BMJ Open

Impact of the test and treat policy on delays in ART initiation among HIV positive patients in Johannesburg, South Africa

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030228
Article Type:	Research
Date Submitted by the Author:	20-Mar-2019
Complete List of Authors:	Onoya, Dorina; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Sineke, Tembeka; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Hendrickson, Cheryl; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Mokhele, Idah; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Maskew, Mhairi; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Long, Lawrence; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office; Boston University, Boston School of Public Health, Department of Global Health Fox, Matt; Boston University, Epidemiology and Global Health; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, PRIMARY CARE

+Working Title:

Impact of UTT and same-day-ART treatment initiation policies delays in ART initiation in Johannesburg, South Africa

Title: Impact of the test and treat policy on delays in ART initiation among HIV positive patients in Johannesburg, South Africa

Authors: Dorina Onoya[1], Tembeka Sineke[1], Cheryl Hendrickson[1], Idah Mokhele[1], Mhairi Maskew[1], Lawrence Long[1,2], Matthew P. Fox[1, 2, 3]

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

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

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

Corresponding author: Dorina Onoya, Health Economics and Epidemiology Research Office, 39 Empire Road, Parktown, Johannesburg, 2193, South Africa, donoya@heroza.org +27 10 001 7930

Keywords: HIV, ART attrition, UTT, same-day-ART

Word count (main body): 2074

Abstract

Objectives To assess delays to antiretroviral therapy (ART) initiation before the Universal Test & Treat (UTT) policy, under UTT and during Same-day-ART policy periods in Johannesburg (South Africa).

Design Prospective cohort study

Setting Patients were recruited from six primary health clinic in Johannesburg.

Participants Overall, 1029 newly diagnosed HIV positive adults (≥18 years) were enrolled between April to December 2015 (Pre-UTT), July-September 2017 (UTT) and October 2017-July 2018 (UTT/Same-day-ART).

Main outcome measures Patient records were reviewed 30 days after HIV diagnosis. Predictors of 30-days-ART initiation were assessed using Cox proportional hazards models. Additionally, predictors of Same-day-ART initiation were evaluated using Poisson Regression modelling.

Results Overall, 740 (71.9%) initiated ART within 30 days (36.9% pre-UTT, 65.9% under UTT and 79.9% under UTT/Same-day-ART). The median days to ART initiation declined from 21.0 days pre-UTT (IQR: 15-30) to eight days (IQR: 6-16) under UTT and five days (IQR: 0-8) under the UTT/Same-day-ART policy. However, only 150 (20.2%) of the UTT/Same-day-ART cohort initiated ART immediately. Living in a two-adult home (adjusted Hazard ratio (aHR) 1.2 vs living alone, 95% Confidence Interval (CI): 1.0-1.4) and travelling >30 minutes to the clinic (aHR 1.3 vs. <15 minute travel, 95% CI: 1.1-1.7) were associated with a higher likelihood of starting ART within 30 days. Participants who lacked 30-days CD4 data were 30% less likely to start ART by 30 days (aHR 0.7 vs CD4<350 cell/µl, 95% CI: 0.6-0.8). The opposite was true for immediate ART initiation among the UTT/Same-day ART cohort (aRR 1.7 for missing vs CD4<350 cell/µl, 95%CI: 1.3-2.4).

Conclusions

Our results highlight a move towards earlier initiation of HIV treatment after the "treat all" policy implementation. However, increases in missing a baseline laboratory data and the low

implementation/uptake of immediate ART highlights potential health infrastructure and human resources limitation critical for sustained policy implementation.

Word count: 350

Strengths and limitations

- Cohorts enrolled across the three most recent ART guideline implementation periods in South Africa, allowing observation of changes over time.
- Cohorts enrolled immediately after HIV diagnosis, allowing for observation of ART initiation and early losses from HIV diagnosis.
- Our results highlight a positive move towards earlier initiation of HIV treatment after the "treat all" policy implementation.
- Although a significant reduction in delays to ART initiation has been achieved, ART initiation on the day of HIV diagnosis is proving more challenging and may require additional resources.
- Increases in missing laboratory tests at diagnosis reduce the strength of laboratory datasets as monitoring tools for the early steps of the HIV treatment cascade and estimation of the impact of the Same-Day ART on patient CD4 profile at diagnosis.

Introduction

South Africa has the largest HIV epidemic in the world, with an estimated 7.9 million people living with HIV, with an ART program covering an estimated 4.4 million (55.7%) HIV infected patients by 2017(1).

In September 2016, South Africa adopted the World Health Organization (WHO) 2015 Universal Test and Treat (UTT) policy making all HIV positive patients eligible for antiretroviral therapy (ART) at diagnosis, irrespective of CD4 count (2-4). South Africa's adoption of the UTT policy was based on the availability of safer, more tolerable drug combinations and reliable evidence of the positive impact of early ART initiation on several treatment outcomes (5-7). Compared to those who deferred treatment, patients who started ART immediately after HIV diagnosis had lower rates of AIDS-related adverse events and improved viral suppression rates with no difference in post-initiation attrition rates (8, 9). Additionally, this "treat all" strategy was also supported by substantial evidence of ART as an HIV prevention strategy (7, 10).

In 2017, the UTT policy in South Africa was updated with a directive to initiate ART on the day of HIV diagnosis (Same-day-ART) (11). While widespread support for the "treat all" policy has created momentum for its promulgation, there remain reservations that health system capacity constraints may limit same-day-ART policy assimilation and result in variations in implementation at facility-level (12). The policy was implemented amid concerns that, under UTT, health facilities in high burden settings, in particular, might struggle with the increased patient burden, potentially reducing the quality of care provided to new and existing patients (13-15). Recent studies show that the implementation of same-day-ART policy is challenged by limited health personnel and infrastructural capacity (13, 16, 17). PHC-level health care providers also raised concern around patient acceptance of same-day-ART, ART refusal or early patient disengagement from care or intermittent adherence after starting ART (18).

The 2017 National HIV survey in South Africa reported welcome increases in the number of HIV positive patients initiated on ART (nearly one million additional patients have been initiated between 2016 and 2017 (3). However, in addition to measuring the program success in expanding access to ART, critical outcomes of the UTT policy and associated interventions are the initiation of relatively asymptomatic individuals on ART, reductions in delays to ART initiation and long-term retention in HIV care.

In this study, we set out to measure the impact of UTT and same-day-ART policies on time to ART initiation and to examine factors associated with initiating ART within 30 days of HIV diagnosis across the three recent ART guideline periods in Johannesburg, South Africa.

Methods

Study Setting and design

This study was conducted at six peri-urban primary healthcare clinics (PHCs) in Johannesburg, South Africa. We conducted a prospective cohort study, enrolling consenting newly diagnosed HIV positive adult (≥18 years) patients from April to December 2015 (Pre-UTT), July-September 2017 (UTT, before same-day-ART) and October 2017-July 2018 (UTT/Same-day-ART). UTT and UTT/Same-day-ART cohorts were only enrolled from two primary health clinics (PHCs) in Johannesburg while the UTT/Same-day-ART cohort included four additional PHCs in Johannesburg. Participant enrolment co-occurred across sites until the total sample size was attained. All patients were enrolled in the study by trained study interviewers via referral from PHC-based lay HIV counsellors. Patients were eligible if they had initiated HIV care after diagnosis. Women who were pregnant at HIV diagnosis were excluded from the study because their in-pregnancy treatment initiation and care processes differ from that of non-pregnant women.

Data Collection

Consenting patients completed an interviewer-administered baseline questionnaire after HIV testing, on the day of HIV diagnosis. The interview included questions on demographic factors, socio-economic status and health-seeking behaviour. Patients were passively followed up for 30 days to determine ART initiation. Routine clinical follow-up data were collected from paper and electronic medical records including laboratory test results.

Patient and Public Involvement

Patients were not directly involved in the design of this study. However information collected from patients in previous studies informed the design, data collection approaches and interpretation of study results. Also, the study implementation was guided by health care workers form participating study sites. Study participants consented to a once-off direct data collection

after HIV diagnosis and passive follow-up data collection via medical record review. Therefore direct result dissemination to patients will not be possible. However we plan to present study results to health care workers and policy-makers at participating PHC clinics and at other policy-relevant forums.

Outcome data and analysis

The primary exposure variable was the HIV testing guidelines at the time of HIV diagnosis categorised as pre-UTT, under UTT but before the same-day ART policy (UTT) and after the same-day ART cohort (Same-day-ART). The outcome event was ART initiation within 30 days of HIV diagnosis. Patients were followed up from the date of HIV diagnosis to ART initiation in the first 30 days of HIV care, time of transfer/ death if these occurred in the first 30 days, at 30 days after HV diagnosis if there was no evidence of transfer or death (patient assumed to be returning).

Predictors of ART initiation in the first 30 days of HIV care were assessed using Cox proportional hazards models, reporting Hazard Ratios (HR). Additionally, predictors of ART initiation on the day of HIV diagnosis were evaluated using Poisson Regression modelling, reporting Relative Risks (RR). The study protocol was reviewed and approved by the Institutional Review Boards of the University of Witwatersrand (M141103) and Boston University (H-33516).

Results

Clinical and demographic characteristics at baseline

The study sample consisted of 1029 adults enrolled immediately after HIV testing, 146 (14.2%) enrolled in the pre-UTT period, 141 (13.7%) under UTT but before the same-day ART directive, 742 (72.1%) under the UTT/same-day ART policy (Table 1, Figure 1). The age and gender distributions of participants were similar across cohorts. Although the proportion of participants who tested with CD4 count<350/mm^3 decreased from 65.8% pre-UTT to 39.7% in the UTT/Same-day-ART cohort, the percentage of patients with missing 30 days (baseline) CD4 count results increased from 3.4% to 34.7%. The proportion of patient with 30 days CD4

count>500 cells/µl did not change substantially across guideline periods (13.5% pre-UTT, 18.1% UTT and 20.0% Same-day-ART).

The majority of participants (72.9%) had less than a grade 12 qualification but, overall, 52.5% were employed. Most participants lived within 15 minutes of the diagnosing clinic (56.9%). However, a small proportion reported travelling over 30 minutes to reach the clinic (12.5% overall, 6.8% pre-UTT, 4.3% under UTT and 15.2% under the Same-day-ART policies).

Time to ART initiation from HIV diagnosis across guideline periods

The overall median days to ART initiation declined from 21 days (IQR: 15-30) to a median of 8 days (IQR: 6-16) after the implementation of the UTT policy and was further reduced to 5 days (IQR: 0-8) after the same-day-ART directive was given (Figure 2). Overall, 71.9% initiated ART within 30 days of HIV diagnosis, 36.9% pre-UTT, 65.9% under UTT and 79.9% under the Same-day-ART periods (Figure 3). Pre-UTT participants were 80% less likely to initiate ART in the first 30 days (adjusted HR (aHR) 0.2, 95% CI: 0.2-0.3) compared to Same-day-ART participants (Table 2). Similarly, patients diagnosed under the UTT policy were 40% less likely to start ART within 30 days of HIV diagnosis (aHR 0.6, 95% CI: 0.5-0.7) compared to UTT/Same-day-ART participants. There was no meaningful difference in the likelihood of 30 days ART initiation across gender and baseline CD4 categories (among those with CD4 data). However, compared to patients with baseline CD4<350 cell/mm^3, participants who were missing 30 days CD4 counts were 30% less likely to start ART within a month (aHR 0.7, 95% CI: 0.6-0.8). While only 12.5% of participants indicated travelling for at least 30 minutes to the clinic, they were 30% more likely to start ART within 30 days compared to those who travelled no more than 15 minutes (aHR 1.3 overall, 95%CI: 1.1-1.7).

Demographic and clinical characteristics associated with immediate ART initiation within the Same-day-ART cohort

Among UTT/Same-day-ART participants, 150 (20.2%) initiated treatment on the day of HIV diagnosis (25.3% of those who initiated within 30 days). Older participants (aRR 0.6 for ≥40 years compared to 18-29.9 years, 95% CI: 0.4-0.9) were less likely to start ART on the day of

HIV testing (Table 3). However, in the Same-day-ART period, missing baseline CD4 data was associated with a 70% higher likelihood of starting ART on the day of HIV diagnosis (aRR 1.7, 95%CI: 1.3-2.4). Although not included in the multivariable model, we also describe a high variability in same-day-ART policy implementation across sites (Table 4).

Discussion

This study highlights a marked reduction in time to ART initiation before the UTT guidelines and after the same-day-ART policy implementation. The most substantial decline in time to ART occurred immediately after September 2016 policy change (from 21 to 8 days) when the "treat all" policy, which did not include a directive to modify ART initiation processes begun, with additional declines s (to 5 days) in delays to ART start after the same-day-ART memorandum was sent to clinics. These declines are consistent with the goals of the WHO HIV treatment guidelines: to initiate patients as early as possible to achieve better clinical outcomes (2-4).

Consistent with previous findings, we found that the majority of patients still present with low CD4 counts (<350 cell/mm^3) (19), with under 10% increase in the proportion of patients presenting at CD4 >500 cells/mm^3 after UTT. These results highlight the need for consistent efforts to increase early HIV testing and ART initiation of asymptomatic as well as older male patients. We also observed a substantial increase in the proportion of patients who lacked baseline CD4 data. For the 30-days-ART outcome, having a missing baseline CD4 was associated with a reduced likelihood of starting ART, suggesting that before the UTT policy, the lack of baseline CD4 was synonymous of early loss from care. However, under the UTT/Same-day-ART policy, missing baseline CD4 data may indicate changes in clinic processes to accommodate the faster ART initiations. This missing data could result from clinic deferral of blood draws (for late initiations/ past blood collection times) or patient impatience with the drawn-out ART initiation processes on the day of testing.

Nearly nine months after the same-day-ART directive, only 20.2% of diagnosed patients under this policy had started ART on the day of diagnosis, highlighting possible facility-level policy implementation challenges. We found marked variability in the buy-in of health care workers and the application of the same-day ART policy across health facilities (20). Healthcare

providers expressed reservations about the acceptability of immediate ART for the majority of their patients and the feasibility of the strategy considering their current workload (20).

Interestingly, participants who travelled over 30 minutes to the diagnosing clinic were more likely to initiate ART on the day of diagnosis, suggesting that motived patients were willing to travel further to clinics perceived to offer a better quality of services (21). Furthermore, younger (<39 years) people may be more informed and see fewer cultural barriers to HIV disclosure and HIV treatment (21).

The strength of the analysis lies in the three prospective cohorts spanning three ART guideline periods in South Africa, allowing direct observation of the changes in ART uptake and treatment outcomes over time. However, the study data is limited by the small number of health facilities assessed and limited information about additional facility level interventions as well as contributions by partner organisations in supporting policy assimilation and implementation. Therefore, other data from a more comprehensive facility survey is needed to better explain the facility-level variations in same-day-ART policy implementation and outcomes. Additionally, we only collected ART initiation data from testing facilities and were not able to determine if some participants had started ART elsewhere. The reason for the higher ART uptake among UTT/Same-day-ART participants require further exploration into ART initiation processes and their potential impact on patient health-seeking behaviour as well as long term on-ART outcomes.

Conclusion

Our results highlight a positive move towards earlier initiation of HIV treatment after the “treat all” policy implementation. However, the results also emphasise a vital need to streamline processes to increase same-day-ART implementation/uptake but also ensure that baseline safety and monitoring blood tests are done timeously. Going forward, the need to improve patient demand for early HIV testing remains pertinent to achieving the prevention and treatment benefits of ART. However, clinic-level infrastructural interventions and human resource support are needed to ensure sustained policy implementation and patient outcomes.

Acknowledgements

We extend our gratitude to the Directors and staff of Primary Health Care Clinics who supported the implementation of the study and our sincere thanks go to the patients attending these clinics for their willingness to participate and share the valuable information that made this study possible.

Author Contributions

DO and MPF had the original idea for the study and paper. TS managed the study implementation and conducted the primary data analysis. TS, CH, IM, implemented the study and contributed to the result interpretation. LL and MM contributed to the results interpretation. All authors wrote the results and the discussion. All authors reviewed and approved the manuscript.

Conflict of Interest

Authors have no conflicts of interest to declare.

Funding

This study has been made possible by the generous support of the American People and the President's Emergency Plan for AIDS Relief (PEPFAR) through United States Agency for International Development (USAID) under the terms of Cooperative Agreements AID-674-A-12-00029 and 72067419CA00004 to HE2RO. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID or the United States Government.

Data Statement

Patient medical records are owned by the study site and the National Department of Health (South Africa) and governed by the Human Research Ethics Committee (University of

Witwatersrand, Johannesburg, South Africa). All relevant data is included in the paper. The full data are available from the Health Economics and Epidemiology Research Office for researchers who meet the criteria for access to confidential data and have approval from the owners of the data (information@heroza.org).

References

1. HSRC. The Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication survey, 2017: HIV Impact Assessment Summary Report. Cape Town, HSRC Press.; 2017.

2. Abuelezam N N, McCormick AW, Fussell T, Afriyie AN, Wood R, DeGruttola V, et al. Can the Heterosexual HIV Epidemic be Eliminated in South Africa Using Combination Prevention? A Modeling Analysis. American journal of epidemiology. 2016;184(3):239-48.

3. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, et al. HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the Potential Impact of Antiretroviral Therapy on HIV Incidence in South Africa. PLOS Medicine. 2012;9(7):e1001245.

4. South African National Department of Health (South Africa). Implementation of Universal Test and Treat Strategy for HIV positive patients and differentiated care for stable patients 2016. Pretoria: National Department of Health 2016. https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf
Accessed October 2018

5. Group TAS, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.

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

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

8. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine. 2015;373(9):795-807.

9. 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;13(5):e1002015.

10. Long LC, Maskew M, Brennan AT, Mongwenyana C, Nyoni C, Malete G, et al. Initiating antiretroviral therapy for HIV at a patient's first clinic visit: a cost-effectiveness analysis of the rapid initiation of treatment randomized controlled trial. Aids. 2017;31(11):1611-9.

11. South African National Department of Health (South Africa). Tracking implementation of the 90-90-90 strategy for HIV, through the implementation of Test and Treat (TT) policy and same-day anti-retroviral therapy (ART) initiation for HIV positive patients 2017. Pretoria: National Department of Health; 2017.

12. Onoya D, Mokhele I, Sineke T, Ngoma B, Moolla A, Vujovic M, Bor J, Langa J, Fox M P. Health provider perspectives on implementation of same-day ART initiation six months after policy change in South Africa. International AIDS Conference (poster); 2018; Amsterdam.

13. Boyer S, Iwuji C, Gosset A, Protopopescu C, Okesola N, Plazy M, et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. AIDS Care. 2016;28(sup3):39-51.

14. Collins S, Geffen N. Community views: balancing the public health benefits of earlier antiretroviral treatment with the implications for individual patients – perspectives from the community. Current Opinion in HIV and AIDS. 2014;9(1):4-10.

15. Kulkarni SP, Shah KR, Sarma KV, Mahajan AP. Clinical Uncertainties, Health Service Challenges, and Ethical Complexities of HIV "Test-and-Treat": A Systematic Review. American Journal of Public Health. 2013;103(6):e14-e23.

16. Cassim N, Coetzee LM, Schnippel K, Glencross DK. Estimating Implementation and Operational Costs of an Integrated Tiered CD4 Service including Laboratory and Point of Care Testing in a Remote Health District in South Africa. PLoS ONE. 2014;9(12):e115420.

17. Skhosana M, Reddy S, Reddy T, Ntoyanto S, Spooner E, Ramjee G, et al. PIMA TM point-of-care testing for CD4 counts in predicting antiretroviral initiation in HIV-infected individuals in KwaZulu-Natal, Durban, South Africa. Southern African Journal of HIV Medicine.2016;17(1).

18. Bigna JJR, Plottel CS, Koulla-Shiro S. Challenges in initiating antiretroviral therapy for all HIV-infected people regardless of CD4 cell count. Infectious Diseases of Poverty. 2016;5(1):85.

19. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002-2013: a meta-analysis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015;60(7):1120-7.

20. Onoya D, Mokhele I, Sineke T, Ngoma B, Vujovic M, Langa J, et al., editors. Health provider perspectives on implementation of same day ART initiation six months after policy change in South Africa. AIDS 2018; 2018; Amsterdam.

21. Human Sciences Research Council (HSRC). The People Living With HIV Stigma Index: South Africa 2014. HSRC Press: 2014 Accessed October 2018 http://www.stigmaindex.org/sites/default/files/reports/Summary-Booklet-on-Stigma-Index-Survey%20South%20Africa.pdf

Table 1: Characteristics of the sample population by Period of HIV testing

	Pre-UTT (n=146)	UTT (n=141)	UTT/Same-day-ART (n=742)	Total (n=1029)
	n (%)	n (%)	n (%)	n (%)
Facility				
PHC1	68 (46.6)	72 (51.1)	80 (10.8)	220 (21.4)
PHC2	78 (53.4)	69 (48.9)	51 (6.9)	198 (19.2)
PHC3	-	-	207 (27.9)	207 (20.1)
PHC4	-	-	125 (16.8)	125 (12.1)
PHC5	-	-	151 (20.4)	151 (14.7)
PHC6	-	-	128 (17.3)	128 (12.4)
Sex				
Female	87 (59.6)	81 (57.4)	461 (62.1)	629 (61.1)
Male	59 (40.4)	60 (42.6)	281 (37.9)	400 (38.9)
Age, (median, IQR)				
18-29.9	52 (35.6)	53 (37.6)	242 (32.6)	347 (33.7)
30 - 34	41 (28.1)	29 (20.6)	177 (23.9)	247 (24.0)
35 - 39	28 (19.2)	31 (22.0)	147 (19.8)	206 (20.0)
40+	25 (17.1)	28 (19.9)	176 (23.7)	229 (22.3)
Baseline CD4				
<350	96 (65.8)	73 (51.8)	296 (39.9)	465 (45.2)
350 - 500	26 (17.8)	22 (15.6)	91 (12.3)	139 (13.5)
≥500	19 (13.0)	21 (14.9)	97 (13.1)	137 (13.3)
Missing	5 (3.4)	25 (17.7)	258 (34.8)	288 (28.0)
Education				
Less than grade 12	97 (66.4)	95 (71.4)	544 (73.9)	736 (72.5)
Senior certificate/Matric or higher	49 (33.6)	38 (28.6)	192 (26.1)	279 (27.5)
Marital Status				
Single	28 (19.2)	18 (12.8)	110 (14.8)	156 (15.2)
In a relationship	92 (63.0)	98 (69.5)	497 (67.1)	687 (66.8)
Married	21 (14.4)	18 (12.8)	112 (15.1)	151 (14.7)
Divorced/widowed	5 (3.4)	7 (5.0)	22 (3.0)	34 (3.3)
Employment Status				
Unemployed	70 (47.9)	66 (46.8)	402 (54.5)	538 (52.5)
Employed	76 (52.1)	75 (53.2)	335 (45.5)	486 (47.5)
Part-time/shifts	19 (25.0)	19 (27.5)	74 (17.2)	112 (19.5)
All day	57 (75.0)	50 (72.5)	355 (82.8)	462 (80.5)
Number of adults in household				
Lives alone	28 (19.2)	21 (15.0)	160 (21.7)	209 (20.5)
Two adult in home	82 (56.2)	81 (57.9)	429 (58.3)	592 (57.9)
≥ three adults	36 (24.7)	38 (27.1)	147 (20.0)	221 (21.6)
Travel time to clinic				
≤15 minutes	90 (61.6)	90 (63.8)	405 (54.6)	585 (56.9)
16-30 minutes	46 (31.5)	45 (31.9)	224 (30.2)	315 (30.6)

>30 minutes	10 (6.8)	6 (4.3)	113 (15.2)	129 (12.5)

Table 2: Demographic and clinical characteristics associated with initiating ART within 30 days of HIV diagnosis

	Initiated ART within 30 days n(%)	Person years	Rates/100 PY (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Guideline periods					
Pre-UTT/ Cohort 1	54 (36.9)	1.19	45.4 (34.8-59.3)	0.3 (0.2-0.3)	0.2 (0.2-0.3)
UTT/ Cohort 2	93 (65.9)	0.79	117.7 (96.1-144.3)	0.6 (0.5-0.7)	0.6 (0.5-0.7)
Same day/ Cohort 3	593 (79.9)	2.71	218.8 (201.7-236.9)	1.0	1.0
Sex					
Male	266 (66.5)	1.97	134.7 (119.4-151.9)	1.0	1.0
Female	474 (75.3)	2.72	174.5 (159.5-190.9)	1.7 (1.4-2.0)	1.2 (1.0-1.4)
Age at testing					
18-29.9	247 (71.1)	1.57	157.3 (138.6-177.8)	1.0	
30 - 34	170 (68.8)	1.10	154.5 (132.9-179.6)	1.0 (0.8-1.2)	
35 - 39	146 (70.8)	0.99	147.5 (125.2-173.1)	1.0 (0.8-1.2)	
40+	177 (77.2)	1.03	171.8 (148-199.9)	1.1 (0.9-1.3)	
Baseline CD4					
<350	146 (62.7)	2.23	154.4 (138.9-171.6)	1.0	1.0
350 - 500	238 (79.9)	0.61	169.6 (139.8-205.7)	1.1 (0.9-1.4)	1.1 (0.9-1.4)
≥500	172 (81.9)	0.5	217.9 (180.6-262.9)	1.3 (1.0-1.6)	1.2 (0.9-1.4)
Missing	194 (63.9)	1.36	135.7 (117.5-156.8)	0.9 (0.8-1.1)	0.7 (0.6-0.8)
Education					
< Grade 12	527 (71.6)	3.41	154.5 (142.1-168.5)	1.0	
≥ Grade 12	203 (72.7)	1.23	165.0 (144.2-189.9)	1.1 (0.9-1.2)	
Marital Status					
Single	114 (73.0)	0.71	160..6 (1.33.6-192.9)	1.00	
In a relationship	483 (70.3)	3.09	156.3 (142.6-170.4)	1.0 (0.8-1.2)	
Married	119 (78.8)	0.69	172.5 (142.7-204.3)	1.1 (0.8-1.4)	
Divorced/widowed	23 (67.6)	0.18	127.8 (83.1-188.3)	0.8 (0.5-1.3)	
Employment Status					
Unemployed	386 (71.7)	2.47	156.3 (141.2-172.3)	1.0	
Employed	351 (72.2)	2.18	161.0 (144.6-178.2)	1.0 (0.9-1.2)	
Employment hours					
Part-time/shifts	82 (73.2)	0.49	167.3 (132.9-204.9)	1.0	
All day	147 (31.8)	2.13	2.13 (138.8-172.2)	1.0 (0.8-1.2)	
# adults in household					
Lives alone	141 (67.4)	1.02	138.2 (117.1-162.9)	1.0	1.0
Two adult in home	442 (74.6)	2.6	170.0 (154.8-186.5)	1.2 (1.0-1.4)	1.2 (1.0-1.4)

≥ three adults	153 (69.2)	1.03	148.5 (126.8-174.1)	1.1 (0.8-1.3)	1.0 (0.8-1.3)
Travel time to clinic					
≤15 minutes	415 (70.9)	2.73	152.0 (138.2-167.5)	1.0	1.0
16-30 minutes	218 (69.2)	1.52	143.4 (125.4-163.5)	1.0 (0.8-1.1)	0.9 (0.8-1.1)
>30 minutes	107 (82.9)	0.44	243.2 (200.9-293.5)	1.5 (1.2-1.8)	1.3 (1.1-1.7)

Table 3: Demographic and clinical characteristics associated with initiating ART on the day of HIV diagnosis

	Initiated ART within same-day n(%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Sex			
Male	44 (15.6)	1.0	1.0
Female	106 (22.9)	1.5 (1.1-2.0)	1.3 (0.9-1.9)
Age at testing			
18-29.9	62 (25.6)	1.0	1.0
30 - 34	38 (21.4)	0.8 (0.6-1.2)	0.9 (0.6-1.2)
35 - 39	24 (16.3)	0.6 (0.4-0.9)	0.7 (0.4-1.0)
40+	26 (14.7)	0.6 (0.4-0.9)	0.6 (0.4-0.9)
Baseline CD4			
<350	44 (17.4)	1.0	1.0
350 - 500	18 (24.6)	1.3 (0.8-2.2)	1.3 (0.8-2.1)
≥500	20 (25.9)	1.4 (0.9-2.2)	1.2 (0.8-1.9)
Missing	68 (35.7)	1.8 (1.3-2.5)	1.7 (1.3-2.4)
Education			
< Grade 12	107 (19.6)	1.0	
≥ Grade 12	43 (22.3)	1.1 (0.8-1.6)	
Marital Status			
Single	17 (15.4)	1.0	
In a relationship	117 (23.5)	1.5 (0.9-2.4)	
Married	16 (14.2)	0.9 (0.5-1.7)	
Divorced/widowed	-		
Employment Status			
Unemployed	76 (18.9)	1.0	
Employed	72 (21.4)	1.1 (0.9-1.5)	
Employment hours			
Part-time/shifts	19 (25.6)	1.0	
All day	63 (17.7)	0.7 (0.4-1.1)	

# adults in household			
Lives alone	30 (18.7)	1.0	
Two adult in home	88 (20.5)	1.1 (0.8-1.6)	
≥ three adults	30 (20.4)	1.1 (0.7-1.7)	
Travel time to clinic			
≤15 minutes	77 (19.0)	1.0	1.0
16-30 minutes	41 (18.3)	0.9 (0.7-1.4)	0.9 (0.7-1.4)
>30 minutes	32 (28.3)	1.5 (1.0-2.1)	1.4 (1.0-2.0)

Table 4: Facility variability associated with ART initiation within 30 days or ART initiation within same-day.

	Initiated ART within 30 days n(%)	Crude HR (95% CI)	Initiated ART within same-day n(%)	Crude RR (95% CI)
Facility				
PHC 1	145 (65.9)	0.5 (0.4-0.7)	8 (10.0)	0.3 (0.2-0.6)
PHC 2	96 (48.4)	0.3 (0.2-0.4)	9 (17.6)	0.5 (0.3-1.0)
PHC 3	169 (81.6)	0.9 (0.7-1.1)	35 (16.9)	0.5 (0.3-0.7)
PHC 4	98 (78.4)	1.00	42 (33.6)	1.0
PHC 5	121 (80.1)	0.8 (0.6-0.9)	46 (30.4)	0.9 (0.6-1.3)
PHC 6	111 (86.7)	0.9 (0.7-1.2)	10 (7.8)	0.2 (0.1-0.4)

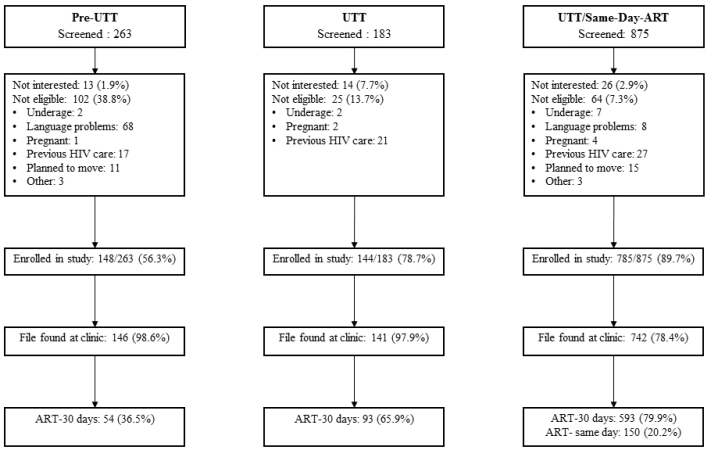


Figure 1. Participant flow in the three recruitment periods

338x190mm (96 x 96 DPI)

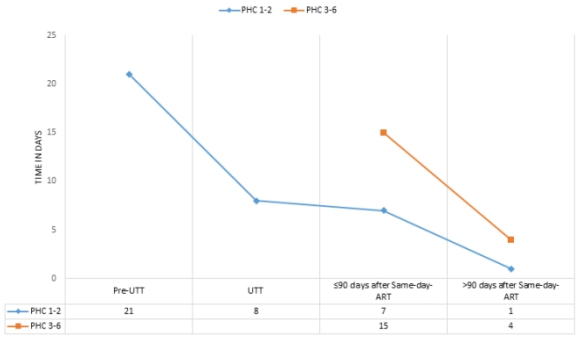


Figure 2. Timing of ART initiation in the first 30 days of HIV care across HIV treatment guideline periods in Johannesburg, South Africa

338x190mm (96 x 96 DPI)

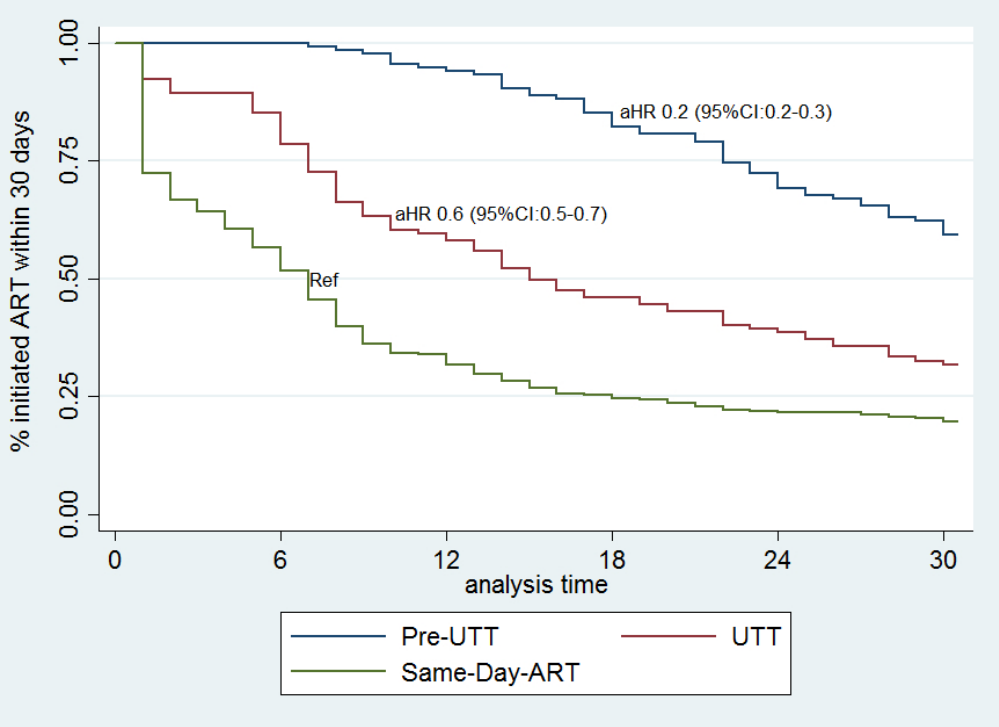


Figure 3. Hazards of starting ART within 30 days of HIV diagnosis by HIV treatment guideline periods in Johannesburg, South Africa

304x221mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	6, Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 2-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	7-8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of the test and treat policy on delays in ART initiation among HIV positive adult patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030228.R1
Article Type:	Original research
Date Submitted by the Author:	26-Aug-2019
Complete List of Authors:	Onoya, Dorina; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Sineke, Tembeka; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Hendrickson, Cheryl; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Mokhele, Idah; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Maskew, Mhairi; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Long, Lawrence; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office; Boston University, Boston School of Public Health, Department of Global Health Fox, Matthew; Boston University, Epidemiology and Global Health; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office
Primary Subject Heading:	Health policy
Secondary Subject Heading:	HIV/AIDS, Public health, Health policy
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, PRIMARY CARE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

+Working Title:

Impact of the test and treat policy on same-day ART delays in HIV treatment initiation in Johannesburg, South Africa

Title: Impact of the test and treat policy on delays in ART initiation among HIV positive adult patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study

Authors: Dorina Onoya[1], Tembeka Sineke[1], Cheryl Hendrickson[1], Idah Mokhele[1], Mhairi Maskew[1], Lawrence Long[1,2], Matthew P. Fox[1, 2, 3]

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

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

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

Corresponding author: Dorina Onoya, Health Economics and Epidemiology Research Office, 39 Empire Road, Parktown, Johannesburg, 2193, South Africa, donoya@heroza.org +27 10 001 7930

Keywords: HIV, ART attrition, UTT, same-day ART

Word count (main body): 3169

Abstract

Objectives To assess delays to antiretroviral therapy (ART) initiation before the Universal Test & Treat (UTT) policy, under UTT and during same-day ART policy periods in Johannesburg, South Africa.

Design Prospective cohort study

Setting Patients were recruited from six primary health clinic in Johannesburg.

Participants Overall, 1029 newly diagnosed HIV positive adults (≥18 years) were consecutively enrolled by referral from the testing HIV counsellor between April to December 2015 (Pre-UTT n=146), July-August 2017 (UTT, n=141) and October 2017-August 2018 (same-day ART, n=742).

Main outcome measures Predictors of 30-days ART initiation uptake were assessed using Cox proportional hazards models. Additionally, predictors of same-day ART initiation were evaluated using Poisson regression modelling.

Results Overall, 30-days ART proportions were 71.9% overall, 36.9% pre-UTT, 65.9% under UTT and 79.9% under the same-day ART policy. The median days to ART initiation declined from 21 pre-UTT (IQR: 15-30) to eight (IQR: 6-16) under UTT and five days (IQR: 0-8) under the same-day ART policy. However, only 150 (20.2%) of the same-day ART cohort initiated ART immediately after HIV diagnosis. Living in a two-adult home (adjusted Hazard ratio (aHR) 1.2 vs living alone, 95% Confidence Interval (CI): 1.0-1.4) increased the likelihood of 30-day ART. Missing baseline CD4 data decreased the likelihood of 30-days ART by 40% (aHR 0.6 vs CD4<350 cell/µl, 95% CI: 0.5-0.7). Women were more likely to take up immediate ART (aRR 1.3, 95%CI: 1.0-1.9). Participants ≥40 years (aRR 0.6 vs 18-24 years old, 95% CI: 0.4-0.9) were less likely to start ART on the day of HIV diagnosis. However, same-day ART rates increased with longer policy implementation time (aRR 0.2 for <3-months vs >10-months, 95%CI: 0.1-0.4).

Conclusions Our results highlight a positive move towards earlier ART initiation during the UTT and same-day ART periods and emphasise a need to increase same-day ART implementation further.

Word count: 300

Strengths and limitations

- Cohorts enrolled across the three most recent ART guideline implementation periods in South Africa, allowing observation of changes over time.
- Participants enrolled immediately after HIV diagnosis, allowing for observation of ART initiation and patient attrition from HIV diagnosis.
- Our results highlight a positive move towards earlier initiation of HIV treatment after the UTT policy implementation.
- Although we demonstrate substantial reductions in delays to ART initiation (median of 21 to five days), ART initiation on the day of HIV diagnosis is limited and requires additional investigations to improve programmatic performance.
- Increases in missing baseline laboratory tests at diagnosis reduce the strength of laboratory datasets as monitoring tools for the early steps of the HIV treatment cascade and delay the assessment of the appropriateness of the initial ART regiment.

Introduction

South Africa has the largest Human Immunodeficiency Virus (HIV) epidemic in the world, with an estimated 7.9 million persons living with HIV (1). To increase access to antiretroviral therapy (ART), the South African government gradually increased the cluster of differentiation four (CD4)-based treatment eligibility threshold from 200 cells/µl in 2004, to 350 cells/µl in 2010 and 500 cells/µl in January 2015 (2-6).

In 2017, an estimated 4.4 million (55.7%) HIV-positive patients had been initiated on ART (1), highlighting the high patient attrition between HIV diagnosis and ART initiation. Determinants of losses in the HIV treatment cascade include cluster of differentiation four (CD4) cell count at diagnosis, gender, socio-economic factors such as disclosure and HIV stigma, access to health care facilities, travel time and cost of attending clinic visits (7-14). In the past, attrition from care after HIV diagnosis was also related to the number of assessment and counselling visits required before treatment initiation for eligible patients and the lack of systematic monitoring of and benefits for patients who were not offered ART (2-6, 14).

In September 2016, South Africa removed the CD4 cell count threshold for ART eligibility and adopted the World Health Organization (WHO) 2015 Universal Test and Treat (UTT) policy making all HIV positive patients eligible for ART at diagnosis (15-17). South Africa's adoption of the UTT policy was based on the availability of safer, more tolerable drug combinations and reliable evidence of the positive impact of early ART initiation on morbidity and viral suppression outcomes (18-20). Clinical trials showed that, compared to patients who deferred ART, patients who started treatment immediately after HIV diagnosis had lower rates of acquired immunodeficiency syndrome (AIDS)-related adverse events and improved viral suppression rates with no difference in post-initiation attrition rates (21-22). Additionally, various studies showed that, compared to patients who deferred ART, patients who started ART immediately after diagnosis were less likely to transmit HIV to HIV-negative partners (16, 21-23).

In September 2017, the UTT policy in South Africa was updated with a directive to initiate ART on the day of HIV diagnosis (same-day ART) (24). While widespread support for the UTT or "treat all" policy has created momentum for its promulgation, there remain reservations from primary health care (PHC) providers that health system capacity constraints may limit same-day

ART policy assimilation and result in variations in implementation at facility-level (25). The policy was implemented amid concerns that, under UTT, health facilities in high burden settings, in particular, might struggle with the increased patient burden, potentially reducing the quality of care provided to new and existing patients (2-4,26-27). There are also concerns around patient acceptance of same-day ART, ART refusal or early patient disengagement from care or intermittent adherence after starting ART (28).

The 2017 National HIV survey in South Africa reported increases in the number of HIV positive patients initiated on ART (nearly one million additional patients have been started on ART between 2016 and 2017 (1). However, in addition to measuring program success in terms of expanded access to ART, critical outcomes of the UTT policy include the initiation of patients with high CD4 cell count, reductions in delays to ART initiation and long-term retention in HIV care.

In this study, we set out to measure ART initiation of newly diagnosed adults in the first 30 days of HIV care (30-day ART), across the three recent ART guideline periods and to examine factors associated with 30-days ART in Johannesburg, South Africa.

Methods

Study Setting and design

This study was conducted at six of 15 peri-urban, public-sector PHCs in the Johannesburg health sub-district A, South Africa. PHC clinics in Johannesburg are mainly nurse-run with the support of one medical doctor and are responsible for HIV testing, ART initiation and primary-level management and monitoring of HIV positive patients. We conducted a prospective cohort study, enrolling consenting newly diagnosed HIV positive adult (≥18 years) patients from April to December 2015 (Pre-UTT period), July-August 2017 (UTT period) and October 2017-August 2018 (same-day ART period). Pre-UTT and UTT cohorts were only enrolled from two PHCs in Johannesburg while the same-day ART cohort included four additional PHCs in the same area (serving similar populations) in Johannesburg (Summarised in Table 1) (10-13). The sample size for the same-day ART cohort was increased to enable a separate assessment of ART refusal and

attrition among participants who initiate ART with high CD4 count (>500 cells/µl). The number of sites was increased to six to allow comparison of the same-day ART across clinics.

Participant enrolment co-occurred across sites until the total planned sample size was attained. Figure one outlines the criteria for being excluded from the study. All patients were enrolled in the study after an HIV-positive diagnosis (before ART eligibility determination) by trained study interviewers via referral from PHC-based lay HIV counsellors. Patients were eligible if they had entered HIV care after an HIV-positive diagnosis. Entering HIV care was defined as providing the first blood sample for baseline safety laboratory tests for the Pre-UTT and UTT cohorts, and defined as having received the HIV positive test result for the same-day ART cohort because new clinic processes meant that patients were likely to start ART before the first blood collection. Women who were pregnant at HIV diagnosis were excluded from the study because their antenatal care ART initiation and monitoring processes differ from that of non-pregnant populations. Study staff cooperated closely with lay HIV counsellors across sites and checked HIV testing records daily to ensure that the maximum number of testers were being referred to study staff for study eligibility assessment.

Data Collection

Consenting patients completed an interviewer-administered baseline questionnaire after HIV testing, on the day of HIV diagnosis. The interview was conducted exclusively in English in the pre-UTT cohort but later translated to Sotho and Zulu as well for the UTT and same-day ART cohorts. The interview included questions on demographic factors, socioeconomic status and health-seeking behaviour. The recency of the HIV diagnosis was determined from patient responses in the baseline questionnaire. Patients were passively followed up by medical record review up to 30 days after the HIV diagnosis to determine ART initiation. Person-time accrued from the date of HIV diagnosis (study enrolment) until ART initiation. We assumed that all patients for whom clinic files were created were in care for the first 30 days unless there was evidence of an official transfer or death in the first 30 days after HIV diagnosis.Trained data collectors captured routine clinical follow-up data of consenting participants from facility-based paper and electronic medical records including laboratory test results from the National Health Laboratory Services (NHLS). We define baseline CD4 as the CD4 results from tests conducted on the first blood specimen drawn after HIV diagnosis. Trained data collectors captured all

patient data on the REDCap (Research Electronic Data Capture) systems (Vanderbilt University, Nashville, Tenessee). All datasets were exported to STATA 14 (StataCorp, College Station, Texas) for the analysis.

Patient and Public Involvement

Patients were not directly involved in the design of this study or reimbursed for their participation in the study. However, information collected from patients in previous studies informed the design, data collection approaches and interpretation of study results (19, 24). Also, the study implementation was guided by health care workers from participating study sites. Study participants consented to a once-off direct data collection after HIV diagnosis and passive follow-up data collection via medical record review. Therefore, direct result dissemination to patients will not be possible. However, we plan to present study results to health care workers and policy-makers at participating PHC clinics and at other policy-relevant forums.

Outcome data and analysis

The primary exposure variable was the ART guidelines at the time of HIV diagnosis categorised as pre-UTT (active between January 2015 and August 2016), under the general UTT (active between September 2016 and August 2017) policy and the same-day ART policy (active from September 2017). The primary outcome was ART initiation up to 30 days after HIV diagnosis (30-day ART), and the secondary outcome is ART initiation immediately after HIV diagnosis, both outcomes were coded Yes (1) or No (0). Final data analysis began in October 2018.

Continuous variables were described using medians and interquartile ranges. Categorical variables were described using percentages. Kaplan Meier analyses were conducted to assess time to ART initiation in the first 30 days of HIV care. Predictors of 30-day ART were modelled using Cox proportional hazards regression, reporting Hazard Ratios (HR). Variables with a p-value <0.1 in crude analyses were entered in the multivariate model. Schoenfeld residuals were used to test the assumption of proportional hazards. Interaction terms with time-varying covariates were created for variables that violated the proportional hazards assumption. Variables were excluded from the model when the inclusion of the interaction term did not resolve the proportional hazards assumption violation. Missing data were accounted for by including a 'not measured/missing' category where necessary. Additionally, predictors of ART initiation on the

day of HIV diagnosis (dichotomised) were evaluated using Poisson Regression modelling, reporting Relative Risks (RR).

All multivariate analyses were adjusted for the time from the period-specific policy announcement to account for the varying lag periods between policy implementation and participant enrolment across cohorts. Additionally, we tested the association between the highest level of education and ART initiation across guidelines period to account for the change in interview language options. The study protocol was reviewed and approved by the Institutional Review Boards of the University of Witwatersrand (M141103) in South Africa and Boston University (H-33516) in the USA.

Results

Clinical and demographic characteristics at baseline

Although 1077 (100% of target sample) HIV positive adults enrolled in the study, medical data was available for 1029 (95.5%), 146 (98.6%) pre-UTT, 141 (97.9%) under UTT, and 742 (78.4%) under the same-day ART policy (Figure 1). The exclusive use of English questionnaires in the pre-UTT cohort was the largest reason for participant non-eligibility (25.9% of total screened). However, the age and gender distributions were similar across cohorts (Median 32.6 years for Pre-UTT, interquartile range (IQR):27.2-37.6; 32.3 years for UTT, IQR: 27.2-38.9; and 32.3 years for same-day ART, IQR: 28.4-39.5) (Table 2). Women (Median 32.6 years, IQR: 27.0-37.7) were slightly younger at HIV diagnosis than men (Median 35.8, IQR: 32.1-41.5) (β_{female} -3.4, 95%CI: -4.4 to -2.4). The pre-UTT cohort had a marginally higher proportion of participants who completed grade 12 (33.6%) compared to 28.6% in the UTT and 26.1% in the same-day ART cohorts. Employment rates were also similar across cohorts (47.9% pre-UTT, 46.8% UTT and 54.5% same-day ART).

Although the proportion of participants who tested with CD4 count<350/mm^3 decreased from 65.8% pre-UTT to 39.7% in the same-day ART cohort, the percentage of patients with missing baseline CD4 count results increased from 3.4% to 34.7%, respectively. Among participant who had CD4 data, the proportion of patient with baseline CD4 count>500 cells/µl did not change substantially across guideline periods (20.0% during same-day ART vs 13.5% Pre-UTT, relative

risk (RR)=1.5 (95%CI: 0.9-2.3) and RR=1.3 (95%CI: 0.9-2.4) for same-day ART vs UTT (18.1%)).

Although most participants lived within 15 minutes of the diagnosing clinic (56.9%), a small proportion reported travelling over 30 minutes to the clinic (12.5% overall, 6.8% pre-UTT, 4.3% under UTT and 15.2% under the same-day ART policies). Travel time varied across clinics such that <12% participants from five of the six recruitment sites reported travelling over 30 minutes to the clinics, but 46.4% of participants from PHC four reported >30-minutes travel time.

Time to ART initiation from HIV diagnosis across guideline periods

The overall median days to ART initiation declined from 21 days (IQR: 15-30) to eight days (IQR: 6-16) after the implementation of the UTT policy. Time to ART start was further reduced to a median of five days (IQR: 0-8) after the same-day ART directive was given (Figure 2), with most reductions observed three months after the same-day ART policy directive was given to PHCs. Overall, 71.9% initiated ART within 30 days of HIV diagnosis, 36.9% pre-UTT (44.3% of those eligible for ART), 65.9% under UTT and 79.9% under the same-day ART periods (Figure 3).

Overall, 30-day ART rates increased with increasing lag time from the prevailing (at the time of participant's HIV diagnosis) policy announcement (adjusted hazard ratio (aHR) 0.4 for ≤3-months vs ≥10-months, 95%CI: 0.2-0.6). The highest level of education was not associated with 30-day ART uptake. After adjusting for the facility of diagnosis and lag time from the policy announcement, pre-UTT participants were 80% less likely to initiate ART in the first 30 days (aHR 0.2, 95% CI: 0.2-0.4) compared to same-day ART participants (Table 3). Similarly, patients diagnosed under the UTT policy were 70% less likely to start ART within 30 days of HIV diagnosis (aHR 0.3, 95% CI: 0.2-0.5) compared to same-day ART participants (Figure 3).

While women had higher 30-day ART rates compared to men (aHR 1.2, 95%CI: 1.0-1.4), there was no meaningful difference in the likelihood of 30-days ART initiation across age, marital status, travel time to the clinic or employment categories. Overall, compared to patients with baseline CD4<350 cell/µl, participants with baseline CD4>500 cells/µl had similar rates of 30-day ART. However, participants who were missing baseline CD4 counts were 40% less likely to start ART within a month (aHR 0.6, 95% CI: 0.5-0.7). Participants who lived in a two-adult home had higher rates of 30-day ART than those who lived alone (aHR 1.2, 95%CI: 1.0-1.5). Women were more likely to live with at least one other adult (RR 1.2, 95%CI: 1.1-1.4) compared to men.

Demographic and clinical characteristics associated with immediate ART initiation within the same-day ART cohort

Within the same-day ART cohort, 150 (20.2%) participants initiated treatment on the day of HIV diagnosis (25.3% of those who initiated ART within 30 days). Women were more likely to take up immediate ART (aRR 1.3, 95%CI: 1.0-1.9). Older participants (aRR 0.6 for patients ≥40 years old compared to patients in the 18-24 years group, 95% CI: 0.4-0.9) were less likely to start ART on the day of HIV diagnosis (Table 4). In the same-day ART period, missing baseline CD4 data did not affect the likelihood of starting ART on the day of HIV diagnosis (aRR 1.5, 95%CI: 0.5-3.7). We also describe a high variability in same-day ART policy implementation across sites (Table 4). However, same-day ART rates increased gradually with longer policy implementation time (aRR 0.2 for <3 months vs >10 months, 95%CI: 0.1-0.4) (Figure 4).

Discussion

This study highlights a marked reduction in time to ART initiation following the implementation of the UTT guidelines, decreasing from a median of 21 days to eight days, despite this policy not including a directive to modify ART initiation times. An additional decline in time to ART start was also observed after the same-day ART memorandum was sent to clinics. These declines are consistent with the goals of the WHO HIV treatment guidelines: to initiate patients as early as possible to achieve better clinical outcomes (15-16).

Consistent with previous findings (29), we found a decrease in the proportion of patients presenting with CD4 <350 cells/µl but little improvement in the CD4>500 cells/µl group between the pre-UTT and same-day ART periods. Overall, nearly two-thirds of participants who had baseline CD4 data were diagnosed with HIV with low CD4 counts (<350 cell/µl). Over one-third of the same-day ART cohort was missing baseline CD4 data.

Missing baseline CD4 data in the same-day ART cohort could have resulted from the lack of clarity in the policy with regards to the need or timing of safety blood tests early in the same-day ART policy implementation or patient impatience with the drawn-out HIV testing and ART initiation processes on the day of HIV testing (17, 25, 30). It is unclear whether this is a result of the change in the definition of entry in HIV care (first blood draw vs HIV diagnosis) for the same-day ART cohort. However, this increase in missing baseline CD4 could also be observed from the pre-UTT cohort to the UTT cohort, at which point clinics already began to reduce time to ART start (to the first week of care for some patients). Nevertheless, having a missing baseline CD4 was associated with a reduced likelihood of 30-day ART compared to patients with lower baseline CD4 values. When we restricted the analysis to the same-day ART cohort, having a missing CD4 count was associated with a non-significant increase in same-day ART rates, which possibly also means that patients diagnosed under the same-day ART policy may start ART before the first blood draw a defer baseline CD4 tests. However, this finding must be explored further.

Interestingly, participants who lived in a two-adult home rather than alone were more likely to initiate ART within 30 days. However, participants who lived in larger households had similar 30-day ART rates to those who lived alone, suggesting persisting fear of confidentiality breaches within homes (5, 8).

Only 20.2% of diagnosed patients under the same-day ART policy started ART on the day of diagnosis, highlighting possible facility-level policy assimilation challenges. In a previous qualitative study involving PHC health providers, we found marked variability in the buy-in of health care workers and the application of the same-day ART policy across health facilities (25). Healthcare providers expressed reservations about the acceptability of immediate ART for the majority of their patients and the feasibility of the strategy considering their current workload (25). However, same-day ART rates steadily increased over time, suggesting improvements

policy assimilation. Rates of ART initiation on the day of HIV diagnosis and up to 30 days after HIV diagnosis were higher among women than men. Women were, on average, younger at HIV diagnosis than men, highlighting the persisting need for consistent efforts to increase early HIV testing and ART initiation of high-CD4 and younger men.

The strength of these analyses lies in the three prospective cohorts, spanning three ART guideline periods in South Africa, allowing direct observation of the changes in ART uptake over time. However, the study data are limited by the small number of health facilities assessed as well as limited information about additional facility-level interventions and the contributions by partner organisations in supporting policy assimilation and implementation. Therefore, other data from a more representative facility survey are needed to better explain the facility-level variations in ART policy implementation and outcomes. Additionally, we only collected ART initiation data from testing facilities with a short follow-up period and were not able to determine if some participants went on to start ART elsewhere. Furthermore, the reason for the higher ART uptake among same-day ART participants require further exploration around the ART initiation processes and their potential impact on patients' future health-seeking behaviour as well as long term on-ART outcomes.

Conclusion

Our results highlight a positive move towards earlier ART initiation after the implementation of the UTT and same-day ART policies. However, the results also emphasise a vital need to streamline processes to increase same-day ART implementation/uptake further but also ensure timeous baseline safety and monitoring blood tests. Going forward, the need to improve patient demand for early HIV testing remains pertinent to achieve the prevention and treatment benefits of ART.

Acknowledgements

We extend our gratitude to the staff of PHC clinics who supported the implementation of the study and our sincere thanks go to the patients attending these clinics for their willingness to participate and share the valuable information that made this study possible.

Author Contributions

DO and MPF had the original idea for the study and paper. TS managed the study implementation and conducted the primary data analysis. TS, CH, IM, implemented the study and contributed to the result interpretation. LL and MM contributed to the interpretation of the results. All authors reviewed and approved the manuscript.

Conflict of Interest

Authors have no conflicts of interest to declare.

Funding

This study has been made possible by the generous support of the American People and the President's Emergency Plan for AIDS Relief (PEPFAR) through United States Agency for International Development (USAID) under the terms of Cooperative Agreements AID-674-A-12-00029 and 72067419CA00004 to HE2RO. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID or the United States Government.

Data Statement

Patient medical records are owned by the study site and the National Department of Health (South Africa) and governed by the Human Research Ethics Committee (University of Witwatersrand, Johannesburg, South Africa). All relevant data is included in the paper.

References

1. HSRC. The Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017: HIV Impact Assessment Summary Report. Cape Town, HSRC Press.; 2017.

2. Boyer S, Iwuji C, Gosset A, Protopopescu C, Okesola N, Plazy M, et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. AIDS Care. 2016;28(sup3):39-51.

3. Collins S, Geffen N. Community views: balancing the public health benefits of earlier antiretroviral treatment with the implications for individual patients – perspectives from the community. Current Opinion in HIV and AIDS. 2014;9(1):4-10.

4. Cassim N, Coetzee LM, Schnippel K, Glencross DK. Estimating Implementation and Operational Costs of an Integrated Tiered CD4 Service including Laboratory and Point of Care Testing in a Remote Health District in South Africa. PLoS ONE. 2014;9(12):e115420.

5. Human Sciences Research Council (HSRC). The People Living With HIV Stigma Index: South Africa 2014. HSRC Press: 2014 Accessed October 2018 http://www.stigmaindex.org/sites/default/files/reports/Summary-Booklet-on-Stigma-Index-Survey%20South%20Africa.pdf

6. Goudge J, Ngoma B, Manderson L, Schneider H. Stigma, identity and resistance among people living with HIV in South Africa. SAHARA-J: Journal of Social Aspects of HIV/AIDS. 2009;6(3):94-104.

7. Abrahams N, Jewkes R. Managing and resisting stigma: a qualitative study among people living with HIV in South Africa. Journal of the International AIDS Society. 2012 Apr;15(2):10-7448.

8. Treves-Kagan S, Steward WT, Ntswane L, Haller R, Gilvydis JM, Gulati H, Barnhart S, Lippman SA. Why increasing availability of ART is not enough: a rapid, community-based study on how HIV-related stigma impacts engagement to care in rural South Africa. BMC public health. 2015 Dec;16(1):87.

9. South African National Department of Health (SA-NDoH). National Antiretroviral Treatment Guidelines, 2004. Pretoria: SA-NDoH;2004.

10. South African National Department of Health (SA-NDoH). National Antiretroviral Treatment Guidelines, 2010. Pretoria: SA-NDoH;2010.

11. South African National Department of Health (SA-NDoH. Circular on new criteria for initiating adults on ART at CD4 count of 350 cells/ml and below 2011. Pretoria: SA-NDoH; 2011.

12. South African National Department of Health (SA-NDoH. National Antiretroviral Treatment Guidelines 2013. Pretoria: SA NDoH;2013.

13. South African National Department of Health (SA-NDoH). National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults 2015: SA NDoH;2015.

14. Ahmed S, Autrey J, Katz IT, Fox MP, Rosen S, Onoya D, et al. Why do people living with HIV not initiate treatment? A systematic review of qualitative evidence from low- and middle-income countries. Social Science & Medicine. 2018;213:72-84.

15. Abuelezam N N, McCormick AW, Fussell T, Afriyie AN, Wood R, DeGruttola V, et al. Can the Heterosexual HIV Epidemic be Eliminated in South Africa Using Combination Prevention? A Modeling Analysis. American journal of epidemiology. 2016;184(3):239-48.

16. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, et al. HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the Potential Impact of Antiretroviral Therapy on HIV Incidence in South Africa. PLOS Medicine. 2012;9(7):e1001245.

17. South African National Department of Health (South Africa). Implementation of Universal Test and Treat Strategy for HIV positive patients and differentiated care for stable patients 2016. Pretoria: National Department of Health, 2016. https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf Accessed October 2018

18. Group TAS, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.

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

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

21. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine. 2015;373(9):795-807.

22. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV. Prevention of HIV-1 infection with early antiretroviral therapy. New England journal of medicine. 2011 Aug 11;365(6):493-505.

23. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013 Feb 22;339(6122):966-71..

24. South African National Department of Health (South Africa). Tracking implementation of the 90-90-90 strategy for HIV, through the implementation of Test and Treat (TT) policy and same-day anti-retroviral therapy (ART) initiation for HIV positive patients 2017. Pretoria: National Department of Health; 2017.

25. Onoya D, Mokhele I, Sineke T, Ngoma B, Moolla A, Vujovic M, Bor J, Langa J, Fox M P. Health provider perspectives on implementation of same-day ART initiation six months after policy change in South Africa. International AIDS Conference (poster); 2018; Amsterdam.

26. Kulkarni SP, Shah KR, Sarma KV, Mahajan AP. Clinical Uncertainties, Health Service Challenges, and Ethical Complexities of HIV "Test-and-Treat": A Systematic Review. American Journal of Public Health. 2013;103(6):e14-e23.

27. Skhosana M, Reddy S, Reddy T, Ntoyanto S, Spooner E, Ramjee G, et al. PIMA TM point-of-care testing for CD4 counts in predicting antiretroviral initiation in HIV-infected individuals in KwaZulu-Natal, Durban, South Africa. Southern African Journal of HIV Medicine.2016;17(1).

28. Bigna JJR, Plottel CS, Koulla-Shiro S. Challenges in initiating antiretroviral therapy for all HIV-infected people regardless of CD4 cell count. Infectious Diseases of Poverty. 2016;5(1):85.

29. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002-2013: a meta-analysis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015;60(7):1120-7.

30. Egbujie BA, Grimwood A, Mothibi-Wabafor EC, Fatti G, Tshabalala AMET, Allie S, et al. Impact of 'Ideal Clinic' implementation on patient waiting time in primary healthcare clinics in KwaZulu-Natal Province, South Africa: A before-and-after evaluation. SAMJ Research. 2018;108(4):311-8.

Table 1. Description of ART guideline changes over time in South Africa

ART Guideline	Guideline eligibility/description	Introduction of guidelines/directive	Study recruitment period
Pre-UTT	Eligible for ART start if CD4 <500 cells/ml	January 2015	April-December 2015
UTT, before same-day ART	Eligible for ART start if HIV-positive, regardless of CD4 count	September 2016	July-September 2017
UTT, with same-day ART	Eligible for ART start if HIV-positive, regardless of CD4 count. Directive to initiate ART on date of HIV-positive diagnosis	September 2017	October 2017-July 2018

Table 2 Characteristics of the sample population by Period of HIV testing

	Pre-UTT (n=146)	UTT (n=141)	Same-day ART (n=742)	Total (N=1029)
	n (%)	n (%)	n (%)	n (%)
Facility				
PHC1	68 (46.6)	72 (51.1)	80 (10.8)	220 (21.4)
PHC2	78 (53.4)	69 (48.9)	51 (6.9)	198 (19.2)
PHC3	-	-	207 (27.9)	207 (20.1)
PHC4	-	-	125 (16.8)	125 (12.1)
PHC5	-	-	151 (20.4)	151 (14.7)
PHC6	-	-	128 (17.3)	128 (12.4)
Time after policy announcement				
≤3 months	1 (0.7)	0	138 (18.6)	139 (13.5)
4-6 months	40 (27.4)	0	183 (24.7)	223 (21.7)
7-9 months	72 (49.3)	2 (1.4)	233 (31.4)	307 (29.8)
≥10 months	33 (22.6)	139 (98.6)	188 (25.4)	360 (35.0)
Sex				
Female	87 (59.6)	81 (57.4)	461 (62.1)	629 (61.1)
Male	59 (40.4)	60 (42.6)	281 (37.9)	400 (38.9)
Age, (median, IQR)				
18 - 24	20 (13.7)	20 (14.2)	82 (11.1)	122 (11.9)
25 - 29	32 (21.9)	33 (23.4)	160 (21.6)	225 (21.9)
30 - 34	41 (28.1)	29 (20.6)	177 (23.9)	247 (24.0)
35 - 39	28 (19.2)	31 (22.0)	147 (19.8)	206 (20.0)
40+	25 (17.1)	28 (19.9)	176 (23.7)	229 (22.3)
Baseline CD4				
<350	96 (65.8)	73 (51.8)	296 (39.9)	465 (45.2)
350 - 500	26 (17.8)	22 (15.6)	91 (12.3)	139 (13.5)
≥500	19 (13.0)	21 (14.9)	97 (13.1)	137 (13.3)
Missing	5 (3.4)	25 (17.7)	258 (34.8)	288 (28.0)
Education				
< Grade 12	97 (66.4)	95 (71.4)	544 (73.9)	736 (72.5)
≥ Grade 12	49 (33.6)	38 (28.6)	192 (26.1)	279 (27.5)
Marital Status				
Single	28 (19.2)	18 (12.8)	110 (14.8)	156 (15.2)
In a relationship	92 (63.0)	98 (69.5)	497 (67.1)	687 (66.8)
Married	21 (14.4)	18 (12.8)	112 (15.1)	151 (14.7)
Divorced/widowed	5 (3.4)	7 (5.0)	22 (3.0)	34 (3.3)
Employment Status				
Unemployed	70 (47.9)	66 (46.8)	402 (54.5)	538 (52.5)
Employed	76 (52.1)	75 (53.2)	335 (45.5)	486 (47.5)
Number of adults in household				
Lives alone	28 (19.2)	21 (15.0)	160 (21.7)	209 (20.5)
Two adult in home	82 (56.2)	81 (57.9)	429 (58.3)	592 (57.9)
≥ three adults	36 (24.7)	38 (27.1)	147 (20.0)	221 (21.6)

Travel time to clinic				
≤15 minutes	90 (61.6)	90 (63.8)	405 (54.6)	585 (56.9)
16-30 minutes	46 (31.5)	45 (31.9)	224 (30.2)	315 (30.6)
>30 minutes	10 (6.8)	6 (4.3)	113 (15.2)	129 (12.5)

Table 3 Demographic and clinical characteristics associated with initiating ART within 30 days of HIV diagnosis

	Initiated ART within 30 days n(%)	Person years	Rates/100 PY (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Facilities					
PHC 1	145 (65.9)	1.1	131.6 (111.8-154.8)	0.5 (0.4-0.7)	1.3 (0.8-2.0)
PHC 2	96 (48.5)	1.4	66.6 (54.5-81.4)	0.3 (0.2-0.4)	0.7 (0.4-1.2)
PHC 3	169 (81.6)	0.7	228.6 (196.6-265.8)	0.9 (0.7-1.1)	0.8 (0.6-1.0)
PHC 4	98 (78.4)	0.4	266.7 (218.8-325.1)	1	1
PHC 5	121 (80.1)	0.6	192.9 (161.4-230.5)	0.8 (0.6-1.0)	0.7 (0.6-1.0)
PHC 6	111 (86.7)	0.4	267.8 (222.3-322.5)	1.0 (0.7-1.3)	0.9 (0.7-1.2)
Guideline periods					
Pre-UTT	54 (36.9)	1.1	45.4 (34.8-59.3)	0.3 (0.2-0.3)	0.2 (0.1-0.4)
UTT	93 (65.9)	0.8	117.7 (96.1-144.3)	0.6 (0.5-0.7)	0.3 (0.2-0.5)
Same-day ART	593 (79.9)	2.7	218.8 (201.7-236.9)	1.0	1.0
Time after policy announcement					
≤3 months	101 (72.7)	0.6	157.4 (129.5-191.3)	0.9 (0.7-1.1)	0.4 (0.2-0.6)
4-6 months	152 (68.2)	1.1	133.0 (113.4-155.9)	0.8 (0.6-1.0)	0.5 (0.4-0.7)
7-9 months	216 (70.4)	1.4	155.8 (136.3-178.0)	0.9 (0.7-1.1)	0.7 (0.6-0.8)
≥10 months	271 (75.3)	1.5	178.3 (158.2-200.8)	1	1
Sex					
Male	266 (66.5)	2.0	134.7 (119.4-151.9)	1.0	1.0
Female	474 (75.3)	2.7	174.5 (159.5-190.9)	1.7 (1.4-2.0)	1.2 (1.0-1.4)
Age at testing					
18 - 24	88 (72.1)	0.5	170.9 (138.7-210.6)	1.0	
25 - 29	159 (70.7)	1.1	150.2 (128.6-175.5)	0.9 (0.7-1.2)	
30 - 34	170 (68.8)	1.1	154.5 (132.9-179.6)	0.9 (0.7-1.2)	
35 - 39	146 (70.8)	1.0	147.5 (125.2-173.1)	0.9 (0.7-1.2)	
40+	177 (77.2)	1.0	171.8 (148-199.9)	1.1 (0.8-1.3)	
Baseline CD4					
<350	146 (62.7)	2.2	154.4 (138.9-171.6)	1.0	1.0
350 - 500	238 (79.9)	0.6	169.6 (139.8-205.7)	1.1 (0.9-1.4)	1.1 (0.9-1.3)
≥500	172 (81.9)	0.5	217.9 (180.6-262.9)	1.3 (1.0-1.6)	1.1 (0.9-1.4)
Missing	194 (63.9)	1.4	135.7 (117.5-156.8)	0.9 (0.8-1.1)	0.6 (0.5-0.7)
Education					
< Grade 12	527 (71.6)	3.4	154.5 (142.1-168.5)	1.0	

≥ Grade 12	203 (72.7)	1.2	165.0 (144.2-189.9)	1.1 (0.9-1.2)	
Marital Status					
Single	114 (73.0)	0.7	160.6 (133.6-192.9)	1.00	
In a relationship	483 (70.3)	3.1	156.3 (142.6-170.4)	1.0 (0.8-1.2)	
Married	119 (78.8)	0.67	172.5 (142.7-204.3)	1.1 (0.8-1.4)	
Divorced/widowed	23 (67.6)	0.2	127.8 (83.1-188.3)	0.8 (0.5-1.3)	
Employment Status					
Unemployed	386 (71.7)	2.5	156.3 (141.2-172.3)	1.0	
Employed	351 (72.2)	2.2	161.0 (144.6-178.2)	1.0 (0.9-1.2)	
# adults in household					
Lives alone	141 (67.4)	1.0	138.2 (117.1-162.9)	1.0	1.0
Two adult in home	442 (74.6)	2.6	170.0 (154.8-186.5)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
≥ three adults	153 (69.2)	1.0	148.5 (126.8-174.1)	1.1 (0.8-1.3)	1.1 (0.9-1.5)
Travel time to clinic					
≤15 minutes	415 (70.9)	2.7	152.0 (138.2-167.5)	1.0	1.0
16-30 minutes	218 (69.2)	1.5	143.4 (125.4-163.5)	1.0 (0.8-1.1)	0.9 (0.8-1.1)
>30 minutes	107 (82.9)	0.4	243.2 (200.9-293.5)	1.5 (1.2-1.8)	1.1 (0.9-1.5)

Table 4 Demographic and clinical characteristics associated with initiating ART on the day of HIV diagnosis

	Initiated ART within same-day n(%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Facility			
PHC 1	8 (10.0)	0.3 (0.2-0.6)	1.5 (0.5-4.3)
PHC 2	9 (17.7)	0.5 (0.3-1.0)	2.1 (0.9-4.9)
PHC 3	35 (16.9)	0.5 (0.3-0.7)	0.7 (0.4-1.0)
PHC 4	42 (33.6)	1	1
PHC 5	46 (30.5)	0.9 (0.6-1.3)	1.3 (0.8-1.9)
PHC 6	10 (7.8)	0.2 (0.1-0.4)	0.3 (0.1-0.5)
Time after policy announcement			
≤3 months	15 (10.9)	0.3 (0.2-0.6)	0.2 (0.1-0.4)
4-6 months	19 (10.4)	0.3 (0.2-0.5)	0.3 (0.2-0.5)
7-9 months	57 (24.5)	0.8 (0.6-1.1)	0.8 (0.6-1.0)
≥10 months	59 (31.4)	1	1
Sex			
Male	44 (15.7)	1	1
Female	106 (23.0)	1.5 (1.1-2.0)	1.3 (1.0-1.9)
Age at testing			
18 - 24	25 (30.5)	1.0	1.0

25 - 29	37 (23.1)	0.8 (0.5-1.2)	0.8 (0.5-1.3)
30 - 34	38 (21.5)	0.7 (0.5-1.1)	0.8 (0.5-1.2)
35 - 39	24 (16.3)	0.5 (0.3-0.9)	0.7 (0.4-1.1)
40+	26 (14.8)	0.5 (0.3-0.8)	0.6 (0.4-0.9)
Baseline CD4			
<350	44 (14.9)	1.0	1.0
350 - 500	18 (19.8)	1.3 (0.8-2.2)	1.0 (0.4-2.6)
≥500	20 (20.6)	1.4 (0.9-2.2)	1.1 (0.4-2.9)
Missing	68 (26.4)	1.8 (1.3-2.5)	1.5 (0.6-3.7)
Education			
< Grade 12	107 (19.7)	1.0	
≥ Grade 12	43 (22.4)	1.1 (0.8-1.6)	
Marital Status			
Single	17 (15.5)	1.0	
In a relationship	117 (23.5)	1.5 (0.9-2.4)	
Married	16 (14.3)	0.9 (0.5-1.7)	
Divorced/widowed	0		
Employment Status			
Unemployed	76 (18.9)	1.0	
Employed	72 (21.5)	1.1 (0.9-1.5)	
# adults in household			
Lives alone	30 (18.7)	1.0	
Two adult in home	88 (20.5)	1.1 (0.8-1.6)	
≥ three adults	30 (20.4)	1.1 (0.7-1.7)	
Travel time to clinic			
≤15 minutes	77 (19.0)	1.0	1.0
16-30 minutes	41 (18.3)	0.9 (0.7-1.4)	1.1 (0.8-1.6)
>30 minutes	32 (28.3)	1.5 (1.0-2.1)	1.3 (0.8-2.0)

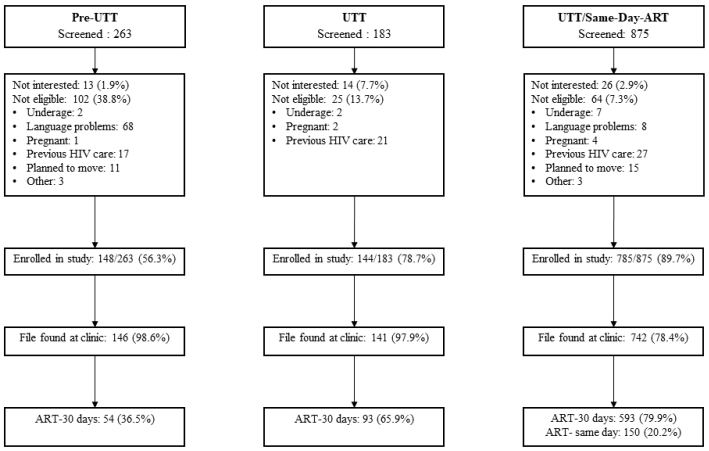


Figure 1. Participant flow through the recruitment process by ART guideline periods

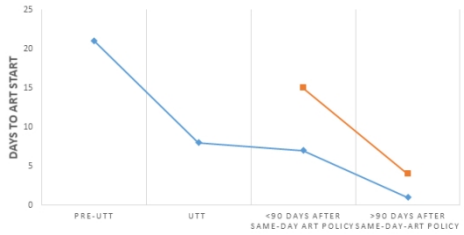


Figure 2. Time to ART initiation in the first 30 days of HIV care pre-UTT, during UTT and under the same-day ART policies in Johannesburg, South Africa.

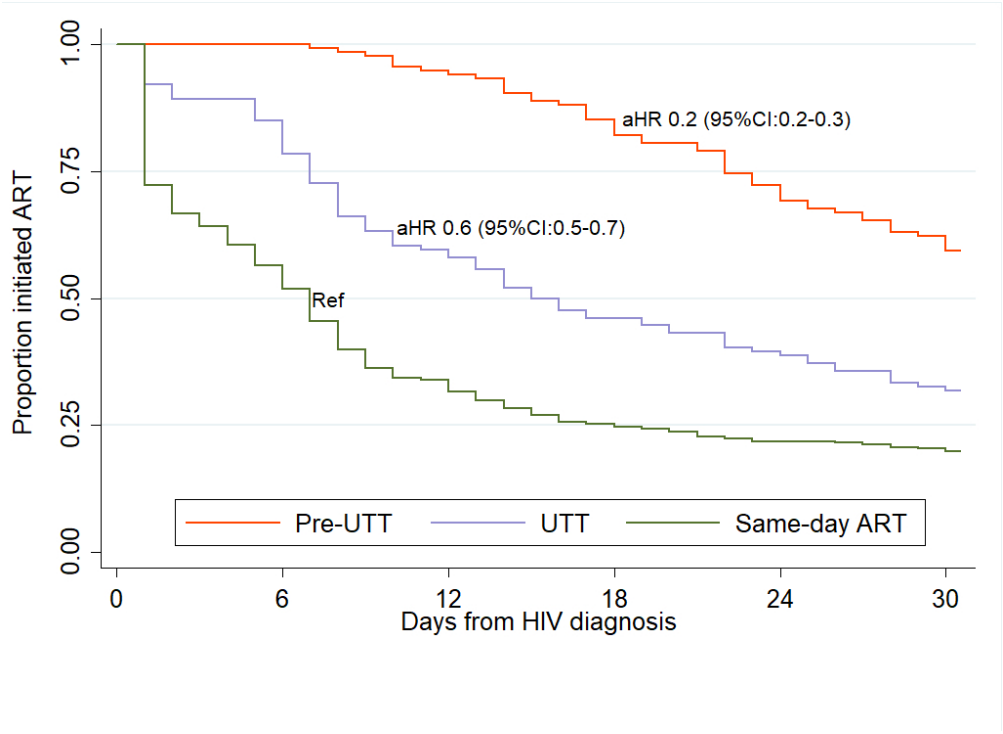


Figure 3. Kaplan Meier curves of ART initiation in the first 30 days of HIV care in Johannesburg, South Africa

361x262mm (72 x 72 DPI)

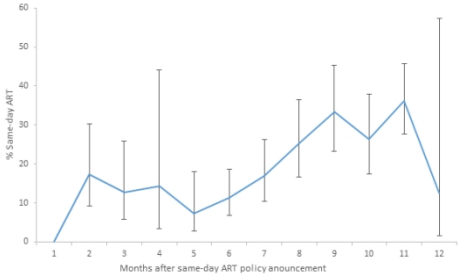


Figure 4. The trend of same-day ART initiations in the first ten months of the same-day ART policy in Johannesburg, South Africa

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	6-7, Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 2-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of the test and treat policy on delays in ART initiation among HIV positive adult patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030228.R2
Article Type:	Original research
Date Submitted by the Author:	27-Nov-2019
Complete List of Authors:	Onoya, Dorina; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Sineke, Tembeka; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Hendrickson, Cheryl; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Mokhele, Idah; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Maskew, Mhairi; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Long, Lawrence; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office; Boston University, Boston School of Public Health, Department of Global Health Fox, Matthew; Boston University, Epidemiology and Global Health; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office
Primary Subject Heading:	Health policy
Secondary Subject Heading:	HIV/AIDS, Public health, Health policy
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, PRIMARY CARE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

+Working Title:

Impact of the test and treat policy on same-day ART delays in HIV treatment initiation in Johannesburg, South Africa

Title: Impact of the test and treat policy on delays in ART initiation among HIV positive adult patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study

Authors: Dorina Onoya[1], Tembeka Sineke[1], Cheryl Hendrickson[1], Idah Mokhele[1], Mhairi Maskew[1], Lawrence Long[1,2], Matthew P. Fox[1, 2, 3]

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

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

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

Corresponding author: Dorina Onoya, Health Economics and Epidemiology Research Office, 39 Empire Road, Parktown, Johannesburg, 2193, South Africa, donoya@heroza.org +27 10 001 7930

Keywords: HIV, ART attrition, UTT, same-day ART

Word count (main body): 3436

Abstract

Objectives To assess delays to antiretroviral therapy (ART) initiation before the Universal Test & Treat (UTT) policy, under UTT and during same-day initiation (SDI) of ART policy periods in Johannesburg, South Africa.

Design Prospective cohort study

Setting Patients were recruited from six primary health clinic in Johannesburg.

Participants Overall, 1029 newly diagnosed HIV positive adults (≥18 years) were consecutively enrolled by referral from the testing HIV counsellor between April- December 2015 (Pre-UTT n=146), July-August 2017 (UTT, n=141) and October 2017-August 2018 (SDI, n=742).

Main outcome measures Predictors of 30-days ART initiation uptake were assessed using Cox proportional hazards models from HIV diagnosis. Additionally, predictors of immediate ART initiation were evaluated using Poisson regression modelling.

Results Overall, 30-days ART proportions were 71.9% overall, 36.9% pre-UTT, 65.9% under UTT and 79.9% under the SDI policy. The median days to ART initiation declined from 21 pre-UTT (IQR: 15-30) to eight (IQR: 6-16) under UTT and five days (IQR: 0-8) under the SDI policy. However, only 150 (20.2%) of the SDI cohort initiated ART immediately after HIV diagnosis. Living in a two-adult home (adjusted Hazard ratio (aHR) 1.2 vs living alone, 95% Confidence Interval (CI): 1.0-1.4) increased the likelihood of 30-day ART. Missing baseline CD4 data decreased the likelihood of 30-days ART by 40% (aHR 0.6 vs CD4<350 cell/µl, 95% CI: 0.5-0.7). Women were more likely to take up immediate ART (aRR 1.3, 95%CI: 1.0-1.9). Participants ≥40 years (aRR 0.6 vs 18-24 years old, 95% CI: 0.4-0.9) were less likely to start ART on the day of HIV diagnosis. However, immediate ART rates increased with longer policy implementation time (aRR 0.2 for <3-months vs >10-months, 95%CI: 0.1-0.4).

Conclusions Our results highlight a positive move towards earlier ART initiation during the UTT and SDI periods and emphasise a need to increase same-day ART implementation further.

Word count: 300

Strengths and limitations

- Cohorts enrolled across the three most recent ART guideline implementation periods in South Africa, allowing observation of changes over time.
- Participants enrolled immediately after HIV diagnosis, allowing for observation of ART initiation and patient attrition from HIV diagnosis.
- Our results highlight a positive move towards earlier initiation of HIV treatment after the UTT policy implementation.
- Although we demonstrate substantial reductions in delays to ART initiation (median of 21 to five days), ART initiation on the day of HIV diagnosis is limited and requires additional investigations to improve programmatic performance.
- Increases in missing baseline laboratory tests at diagnosis reduce the strength of laboratory datasets as monitoring tools for the early steps of the HIV treatment cascade and delay the assessment of the appropriateness of the initial ART regiment.

Introduction

South Africa has the largest Human Immunodeficiency Virus (HIV) epidemic in the world, with an estimated 7.9 million persons living with HIV (1). Over the years, the South African government gradually increased the cluster of differentiation four (CD4)-based antiretroviral therapy (ART) eligibility threshold from 200 cells/µl in 2004, to 350 cells/µl in 2010 and 500 cells/µl in January 2015 (2-6). These thresholds both capped the number of persons initiating ART and negatively affected the retention of pre-ART patients. In the past, attrition from care after HIV diagnosis was also related to the number of assessment and counselling visits required before treatment initiation for eligible patients and the lack of systematic monitoring of and benefits for patients who were not offered ART (2-7). Additional pre-ART determinants of losses from the HIV treatment cascade include gender, requirement for a treatment buddy/disclosure and HIV stigma, and the high cost of attending clinic visits (7-14).

In September 2016, South Africa removed the CD4 cell count threshold for ART eligibility and adopted the World Health Organization (WHO) 2015 Universal Test and Treat (UTT) policymaking all HIV positive patients eligible for ART at diagnosis (15-17). Clinical trials showed that, compared to patients who deferred ART, patients who started treatment immediately after HIV diagnosis had lower rates of acquired immunodeficiency syndrome (AIDS)-related adverse events and improved viral suppression rates with no difference in post-initiation attrition rates (18-22). Moreover, patients who started ART immediately after diagnosis were less likely to transmit HIV than patients who deferred ART (16, 21-23).

In September 2017, the general UTT policy was updated with a directive to initiate ART on the day of HIV diagnosis (same-day initiation - SDI) (24). While widespread support for the UTT policy has created momentum for its promulgation, there remained reservations from primary health care (PHC) providers that health system capacity constraints may limit same-day ART policy assimilation and result in variations in implementation at facility-level (25). The policy was implemented amid concerns that, under UTT, health facilities in high burden settings, in particular, might struggle with the increased patient burden, potentially reducing the quality of care provided to new and existing patients (2-4, 26-27). There were also concerns around patient acceptance of same-day ART, ART refusal or early patient disengagement from care or intermittent adherence after starting ART (28).

In 2017, an estimated 4.4 million (55.7%) South African HIV-positive patients had started ART (1). While this constituted an in increases in the number of HIV positive patients initiated on ART (nearly one million additional patients started ART between 2016 and 2017), the proportions also suggested continued challenges with patient linkage to ART after HIV diagnosis (1). Furthermore, in addition to measuring program success in terms of expanded access to ART, critical outcomes of the UTT policy include the initiation of patients with high CD4 cell count, reductions in delays to ART initiation and long-term retention in HIV care.

In this study, we set out to measure ART initiation of newly diagnosed adults in the first 30 days of HIV care (30-day ART) across the three recent ART guideline periods and to examine factors associated with 30-days ART at six primary healthcare clinics (PHC) in Johannesburg, South Africa. Additionally, we examined rates and factors associated with initiating ART on the day of HIV diagnosis among participants diagnosed under the SDI policy.

Methods

Study Setting and design

The city of Johannesburg (JHB) is the largest of five health districts in the Gauteng province in South Africa. Johannesburg had an estimated HIV prevalence of 12.9% (>500,000 persons living with HIV) in 2017, with 60.7% of diagnosed persons currently receiving ART. Johannesburg comprises 108 PHC (facilities subdivided into seven regions or sub-districts (denoted A-G) covering about 75% of the population (uninsured). This study was conducted at six (of 13) conveniently selected public-sector PHCs in the JHB health sub-district A. PHC clinics in Johannesburg are mainly nurse-run with the support of one medical doctor and are responsible for HIV testing, ART initiation and primary-level management and monitoring of HIV positive patients.

We conducted a prospective cohort study, enrolling consenting newly diagnosed HIV positive adult (≥18 years) patients from April to December 2015 (CD4<500 or Pre-UTT period), July-August 2017 (UTT period) and October 2017-August 2018 (SDI period) (Summarised in Table 1). Pre-UTT and UTT cohorts were only enrolled from two PHCs in Johannesburg while the SDI cohort included four additional PHCs in the same area (serving similar populations) in

Johannesburg (Table 2) (11-14). We assumed that 70% of HIV positive patients with CD4 counts > 350 cells/µl would become lost from HIV care in the first year after HIV diagnosis compared to 60% among patients with CD4 ≤ 350. We further hypothesised a 20% reduction in overall attrition between the pre-UTT and UTT periods. Additionally, the sample size for the SDI cohort was increased to enable a separate assessment of ART refusal (hypothesised 20% refusal by six-month post-HIV diagnosis) and attrition among participants who initiate ART with high CD4 count (>500 cells/µl). The ART refusal analysis will be presented in future manuscript. The number of sites was also increased to six to allow comparison of the same-day ART across clinics.

Participant enrolment co-occurred across sites until 100% sample size was attained at each site (Figure 1). All patients were enrolled in the study after a new (self-reported) HIV-positive diagnosis (before ART eligibility determination) by trained study interviewers via referral from PHC-based lay HIV counsellors. We included newly diagnosed adult patients (18 years or older) who were able to speak English, Zulu and Sotho. Patients were eligible if they had entered HIV care after an HIV-positive diagnosis. Entering HIV care was defined as providing the first blood sample for baseline safety laboratory tests for the Pre-UTT and UTT cohorts, and defined as having received the HIV positive test result for the same-day ART cohort because new clinic processes meant that patients were likely to start ART before the first blood collection. Women who were pregnant at HIV diagnosis were excluded from the study because their antenatal care ART initiation and monitoring processes differ from that of non-pregnant populations. Study staff cooperated closely with lay HIV counsellors across sites and checked HIV testing records daily to ensure that all testers who were diagnosed with HIV were being referred to study staff for study eligibility assessment.

Data Collection

Patients provided written consent for all study procedures and completed an interviewer-administered baseline questionnaire after HIV testing, on the day of HIV diagnosis. The consent process and interviews were conducted exclusively in English in the pre-UTT cohort because we assumed that the urban Johannesburg population would be conversant in English but later translated to Sotho and Zulu as well for the UTT and SDI cohorts. The interview included questions on demographic factors, socioeconomic status and health-seeking behaviour. The

recency of the HIV diagnosis was determined from HIV testing history questions at baseline. Patients were passively followed up by medical record review up to 30 days after HIV diagnosis to determine ART initiation.

Person-time accrued from the date of HIV diagnosis (study enrolment) until ART initiation. We assumed that all patients for whom clinic files were created were in care for the first 30 days unless there was evidence of an official transfer or death in the first 30 days after HIV diagnosis. Trained data collectors captured routine clinical follow-up data of consenting participants from facility-based paper and electronic medical records, including laboratory test results from the National Health Laboratory Services (NHLS). We define baseline CD4 as the first CD4 results in up to 30 days after HIV diagnosis. Trained data collectors captured all routine clinical follow-up data on the REDCap (Research Electronic Data Capture) systems (Vanderbilt University, Nashville, Tenessee). All datasets were exported to STATA 14 (StataCorp, College Station, Texas) for the analysis.

Patient and Public Involvement

Patients of the current study were not directly involved in the design of this study or reimbursed for their participation in the study. However, information collected from patients in previous studies informed the design, data collection approaches and interpretation of study results (19, 24). Also, the study implementation was guided by health care workers from the participating study sites. Study participants consented to a once-off direct data collection after HIV diagnosis and passive follow-up data collection via medical record review. Therefore, direct result dissemination to patients will not be possible. However, we plan to present study results to health care workers and policy-makers at participating PHC clinics and at other policy-relevant forums.

Outcome data and analysis

The primary exposure variable was the ART policy at the time of HIV diagnosis, categorised as pre-UTT (policy active between January 2015 and August 2016), under the general UTT (active between September 2016 and August 2017) policy and the SDI policy (active from September 2017 onward) (14, 17, 24). The primary outcome was ART initiation up to 30 days after HIV diagnosis (30-day ART), and the secondary outcome is ART initiation immediately after HIV

diagnosis (Immediate ART), both outcomes were coded Yes (1) or No (0). Final data analysis began in October 2018.

Continuous variables were described using medians and interquartile ranges. Categorical variables were described using percentages. Kaplan Meier analyses were conducted to assess time to ART initiation in the first 30 days of HIV care. Predictors of 30-day ART were modelled using Cox proportional hazards regression, reporting Hazard Ratios (HR). Variables with a p-value <0.1 in crude analyses were entered in the multivariate model. Schoenfeld residuals were used to test the assumption of proportional hazards. Interaction terms with time-varying covariates were created for variables that violated the proportional hazards assumption. Variables were excluded from the model when the inclusion of the interaction term did not resolve the proportional hazards assumption violation. Missing data were accounted for by including a 'not measured/missing' category where necessary. Additionally, predictors of ART initiation on the day of HIV diagnosis (dichotomised) were evaluated using Poisson Regression modelling, reporting Relative Risks (RR).

All multivariate analyses were adjusted for the time from the period-specific policy announcement to account for the varying lag periods between policy implementation and participant enrolment across cohorts. Additionally, we tested the association between the highest level of education and ART initiation across guideline periods to account for the change in interview language options. The study protocol was reviewed and approved by the Institutional Review Boards of the University of Witwatersrand (M141103) in South Africa and Boston University (H-33516) in the USA.

Results

Clinical and demographic characteristics at baseline

Although 1167 (100% of target sample) HIV positive adults enrolled in the study, this analysis was limited to 1029 (88.2%) for whom an outcome could be ascertained (medical data was available), 146 (98.6%) pre-UTT, 141 (97.9%) under UTT, and 742 (94.5%) under the SDI policy (Figure 1). The exclusive use of English questionnaires in the pre-UTT cohort was the most significant reason for participant non-eligibility (25.9% of total screened). However, the age and gender distributions were similar across cohorts (Median 32.6 years for Pre-UTT,

interquartile range (IQR):27.2-37.6; 32.3 years for UTT, IQR: 27.2-38.9; and 32.3 years for SDI, IQR: 28.4-39.5) (Table 2). Women (Median 32.6 years, IQR: 27.0-37.7) were slightly younger at HIV diagnosis than men (Median 35.8, IQR: 32.1-41.5) (β_{female} -3.4, 95%CI: -4.4 to -2.4). The pre-UTT cohort had a marginally higher proportion of participants who completed grade 12 (33.6%) compared to 28.6% in the UTT and 26.1% in the SDI cohorts. Employment rates were also similar across cohorts (47.9% pre-UTT, 46.8% UTT and 54.5% SDI).

Although the proportion of participants who tested with CD4 count<350/mm^3 decreased from 65.8% pre-UTT to 39.7% in the same-day ART cohort, the percentage of patients with missing baseline CD4 count results increased from 3.4% to 34.7%, respectively. Among participant who had CD4 data, the proportion of patient with baseline CD4 count>500 cells/µl did not change substantially across guideline periods (20.0% during SDI vs 13.5% Pre-UTT, relative risk (RR)=1.5 (95%CI: 0.9-2.3) and RR=1.3 (95%CI: 0.9-2.4) for SDI vs UTT (18.1%)).

Although most participants lived within 15 minutes of the diagnosing clinic (56.9%), a small proportion reported travelling over 30 minutes to the clinic (12.5% overall, 6.8% pre-UTT, 4.3% under UTT and 15.2% under SDI policies). Travel time varied across clinics such that <12% participants from five of the six recruitment sites reported travelling over 30 minutes to the clinics, but 46.4% of participants from PHC four reported >30-minutes travel time.

Time to ART initiation from HIV diagnosis across guideline periods

Overall, 71.9% participants initiated ART within 30 days of HIV diagnosis, 36.5% pre-UTT (44.3% of those eligible for ART), 65.9% under UTT and 79.9% in the SDI period (Figure 3). The overall median days to ART initiation declined from 21 days (IQR: 15-30) to eight days (IQR: 6-16) after the implementation of the UTT policy. Time to ART start was further reduced to a median of five days (IQR: 0-8) after the SDI directive was given (Figure 2), with most reductions observed three months after the SDI policy directive was given to PHCs.

Overall, 30-day ART rates increased with increasing lag time from the prevailing (at the time of participant's HIV diagnosis) policy announcement (adjusted hazard ratio (aHR) 0.4 for ≤3-months vs ≥10-months, 95%CI: 0.2-0.6). The highest level of education was not associated with 30-day ART uptake. After adjusting for the facility of diagnosis and lag time from the policy announcement, pre-UTT participants were 80% less likely to initiate ART in the first 30 days (aHR 0.2, 95% CI: 0.2-0.4) compared to SDI participants (Table 3). Similarly, patients diagnosed under the UTT policy were 70% less likely to start ART within 30 days of HIV diagnosis (aHR 0.3, 95% CI: 0.2-0.5) compared to SDI participants (Figure 3).

While women had higher 30-day ART rates compared to men (aHR 1.2, 95%CI: 1.0-1.4), there was no meaningful difference in the likelihood of 30-days ART initiation across age, marital status, travel time to the clinic or employment categories. Overall, compared to patients with baseline CD4<350 cell/µl, participants with baseline CD4>500 cells/µl had similar rates of 30-day ART. However, participants who were missing baseline CD4 counts were 40% less likely to start ART within a month (aHR 0.6, 95% CI: 0.5-0.7). Participants who lived in a two-adult home had higher rates of 30-day ART than those who lived alone (aHR 1.2, 95%CI: 1.0-1.5). Women were more likely to live with at least one other adult (RR 1.2, 95%CI: 1.1-1.4) compared to men.

Demographic and clinical characteristics associated with immediate ART initiation within the SDI cohort

Within the SDI cohort, 150 (20.2%) participants initiated treatment on the day of HIV diagnosis (25.3% of those who initiated ART within 30 days). Women were more likely to take up immediate ART (aRR 1.3, 95%CI: 1.0-1.9) than men. Older participants (aRR 0.6 for patients ≥40 years old compared to patients in the 18-24 years group, 95% CI: 0.4-0.9) were less likely to start ART on the day of HIV diagnosis (Table 4). In the SDI period, missing baseline CD4 data

did not affect the likelihood of starting ART on the day of HIV diagnosis (aRR 1.5, 95%CI: 0.5-3.7). We also describe a high variability in SDI policy implementation across sites (Table 4). However, immediate ART rates increased gradually with longer policy implementation time (aRR 0.2 for <3 months vs >10 months, 95%CI: 0.1-0.4) (Figure 4).

Discussion

This study highlights a marked reduction in time to ART initiation following the implementation of the UTT guidelines, decreasing from a median of 21 days to eight days, despite this policy not including a directive to modify ART initiation times. An additional decline in time to ART start was also observed after the same-day ART memorandum was sent to clinics. These declines are consistent with the goals of the WHO HIV treatment guidelines: to initiate patients as early as possible to achieve better clinical outcomes (15-16).

Consistent with previous findings (29), we found a decrease in the proportion of patients presenting with CD4 <350 cells/µl but little improvement in the CD4>500 cells/µl group between the pre-UTT and SDI periods. Overall, nearly two-thirds of participants who had baseline CD4 data were diagnosed with HIV with low CD4 counts (<350 cell/µl). Over a third of the SDI cohort was missing baseline CD4 data.

Missing baseline CD4 data in the SDI cohort could have resulted from the lack of clarity in the policy with regards to the need or timing of safety blood tests early in the same-day ART policy implementation or patient impatience with the drawn-out HIV testing and ART initiation processes on the day of HIV testing (17, 25, 30). It is unclear whether this is a result of the change in the definition of entry in HIV care (first blood draw vs HIV diagnosis) for the SDI cohort. However, this increase in missing baseline CD4 was observed from the pre-UTT cohort to the UTT cohort, at which point clinics already began to reduce time to ART start (to the first week of care for some patients). Nevertheless, having a missing baseline CD4 was associated with a reduced likelihood of 30-day ART compared to patients with lower baseline CD4 values. When we restricted the analysis to the SDI cohort, having a missing CD4 count was associated with a non-significant increase in immediate ART rates, which possibly also means that patients diagnosed under the SDI policy may start ART before the first blood draw and defer baseline CD4 tests. However, this finding requires further exploration.

Interestingly, participants who lived in a two-adult home rather than alone were more likely to initiate ART within 30 days. However, participants who lived in larger households had similar 30-day ART rates to those who lived alone, suggesting persisting fear of confidentiality breaches within homes (5, 9).

Only 20.2% of patients diagnosed under the SDI policy started ART on the day of diagnosis, highlighting possible facility-level policy assimilation challenges. Rates of immediate ART and 30-days ART were also higher among non-pregnant women than men. Immediate ART has been available to South African HIV positive pregnant women since 2013 with relatively few patients or provider acceptability challenges (13, 31-33). However, health provider concerns about the SDI policy for the general population may have affected the pace of the policy implementation (25). In a previous qualitative study, Healthcare providers expressed reservations about the acceptability of immediate ART for the majority of their patients and the feasibility of the strategy considering their current workload (25). However, immediate ART rates steadily increased over time, suggesting improvements policy assimilation, albeit with some variability across sites. While CD4 count did not influence immediate ART uptake, women were younger at HIV diagnosis than men, highlighting the persisting need for consistent efforts to increase early HIV testing and ART initiation younger men (1, 31).

The strength of these analyses lies in the three prospective cohorts, spanning three ART guideline periods in South Africa, allowing direct observation of the changes in ART uptake over time. This study improves on a possible retrospective review by the collection of extensive personal and contextual data that are not routinely collected. However, the study data are limited by the small number of health facilities assessed, limited information about additional facility-level interventions as well as the contributions by partner organisations in supporting policy assimilation and implementation. Therefore, a more representative facility survey is needed to better explain the facility-level variations in ART policy implementation and outcomes. Additionally, we only collected ART initiation data from testing facilities with a short follow-up period and were not able to determine if some participants went on to start ART elsewhere.

Furthermore, the reason for the higher ART uptake among same-day ART participants require further exploration around the ART initiation processes and their potential impact on patients' future health-seeking behaviour as well as long term on-ART outcomes. The sample size did

influence the duration of the enrolment process. However, the date of enrolment start depended on ethics approval. Unfortunately, we were negatively affected by university student protests that caused the Human Research Ethics department to stop operations for a while, resulting in a backlog of applications. To compensate for this, we adjusted all multivariate analyses by the lag period between the policy directive to the clinics and the date of patient's HIV diagnosis.

Conclusion

Our results highlight a positive move towards earlier ART initiation after the implementation of the UTT and SDI policies. However, the results also emphasise a vital need to not only streamline processes to increase immediate ART implementation/uptake further but also ensure timeous baseline safety and monitoring blood tests. Going forward, the need to improve patient demand for early HIV testing remains pertinent to achieve the prevention and treatment benefits of ART.

Acknowledgements

We extend our gratitude to the staff of PHC clinics who supported the implementation of the study and our sincere thanks go to the patients attending these clinics for their willingness to participate and share the valuable information that made this study possible.

Author Contributions

DO and MPF conceptualized the study and paper. TS managed the study implementation and conducted the primary data analysis. TS, CH, IM, implemented the study and contributed to the result interpretation. LL and MM contributed to the interpretation of the results. All authors reviewed and approved the manuscript.

Conflict of Interest

Authors have no conflicts of interest to declare.

Funding

This study has been made possible by the generous support of the American People and the President's Emergency Plan for AIDS Relief (PEPFAR) through United States Agency for International Development (USAID) under the terms of Cooperative Agreements AID-674-A-12-00029 and 72067419CA00004 to HE2RO. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID or the United States Government.

Data Statement

Patient medical records are owned by the study site and the National Department of Health (South Africa) and governed by the Human Research Ethics Committee (University of Witwatersrand, Johannesburg, South Africa). All relevant data is included in the paper.

References

1. HSRC. The Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017: HIV Impact Assessment Summary Report. Cape Town, HSRC Press.; 2017.

2. Boyer S, Iwuji C, Gosset A, Protopopescu C, Okesola N, Plazy M, et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. AIDS Care. 2016;28(sup3):39-51.

3. Collins S, Geffen N. Community views: balancing the public health benefits of earlier antiretroviral treatment with the implications for individual patients – perspectives from the community. Current Opinion in HIV and AIDS. 2014;9(1):4-10.

4. Cassim N, Coetzee LM, Schnippel K, Glencross DK. Estimating Implementation and Operational Costs of an Integrated Tiered CD4 Service including Laboratory and Point of Care Testing in a Remote Health District in South Africa. PLoS ONE. 2014;9(12):e115420.

5. Human Sciences Research Council (HSRC). The People Living With HIV Stigma Index: South Africa 2014. HSRC Press: 2014 Accessed October 2018

http://www.stigmaindex.org/sites/default/files/reports/Summary-Booklet-on-Stigma-Index-Survey%20South%20Africa.pdf

6. Goudge J, Ngoma B, Manderson L, Schneider H. Stigma, identity and resistance among people living with HIV in South Africa. SAHARA-J: Journal of Social Aspects of HIV/AIDS. 2009;6(3):94-104.

7. Ahmed S, Autrey J, Katz IT, Fox MP, Rosen S, Onoya D, et al. Why do people living with HIV not initiate treatment? A systematic review of qualitative evidence from low- and middle-income countries. Social Science & Medicine. 2018;213:72-84.

8. Abrahams N, Jewkes R. Managing and resisting stigma: a qualitative study among people living with HIV in South Africa. Journal of the International AIDS Society. 2012 Apr;15(2):10-7448.

9. Treves-Kagan S, Steward WT, Ntswane L, Haller R, Gilvydis JM, Gulati H, Barnhart S, Lippman SA. Why increasing availability of ART is not enough: a rapid, community-based study on how HIV-related stigma impacts engagement to care in rural South Africa. BMC public health. 2015 Dec;16(1):87.

10. South African National Department of Health (SA-NDoH). National Antiretroviral Treatment Guidelines, 2004. Pretoria: SA-NDoH;2004.

11. South African National Department of Health (SA-NDoH). National Antiretroviral Treatment Guidelines, 2010. Pretoria: SA-NDoH;2010.

12. South African National Department of Health (SA-NDoH. Circular on new criteria for initiating adults on ART at CD4 count of 350 cells/ml and below 2011. Pretoria: SA-NDoH; 2011.

13. South African National Department of Health (SA-NDoH. National Antiretroviral Treatment Guidelines 2013. Pretoria: SA NDoH;2013.

14. South African National Department of Health (SA-NDoH). National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults 2015: SA NDoH;2015.

15. Abuelezam N N, McCormick AW, Fussell T, Afriyie AN, Wood R, DeGruttola V, et al. Can the Heterosexual HIV Epidemic be Eliminated in South Africa Using Combination Prevention? A Modeling Analysis. American journal of epidemiology. 2016;184(3):239-48.

16. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, et al. HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the

Potential Impact of Antiretroviral Therapy on HIV Incidence in South Africa. PLOS Medicine. 2012;9(7):e1001245.

17. South African National Department of Health (South Africa). Implementation of Universal Test and Treat Strategy for HIV positive patients and differentiated care for stable patients 2016. Pretoria: National Department of Health, 2016. https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf Accessed October 2018

18. Group TAS, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.

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

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

21. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine. 2015;373(9):795-807.

22. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV. Prevention of HIV-1 infection with early antiretroviral therapy. New England journal of medicine. 2011 Aug 11;365(6):493-505.

23. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013 Feb 22;339(6122):966-71..

24. South African National Department of Health (South Africa). Tracking implementation of the 90-90-90 strategy for HIV, through the implementation of Test and Treat (TT) policy and same-day anti-retroviral therapy (ART) initiation for HIV positive patients 2017. Pretoria: National Department of Health; 2017.

25. Onoya D, Mokhele I, Sineke T, Ngoma B, Moolla A, Vujovic M, Bor J, Langa J, Fox M P. Health provider perspectives on implementation of same-day ART initiation six months after policy change in South Africa. International AIDS Conference (poster); 2018; Amsterdam.

26. Kulkarni SP, Shah KR, Sarma KV, Mahajan AP. Clinical Uncertainties, Health Service Challenges, and Ethical Complexities of HIV "Test-and-Treat": A Systematic Review. American Journal of Public Health. 2013;103(6):e14-e23.

27. Skhosana M, Reddy S, Reddy T, Ntoyanto S, Spooner E, Ramjee G, et al. PIMA TM point-of-care testing for CD4 counts in predicting antiretroviral initiation in HIV-infected individuals in KwaZulu-Natal, Durban, South Africa. Southern African Journal of HIV Medicine.2016;17(1).

28. Bigna JJR, Plottel CS, Koulla-Shiro S. Challenges in initiating antiretroviral therapy for all HIV-infected people regardless of CD4 cell count. Infectious Diseases of Poverty. 2016;5(1):85.

29. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002-2013: a meta-analysis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015;60(7):1120-7.

30. Egbujie BA, Grimwood A, Mothibi-Wabafor EC, Fatti G, Tshabalala AMET, Allie S, et al. Impact of 'Ideal Clinic' implementation on patient waiting time in primary healthcare clinics in KwaZulu-Natal Province, South Africa: A before-and-after evaluation. SAMJ Research. 2018;108(4):311-8.

31. Langwenya N, Phillips TK, Brittain K, Zerbe A, Abrams EJ, Myer L. Same-day antiretroviral therapy (ART) initiation in pregnancy is not associated with viral suppression or engagement in care: A cohort study. Journal of the International AIDS Society. 2018;21(6):e25133.

32. Garrett N, Norman E, Leask K, Naicker N, Asari V, Majola N, et al. Acceptability of Early Antiretroviral Therapy Among South African Women. AIDS Behav. 2018;22(3):1018-24.

33. Black S, Zulliger R, Marcus R, Mark D, Myer L, Bekker L-G. Acceptability and challenges of rapid ART initiation among pregnant women in a pilot programme, Cape Town, South Africa. AIDS Care. 2014;26(6):736-41.

34.

Table 1. Description of ART guideline changes over time in South Africa

ART Guidelines	Guideline eligibility/description	Introduction of guidelines/directive	Study recruitment period
Pre-UTT	Eligible for ART start if CD4 <500 cells/ml	January 2015	April-December 2015
UTT, before SDI	Eligible for ART upon HIV-positive diagnosis, regardless of CD4 count	September 2016	July-August 2017
UTT + SDI	Eligible for ART upon HIV-positive diagnosis, regardless of CD4 count. Initiate ART on day of HIV-positive diagnosis	September 2017	October 2017-August 2018

Table 2 Characteristics of the sample population by Period of HIV testing

	Pre-UTT N=146		UTT N=141		SDI N=742		Total N=1029	
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
Facility								
PHC1	68	46.6 (38.6-54.8)	72	51.1 (42.8-59.3)	80	10.8 (8.7-13.2)	220	21.4 (18.9-23.9)
PHC2	78	53.4 (45.2-61.4)	69	48.9 (40.7-57.2)	51	6.9 (5.2-8.9)	198	19.2 (16.9-21.8)
PHC3	-	-	-	-	207	27.9 (24.8-31.2)	207	20.1 (17.7-22.7)
PHC4	-	-	-	-	125	16.8 (14.3-19.7)	125	12.1 (10.3-14.3)
PHC5	-	-	-	-	151	20.3 (17.6-23.4)	151	14.6 (12.6-16.9)
PHC6	-	-	-	-	128	17.3 (14.7-20.1)	128	12.4 (10.6-14.6)
Time after policy announcement								
≤3 months	1	0.6 (0.09-4.8)	0	0	138	18.6 (15.9-21.6)	139	13.5 (11.5-15.7)
4-6 months	40	27.4 (20.7-35.3)	0	0	183	24.6 (21.7-27.9)	223	21.6 (19.3-24.3)
7-9 months	72	49.3 (41.2-57.5)	2	1.4 (0.3-5.6)	233	31.4 (28.2-34.8)	307	29.8 (27.1-32.7)
≥10 months	33	22.6 (16.5-30.2)	139	98.6 (94.4-99.7)	188	25.3 (22.3-28.6)	360	34.9 (32.1-37.9)
Sex								
Female	87	40.4 (32.7-48.7)	81	42.6 (34.6-50.9)	461	37.8 (34.4-41.4)	629	38.9 (35.9-41.9)
Male	59	59.6 (51.3-67.3)	60	57.4 (49.1-65.4)	281	62.1 (58.6-65.6)	400	61.1 (58.1-64.1)
Age (median. IQR)								
Median (IQR)		32.6 (27.2-37-6)		32.8 (27.238.9)		33.3 (28.4-33.3)		33.2 (28.2-39.3)
18 - 24	20	13.7 (8.9-20.4)	20	14.2 (9.2-21.1)	82	10.9 (8.7-13.4)	122	11.8 (9.9-13.9)
25 - 29	32	21.9 (15.9-29.4)	33	23.4 (17.1-31.2)	160	21.6 (18.7-24.7)	225	21.9 (19.4-24.5)
30 - 34	41	28.1 (21.3-36.0)	29	20.6 (14.6-28.1)	177	23.9 (20.9-27.1)	247	24.0 (21.5-26.7)
35 - 39	28	19.2 (13.5-26.5)	31	21.9 (15.8-29.7)	147	19.8 (17.1-22.8)	206	20.0 (17.7-22.6)
40+	25	17.1 (11.8-24.2)	28	19.9 (14.0-27.4)	176	23.8 (20.9-27.1)	229	22.3 (19.9-25.0)
Baseline CD4								

<350	96	65.7 (57.6-73.1)	73	51.8 (43.5-59.9)	296	39.9 (36.4-43.5)	465	45.1 (42.2-48.2)
350 - 500	26	17.8 (12.4-24.9)	22	15.6 (10.4-22.7)	91	12.3 (10.1-14.8)	139	13.5 (11.5-15.7)
≥500	19	13.0 (8.4-19.6)	21	14.9 (9.8-21.9)	97	13.1 (10.8-15.7)	137	13.3 (11.4-15.5)
Missing	5	3.4 (1.4-8.0)	25	17.7 (12.2-25.0)	258	34.8 (31.4-38.3)	288	27.9 (25.3-30.8)
Education								
< Grade 12	97	66.4 (58.3-73.7)	95	71.4 (63.1-78.5)	544	73.9 (70.6-76.9)	736	72.5 (69.7-75.2)
≥ Grade 12	49	33.5 (26.3-41.7)	38	28.6 (21.5-36.9)	192	26.1 (23.0-29.4)	279	27.5 (24.8-30.3)
Marital Status								
Single	28	19.2 (13.5-26.5)	18	12.8 (8.1-19.4)	110	14.8 (12.5-17.6)	156	15.1 (13.1-17.5)
In a relationship	92	63.0 (54.8-70.5)	98	69.5 (61.3-76.6)	497	67.1 (63.6-70.4)	687	66.8 (63.9-69.6)
Married	21	14.4 (9.5-21.1)	18	12.8 (8.1-19.4)	112	15.1 (12.7-17.9)	151	14.7 (12.7-16.9)
Divorced/widowed	5	3.4 (1.4-8.0)	7	4.9 (2.4-10.1)	22	2.9 (1.9-4.5)	34	3.3 (2.3-4.5)
Employment Status								
Unemployed	70	25.0 (16.4-36.2)	66	46.8 (38.6-55.2)	402	54.5 (50.9-58.1)	538	52.5 (49.5-55.6)
Employed	76	75.0 (63.8-83.6)	75	53.2 (44.8-61.4)	335	45.5 (41.9-49.1)	486	47.5 (44.4-50.5)
Number of adults in household								
Lives alone	28	19.2 (13.5-26.5)	21	15.0 (9.9-22.0)	160	21.7 (18.9-24.9)	209	20.4 (18.1-23.0)
Two adult in home	82	56.2 (47.9-64.1)	81	57.9 (49.4-65.8)	429	58.3 (54.7-61.8)	592	57.9 (54.9-60.9)
≥ three adults	36	24.7 (18.3-32.4)	38	27.1 (20.4-35.2)	147	19.9 (17.2-23.0)	221	21.6 (19.2-24.3)
Travel time to clinic								
≤15 minutes	90	61.6 (53.4-69.3)	90	63.8 (55.5-71.4)	405	54.6 (50.9-58.1)	585	56.8 (53.8-59.9)
16-30 minutes	46	31.5 (24.4-39.6)	45	31.9 (24.7-40.1)	224	30.2 (26.9-33.6)	315	30.6 (27.9-33.5)
>30 minutes	10	6.8 (3.6-12.3)	6	4.3 (1.9-9.2)	113	15.2 (12.8-18.0)	129	12.5 (10.6-14.7)

Table 3 Demographic and clinical characteristics associated with initiating ART within 30 days of HIV diagnosis

	30-days ART n(%)	Person years	Incidence rates/100 PY (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Facilities					
PHC 1	145 (65.9)	1.1	131.6 (111.8-154.8)	0.5 (0.4-0.7)	1.3 (0.8-2.0)
PHC 2	96 (48.5)	1.4	66.6 (54.5-81.4)	0.3 (0.2-0.4)	0.7 (0.4-1.2)
PHC 3	169 (81.6)	0.7	228.6 (196.6-265.8)	0.9 (0.7-1.1)	0.8 (0.6-1.0)
PHC 4	98 (78.4)	0.4	266.7 (218.8-325.1)	1	1
PHC 5	121 (80.1)	0.6	192.9 (161.4-230.5)	0.8 (0.6-1.0)	0.7 (0.6-1.0)
PHC 6	111 (86.7)	0.4	267.8 (222.3-322.5)	1.0 (0.7-1.3)	0.9 (0.7-1.2)
Guideline periods					
Pre-UTT	54 (36.9)	1.1	45.4 (34.8-59.3)	0.3 (0.2-0.3)	0.2 (0.1-0.4)
UTT	93 (65.9)	0.8	117.7 (96.1-144.3)	0.6 (0.5-0.7)	0.3 (0.2-0.5)
Same-day ART	593 (79.9)	2.7	218.8 (201.7-236.9)	1.0	1.0
Time after policy announcement					
≤3 months	101 (72.7)	0.6	157.4 (129.5-191.3)	0.9 (0.7-1.1)	0.4 (0.2-0.6)
4-6 months	152 (68.2)	1.1	133.0 (113.4-155.9)	0.8 (0.6-1.0)	0.5 (0.4-0.7)
7-9 months	216 (70.4)	1.4	155.8 (136.3-178.0)	0.9 (0.7-1.1)	0.7 (0.6-0.8)

≥10 months	271 (75.3)	1.5	178.3 (158.2-200.8)	1	1
Sex					
Male	266 (66.5)	2.0	134.7 (119.4-151.9)	1.0	1.0
Female	474 (75.3)	2.7	174.5 (159.5-190.9)	1.7 (1.4-2.0)	1.2 (1.0-1.4)
Age at testing					
18 - 24	88 (72.1)	0.5	170.9 (138.7-210.6)	1.0	
25 - 29	159 (70.7)	1.1	150.2 (128.6-175.5)	0.9 (0.7-1.2)	
30 - 34	170 (68.8)	1.1	154.5 (132.9-179.6)	0.9 (0.7-1.2)	
35 - 39	146 (70.8)	1.0	147.5 (125.2-173.1)	0.9 (0.7-1.2)	
40+	177 (77.2)	1.0	171.8 (148-199.9)	1.1 (0.8-1.3)	
Baseline CD4					
<350	146 (62.7)	2.2	154.4 (138.9-171.6)	1.0	1.0
350 - 500	238 (79.9)	0.6	169.6 (139.8-205.7)	1.1 (0.9-1.4)	1.1 (0.9-1.3)
≥500	172 (81.9)	0.5	217.9 (180.6-262.9)	1.3 (1.0-1.6)	1.1 (0.9-1.4)
Missing	194 (63.9)	1.4	135.7 (117.5-156.8)	0.9 (0.8-1.1)	0.6 (0.5-0.7)
Education					
< Grade 12	527 (71.6)	3.4	154.5 (142.1-168.5)	1.0	
≥ Grade 12	203 (72.7)	1.2	165.0 (144.2-189.9)	1.1 (0.9-1.2)	
Marital Status					
Single	114 (73.0)	0.7	160.6 (133.6-192.9)	1.00	
In a relationship	483 (70.3)	3.1	156.3 (142.6-170.4)	1.0 (0.8-1.2)	
Married	119 (78.8)	0.67	172.5 (142.7-204.3)	1.1 (0.8-1.4)	
Divorced/widowed	23 (67.6)	0.2	127.8 (83.1-188.3)	0.8 (0.5-1.3)	
Employment Status					
Unemployed	386 (71.7)	2.5	156.3 (141.2-172.3)	1.0	
Employed	351 (72.2)	2.2	161.0 (144.6-178.2)	1.0 (0.9-1.2)	
# adults in household					
Lives alone	141 (67.4)	1.0	138.2 (117.1-162.9)	1.0	1.0
Two adult in home	442 (74.6)	2.6	170.0 (154.8-186.5)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
≥ three adults	153 (69.2)	1.0	148.5 (126.8-174.1)	1.1 (0.8-1.3)	1.1 (0.9-1.5)
Travel time to clinic					
≤15 minutes	415 (70.9)	2.7	152.0 (138.2-167.5)	1.0	1.0
16-30 minutes	218 (69.2)	1.5	143.4 (125.4-163.5)	1.0 (0.8-1.1)	0.9 (0.8-1.1)
>30 minutes	107 (82.9)	0.4	243.2 (200.9-293.5)	1.5 (1.2-1.8)	1.1 (0.9-1.5)

Table 4 Demographic and clinical characteristics associated with initiating ART on the day of HIV diagnosis

	Immediate ART n(%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Facility			
PHC 1	8 (10.0)	0.3 (0.2-0.6)	1.5 (0.5-4.3)

PHC 2	9 (17.7)	0.5 (0.3-1.0)	2.1 (0.9-4.9)
PHC 3	35 (16.9)	0.5 (0.3-0.7)	0.7 (0.4-1.0)
PHC 4	42 (33.6)	1	1
PHC 5	46 (30.5)	0.9 (0.6-1.3)	1.3 (0.8-1.9)
PHC 6	10 (7.8)	0.2 (0.1-0.4)	0.3 (0.1-0.5)
Time after policy announcement			
≤3 months	15 (10.9)	0.3 (0.2-0.6)	0.2 (0.1-0.4)
4-6 months	19 (10.4)	0.3 (0.2-0.5)	0.3 (0.2-0.5)
7-9 months	57 (24.5)	0.8 (0.6-1.1)	0.8 (0.6-1.0)
≥10 months	59 (31.4)	1	1
Sex			
Male	44 (15.7)	1	1
Female	106 (23.0)	1.5 (1.1-2.0)	1.3 (1.0-1.9)
Age at testing			
18 - 24	25 (30.5)	1.0	1.0
25 - 29	37 (23.1)	0.8 (0.5-1.2)	0.8 (0.5-1.3)
30 - 34	38 (21.5)	0.7 (0.5-1.1)	0.8 (0.5-1.2)
35 - 39	24 (16.3)	0.5 (0.3-0.9)	0.7 (0.4-1.1)
40+	26 (14.8)	0.5 (0.3-0.8)	0.6 (0.4-0.9)
Baseline CD4			
<350	44 (14.9)	1.0	1.0
350 - 500	18 (19.8)	1.3 (0.8-2.2)	1.0 (0.4-2.6)
≥500	20 (20.6)	1.4 (0.9-2.2)	1.1 (0.4-2.9)
Missing	68 (26.4)	1.8 (1.3-2.5)	1.5 (0.6-3.7)
Education			
< Grade 12	107 (19.7)	1.0	
≥ Grade 12	43 (22.4)	1.1 (0.8-1.6)	
Marital Status			
Single	17 (15.5)	1.0	
In a relationship	117 (23.5)	1.5 (0.9-2.4)	
Married	16 (14.3)	0.9 (0.5-1.7)	
Divorced/widowed	0		
Employment Status			
Unemployed	76 (18.9)	1.0	
Employed	72 (21.5)	1.1 (0.9-1.5)	
# adults in household			
Lives alone	30 (18.7)	1.0	
Two adult in home	88 (20.5)	1.1 (0.8-1.6)	
≥ three adults	30 (20.4)	1.1 (0.7-1.7)	
Travel time to clinic			
≤15 minutes	77 (19.0)	1.0	1.0

16-30 minutes	41 (18.3)	0.9 (0.7-1.4)	1.1 (0.8-1.6)
>30 minutes	32 (28.3)	1.5 (1.0-2.1)	1.3 (0.8-2.0)

Figure 1. Participants flow from screening to ART initiation in the first 30 days of care by ART policy periods

Figure 2. Time to ART start in the first 30 days of HIV care by ART policy periods

Figure 3. Kaplan Meier curve of ART initiation in the first 30 days of HIV care by ART policy periods

Figure 4. Immediate ART uptake in the first 12 months of the SDI policy implementation

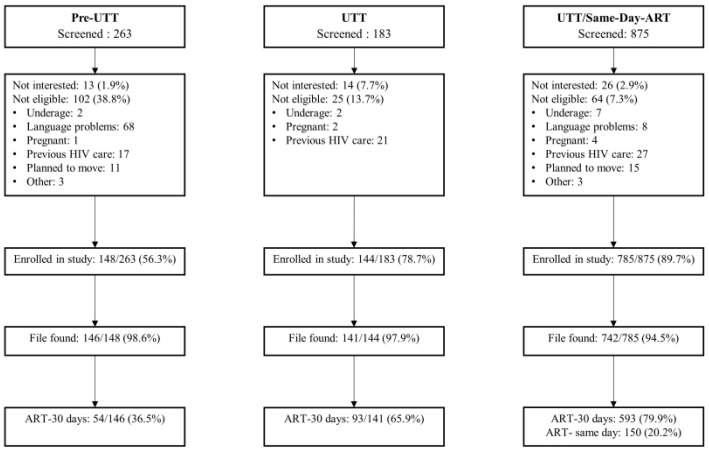


Figure 1. Participants flow from screening to ART initiation in the first 30 days of care by ART policy periods

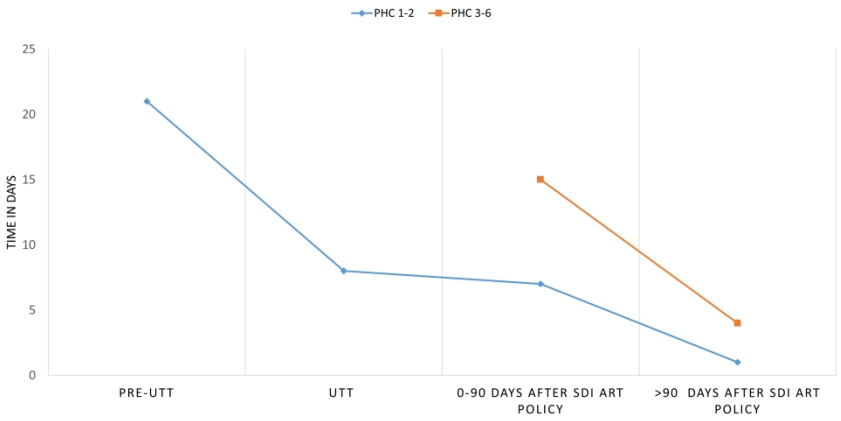


Figure 2. Time to ART start in the first 30 days of HIV care by ART policy periods

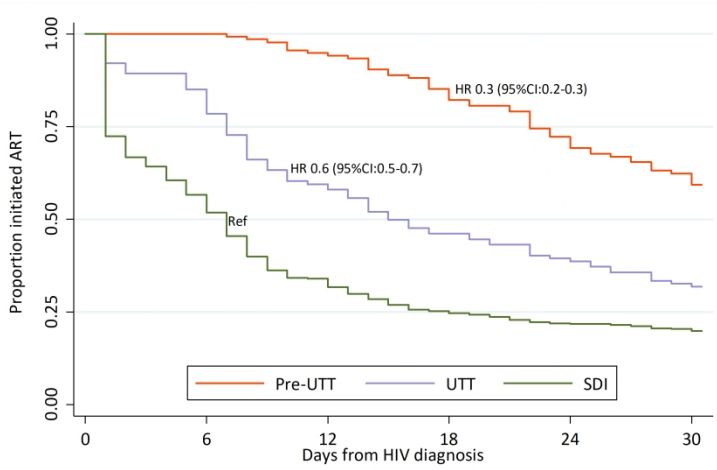


Figure 3. Kaplan Meier curve of ART initiation in the first 30 days of HIV care by ART policy periods

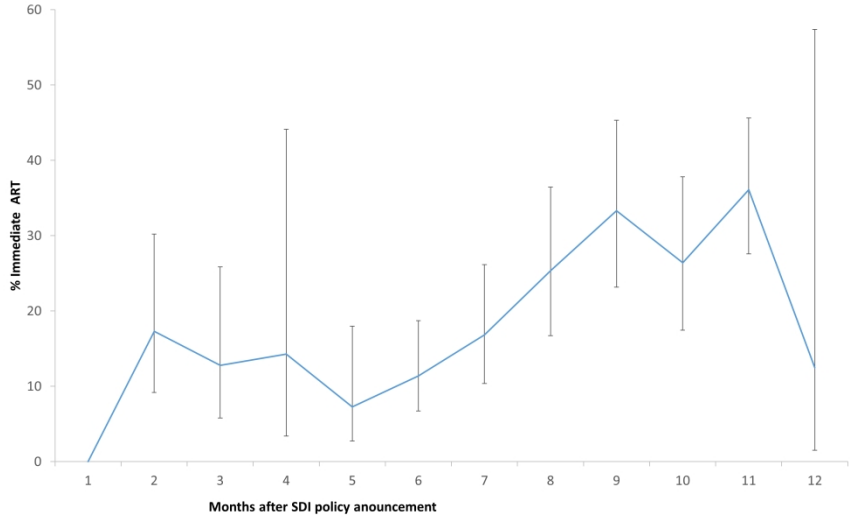


Figure 4. Immediate ART uptake in the first 12 months of the SDI policy implementation

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	6-7, Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 2-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of the test and treat policy on delays in antiretroviral therapy initiation among adult HIV positive patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030228.R3
Article Type:	Original research
Date Submitted by the Author:	05-Feb-2020
Complete List of Authors:	Onoya, Dorina; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Sineke, Tembeka; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Hendrickson, Cheryl; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Mokhele, Idah; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Maskew, Mhairi; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Long, Lawrence; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office; Boston University, Boston School of Public Health, Department of Global Health Fox, Matthew; Boston University, Epidemiology and Global Health
Primary Subject Heading:	Health policy
Secondary Subject Heading:	HIV/AIDS, Public health, Health policy
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, PRIMARY CARE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

+Working Title:

Impact of the test and treat policy on delays in HIV treatment initiation in Johannesburg, South Africa

Title: Impact of the test and treat policy on delays in antiretroviral therapy initiation among adult HIV positive patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study

Authors: Dorina Onoya[1], Tembeka Sineke[1], Cheryl Hendrickson[1], Idah Mokhele[1], Mhairi Maskew[1], Lawrence Long[1,2], Matthew P. Fox[1, 2, 3]

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

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

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

Corresponding author: Dorina Onoya, Health Economics and Epidemiology Research Office, 39 Empire Road, Parktown, Johannesburg, 2193, South Africa, donoya@heroza.org +27 10 001 7930

Keywords: HIV, ART attrition, UTT, same-day ART

Word count (main body): 3436

Abstract

Objectives To assess delays to antiretroviral therapy (ART) initiation before and after the Universal Test & Treat (UTT) and the same-day initiation (SDI) of ART policy periods in Johannesburg, South Africa.

Design Prospective cohort study

Setting Patients were recruited from six primary health clinics in Johannesburg.

Participants Overall, 1029 newly diagnosed HIV positive adults (≥18 years) were consecutively enrolled by referral from the testing counsellor between April- December 2015 (Pre-UTT n=146), July-August 2017 (UTT, n=141) and October 2017-August 2018 (SDI, n=742).

Main outcome measures Cox proportional hazards regression was used to assess predictors of 30-days ART initiation. Additionally, predictors of immediate ART initiation were evaluated using Poisson regression.

Results Overall, 30-days ART proportions were 71.9% overall, 36.9% pre-UTT (44.3% of those eligible), 65.9% under UTT and 79.9% under the SDI policy. The median days to ART initiation declined from 21 pre-UTT (Interquartile range (IQR): 15-30) to eight (IQR: 6-16) under UTT and five days (IQR: 0-8) under the SDI policy. However, only 150 (20.2%) of the SDI cohort initiated ART immediately after HIV diagnosis. Living in a two-adult home (adjusted Hazard ratio (aHR) 1.2 vs living alone, 95% Confidence Interval (CI): 1.0-1.5) increased the likelihood of 30-day ART. Missing baseline CD4 data decreased the likelihood of 30-days ART by 40% (aHR 0.6 vs CD4<350 cell/µl, 95% CI: 0.5-0.7). More women took up immediate ART (adjusted relative risk (aRR) 1.3, 95%CI: 1.0-1.9). Participants ≥40 years (aRR 0.6 vs 18-24 years, 95% CI: 0.4-0.9) were less likely to start ART immediately after HIV diagnosis. However, immediate ART rates increased with longer policy implementation time (aRR 0.2 for <3-months vs >10-months, 95%CI: 0.1-0.4).

Conclusions The study results highlight a positive move towards earlier ART initiation during the UTT and SDI periods and emphasise a need to increase same-day ART implementation further.

Word count: 300

Strengths and limitations

- Cohorts enrolled across the three most recent ART guideline implementation periods in South Africa, allowing observation of changes over time.
- Participants were enrolled immediately after HIV diagnosis, allowing for observation of ART initiation and patient attrition from HIV diagnosis over time.
- The results highlight a positive move towards earlier initiation of HIV treatment after the UTT policy implementation.
- Although we demonstrate substantial reductions in delays to ART initiation (median of 21 to five days), ART initiation on the day of HIV diagnosis is limited and requires additional investigations to improve programmatic performance.
- Increases in missing baseline laboratory tests at diagnosis reduce the strength of laboratory datasets as monitoring tools for the early steps of the HIV treatment cascade and delay the assessment of the appropriateness of the initial ART regiment.

Introduction

South Africa has the largest Human Immunodeficiency Virus (HIV) epidemic in the world, with an estimated 7.9 million persons living with HIV (1). Over the years, the South African government gradually increased the cluster of differentiation four (CD4)-based antiretroviral therapy (ART) eligibility threshold from 200 cells/µl in 2004, to 350 cells/µl in 2010 and 500 cells/µl in January 2015 (2-6). These thresholds both capped the number of persons initiating ART and negatively affected the retention of pre-ART patients. In the past, attrition from care after HIV diagnosis was also related to the number of assessment and counselling visits required before treatment initiation for eligible patients and the lack of systematic monitoring of and benefits for patients who were not offered ART (2-7). Additional pre-ART determinants of losses from the HIV treatment cascade include gender, requirement for a treatment buddy/disclosure and HIV stigma, and the high cost of attending clinic visits (7-14).

In September 2016, South Africa removed the CD4 cell count threshold for ART eligibility and adopted the World Health Organization (WHO) 2015 Universal Test and Treat (UTT) policy, making all HIV positive patients eligible for ART at diagnosis (15-17). Clinical trials showed that, compared to patients who deferred ART, patients who started treatment immediately after HIV diagnosis had lower rates of acquired immunodeficiency syndrome (AIDS)-related adverse events and improved viral suppression rates with no difference in post-initiation attrition rates (18-22). Moreover, patients who started ART immediately after diagnosis were less likely to transmit HIV than patients who deferred ART (16, 21-23).

In September 2017, the general UTT policy was updated with a directive to initiate ART on the day of HIV diagnosis (same-day initiation - SDI) (24). While widespread support for the UTT policy has created momentum for its promulgation, there remained reservations from primary health care (PHC) providers that health system capacity constraints may limit same-day ART policy assimilation and result in variations in implementation at facility-level (25). The policy was implemented amid concerns that, under UTT, health facilities in high burden settings, in particular, might struggle with the increased patient burden, potentially reducing the quality of care provided to new and existing patients (2-4, 26-27). There were also concerns around patient acceptance of same-day ART, ART refusal or early patient disengagement from care or intermittent adherence after starting ART (28).

In 2017, an estimated 4.4 million (55.7%) South African HIV-positive patients had started ART (1). While this constituted a major increase in the number of HIV positive patients initiated on ART (nearly one million additional patients started ART between 2016 and 2017), the proportions also suggested continued challenges with patient linkage to ART after HIV diagnosis (1). Furthermore, in addition to measuring program success in terms of expanded access to ART, critical outcomes of the UTT policy include the initiation of patients with high CD4 (>500) count, reductions in delays to ART initiation and long-term retention in HIV care.

In this study, we set out to measure ART initiation of newly HIV diagnosed adults in the first 30 days of HIV care (30-day ART) across the three recent ART guideline periods and examine factors associated with 30-days ART at six primary healthcare clinics (PHC) in Johannesburg, South Africa. Additionally, we examined rates and predictors of initiating ART on the day of HIV diagnosis among patients diagnosed under the SDI policy.

Methods

Study Setting and design

The city of Johannesburg is the largest of five health districts in the Gauteng province in South Africa. Johannesburg had an estimated HIV prevalence of 12.9% (>500,000 persons living with HIV) in 2017, with 60.7% of diagnosed persons currently receiving ART. Johannesburg comprises 108 PHCs subdivided into seven regions or sub-districts (denoted A-G) covering about 75% of the population (mainly uninsured). This study was conducted at six (of 13) conveniently selected public-sector PHCs in the Johannesburg health sub-district A. PHCs in Johannesburg are mainly nurse-run with the support of one medical doctor and are responsible for HIV testing, ART initiation and primary-level management and monitoring of HIV positive patients.

We conducted a prospective cohort study, enrolling consenting newly diagnosed HIV positive adult (≥18 years) patients from April to December 2015 (CD4<500 or Pre-UTT period), July-August 2017 (UTT period) and October 2017-August 2018 (SDI period) (Summarised in Table 1). Pre-UTT and UTT cohorts were only enrolled from two PHCs in Johannesburg while the SDI cohort included four additional PHCs serving similar populations in the same area in

Johannesburg (Table 2) (11-14). We assumed that 70% of HIV positive patients with CD4 counts > 350 cells/µl would become lost from HIV care in the first year after HIV diagnosis compared to 60% among patients with CD4 ≤ 350. We further hypothesised a 20% reduction in overall attrition between the pre-UTT and UTT periods. Additionally, the sample size for the SDI cohort was increased to enable a separate assessment of ART refusal (hypothesised 20% refusal by six-month post-HIV diagnosis) and attrition among participants who initiate ART with high CD4 count (>500 cells/µl). The ART refusal analysis will be presented in future manuscripts. The number of sites was also increased to six to allow comparison of the same-day ART across clinics.

Participant enrolment co-occurred across sites until 100% sample size was attained at each site (Figure 1). All patients were enrolled in the study after a new (self-reported) HIV-positive diagnosis (before ART eligibility determination) by trained study interviewers via referral from PHC-based lay HIV counsellors. We included newly diagnosed adult patients (18 years or older) who were able to speak English, Zulu and Sotho. Patients were eligible if they had entered HIV care after an HIV-positive diagnosis. Entering HIV care was defined as providing the first blood sample for baseline safety laboratory tests for the Pre-UTT and UTT cohorts, and defined as having received the HIV positive test result for the same-day ART cohort because new clinic processes meant that patients were likely to start ART before the first blood collection. The first blood tests were necessary to determine patients' CD4 count eligibility for ART and the appropriate initial ART regiment, hence the term "safety bloods". Women who were pregnant at HIV diagnosis were excluded from the study because ART initiation and monitoring processes in antenatal care differ from that of non-pregnant populations. Study staff cooperated closely with lay HIV counsellors across sites and checked HIV testing records daily to ensure that all testers who were diagnosed with HIV were being referred to study staff for study eligibility assessment.

Data Collection

Patients provided written consent for all study procedures and completed an interviewer-administered baseline questionnaire after HIV testing, on the day of HIV diagnosis. The consent process and interviews were conducted exclusively in English in the pre-UTT cohort because we assumed that the urban Johannesburg population would be conversant in English but later translated to Sotho and Zulu as well for the UTT and SDI cohorts. The interview included

questions on demographic factors, socioeconomic status and health-seeking behaviour. The recency of the HIV diagnosis was determined from HIV testing history questions at baseline. Patients were passively followed up by paper and electronic (including laboratory data) medical record review up to 30 days after HIV diagnosis to determine ART initiation.

Person-time accrued from the date of HIV diagnosis (study enrolment) until ART initiation. We assumed that all patients for whom clinic files were created were in care for the first 30 days unless there was evidence of an official transfer or death in the first 30 days after HIV diagnosis. Trained data collectors captured routine clinical follow-up data of consenting participants from facility-based paper and electronic medical records, including laboratory test results from the National Health Laboratory Services (NHLS). We define baseline CD4 as the first CD4 results in up to 30 days after HIV diagnosis. Trained data collectors captured all routine clinical follow-up data on the REDCap (Research Electronic Data Capture) systems (Vanderbilt University, Nashville, Tenessee). All datasets were exported to STATA 14 (StataCorp, College Station, Texas) for the analysis.

Patient and Public Involvement

Patients of the current study were not directly involved in the design of this study or reimbursed for their participation in the study. However, information collected from patients in previous studies informed the design, data collection approaches and interpretation of study results (19, 24). Also, the study implementation was guided by health care workers from the participating study sites. Study participants consented to a once-off direct data collection after HIV diagnosis and passive follow-up data collection via medical record review. Therefore, direct result dissemination to patients will not be possible. However, we plan to present study results to health care workers and policy-makers at participating PHC clinics and at other policy-relevant forums.

Outcome data and analysis

The primary exposure variable was the ART policy period at the time of HIV diagnosis, categorised as pre-UTT (policy active between January 2015 and August 2016), under the general UTT (active between September 2016 and August 2017) policy and the SDI policy (active from September 2017 onward) (14, 17, 24). The primary outcome was ART initiation up to 30 days after HIV diagnosis (30-day ART), and the secondary outcome is ART initiation

immediately after HIV diagnosis (Immediate ART), both outcomes were coded Yes (1) or No (0). Final data analysis began in October 2018.

Continuous variables were described using medians and interquartile ranges. Categorical variables were described using percentages. Kaplan Meier analyses were conducted to assess time to ART initiation in the first 30 days of HIV care. Predictors of 30-day ART were modelled using Cox proportional hazards regression, reporting Hazard Ratios (HR). Variables with a p-value <0.1 in crude analyses were entered in the multivariate model. Schoenfeld residuals were used to test the assumption of proportional hazards. Interaction terms with time-varying covariates were created for variables that violated the proportional hazards assumption. Variables were excluded from the model when the inclusion of the interaction term did not resolve the proportional hazards assumption violation. Missing data were accounted for by including a 'not measured/missing' category where necessary. Additionally, predictors of ART initiation on the day of HIV diagnosis (dichotomised) were evaluated using Poisson Regression modelling, reporting Relative Risks (RR).

All multivariate analyses were adjusted for the time from the period-specific policy announcement to account for the varying lag periods between policy implementation and participant enrolment (policy-months at HIV diagnosis) across cohorts. Additionally, we tested the association between the highest level of education and ART initiation across guideline periods to account for the change in interview language options. The study protocol was reviewed and approved by the Institutional Review Boards of the University of Witwatersrand (M141103) in South Africa and Boston University (H-33516) in the USA.

Results

Clinical and demographic characteristics at baseline

Although 1167 (100% of target sample) HIV positive adults enrolled in the study, this analysis was limited to 1029 (88.2%) for whom an outcome could be ascertained (medical data was available), 146 (98.6%) pre-UTT, 141 (97.9%) under UTT, and 742 (94.5%) under the SDI policy (Figure 1). The survival analyses included only participants who were eligible for ART at the time of HIV diagnosis (n=1004). The exclusive use of English questionnaires in the pre-UTT cohort was the most significant reason for participant non-eligibility (25.9% of total screened).

However, the age and gender distributions were similar across cohorts (Median 32.6 years for Pre-UTT, interquartile range (IQR):27.2-37.6; 32.3 years for UTT, IQR: 27.2-38.9; and 32.3 years for SDI, IQR: 28.4-39.5) (Table 2). Women (Median 32.6 years, IQR: 27.0-37.7) were slightly younger at HIV diagnosis than men (Median 35.8, IQR: 32.1-41.5) (β_{female} -3.4, 95%CI: -4.4 to -2.4). The pre-UTT cohort had a marginally higher proportion of participants who completed grade 12 (33.6%) compared to 28.6% in the UTT and 26.1% in the SDI cohorts. Employment rates were also similar across cohorts (47.9% pre-UTT, 46.8% UTT and 54.5% SDI). Among the 146 pre-UTT participants, 122 (83.6%) were eligible for ART.

Although the proportion of participants who tested with CD4 count<350/mm^3 decreased from 65.8% pre-UTT to 39.7% in the same-day ART cohort, the percentage of patients with missing baseline CD4 count results increased from 3.4% to 34.7%, respectively. Among participant who had CD4 data, the proportion of patient with baseline CD4 count>500 cells/µl did not change substantially across guideline periods (20.0% during SDI vs 13.5% Pre-UTT, relative risk (RR)=1.5 (95%CI: 0.9-2.3) and RR=1.3 (95%CI: 0.9-2.4) for SDI vs UTT (18.1%)).

Although most participants lived within 15 minutes of the diagnosing clinic (56.9%), a small proportion reported travelling over 30 minutes to the clinic (12.5% overall, 6.8% pre-UTT, 4.3% under UTT and 15.2% under SDI policies). Travel time varied across clinics such that <12% participants from five of the six recruitment sites reported travelling over 30 minutes to the clinics, but 46.4% of participants from PHC four reported >30-minutes travel time.

Time to ART initiation from HIV diagnosis across guideline periods

Overall, 71.9% participants initiated ART within 30 days of HIV diagnosis, 36.5% pre-UTT (44.3% of those eligible for ART), 65.9% under UTT and 79.9% in the SDI period . The overall median days to ART initiation declined from 21 days (IQR: 15-30) to eight days (IQR: 6-16) after the implementation of the UTT policy. Time to ART start was further reduced to a median of five days (IQR: 0-8) after the SDI directive was given (Figure 2), with most reductions observed three months after the SDI policy directive was given to PHCs.

Overall, 30-day ART rates increased with increasing lag time from the prevailing (at the time of participant's HIV diagnosis) policy announcement (adjusted hazard ratio (aHR) 0.4 for ≤3-months vs ≥10-months, 95%CI: 0.3-0.6). The highest level of education was not associated with 30-day ART uptake. After adjusting for the facility of diagnosis and lag time from the policy announcement, pre-UTT participants were 80% less likely to initiate ART in the first 30 days (aHR 0.2, 95% CI: 0.1-0.3) compared to SDI participants (Table 3). Similarly, patients diagnosed under the UTT policy were 70% less likely to start ART within 30 days of HIV diagnosis (aHR 0.3, 95% CI: 0.2-0.5) compared to SDI participants (Figure 3).

While women had higher 30-day ART rates compared to men (aHR 1.2, 95%CI: 1.0-1.4), there was no meaningful difference in the likelihood of 30-days ART initiation across age, marital status, travel time to the clinic or employment categories. Overall, compared to patients with baseline CD4<350 cell/µl, participants with baseline CD4>500 cells/µl had similar rates of 30-day ART. However, participants who were missing baseline CD4 counts were 40% less likely to start ART within a month (aHR 0.6, 95% CI: 0.5-0.7). Participants who lived in a two-adult home had higher rates of 30-day ART than those who lived alone (aHR 1.2, 95%CI: 1.0-1.5). Women were more likely to live with at least one other adult (RR 1.2, 95%CI: 1.1-1.4) compared to men.

Demographic and clinical characteristics associated with immediate ART initiation within the SDI cohort

Within the SDI cohort, 150 (20.2%) participants initiated treatment on the day of HIV diagnosis (25.3% of those who initiated ART within 30 days). Women were more likely to take up immediate ART (aRR 1.3, 95%CI: 1.0-1.9) than men. Older participants (aRR 0.6 for patients ≥40 years old compared to patients in the 18-24 age group, 95% CI: 0.4-0.9) were less likely to start ART on the day of HIV diagnosis (Table 4). In the SDI period, missing baseline CD4 data

did not affect the likelihood of starting ART on the day of HIV diagnosis (aRR 1.5, 95%CI: 0.5-3.7). We also describe a high variability in SDI policy implementation across sites (Table 4). Figure four illustrates the rates of immediate ART by SDI policy-month with 95% confidence intervals for the proportions. However, immediate ART rates increased gradually with longer policy implementation time (aRR 0.2 for <3 months vs >10 months, 95%CI: 0.1-0.4) (Figure 4).

Discussion

This study highlights a marked reduction in time to ART initiation following the implementation of the UTT guidelines, decreasing from a median of 21 days to eight days, despite this policy not including a directive to modify ART initiation times. An additional decline in time to ART start was also observed after the same-day ART memorandum was sent to clinics. These declines in time-to-ART are consistent with the goals of the WHO HIV treatment guidelines: to initiate patients as early as possible to achieve better clinical outcomes (15-16).

Consistent with previous findings (29), we found a decrease in the proportion of patients presenting at PHCs for HIV diagnosis with CD4 <350 cells/µl but little improvement in the CD4>500 cells/µl group between the pre-UTT and SDI periods. Overall, nearly two-thirds of participants who had baseline CD4 data were diagnosed with HIV with low CD4 counts (<350 cell/µl).

Over a third of the SDI cohort was missing baseline CD4 data. Missing baseline CD4 data in the SDI cohort could have resulted from the lack of clarity in the policy with regards to the need or timing of safety blood tests early in the same-day ART policy implementation or patient impatience with the drawn-out HIV testing and ART initiation processes on the day of HIV testing (17, 25, 30). It is unclear whether this is a result of the change in the definition of entry in HIV care (first blood draw vs HIV diagnosis) for the SDI cohort. However, this increase in missing baseline CD4 was observed from the pre-UTT cohort to the UTT cohort, at which point clinics already began to reduce time to ART start (to the first week of care for some patients). Nevertheless, having a missing baseline CD4 was associated with a reduced likelihood of 30-day ART compared to patients with lower baseline CD4 values. When we restricted the analysis to the SDI cohort, having a missing CD4 count was associated with a non-significant increase in immediate ART rates, which possibly also means that patients diagnosed under the SDI policy

may start ART before the first blood draw and defer baseline CD4 tests. However, this finding requires further exploration.

Women were more likely to start ART within 30 days than men. Interestingly, participants who lived in a two-adult home rather than alone were more likely to initiate ART within 30 days. This may also be indirectly associated with gender as men were more likely to live alone than women. However, participants who lived in larger households had similar 30-day ART rates to those who lived alone, suggesting persisting fear of confidentiality breaches within homes (5, 9).

Only 20.2% of patients diagnosed under the SDI policy started ART on the day of diagnosis, highlighting possible facility-level policy assimilation challenges. Rates of immediate ART and 30-days ART were also higher among non-pregnant women than men. Immediate ART has been available to South African HIV positive pregnant women since 2013 with relatively few patients or provider acceptability challenges (13, 31-33). However, health provider concerns about the SDI policy for the general population may have affected the pace of the policy implementation (25). In a previous qualitative study, Healthcare providers expressed reservations about the acceptability of immediate ART for the majority of their patients and the feasibility of the strategy considering their current workload (25). However, immediate ART rates steadily increased over time, suggesting improvements policy assimilation, albeit with some variability across sites. While CD4 count did not influence immediate ART uptake, women were younger at HIV diagnosis than men, highlighting the persisting need for consistent efforts to increase early HIV testing and ART initiation younger men (1, 31).

The strength of these analyses lies in the three prospective cohorts, spanning three ART guideline periods in South Africa, allowing direct observation of the changes in ART uptake over time. This study improves on a possible retrospective review by the collection of extensive personal and contextual data that are not routinely collected. However, the study data are limited by the small number of health facilities assessed, limited information about additional facility-level interventions as well as the contributions by partner organisations in supporting policy assimilation and implementation. Therefore, a more representative facility survey is needed to better explain the facility-level variations in ART policy implementation and outcomes. Additionally, we only collected ART initiation data from testing facilities with a short follow-up period and were not able to determine if some participants went on to start ART elsewhere.

Furthermore, the reason for the higher ART uptake among same-day ART participants require further exploration around the ART initiation processes and their potential impact on patients' future health-seeking behaviour as well as long term on-ART outcomes. The sample size did influence the duration of the enrolment process. However, the date of enrolment start depended on ethics approval. Unfortunately, we were negatively affected by university student protests that caused the Human Research Ethics department to stop operations for a while, resulting in a backlog of applications. To compensate for this, we adjusted all multivariate analyses by the lag period between the policy directive to the clinics and the date of patient's HIV diagnosis.

Conclusion

Our results highlight a positive move towards earlier ART initiation after the implementation of the UTT and SDI policies. However, the results also emphasise a vital need to not only streamline processes to increase immediate ART implementation/uptake further but also ensure timeous baseline safety and monitoring blood tests. Going forward, the need to improve patient demand for early HIV testing remains pertinent to achieve the prevention and treatment benefits of ART.

Acknowledgements

We extend our gratitude to the staff of PHC clinics who supported the implementation of the study and our sincere thanks go to the patients attending these clinics for their willingness to participate and share the valuable information that made this study possible.

Author Contributions

DO and MPF conceptualized the study and paper. TS managed the study implementation and conducted the primary data analysis. TS, CH, IM, implemented the study and contributed to the result interpretation. LL and MM contributed to the interpretation of the results. All authors reviewed and approved the manuscript.

Conflict of Interest

Authors have no conflicts of interest to declare.

Funding

This study has been made possible by the generous support of the American People and the President's Emergency Plan for AIDS Relief (PEPFAR) through United States Agency for International Development (USAID) under the terms of Cooperative Agreements AID-674-A-12-00029 and 72067419CA00004 to HE2RO. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID or the United States Government.

Data Statement

Patient medical records are owned by the study site and the National Department of Health (South Africa) and governed by the Human Research Ethics Committee (University of Witwatersrand, Johannesburg, South Africa). All relevant data is included in the paper.

References

1. HSRC. The Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017: HIV Impact Assessment Summary Report. Cape Town, HSRC Press.; 2017.

2. Boyer S, Iwuji C, Gosset A, Protopopescu C, Okesola N, Plazy M, et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. AIDS Care. 2016;28(sup3):39-51.

3. Collins S, Geffen N. Community views: balancing the public health benefits of earlier antiretroviral treatment with the implications for individual patients – perspectives from the community. Current Opinion in HIV and AIDS. 2014;9(1):4-10.

4. Cassim N, Coetzee LM, Schnippel K, Glencross DK. Estimating Implementation and Operational Costs of an Integrated Tiered CD4 Service including Laboratory and Point of Care Testing in a Remote Health District in South Africa. PLoS ONE. 2014;9(12):e115420.

5. Human Sciences Research Council (HSRC). The People Living With HIV Stigma Index: South Africa 2014. HSRC Press: 2014 Accessed October 2018 http://www.stigmaindex.org/sites/default/files/reports/Summary-Booklet-on-Stigma-Index-Survey%20South%20Africa.pdf

6. Goudge J, Ngoma B, Manderson L, Schneider H. Stigma, identity and resistance among people living with HIV in South Africa. SAHARA-J: Journal of Social Aspects of HIV/AIDS. 2009;6(3):94-104.

7. Ahmed S, Autrey J, Katz IT, Fox MP, Rosen S, Onoya D, et al. Why do people living with HIV not initiate treatment? A systematic review of qualitative evidence from low- and middle-income countries. Social Science & Medicine. 2018;213:72-84.

8. Abrahams N, Jewkes R. Managing and resisting stigma: a qualitative study among people living with HIV in South Africa. Journal of the International AIDS Society. 2012 Apr;15(2):10-7448.

9. Treves-Kagan S, Steward WT, Ntswane L, Haller R, Gilvydis JM, Gulati H, Barnhart S, Lippman SA. Why increasing availability of ART is not enough: a rapid, community-based study on how HIV-related stigma impacts engagement to care in rural South Africa. BMC public health. 2015 Dec;16(1):87.

10. South African National Department of Health (SA-NDoH). National Antiretroviral Treatment Guidelines, 2004. Pretoria: SA-NDoH;2004.

11. South African National Department of Health (SA-NDoH). National Antiretroviral Treatment Guidelines, 2010. Pretoria: SA-NDoH;2010.

12. South African National Department of Health (SA-NDoH. Circular on new criteria for initiating adults on ART at CD4 count of 350 cells/ml and below 2011. Pretoria: SA-NDoH; 2011.

13. South African National Department of Health (SA-NDoH. National Antiretroviral Treatment Guidelines 2013. Pretoria: SA NDoH;2013.

14. South African National Department of Health (SA-NDoH). National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults 2015: SA NDoH;2015.

15. Abuelezam N N, McCormick AW, Fussell T, Afriyie AN, Wood R, DeGruttola V, et al. Can the Heterosexual HIV Epidemic be Eliminated in South Africa Using Combination Prevention? A Modeling Analysis. American journal of epidemiology. 2016;184(3):239-48.

16. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, et al. HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the Potential Impact of Antiretroviral Therapy on HIV Incidence in South Africa. PLOS Medicine. 2012;9(7):e1001245.

17. South African National Department of Health (South Africa). Implementation of Universal Test and Treat Strategy for HIV positive patients and differentiated care for stable patients 2016. Pretoria: National Department of Health, 2016. https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf Accessed October 2018

18. Group TAS, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.

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

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

21. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine. 2015;373(9):795-807.

22. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV. Prevention of HIV-1 infection with early antiretroviral therapy. New England journal of medicine. 2011 Aug 11;365(6):493-505.

23. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013 Feb 22;339(6122):966-71..

24. South African National Department of Health (South Africa). Tracking implementation of the 90-90-90 strategy for HIV, through the implementation of Test and Treat (TT) policy

and same-day anti-retroviral therapy (ART) initiation for HIV positive patients 2017. Pretoria: National Department of Health; 2017.

25. Onoya D, Mokhele I, Sineke T, Ngoma B, Moolla A, Vujovic M, Bor J, Langa J, Fox M P. Health provider perspectives on implementation of same-day ART initiation six months after policy change in South Africa. International AIDS Conference (poster); 2018; Amsterdam.

26. Kulkarni SP, Shah KR, Sarma KV, Mahajan AP. Clinical Uncertainties, Health Service Challenges, and Ethical Complexities of HIV "Test-and-Treat": A Systematic Review. American Journal of Public Health. 2013;103(6):e14-e23.

27. Skhosana M, Reddy S, Reddy T, Ntoyanto S, Spooner E, Ramjee G, et al. PIMA TM point-of-care testing for CD4 counts in predicting antiretroviral initiation in HIV-infected individuals in KwaZulu-Natal, Durban, South Africa. Southern African Journal of HIV Medicine.2016;17(1).

28. Bigna JJR, Plottel CS, Koulla-Shiro S. Challenges in initiating antiretroviral therapy for all HIV-infected people regardless of CD4 cell count. Infectious Diseases of Poverty. 2016;5(1):85.

29. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002-2013: a meta-analysis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015;60(7):1120-7.

30. Egbujie BA, Grimwood A, Mothibi-Wabafor EC, Fatti G, Tshabalala AMET, Allie S, et al. Impact of 'Ideal Clinic' implementation on patient waiting time in primary healthcare clinics in KwaZulu-Natal Province, South Africa: A before-and-after evaluation. SAMJ Research. 2018;108(4):311-8.

31. Langwenya N, Phillips TK, Brittain K, Zerbe A, Abrams EJ, Myer L. Same-day antiretroviral therapy (ART) initiation in pregnancy is not associated with viral suppression or engagement in care: A cohort study. Journal of the International AIDS Society. 2018;21(6):e25133.

32. Garrett N, Norman E, Leask K, Naicker N, Asari V, Majola N, et al. Acceptability of Early Antiretroviral Therapy Among South African Women. AIDS Behav. 2018;22(3):1018-24.

33. Black S, Zulliger R, Marcus R, Mark D, Myer L, Bekker L-G. Acceptability and challenges of rapid ART initiation among pregnant women in a pilot programme, Cape Town, South Africa. AIDS Care. 2014;26(6):736-41.

34.

Table 1. Description of ART guideline changes over time in South Africa

ART Guidelines	Guideline eligibility/description	Introduction of guidelines/directive	Study recruitment period
Pre-UTT	Eligible for ART start if CD4 <500 cells/ml	January 2015	April-December 2015
UTT, before SDI	Eligible for ART upon HIV-positive diagnosis, regardless of CD4 count	September 2016	July-August 2017
UTT + SDI	Eligible for ART upon HIV-positive diagnosis, regardless of CD4 count. Initiate ART on day of HIV-positive diagnosis	September 2017	October 2017-August 2018

Table 2 Characteristics of the sample population by Period of HIV testing

	Pre-UTT N=146		UTT N=141		SDI N=742		Total N=1029	
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
Facility								
PHC1	68	46.6 (38.6-54.8)	72	51.1 (42.8-59.3)	80	10.8 (8.7-13.2)	220	21.4 (18.9-23.9)
PHC2	78	53.4 (45.2-61.4)	69	48.9 (40.7-57.2)	51	6.9 (5.2-8.9)	198	19.2 (16.9-21.8)
PHC3	-	-	-	-	207	27.9 (24.8-31.2)	207	20.1 (17.7-22.7)
PHC4	-	-	-	-	125	16.8 (14.3-19.7)	125	12.1 (10.3-14.3)
PHC5	-	-	-	-	151	20.3 (17.6-23.4)	151	14.6 (12.6-16.9)
PHC6	-	-	-	-	128	17.3 (14.7-20.1)	128	12.4 (10.6-14.6)
Time after policy announcement								
≤3 months	1	0.6 (0.09-4.8)	0	0	138	18.6 (15.9-21.6)	139	13.5 (11.5-15.7)
4-6 months	40	27.4 (20.7-35.3)	0	0	183	24.6 (21.7-27.9)	223	21.6 (19.3-24.3)
7-9 months	72	49.3 (41.2-57.5)	2	1.4 (0.3-5.6)	233	31.4 (28.2-34.8)	307	29.8 (27.1-32.7)
≥10 months	33	22.6 (16.5-30.2)	139	98.6 (94.4-99.7)	188	25.3 (22.3-28.6)	360	34.9 (32.1-37.9)
Sex								
Female	87	40.4 (32.7-48.7)	81	42.6 (34.6-50.9)	461	37.8 (34.4-41.4)	629	38.9 (35.9-41.9)
Male	59	59.6 (51.3-67.3)	60	57.4 (49.1-65.4)	281	62.1 (58.6-65.6)	400	61.1 (58.1-64.1)
Age (median. IQR)								
Median (IQR)		32.6 (27.2-37-6)		32.8 (27.238.9)		33.3 (28.4-33.3)		33.2 (28.2-39.3)
18 - 24	20	13.7 (8.9-20.4)	20	14.2 (9.2-21.1)	82	10.9 (8.7-13.4)	122	11.8 (9.9-13.9)
25 - 29	32	21.9 (15.9-29.4)	33	23.4 (17.1-31.2)	160	21.6 (18.7-24.7)	225	21.9 (19.4-24.5)
30 - 34	41	28.1 (21.3-36.0)	29	20.6 (14.6-28.1)	177	23.9 (20.9-27.1)	247	24.0 (21.5-26.7)
35 - 39	28	19.2 (13.5-26.5)	31	21.9 (15.8-29.7)	147	19.8 (17.1-22.8)	206	20.0 (17.7-22.6)
40+	25	17.1 (11.8-24.2)	28	19.9 (14.0-27.4)	176	23.8 (20.9-27.1)	229	22.3 (19.9-25.0)
Baseline CD4								

<350	96	65.7 (57.6-73.1)	73	51.8 (43.5-59.9)	296	39.9 (36.4-43.5)	465	45.1 (42.2-48.2)
350 - 500	26	17.8 (12.4-24.9)	22	15.6 (10.4-22.7)	91	12.3 (10.1-14.8)	139	13.5 (11.5-15.7)
≥500	19	13.0 (8.4-19.6)	21	14.9 (9.8-21.9)	97	13.1 (10.8-15.7)	137	13.3 (11.4-15.5)
Missing	5	3.4 (1.4-8.0)	25	17.7 (12.2-25.0)	258	34.8 (31.4-38.3)	288	27.9 (25.3-30.8)
Education								
< Grade 12	97	66.4 (58.3-73.7)	95	71.4 (63.1-78.5)	544	73.9 (70.6-76.9)	736	72.5 (69.7-75.2)
≥ Grade 12	49	33.5 (26.3-41.7)	38	28.6 (21.5-36.9)	192	26.1 (23.0-29.4)	279	27.5 (24.8-30.3)
Marital Status								
Single	28	19.2 (13.5-26.5)	18	12.8 (8.1-19.4)	110	14.8 (12.5-17.6)	156	15.1 (13.1-17.5)
In a relationship	92	63.0 (54.8-70.5)	98	69.5 (61.3-76.6)	497	67.1 (63.6-70.4)	687	66.8 (63.9-69.6)
Married	21	14.4 (9.5-21.1)	18	12.8 (8.1-19.4)	112	15.1 (12.7-17.9)	151	14.7 (12.7-16.9)
Divorced/widowed	5	3.4 (1.4-8.0)	7	4.9 (2.4-10.1)	22	2.9 (1.9-4.5)	34	3.3 (2.3-4.5)
Employment Status								
Unemployed	70	25.0 (16.4-36.2)	66	46.8 (38.6-55.2)	402	54.5 (50.9-58.1)	538	52.5 (49.5-55.6)
Employed	76	75.0 (63.8-83.6)	75	53.2 (44.8-61.4)	335	45.5 (41.9-49.1)	486	47.5 (44.4-50.5)
Number of adults in household								
Lives alone	28	19.2 (13.5-26.5)	21	15.0 (9.9-22.0)	160	21.7 (18.9-24.9)	209	20.4 (18.1-23.0)
Two adult in home	82	56.2 (47.9-64.1)	81	57.9 (49.4-65.8)	429	58.3 (54.7-61.8)	592	57.9 (54.9-60.9)
≥ three adults	36	24.7 (18.3-32.4)	38	27.1 (20.4-35.2)	147	19.9 (17.2-23.0)	221	21.6 (19.2-24.3)
Travel time to clinic								
≤15 minutes	90	61.6 (53.4-69.3)	90	63.8 (55.5-71.4)	405	54.6 (50.9-58.1)	585	56.8 (53.8-59.9)
16-30 minutes	46	31.5 (24.4-39.6)	45	31.9 (24.7-40.1)	224	30.2 (26.9-33.6)	315	30.6 (27.9-33.5)
>30 minutes	10	6.8 (3.6-12.3)	6	4.3 (1.9-9.2)	113	15.2 (12.8-18.0)	129	12.5 (10.6-14.7)

Table 3 Demographic and clinical characteristics associated with initiating ART within 30 days of HIV diagnosis

	30-days ART n(%)	Person years	Incidence rates/100 PY (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Facilities					
PHC 1	145 (70.0)	1.0	146.9 (124.9-172.9)	0.6 (0.5-0.8)	1.3 (0.8-2.0)
PHC 2	96 (51.3)	1.4	70.8 (58.0-86.5)	0.3 (0.2-0.4)	0.7 (0.4-1.2)
PHC 3	169 (81.6)	0.7	228.6 (196.6-265.8)	0.9 (0.7-1.1)	0.8 (0.6-1.0)
PHC 4	98 (78.4)	0.4	266.7 (218.8-325.1)	1	1
PHC 5	121 (80.1)	0.6	192.9 (161.4-230.5)	0.7 (0.6-1.0)	0.7 (0.6-1.0)
PHC 6	111 (86.7)	0.4	267.8 (222.3-322.5)	1.0 (0.7-1.3)	0.9 (0.7-1.2)
Guideline periods					
Pre-UTT	54 (44.3)	1.0	54.6 (41.8-71.3)	0.3 (0.2-0.4)	0.2 (0.1-0.3)
UTT	93 (66.0)	0.8	117.8 (96.1-144.3)	0.6 (0.5-0.7)	0.3 (0.2-0.5)
Same-day ART	593 (79.9)	2.7	218.6 (201.7-236.9)	1	1
Months after policy announcement					
≤3 months	101 (73.2)	0.6	159.9 (131.6-194.4)	0.9 (0.7-1.1)	0.4 (0.3-0.6)
4-6 months	152 (69.7)	1.1	138.2 (117.9-162.0)	0.8 (0.7-1.0)	0.5 (0.4-0.7)
7-9 months	216 (74.0)	1.3	170.2 (148.9-194.4)	1.0 (0.8-1.1)	0.7 (0.6-0.9)

≥10 months	271 (75.9)	1.5	181.8 (161.4-204.8)	1	1
Sex					
Male	266 (68.0)	1.9	139.8 (123.9-157.6)	1	1
Female	474 (77.2)	2.6	183.1 (167.4-200.4)	1.3 (1.1-1.5)	1.2 (1.0-1.4)
Age at testing					
18 - 24	87 (74.4)	0.5	180.4 (146.2-222.6)	1	
25 - 29	159 (73.3)	1.0	161.4 (138.2-188.6)	0.9 (0.7-1.2)	
30 - 34	170 (71.1)	1.0	162.4 (139.8-188.8)	0.9 (0.7-1.2)	
35 - 39	146 (72.3)	1.0	153.5 (130.5-180.5)	0.9 (0.7-1.1)	
40+	178 (77.4)	1.0	173.4 (149.7-200.9)	1.0 (0.7-1.2)	
Baseline CD4					
<350	344 (74.0)	2.2	154.4 (138.9-171.6)	1	1
350 - 500	103 (74.1)	0.6	169.6 (139.8-205.7)	1.1 (0.9-1.4)	1.1 (0.8-1.3)
≥500	109 (92.4)	0.4	310.4 (257.3-374.5)	1.7 (1.3-2.1)	1.2 (1.0-1.5)
Missing	184 (65.0)	1.3	141 (122.0-162.9)	1.0 (0.8-1.1)	0.6 (0.5-0.7)
Education					
< Grade 12	527 (73.0)	3.3	160.6 (147.4-174.9)	1	
≥ Grade 12	203 (75.5)	1.2	176.4 (153.7-202.4)	1.1 (0.9-1.3)	
Marital Status					
Single	114 (74.5)	0.7	165.5 (137.8-198.9)	1	
In a relationship	483 (72.2)	3.0	163.7 (149.7-179.0)	1.0 (0.8-1.2)	
Married	119 (79.9)	0.7	175.9 (146.9-210.5)	1.0 (0.8-1.4)	
Divorced/widowed	23 (69.7)	0.2	132.4 (88.0-199.3)	0.8 (0.5-1.3)	
Employment Status					
Unemployed	386 (73.4)	2.4	163.5 (148.0-180.6)	1	
Employed	351 (74.1)	2.1	167.1 (150.5-185.5)	1.0 (0.9-1.2)	
# adults in household					
Lives alone	141 (69.1)	1.0	144 (122.1-169.9)	1	1
Two adult in home	442 (76.5)	2.5	178.6 (162.7-196.1)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
≥ three adults	153 (70.8)	1.0	153.2 (130.7-179.5)	1.0 (0.8-1.3)	1.1 (0.9-1.5)
Travel time to clinic					
≤15 minutes	415 (73.2)	2.6	161 (146.3-177.3)	1	1
16-30 minutes	218 (70.3)	1.5	146.9 (128.7-167.8)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
>30 minutes	107 (83.6)	0.4	248.6 (205.7-300.4)	1.4 (1.1-1.8)	1.1 (0.9-1.4)

Table 4 Demographic and clinical characteristics associated with initiating ART on the day of HIV diagnosis

	Immediate ART n(%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Facility			
PHC 1	8 (10.0)	0.3 (0.2-0.6)	1.5 (0.5-4.3)

PHC 2	9 (17.7)	0.5 (0.3-1.0)	2.1 (0.9-4.9)
PHC 3	35 (16.9)	0.5 (0.3-0.7)	0.7 (0.4-1.0)
PHC 4	42 (33.6)	1	1
PHC 5	46 (30.5)	0.9 (0.6-1.3)	1.3 (0.8-1.9)
PHC 6	10 (7.8)	0.2 (0.1-0.4)	0.3 (0.1-0.5)
Months after policy announcement			
≤3 months	15 (10.9)	0.3 (0.2-0.6)	0.2 (0.1-0.4)
4-6 months	19 (10.4)	0.3 (0.2-0.5)	0.3 (0.2-0.5)
7-9 months	57 (24.5)	0.8 (0.6-1.1)	0.8 (0.6-1.0)
≥10 months	59 (31.4)	1	1
Sex			
Male	44 (15.7)	1	1
Female	106 (23.0)	1.5 (1.1-2.0)	1.3 (1.0-1.9)
Age at testing			
18 - 24	25 (30.5)	1.0	1.0
25 - 29	37 (23.1)	0.8 (0.5-1.2)	0.8 (0.5-1.3)
30 - 34	38 (21.5)	0.7 (0.5-1.1)	0.8 (0.5-1.2)
35 - 39	24 (16.3)	0.5 (0.3-0.9)	0.7 (0.4-1.1)
40+	26 (14.8)	0.5 (0.3-0.8)	0.6 (0.4-0.9)
Baseline CD4			
<350	44 (14.9)	1.0	1.0
350 - 500	18 (19.8)	1.3 (0.8-2.2)	1.0 (0.4-2.6)
≥500	20 (20.6)	1.4 (0.9-2.2)	1.1 (0.4-2.9)
Missing	68 (26.4)	1.8 (1.3-2.5)	1.5 (0.6-3.7)
Education			
< Grade 12	107 (19.7)	1.0	
≥ Grade 12	43 (22.4)	1.1 (0.8-1.6)	
Marital Status			
Single	17 (15.5)	1.0	
In a relationship	117 (23.5)	1.5 (0.9-2.4)	
Married	16 (14.3)	0.9 (0.5-1.7)	
Divorced/widowed	0		
Employment Status			
Unemployed	76 (18.9)	1.0	
Employed	72 (21.5)	1.1 (0.9-1.5)	
# adults in household			
Lives alone	30 (18.7)	1.0	
Two adult in home	88 (20.5)	1.1 (0.8-1.6)	
≥ three adults	30 (20.4)	1.1 (0.7-1.7)	
Travel time to clinic			
≤15 minutes	77 (19.0)	1.0	1.0

16-30 minutes	41 (18.3)	0.9 (0.7-1.4)	1.1 (0.8-1.6)
>30 minutes	32 (28.3)	1.5 (1.0-2.1)	1.3 (0.8-2.0)

Figure 1. Participants flow from screening to ART initiation in the first 30 days of care by ART policy periods

Figure 2. Median time to ART start in the first 30 days of HIV care by ART policy periods

Figure 3. Kaplan Meier curve of ART initiation in the first 30 days of HIV care by ART policy periods

Figure 4. Immediate ART uptake in the first 12 months of the SDI policy implementation

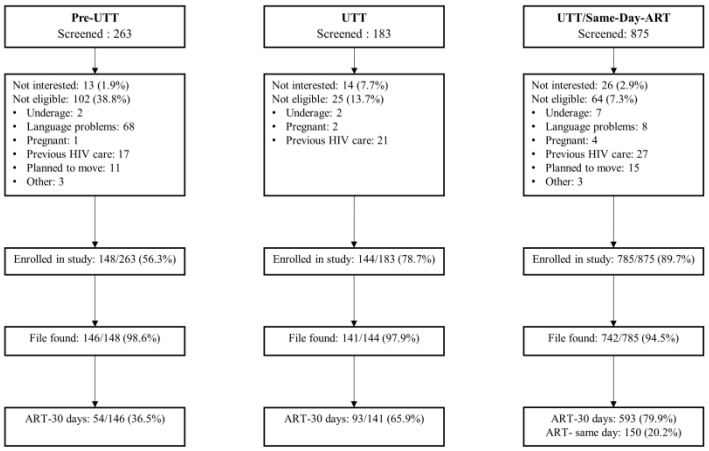
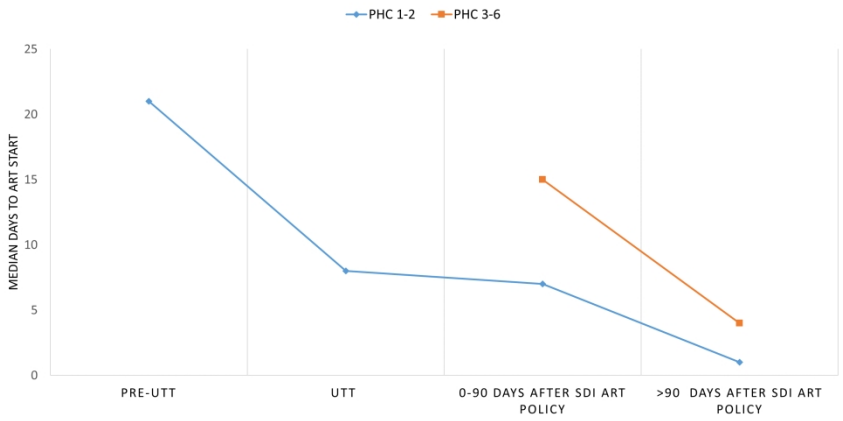
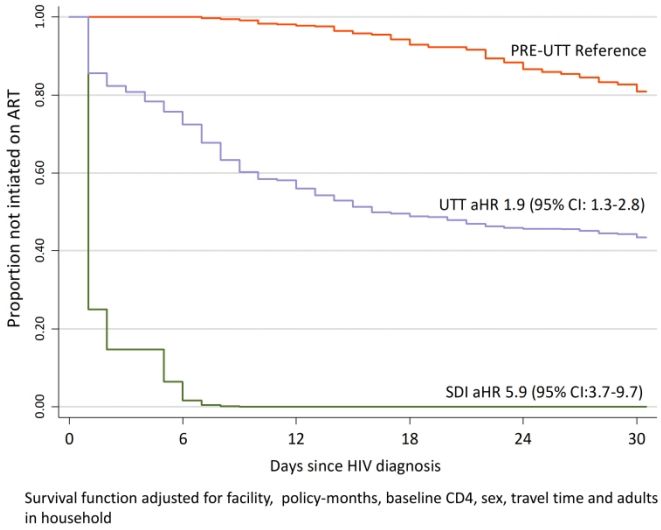


Figure 1. Participants flow from screening to ART initiation in the first 30 days of care by ART policy periods



Median time to ART start in the first 30 days of HIV care by ART policy periods



Kaplan Meier curve of ART initiation in the first 30 days of HIV care by ART policy periods

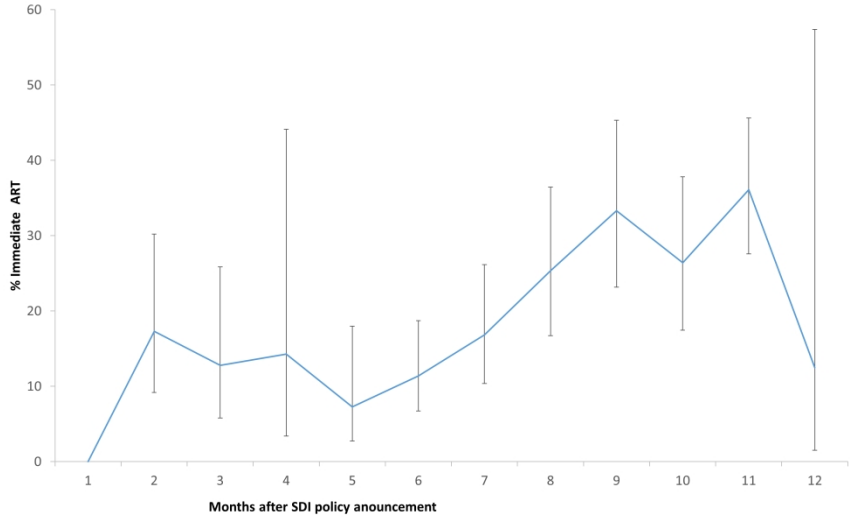


Figure 4. Immediate ART uptake in the first 12 months of the SDI policy implementation

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	6-7, Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 2-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of the test and treat policy on delays in antiretroviral therapy initiation among adult HIV positive patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030228.R4
Article Type:	Original research
Date Submitted by the Author:	26-Feb-2020
Complete List of Authors:	Onoya, Dorina; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Sineke, Tembeka; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Hendrickson, Cheryl; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Mokhele, Idah; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Maskew, Mhairi; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office Long, Lawrence; University of the Witwatersrand, School of Clinical Medicine, Health Economics & Epidemiology Research Office; Boston University, Boston School of Public Health, Department of Global Health Fox, Matthew; Boston University, Epidemiology and Global Health
Primary Subject Heading:	Health policy
Secondary Subject Heading:	HIV/AIDS, Public health, Health policy
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, PRIMARY CARE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

+Working Title:

Impact of the test and treat policy on delays in HIV treatment initiation in Johannesburg, South Africa

Title: Impact of the test and treat policy on delays in antiretroviral therapy initiation among adult HIV positive patients from six clinics in Johannesburg, South Africa: results from a prospective cohort study

Authors: Dorina Onoya[1], Tembeka Sineke[1], Cheryl Hendrickson[1], Idah Mokhele[1], Mhairi Maskew[1], Lawrence Long[1,2], Matthew P. Fox[1, 2, 3]

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

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

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

Corresponding author: Dorina Onoya, Health Economics and Epidemiology Research Office, 39 Empire Road, Parktown, Johannesburg, 2193, South Africa, donoya@heroza.org +27 10 001 7930

Keywords: HIV, ART attrition, UTT, same-day ART

Word count (main body): 3436

Abstract

Objectives To assess delays to antiretroviral therapy (ART) initiation before and after the Universal Test & Treat (UTT) and the same-day initiation (SDI) of ART policy periods in Johannesburg, South Africa.

Design Prospective cohort study

Setting Patients were recruited from six primary health clinics in Johannesburg.

Participants Overall, 1029 newly diagnosed HIV positive adults (≥18 years) were consecutively enrolled by referral from the testing counsellor between April- December 2015 (Pre-UTT n=146), July-August 2017 (UTT, n=141) and October 2017-August 2018 (SDI, n=742).

Main outcome measures Cox proportional hazards regression was used to assess predictors of 30-days ART initiation. Additionally, predictors of immediate ART initiation were evaluated using Poisson regression.

Results Overall, 30-days ART proportions were 71.9% overall, 36.9% pre-UTT (44.3% of those eligible), 65.9% under UTT and 79.9% under the SDI policy. The median days to ART initiation declined from 21 pre-UTT (Interquartile range (IQR): 15-30) to eight (IQR: 6-16) under UTT and five days (IQR: 0-8) under the SDI policy. However, only 150 (20.2%) of the SDI cohort initiated ART immediately after HIV diagnosis. Living in a two-adult home (adjusted Hazard ratio (aHR) 1.2 vs living alone, 95% Confidence Interval (CI): 1.0-1.5) increased the likelihood of 30-day ART. Missing baseline CD4 data decreased the likelihood of 30-days ART by 40% (aHR 0.6 vs CD4<350 cell/µl, 95% CI: 0.5-0.7). More women took up immediate ART (adjusted relative risk (aRR) 1.3, 95%CI: 1.0-1.9). Participants ≥40 years (aRR 0.6 vs 18-24 years, 95% CI: 0.4-0.9) were less likely to start ART immediately after HIV diagnosis. However, immediate ART rates increased with longer policy implementation time (aRR 0.2 for <3-months vs >10-months, 95%CI: 0.1-0.4).

Conclusions The study results highlight a positive move towards earlier ART initiation during the UTT and SDI periods and emphasise a need to increase same-day ART implementation further.

Word count: 300

Strengths and limitations

- Cohorts enrolled across the three most recent ART guideline implementation periods in South Africa, allowing observation of changes over time.
- Participants were enrolled immediately after HIV diagnosis, allowing for observation of ART initiation and patient attrition from HIV diagnosis over time.
- The results highlight a positive move towards earlier initiation of HIV treatment after the UTT policy implementation.
- Although we demonstrate substantial reductions in delays to ART initiation (median of 21 to five days), ART initiation on the day of HIV diagnosis is limited and requires additional investigations to improve programmatic performance.
- Increases in missing baseline laboratory tests at diagnosis reduce the strength of laboratory datasets as monitoring tools for the early steps of the HIV treatment cascade and delay the assessment of the appropriateness of the initial ART regiment.

Introduction

South Africa has the largest Human Immunodeficiency Virus (HIV) epidemic in the world, with an estimated 7.9 million persons living with HIV (1). Over the years, the South African government gradually increased the cluster of differentiation four (CD4)-based antiretroviral therapy (ART) eligibility threshold from 200 cells/µl in 2004, to 350 cells/µl in 2010 and 500 cells/µl in January 2015 (2-6). These thresholds both capped the number of persons initiating ART and negatively affected the retention of pre-ART patients. In the past, attrition from care after HIV diagnosis was also related to the number of assessment and counselling visits required before treatment initiation for eligible patients and the lack of systematic monitoring of and benefits for patients who were not offered ART (2-7). Additional pre-ART determinants of losses from the HIV treatment cascade include gender, requirement for a treatment buddy/disclosure and HIV stigma, and the high cost of attending clinic visits (7-14).

In September 2016, South Africa removed the CD4 cell count threshold for ART eligibility and adopted the World Health Organization (WHO) 2015 Universal Test and Treat (UTT) policy, making all HIV positive patients eligible for ART at diagnosis (15-17). Clinical trials showed that, compared to patients who deferred ART, patients who started treatment immediately after HIV diagnosis had lower rates of acquired immunodeficiency syndrome (AIDS)-related adverse events and improved viral suppression rates with no difference in post-initiation attrition rates (18-22). Moreover, patients who started ART immediately after diagnosis were less likely to transmit HIV than patients who deferred ART (16, 21-23).

In September 2017, the general UTT policy was updated with a directive to initiate ART on the day of HIV diagnosis (same-day initiation - SDI) (24). While widespread support for the UTT policy has created momentum for its promulgation, there remained reservations from primary health care (PHC) providers that health system capacity constraints may limit same-day ART policy assimilation and result in variations in implementation at facility-level (25). The policy was implemented amid concerns that, under UTT, health facilities in high burden settings, in particular, might struggle with the increased patient burden, potentially reducing the quality of care provided to new and existing patients (2-4, 26-27). There were also concerns around patient acceptance of same-day ART, ART refusal or early patient disengagement from care or intermittent adherence after starting ART (28).

In 2017, an estimated 4.4 million (55.7%) South African HIV-positive patients had started ART (1). While this constituted a major increase in the number of HIV positive patients initiated on ART (nearly one million additional patients started ART between 2016 and 2017), the proportions also suggested continued challenges with patient linkage to ART after HIV diagnosis (1). Furthermore, in addition to measuring program success in terms of expanded access to ART, critical outcomes of the UTT policy include the initiation of patients with high CD4 (>500) count, reductions in delays to ART initiation and long-term retention in HIV care.

In this study, we set out to measure ART initiation of newly HIV diagnosed adults in the first 30 days of HIV care (30-day ART) across the three recent ART guideline periods and examine factors associated with 30-days ART at six primary healthcare clinics (PHC) in Johannesburg, South Africa. Additionally, we examined rates and predictors of initiating ART on the day of HIV diagnosis among patients diagnosed under the SDI policy.

Methods

Study Setting and design

The city of Johannesburg is the largest of five health districts in the Gauteng province in South Africa. Johannesburg had an estimated HIV prevalence of 12.9% (>500,000 persons living with HIV) in 2017, with 60.7% of diagnosed persons currently receiving ART. Johannesburg comprises 108 PHCs subdivided into seven regions or sub-districts (denoted A-G) covering about 75% of the population (mainly uninsured). This study was conducted at six (of 13) conveniently selected public-sector PHCs in the Johannesburg health sub-district A. PHCs in Johannesburg are mainly nurse-run with the support of one medical doctor and are responsible for HIV testing, ART initiation and primary-level management and monitoring of HIV positive patients.

We conducted a prospective cohort study, enrolling consenting newly diagnosed HIV positive adult (≥18 years) patients from April to December 2015 (CD4<500 or Pre-UTT period), July-August 2017 (UTT period) and October 2017-August 2018 (SDI period) (Summarised in Table 1). Pre-UTT and UTT cohorts were only enrolled from two PHCs in Johannesburg while the SDI

cohort included four additional PHCs serving similar populations in the same area in Johannesburg (Table 2) (11-14).

Participant enrolment co-occurred across sites until 100% sample size was attained at each site (Figure 1). All patients were enrolled in the study after a new (self-reported) HIV-positive diagnosis (before ART eligibility determination) by trained study interviewers via referral from PHC-based lay HIV counsellors. We included newly diagnosed adult patients (18 years or older) who were able to speak English, Zulu and Sotho. Patients were eligible if they had entered HIV care after an HIV-positive diagnosis. Entering HIV care was defined as providing the first blood sample for baseline safety laboratory tests for the Pre-UTT and UTT cohorts, and defined as having received the HIV positive test result for the same-day ART cohort because new clinic processes meant that patients were likely to start ART before the first blood collection. The first blood tests were necessary to determine patients' CD4 count eligibility for ART and the appropriate initial ART regiment, hence the term "safety bloods". Women who were pregnant at HIV diagnosis were excluded from the study because ART initiation and monitoring processes in antenatal care differ from that of non-pregnant populations. Study staff cooperated closely with lay HIV counsellors across sites and checked HIV testing records daily to ensure that all testers who were diagnosed with HIV were being referred to study staff for study eligibility assessment.

Study sample size

We assumed that 70% of HIV positive patients with CD4 counts > 350 cells/µl would become lost from HIV care in the first year after HIV diagnosis compared to 60% among patients with CD4 ≤ 350 (29-30). We further hypothesised a 20% reduction in overall attrition between the pre-UTT and UTT periods. Additionally, the sample size for the SDI cohort was increased to enable a separate assessment of ART refusal (hypothesised 20% refusal by six-month post-HIV diagnosis) and attrition among participants who initiate ART with high CD4 count (>500 cells/µl)(31). The ART refusal analysis will be presented in future manuscripts. The number of sites was also increased to six to allow comparison of the same-day ART across clinics.

Data Collection

Patients provided written consent for all study procedures and completed an interviewer-administered baseline questionnaire after HIV testing, on the day of HIV diagnosis. Additionally,

participants were assured that participation in the study would in no way amend the care that they received at the clinic, including their future schedule of visits at the clinic. The consent process and interviews were conducted exclusively in English in the pre-UTT cohort because we assumed that the urban Johannesburg population would be conversant in English but later translated to Sotho and Zulu as well for the UTT and SDI cohorts. The interview included questions on demographic factors, socioeconomic status and health-seeking behaviour. The recency of the HIV diagnosis was determined from HIV testing history questions at baseline. Patients were passively followed up by paper and electronic (including laboratory data) medical record review up to 30 days after HIV diagnosis to determine ART initiation.

Person-time accrued from the date of HIV diagnosis (study enrolment) until ART initiation. We assumed that all patients for whom clinic files were created were in care for the first 30 days unless there was evidence of an official transfer or death in the first 30 days after HIV diagnosis. Trained data collectors captured routine clinical follow-up data of consenting participants from facility-based paper and electronic medical records, including laboratory test results from the National Health Laboratory Services (NHLS). We define baseline CD4 as the first CD4 results in up to 30 days after HIV diagnosis. Trained data collectors captured all routine clinical follow-up data on the REDCap (Research Electronic Data Capture) systems (Vanderbilt University, Nashville, Tenessee). All datasets were exported to STATA 14 (StataCorp, College Station, Texas) for the analysis.

Patient and Public Involvement

Patients of the current study were not directly involved in the design of this study or reimbursed for their participation in the study. However, information collected from patients in previous studies informed the design, data collection approaches and interpretation of study results (19, 24). Also, the study implementation was guided by health care workers from the participating study sites. Study participants consented to a once-off direct data collection after HIV diagnosis and passive follow-up data collection via medical record review. Therefore, direct result dissemination to patients will not be possible. However, we plan to present study results to health care workers and policy-makers at participating PHC clinics and at other policy-relevant forums.

Outcome data and analysis

The primary exposure variable was the ART policy period at the time of HIV diagnosis, categorised as pre-UTT (policy active between January 2015 and August 2016), under the general UTT (active between September 2016 and August 2017) policy and the SDI policy (active from September 2017 onward) (14, 17, 24). The primary outcome was ART initiation up to 30 days after HIV diagnosis (30-day ART), and the secondary outcome is ART initiation immediately after HIV diagnosis (Immediate ART), both outcomes were coded Yes (1) or No (0). Final data analysis began in October 2018.

Continuous variables were described using medians and interquartile ranges. Categorical variables were described using percentages. Kaplan Meier analyses were conducted to assess time to ART initiation in the first 30 days of HIV care. Predictors of 30-day ART were modelled using Cox proportional hazards regression, reporting Hazard Ratios (HR). Variables with a p-value <0.1 in crude analyses were entered in the multivariate model. Schoenfeld residuals were used to test the assumption of proportional hazards. Interaction terms with time-varying covariates were created for variables that violated the proportional hazards assumption. Variables were excluded from the model when the inclusion of the interaction term did not resolve the proportional hazards assumption violation. Missing data, (where more than 5% of the data was missing) were accounted for by including a "not measured/missing'" category where necessary. Additionally, predictors of ART initiation on the day of HIV diagnosis (dichotomised) were evaluated using Poisson Regression modelling, reporting Relative Risks (RR).

All multivariate analyses were adjusted for the time from the period-specific policy announcement to account for the varying lag periods between policy implementation and participant enrolment (policy-months at HIV diagnosis) across cohorts. Additionally, we tested the association between the highest level of education and ART initiation across guideline periods to account for the change in interview language options. The study protocol was reviewed and approved by the Institutional Review Boards of the University of Witwatersrand (M141103) in South Africa and Boston University (H-33516) in the USA.

Results

Clinical and demographic characteristics at baseline

Although 1167 (100% of target sample) HIV positive adults enrolled in the study, this analysis was limited to 1029 (88.2%) for whom an outcome could be ascertained (medical data was available), 146 (98.6%) pre-UTT, 141 (97.9%) under UTT, and 742 (94.5%) under the SDI policy (Figure 1). The survival analyses included only participants who were eligible for ART at the time of HIV diagnosis (n=1004). The exclusive use of English questionnaires in the pre-UTT cohort was the most significant reason for participant non-eligibility (25.9% of total screened). However, the age and gender distributions were similar across cohorts (Median 32.6 years for Pre-UTT, interquartile range (IQR):27.2-37.6; 32.3 years for UTT, IQR: 27.2-38.9; and 32.3 years for SDI, IQR: 28.4-39.5) (Table 2). Women (Median 32.6 years, IQR: 27.0-37.7) were slightly younger at HIV diagnosis than men (Median 35.8, IQR: 32.1-41.5) (β_{female} -3.4, 95%CI: -4.4 to -2.4). The pre-UTT cohort had a marginally higher proportion of participants who completed grade 12 (33.6%) compared to 28.6% in the UTT and 26.1% in the SDI cohorts. Employment rates were also similar across cohorts (47.9% pre-UTT, 46.8% UTT and 54.5% SDI). Among the 146 pre-UTT participants, 122 (83.6%) were eligible for ART.

Although the proportion of participants who tested with CD4 count<350/mm^3 decreased from 65.8% pre-UTT to 39.7% in the same-day ART cohort, the percentage of patients with missing baseline CD4 count results increased from 3.4% to 34.7%, respectively. Among participant who had CD4 data, the proportion of patient with baseline CD4 count>500 cells/µl did not change substantially across guideline periods (20.0% during SDI vs 13.5% Pre-UTT, relative risk (RR)=1.5 (95%CI: 0.9-2.3) and RR=1.3 (95%CI: 0.9-2.4) for SDI vs UTT (18.1%)).

Although most participants lived within 15 minutes of the diagnosing clinic (56.9%), a small proportion reported travelling over 30 minutes to the clinic (12.5% overall, 6.8% pre-UTT, 4.3% under UTT and 15.2% under SDI policies). Travel time varied across clinics such that <12% participants from five of the six recruitment sites reported travelling over 30 minutes to the clinics, but 46.4% of participants from PHC four reported >30-minutes travel time.

Time to ART initiation from HIV diagnosis across guideline periods

Overall, 71.9% participants initiated ART within 30 days of HIV diagnosis, 36.5% pre-UTT (44.3% of those eligible for ART), 65.9% under UTT and 79.9% in the SDI period. The overall median days to ART initiation declined from 21 days (IQR: 15-30) to eight days (IQR: 6-16) after the implementation of the UTT policy. Time to ART start was further reduced to a median of five days (IQR: 0-8) after the SDI directive was given (Figure 2), with most reductions observed three months after the SDI policy directive was given to PHCs.

Overall, 30-day ART rates increased with increasing lag time from the prevailing (at the time of participant's HIV diagnosis) policy announcement (adjusted hazard ratio (aHR) 0.4 for ≤3-months vs ≥10-months, 95%CI: 0.3-0.6). The highest level of education was not associated with 30-day ART uptake. After adjusting for the facility of diagnosis and lag time from the policy announcement, pre-UTT participants were 80% less likely to initiate ART in the first 30 days (aHR 0.2, 95% CI: 0.1-0.3) compared to SDI participants (Table 3). Similarly, patients diagnosed under the UTT policy were 70% less likely to start ART within 30 days of HIV diagnosis (aHR 0.3, 95% CI: 0.2-0.5) compared to SDI participants (Figure 3).

While women had higher 30-day ART rates compared to men (aHR 1.2, 95%CI: 1.0-1.4), there was no meaningful difference in the likelihood of 30-days ART initiation across age, marital status, travel time to the clinic or employment categories. Overall, compared to patients with baseline CD4<350 cell/µl, participants with baseline CD4>500 cells/µl had similar rates of 30-day ART. However, participants who were missing baseline CD4 counts were 40% less likely to start ART within a month (aHR 0.6, 95% CI: 0.5-0.7). Participants who lived in a two-adult home had higher rates of 30-day ART than those who lived alone (aHR 1.2, 95%CI: 1.0-1.5). Women were more likely to live with at least one other adult (RR 1.2, 95%CI: 1.1-1.4) compared to men.

Demographic and clinical characteristics associated with immediate ART initiation within the SDI cohort

Within the SDI cohort, 150 (20.2%) participants initiated treatment on the day of HIV diagnosis (25.3% of those who initiated ART within 30 days). Women were more likely to take up immediate ART (aRR 1.3, 95%CI: 1.0-1.9) than men. Older participants (aRR 0.6 for patients ≥40 years old compared to patients in the 18-24 age group, 95% CI: 0.4-0.9) were less likely to start ART on the day of HIV diagnosis (Table 4). In the SDI period, missing baseline CD4 data

did not affect the likelihood of starting ART on the day of HIV diagnosis (aRR 1.5, 95%CI: 0.5-3.7). We also describe a high variability in SDI policy implementation across sites (Table 4). Clinic four had the highest proportion of same-day ART initiates and was used as the reference category across all analyses. Figure four illustrates the rates of immediate ART by SDI policy-month with 95% confidence intervals for the proportions. However, immediate ART rates increased gradually with longer policy implementation time (aRR 0.2 for <3-months vs >10 months, 95%CI: 0.1-0.4) (Figure 4).

Discussion

This study highlights a marked reduction in time to ART initiation following the implementation of the UTT guidelines, decreasing from a median of 21 days to eight days, despite this policy not including a directive to modify ART initiation times. An additional decline in time to ART start was also observed after the same-day ART memorandum was sent to clinics. These declines in time-to-ART are consistent with the goals of the WHO HIV treatment guidelines: to initiate patients as early as possible to achieve better clinical outcomes (15-16).

Consistent with previous findings (32), we found a decrease in the proportion of patients presenting at PHCs for HIV diagnosis with CD4 <350 cells/µl but little improvement in the CD4>500 cells/µl group between the pre-UTT and SDI periods. Overall, nearly two-thirds of participants who had baseline CD4 data were diagnosed with HIV with low CD4 counts (<350 cell/µl).

Over a third of the SDI cohort was missing baseline CD4 data. Missing baseline CD4 data in the SDI cohort could have resulted from the lack of clarity in the policy with regards to the need or timing of safety blood tests early in the same-day ART policy implementation or patient impatience with the drawn-out HIV testing and ART initiation processes on the day of HIV testing (17, 25, 33). It is unclear whether this is a result of the change in the definition of entry in HIV care (first blood draw vs HIV diagnosis) for the SDI cohort. However, this increase in missing baseline CD4 was observed from the pre-UTT cohort to the UTT cohort, at which point clinics already began to reduce time to ART start (to the first week of care for some patients). Nevertheless, having a missing baseline CD4 was associated with a reduced likelihood of 30-day ART compared to patients with lower baseline CD4 values. When we restricted the analysis to

the SDI cohort, having a missing CD4 count was associated with a non-significant increase in immediate ART rates, which possibly also means that patients diagnosed under the SDI policy may start ART before the first blood draw and defer baseline CD4 tests. However, this finding requires further exploration.

Women were more likely to start ART within 30 days than men. Interestingly, participants who lived in a two-adult home rather than alone were more likely to initiate ART within 30 days. This may also be indirectly associated with gender as men were more likely to live alone than women. However, participants who lived in larger households had similar 30-day ART rates to those who lived alone, suggesting persisting fear of confidentiality breaches within homes (5, 9).

Only 20.2% of patients diagnosed under the SDI policy started ART on the day of diagnosis, highlighting possible facility-level policy assimilation challenges. Rates of immediate ART and 30-days ART were also higher among non-pregnant women than men. Immediate ART has been available to South African HIV positive pregnant women since 2013 with relatively few patients or provider acceptability challenges (13, 34-36). However, health provider concerns about the SDI policy for the general population may have affected the pace of the policy implementation (25). In a previous qualitative study, Healthcare providers expressed reservations about the acceptability of immediate ART for the majority of their patients and the feasibility of the strategy considering their current workload (25). However, immediate ART rates steadily increased over time, suggesting improvements policy assimilation, albeit with some variability across sites. While CD4 count did not influence immediate ART uptake, women were younger at HIV diagnosis than men, highlighting the persisting need for consistent efforts to increase early HIV testing and ART initiation younger men (1, 34).

The strength of these analyses lies in the three prospective cohorts, spanning three ART guideline periods in South Africa, allowing direct observation of the changes in ART uptake over time. This study improves on a possible retrospective review by the collection of extensive personal and contextual data that are not routinely collected. However, the study data are limited by the small number of health facilities assessed, limited information about additional facility-level interventions as well as the contributions by partner organisations in supporting policy assimilation and implementation. Therefore, a more representative facility survey is needed to better explain the facility-level variations in ART policy implementation and outcomes.

Additionally, we only collected ART initiation data from testing facilities with a short follow-up period and were not able to determine if some participants went on to start ART elsewhere.

Furthermore, the reason for the higher ART uptake among same-day ART participants require further exploration around the ART initiation processes and their potential impact on 'patients' future health-seeking behaviour as well as long term on-ART outcomes. The sample size did influence the duration of the enrolment process. However, the date of enrolment start depended on ethics approval. Unfortunately, we were negatively affected by university student protests that caused the Human Research Ethics department to stop operations for a while, resulting in a backlog of applications. To compensate for this, we adjusted all multivariate analyses by the lag period between the policy directive to the clinics and the date of ' 'patient's HIV diagnosis.

Conclusion

Our results highlight a positive move towards earlier ART initiation after the implementation of the UTT and SDI policies. However, the results also emphasise a vital need to not only streamline processes to increase immediate ART implementation/uptake further but also ensure timeous baseline safety and monitoring blood tests. Going forward, the need to improve patient demand for early HIV testing remains pertinent to achieve the prevention and treatment benefits of ART.

Acknowledgements

We extend our gratitude to the staff of PHC clinics who supported the implementation of the study and our sincere thanks go to the patients attending these clinics for their willingness to participate and share the valuable information that made this study possible.

Author Contributions

DO and MPF conceptualised the study and paper. TS managed the study implementation and conducted the primary data analysis. TS, CH, IM, implemented the study and contributed to the result interpretation. LL and MM contributed to the interpretation of the results. All authors reviewed and approved the manuscript.

Conflict of Interest

Authors have no conflicts of interest to declare.

Funding

This study has been made possible by the generous support of the American People and the "President's Emergency Plan for AIDS Relief (PEPFAR) through United States Agency for International Development (USAID) under the terms of Cooperative Agreements AID-674-A-12-00029 and 72067419CA00004 to HE2RO. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID or the United States Government.

Data Statement

Patient medical records are owned by the study site and the National Department of Health (South Africa) and governed by the Human Research Ethics Committee (University of Witwatersrand, Johannesburg, South Africa). All relevant data is included in the paper.

References

1. HSRC. The Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017: HIV Impact Assessment Summary Report. Cape Town, HSRC Press.; 2017.
2. Boyer S, Iwuji C, Gosset A, Protopopescu C, Okesola N, Plazy M, et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. AIDS Care. 2016;28(sup3):39-51.
3. Collins S, Geffen N. Community views: balancing the public health benefits of earlier antiretroviral treatment with the implications for individual patients – perspectives from the community. Current Opinion in HIV and AIDS. 2014;9(1):4-10.

4. Cassim N, Coetzee LM, Schnippel K, Glencross DK. Estimating Implementation and Operational Costs of an Integrated Tiered CD4 Service including Laboratory and Point of Care Testing in a Remote Health District in South Africa. PLoS ONE. 2014;9(12):e115420.

5. Human Sciences Research Council (HSRC). The People Living With HIV Stigma Index: South Africa 2014. HSRC Press: 2014 Accessed October 2018 http://www.stigmaindex.org/sites/default/files/reports/Summary-Booklet-on-Stigma-Index-Survey%20South%20Africa.pdf

6. Goudge J, Ngoma B, Manderson L, Schneider H. Stigma, identity and resistance among people living with HIV in South Africa. SAHARA-J: Journal of Social Aspects of HIV/AIDS. 2009;6(3):94-104.

7. Ahmed S, Autrey J, Katz IT, Fox MP, Rosen S, Onoya D, et al. Why do people living with HIV not initiate treatment? A systematic review of qualitative evidence from low- and middle-income countries. Social Science & Medicine. 2018;213:72-84.

8. Abrahams N, Jewkes R. Managing and resisting stigma: a qualitative study among people living with HIV in South Africa. Journal of the International AIDS Society. 2012 Apr;15(2):10-7448.

9. Treves-Kagan S, Steward WT, Ntswane L, Haller R, Gilvydis JM, Gulati H, Barnhart S, Lippman SA. Why increasing availability of ART is not enough: a rapid, community-based study on how HIV-related stigma impacts engagement to care in rural South Africa. BMC public health. 2015 Dec;16(1):87.

10. South African National Department of Health (SA-NDoH). National Antiretroviral Treatment Guidelines, 2004. Pretoria: SA-NDoH;2004.

11. South African National Department of Health (SA-NDoH). National Antiretroviral Treatment Guidelines, 2010. Pretoria: SA-NDoH;2010.

12. South African National Department of Health (SA-NDoH. Circular on new criteria for initiating adults on ART at CD4 count of 350 cells/ml and below 2011. Pretoria: SA-NDoH; 2011.

13. South African National Department of Health (SA-NDoH. National Antiretroviral Treatment Guidelines 2013. Pretoria: SA NDoH;2013.

14. South African National Department of Health (SA-NDoH). National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults 2015: SA NDoH;2015.

15. Abuelezam N N, McCormick AW, Fussell T, Afriyie AN, Wood R, DeGruttola V, et al. Can the Heterosexual HIV Epidemic be Eliminated in South Africa Using Combination Prevention? A Modeling Analysis. American journal of epidemiology. 2016;184(3):239-48.

16. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, et al. HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the Potential Impact of Antiretroviral Therapy on HIV Incidence in South Africa. PLOS Medicine. 2012;9(7):e1001245.

17. South African National Department of Health (South Africa). Implementation of Universal Test and Treat Strategy for HIV positive patients and differentiated care for stable patients 2016. Pretoria: National Department of Health, 2016. https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf Accessed October 2018

18. Group TAS, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.

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

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

21. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine. 2015;373(9):795-807.

22. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV. Prevention of HIV-1 infection with early antiretroviral therapy. New England journal of medicine. 2011 Aug 11;365(6):493-505.

23. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013 Feb 22;339(6122):966-71..

24. South African National Department of Health (South Africa). Tracking implementation of the 90-90-90 strategy for HIV, through the implementation of Test and Treat (TT) policy

and same-day anti-retroviral therapy (ART) initiation for HIV positive patients 2017. Pretoria: National Department of Health; 2017.

25. Onoya D, Mokhele I, Sineke T, Ngoma B, Moolla A, Vujovic M, Bor J, Langa J, Fox M P. Health provider perspectives on implementation of same-day ART initiation six months after policy change in South Africa. International AIDS Conference (poster); 2018; Amsterdam.

26. Kulkarni SP, Shah KR, Sarma KV, Mahajan AP. Clinical Uncertainties, Health Service Challenges, and Ethical Complexities of HIV """Test-and-Treat""": A Systematic Review. American Journal of Public Health. 2013;103(6):e14-e23.

27. Skhosana M, Reddy S, Reddy T, Ntoyanto S, Spooner E, Ramjee G, et al. PIMA TM point-of-care testing for CD4 counts in predicting antiretroviral initiation in HIV-infected individuals in KwaZulu-Natal, Durban, South Africa. Southern African Journal of HIV Medicine.2016;17(1).

28. Bigna JJR, Plottel CS, Koulla-Shiro S. Challenges in initiating antiretroviral therapy for all HIV-infected people regardless of CD4 cell count. Infectious Diseases of Poverty. 2016;5(1):85.

29. Larson BA, Brennan A, McNamara L, Long L, Rosen S, Sanne I. Early loss to follow-up after enrolment in pre-ART care at a large public clinic in Johannesburg, South Africa. Tropical Medicine and International Health. 2010; 15(S1): 43-47.

30. Lessells RJ, Mutevedzi PC, Cooke GS, Newell ML. Retention in HIV care for individuals not yet eligible for antiretroviral therapy: rural KwaZulu-Natal, South Africa. Journal of Acquired immune deficiency Syndrome. 2011; 56(3): e79-e86.

31. Katz IT, Essien T, Marinda ET, et al. Antiretroviral Refusal among Newly Diagnosed HIV-Infected Adults in Soweto, South Africa. AIDS (London, England). 2011;25(17):2177-2181.

32. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002-2013: a meta-analysis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015;60(7):1120-7.

33. Egbujie BA, Grimwood A, Mothibi-Wabafor EC, Fatti G, Tshabalala AMET, Allie S, et al. Impact of 'Ideal 'Clinic' implementation on patient waiting time in primary healthcare

clinics in KwaZulu-Natal Province, South Africa: A before-and-after evaluation. SAMJ Research. 2018;108(4):311-8.

34. Langwenya N, Phillips TK, Brittain K, Zerbe A, Abrams EJ, Myer L. Same-day antiretroviral therapy (ART) initiation in pregnancy is not associated with viral suppression or engagement in care: A cohort study. Journal of the International AIDS Society. 2018;21(6):e25133.

35. Garrett N, Norman E, Leask K, Naicker N, Asari V, Majola N, et al. Acceptability of Early Antiretroviral Therapy Among South African Women. AIDS Behav. 2018;22(3):1018-24.

36. Black S, Zulliger R, Marcus R, Mark D, Myer L, Bekker L-G. Acceptability and challenges of rapid ART initiation among pregnant women in a pilot programme, Cape Town, South Africa. AIDS Care. 2014;26(6):736-41.

Table 1. Description of ART guideline changes over time in South Africa

ART Guidelines	Guideline eligibility/description	Introduction of guidelines/directive	Study recruitment period
Pre-UTT	Eligible for ART start if CD4 <500 cells/ml	January 2015	April-December 2015
UTT, before SDI	Eligible for ART upon HIV-positive diagnosis, regardless of CD4 count	September 2016	July-August 2017
UTT + SDI	Eligible for ART upon HIV-positive diagnosis, regardless of CD4 count. Initiate ART on day of HIV-positive diagnosis	September 2017	October 2017-August 2018

Table 2 Characteristics of the sample population by Period of HIV testing

	Pre-UTT N=146		UTT N=141		SDI N=742		Total N=1029	
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
Facility								
PHC1	68	46.6 (38.6-54.8)	72	51.1 (42.8-59.3)	80	10.8 (8.7-13.2)	220	21.4 (18.9-23.9)
PHC2	78	53.4 (45.2-61.4)	69	48.9 (40.7-57.2)	51	6.9 (5.2-8.9)	198	19.2 (16.9-21.8)
PHC3	-	-	-	-	207	27.9 (24.8-31.2)	207	20.1 (17.7-22.7)
PHC4	-	-	-	-	125	16.8 (14.3-19.7)	125	12.1 (10.3-14.3)
PHC5	-	-	-	-	151	20.3 (17.6-23.4)	151	14.6 (12.6-16.9)
PHC6	-	-	-	-	128	17.3 (14.7-20.1)	128	12.4 (10.6-14.6)
Time after policy announcement								
≤3 months	1	0.6 (0.09-4.8)	0	0	138	18.6 (15.9-21.6)	139	13.5 (11.5-15.7)
4-6 months	40	27.4 (20.7-35.3)	0	0	183	24.6 (21.7-27.9)	223	21.6 (19.3-24.3)
7-9 months	72	49.3 (41.2-57.5)	2	1.4 (0.3-5.6)	233	31.4 (28.2-34.8)	307	29.8 (27.1-32.7)
≥10 months	33	22.6 (16.5-30.2)	139	98.6 (94.4-99.7)	188	25.3 (22.3-28.6)	360	34.9 (32.1-37.9)
Sex								
Female	87	40.4 (32.7-48.7)	81	42.6 (34.6-50.9)	461	37.8 (34.4-41.4)	629	38.9 (35.9-41.9)
Male	59	59.6 (51.3-67.3)	60	57.4 (49.1-65.4)	281	62.1 (58.6-65.6)	400	61.1 (58.1-64.1)
Age (median. IQR)								
Median (IQR)		32.6 (27.2-37-6)		32.8 (27.238.9)		33.3 (28.4-33.3)		33.2 (28.2-39.3)
18 - 24	20	13.7 (8.9-20.4)	20	14.2 (9.2-21.1)	82	10.9 (8.7-13.4)	122	11.8 (9.9-13.9)
25 - 29	32	21.9 (15.9-29.4)	33	23.4 (17.1-31.2)	160	21.6 (18.7-24.7)	225	21.9 (19.4-24.5)
30 - 34	41	28.1 (21.3-36.0)	29	20.6 (14.6-28.1)	177	23.9 (20.9-27.1)	247	24.0 (21.5-26.7)
35 - 39	28	19.2 (13.5-26.5)	31	21.9 (15.8-29.7)	147	19.8 (17.1-22.8)	206	20.0 (17.7-22.6)
40+	25	17.1 (11.8-24.2)	28	19.9 (14.0-27.4)	176	23.8 (20.9-27.1)	229	22.3 (19.9-25.0)
Baseline CD4								

<350	96	65.7 (57.6-73.1)	73	51.8 (43.5-59.9)	296	39.9 (36.4-43.5)	465	45.1 (42.2-48.2)
350 - 500	26	17.8 (12.4-24.9)	22	15.6 (10.4-22.7)	91	12.3 (10.1-14.8)	139	13.5 (11.5-15.7)
≥500	19	13.0 (8.4-19.6)	21	14.9 (9.8-21.9)	97	13.1 (10.8-15.7)	137	13.3 (11.4-15.5)
Missing	5	3.4 (1.4-8.0)	25	17.7 (12.2-25.0)	258	34.8 (31.4-38.3)	288	27.9 (25.3-30.8)
Education								
< Grade 12	97	66.4 (58.3-73.7)	95	71.4 (63.1-78.5)	544	73.9 (70.6-76.9)	736	72.5 (69.7-75.2)
≥ Grade 12	49	33.5 (26.3-41.7)	38	28.6 (21.5-36.9)	192	26.1 (23.0-29.4)	279	27.5 (24.8-30.3)
Marital Status								
Single	28	19.2 (13.5-26.5)	18	12.8 (8.1-19.4)	110	14.8 (12.5-17.6)	156	15.1 (13.1-17.5)
In a relationship	92	63.0 (54.8-70.5)	98	69.5 (61.3-76.6)	497	67.1 (63.6-70.4)	687	66.8 (63.9-69.6)
Married	21	14.4 (9.5-21.1)	18	12.8 (8.1-19.4)	112	15.1 (12.7-17.9)	151	14.7 (12.7-16.9)
Divorced/widowed	5	3.4 (1.4-8.0)	7	4.9 (2.4-10.1)	22	2.9 (1.9-4.5)	34	3.3 (2.3-4.5)
Employment Status								
Unemployed	70	25.0 (16.4-36.2)	66	46.8 (38.6-55.2)	402	54.5 (50.9-58.1)	538	52.5 (49.5-55.6)
Employed	76	75.0 (63.8-83.6)	75	53.2 (44.8-61.4)	335	45.5 (41.9-49.1)	486	47.5 (44.4-50.5)
Number of adults in household								
Lives alone	28	19.2 (13.5-26.5)	21	15.0 (9.9-22.0)	160	21.7 (18.9-24.9)	209	20.4 (18.1-23.0)
Two adult in home	82	56.2 (47.9-64.1)	81	57.9 (49.4-65.8)	429	58.3 (54.7-61.8)	592	57.9 (54.9-60.9)
≥ three adults	36	24.7 (18.3-32.4)	38	27.1 (20.4-35.2)	147	19.9 (17.2-23.0)	221	21.6 (19.2-24.3)
Travel time to clinic								
≤15 minutes	90	61.6 (53.4-69.3)	90	63.8 (55.5-71.4)	405	54.6 (50.9-58.1)	585	56.8 (53.8-59.9)
16-30 minutes	46	31.5 (24.4-39.6)	45	31.9 (24.7-40.1)	224	30.2 (26.9-33.6)	315	30.6 (27.9-33.5)
>30 minutes	10	6.8 (3.6-12.3)	6	4.3 (1.9-9.2)	113	15.2 (12.8-18.0)	129	12.5 (10.6-14.7)

Table 3 Demographic and clinical characteristics associated with initiating ART within 30 days of HIV diagnosis

	30-days ART n(%)	Person years	Incidence rates/100 PY (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Facilities					
PHC 1	145 (70.0)	1.0	146.9 (124.9-172.9)	0.6 (0.5-0.8)	1.3 (0.8-2.0)
PHC 2	96 (51.3)	1.4	70.8 (58.0-86.5)	0.3 (0.2-0.4)	0.7 (0.4-1.2)
PHC 3	169 (81.6)	0.7	228.6 (196.6-265.8)	0.9 (0.7-1.1)	0.8 (0.6-1.0)
PHC 4	98 (78.4)	0.4	266.7 (218.8-325.1)	1	1
PHC 5	121 (80.1)	0.6	192.9 (161.4-230.5)	0.7 (0.6-1.0)	0.7 (0.6-1.0)
PHC 6	111 (86.7)	0.4	267.8 (222.3-322.5)	1.0 (0.7-1.3)	0.9 (0.7-1.2)
Guideline periods					
Pre-UTT	54 (44.3)	1.0	54.6 (41.8-71.3)	0.3 (0.2-0.4)	0.2 (0.1-0.3)
UTT	93 (66.0)	0.8	117.8 (96.1-144.3)	0.6 (0.5-0.7)	0.3 (0.2-0.5)
Same-day ART	593 (79.9)	2.7	218.6 (201.7-236.9)	1	1
Months after policy announcement					
≤3 months	101 (73.2)	0.6	159.9 (131.6-194.4)	0.9 (0.7-1.1)	0.4 (0.3-0.6)
4-6 months	152 (69.7)	1.1	138.2 (117.9-162.0)	0.8 (0.7-1.0)	0.5 (0.4-0.7)
7-9 months	216 (74.0)	1.3	170.2 (148.9-194.4)	1.0 (0.8-1.1)	0.7 (0.6-0.9)

≥10 months	271 (75.9)	1.5	181.8 (161.4-204.8)	1	1
Sex					
Male	266 (68.0)	1.9	139.8 (123.9-157.6)	1	1
Female	474 (77.2)	2.6	183.1 (167.4-200.4)	1.3 (1.1-1.5)	1.2 (1.0-1.4)
Age at testing					
18 - 24	87 (74.4)	0.5	180.4 (146.2-222.6)	1	
25 - 29	159 (73.3)	1.0	161.4 (138.2-188.6)	0.9 (0.7-1.2)	
30 - 34	170 (71.1)	1.0	162.4 (139.8-188.8)	0.9 (0.7-1.2)	
35 - 39	146 (72.3)	1.0	153.5 (130.5-180.5)	0.9 (0.7-1.1)	
40+	178 (77.4)	1.0	173.4 (149.7-200.9)	1.0 (0.7-1.2)	
Baseline CD4					
<350	344 (74.0)	2.2	154.4 (138.9-171.6)	1	1
350 - 500	103 (74.1)	0.6	169.6 (139.8-205.7)	1.1 (0.9-1.4)	1.1 (0.8-1.3)
≥500	109 (92.4)	0.4	310.4 (257.3-374.5)	1.7 (1.3-2.1)	1.2 (1.0-1.5)
Missing	184 (65.0)	1.3	141 (122.0-162.9)	1.0 (0.8-1.1)	0.6 (0.5-0.7)
Education					
< Grade 12	527 (73.0)	3.3	160.6 (147.4-174.9)	1	
≥ Grade 12	203 (75.5)	1.2	176.4 (153.7-202.4)	1.1 (0.9-1.3)	
Marital Status					
Single	114 (74.5)	0.7	165.5 (137.8-198.9)	1	
In a relationship	483 (72.2)	3.0	163.7 (149.7-179.0)	1.0 (0.8-1.2)	
Married	119 (79.9)	0.7	175.9 (146.9-210.5)	1.0 (0.8-1.4)	
Divorced/widowed	23 (69.7)	0.2	132.4 (88.0-199.3)	0.8 (0.5-1.3)	
Employment Status					
Unemployed	386 (73.4)	2.4	163.5 (148.0-180.6)	1	
Employed	351 (74.1)	2.1	167.1 (150.5-185.5)	1.0 (0.9-1.2)	
# adults in household					
Lives alone	141 (69.1)	1.0	144 (122.1-169.9)	1	1
Two adult in home	442 (76.5)	2.5	178.6 (162.7-196.1)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
≥ three adults	153 (70.8)	1.0	153.2 (130.7-179.5)	1.0 (0.8-1.3)	1.1 (0.9-1.5)
Travel time to clinic					
≤15 minutes	415 (73.2)	2.6	161 (146.3-177.3)	1	1
16-30 minutes	218 (70.3)	1.5	146.9 (128.7-167.8)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
>30 minutes	107 (83.6)	0.4	248.6 (205.7-300.4)	1.4 (1.1-1.8)	1.1 (0.9-1.4)

Table 4 Demographic and clinical characteristics associated with initiating ART on the day of HIV diagnosis

	Immediate ART n(%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Facility			
PHC 1	8 (10.0)	0.3 (0.2-0.6)	1.5 (0.5-4.3)

PHC 2	9 (17.7)	0.5 (0.3-1.0)	2.1 (0.9-4.9)
PHC 3	35 (16.9)	0.5 (0.3-0.7)	0.7 (0.4-1.0)
PHC 4	42 (33.6)	1	1
PHC 5	46 (30.5)	0.9 (0.6-1.3)	1.3 (0.8-1.9)
PHC 6	10 (7.8)	0.2 (0.1-0.4)	0.3 (0.1-0.5)
Months after policy announcement			
≤3 months	15 (10.9)	0.3 (0.2-0.6)	0.2 (0.1-0.4)
4-6 months	19 (10.4)	0.3 (0.2-0.5)	0.3 (0.2-0.5)
7-9 months	57 (24.5)	0.8 (0.6-1.1)	0.8 (0.6-1.0)
≥10 months	59 (31.4)	1	1
Sex			
Male	44 (15.7)	1	1
Female	106 (23.0)	1.5 (1.1-2.0)	1.3 (1.0-1.9)
Age at testing			
18 - 24	25 (30.5)	1.0	1.0
25 - 29	37 (23.1)	0.8 (0.5-1.2)	0.8 (0.5-1.3)
30 - 34	38 (21.5)	0.7 (0.5-1.1)	0.8 (0.5-1.2)
35 - 39	24 (16.3)	0.5 (0.3-0.9)	0.7 (0.4-1.1)
40+	26 (14.8)	0.5 (0.3-0.8)	0.6 (0.4-0.9)
Baseline CD4			
<350	44 (14.9)	1.0	1.0
350 - 500	18 (19.8)	1.3 (0.8-2.2)	1.0 (0.4-2.6)
≥500	20 (20.6)	1.4 (0.9-2.2)	1.1 (0.4-2.9)
Missing	68 (26.4)	1.8 (1.3-2.5)	1.5 (0.6-3.7)
Education			
< Grade 12	107 (19.7)	1.0	
≥ Grade 12	43 (22.4)	1.1 (0.8-1.6)	
Marital Status			
Single	17 (15.5)	1.0	
In a relationship	117 (23.5)	1.5 (0.9-2.4)	
Married	16 (14.3)	0.9 (0.5-1.7)	
Divorced/widowed	0		
Employment Status			
Unemployed	76 (18.9)	1.0	
Employed	72 (21.5)	1.1 (0.9-1.5)	
# adults in household			
Lives alone	30 (18.7)	1.0	
Two adult in home	88 (20.5)	1.1 (0.8-1.6)	
≥ three adults	30 (20.4)	1.1 (0.7-1.7)	
Travel time to clinic			
≤15 minutes	77 (19.0)	1.0	1.0

16-30 minutes	41 (18.3)	0.9 (0.7-1.4)	1.1 (0.8-1.6)
>30 minutes	32 (28.3)	1.5 (1.0-2.1)	1.3 (0.8-2.0)

Figure 1. Participants flow from screening to ART initiation in the first 30 days of care by ART policy periods

Figure 2. Median time to ART start in the first 30 days of HIV care by ART policy periods

Figure 3. Kaplan Meier curve of ART initiation in the first 30 days of HIV care by ART policy periods

Figure 4. Immediate ART uptake in the first 12 months of the SDI policy implementation

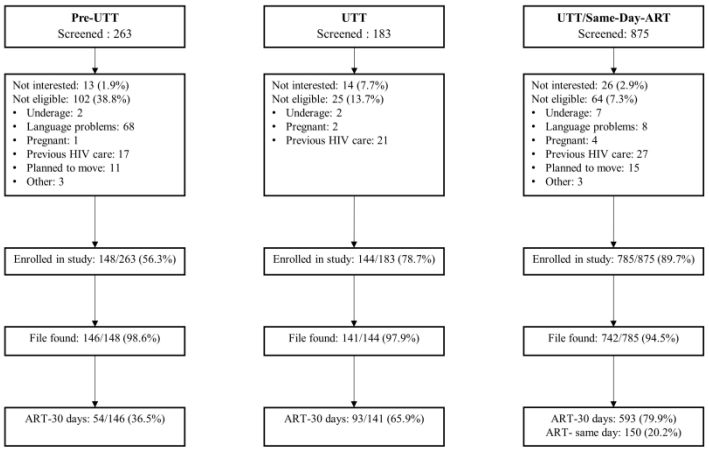
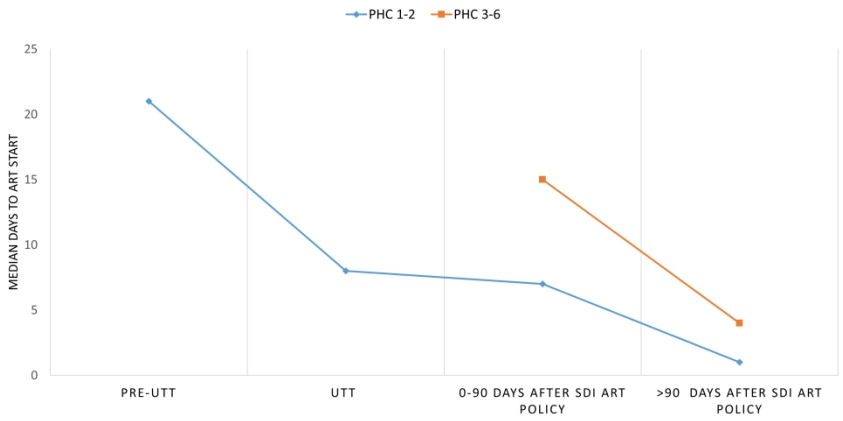
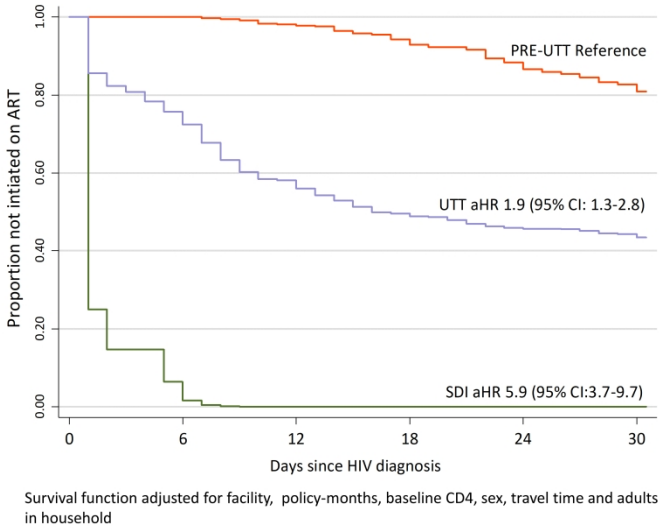


Figure 1. Participants flow from screening to ART initiation in the first 30 days of care by ART policy periods



Median time to ART start in the first 30 days of HIV care by ART policy periods



Kaplan Meier curve of ART initiation in the first 30 days of HIV care by ART policy periods

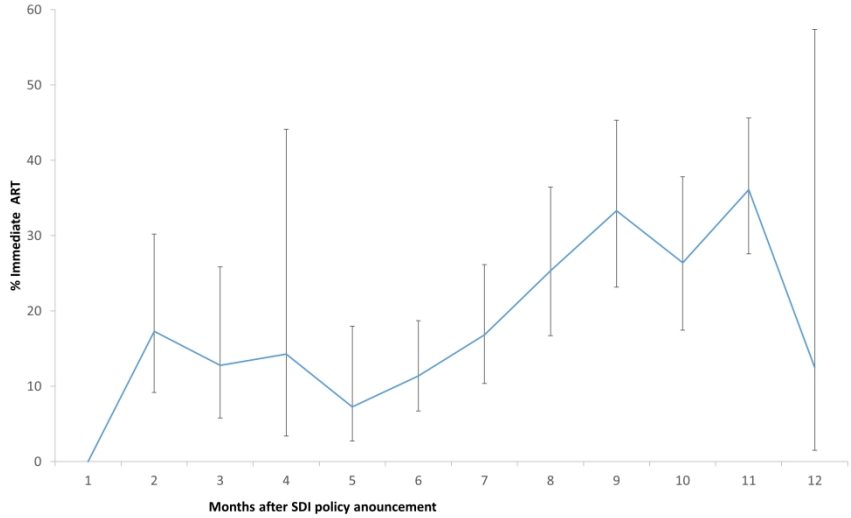


Figure 4. Immediate ART uptake in the first 12 months of the SDI policy implementation

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	6-7, Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 2-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.