraman (IK) bandwidths derived from all data available within two years before and after the threshold to estimate the difference in local linear predictions. The bandwidth defines the area on each side of the threshold where the relationship between antiretroviral therapy (ART) start and viral load monitoring is assumed to be linear in local linear regression models.

† Slope comparison is from separate linear regression models comparing the percentage point change per month before and after Treat-All using all data available within two years before and after national Treat-All adoption.

Table 5:

Percentage with viral load monitoring before and after national Treat-All policy adoption by country and sex.

	Lesotho	Malawi	Mozambique	South Africa	Zambia	Zimbabwe
Female patients	861 (100%)	6,493 (100%)	4,921 (100%)	10,743 (100%)	69,687 (100%)	3,865 (100%)
before Treat-All	416 (48%)	4,096 (63%)	2,412 (49%)	5,768 (54%)	36,618 (53%)	2,244 (58%)
after Treat-All	445 (52%)	2,397 (37%)	2,509 (51%)	4,975 (46%)	33,069 (47%)	1,621 (42%)
Risk difference at threshold*	−0.2	−4.4	3.3	**7.1**	0.6	1.4
(95% CI)	(−5.8, 5.3)	(−10.3, 1.5)	(−0.7, 7.3)	(1.1, 13.0)	(−1.3, 2.5)	(−2.9, 5.6)
p-value	0.944	0.142	0.106	**0.020**	0.552	0.525
IK bandwidth (days)	402	131	135	147	143	373
patients within bandwidth	498	1,810	968	2,778	17,043	2,182
Male patients	448 (100%)	3,422 (100%)	2,374 (100%)	4,873 (100%)	39,849 (100%)	2,110 (100%)
before Treat-All	210 (47%)	1,975 (58%)	1,009 (42%)	2,548 (52%)	20,333 (51%)	1,105 (52%)
after Treat-All	238 (53%)	1,447 (42%)	1,365 (58%)	2,325 (48%)	19,516 (49%)	1,005 (48%)
Risk difference at threshold*	NA	3.3	0.7	−4.2	1.7	0.1
(95% CI)	NA	(−5.5, 12.1)	(−2.2, 3.7)	(−9.8, 1.4)	(−0.8, 4.1)	(−6.4, 6.6)
p-value	NA	0.464	0.627	0.144	0.178	0.967
IK bandwidth (days)	NA	117	208	356	181	224
patients within bandwidth	NA	941	803	3,187	12,218	808

Abbreviation: CI, confidence interval.

*Risk differences at the national Treat-All policy adoption threshold are from regression discontinuity analyses using Imbens-Kalyanaraman (IK) bandwidths derived from all data available within two years before and after the threshold to estimate the difference in local linear predictions. The bandwidth defines the area on each side of the threshold where the relationship between antiretroviral therapy (ART) start and viral load monitoring is assumed to be linear in local linear regression models.