Rapid Antiretroviral Therapy Initiation in the Botswana Combination Prevention Project

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Abstract (294 words)

Background

We evaluated the acceptability, feasibility and outcomes of rapid ART initiation in the Botswana Combination Prevention Project (BCPP).

Methods

BCPP was a community-randomized HIV-prevention trial performed from 2013-2018. In June 2016 universal HIV-treatment and rapid ART initiation with dolutegravir-based ART were introduced; same-day ART initiation was offered at the first clinic visit. We determined time to ART initiation, and rates of retention in care and viral suppression at one year.

Findings

1,717 eligible adults linked to study clinics prior to and 800 after rapid ART introduction. During the rapid ART period 57.1% (95% confidence interval [CI] 53.7-60.6%) of linked individuals initiated ART within 1 day of linkage, 73.7% (95%CI 70.6-76.7%) within 1 week of linkage, 84.9% (95%CI 82.4-87.3%) within 1 month, and 93.5% (95%CI 91.6-95.1%) within 1 year. Prior to the introduction of rapid ART 16.1% (95%CI 14.4-17.9%) of linked individuals initiated ART within 1 week of linkage, 48.9% (95%CI 46.5-51.3%) within 1 month, and 89.2% (95%CI 87.7-90.6%) within 1 year. One year after ART initiation 90.5% (95%CI 87.4%-92.8%) of individuals who linked in the standard ART period were in care and had a viral load <400 copies/ml, compared to 91.6% (95%CI 88.1%-94.1%) in the rapid ART period (odds ratio 1.20, 95%CI 0.86-1.67, p=0.294). Median time from linkage to documented viral suppression was 99 days following introduction of rapid ART initiation (interquartile range [IQR] 86-166 days) compared to 186 days (IQR 116-323 days) prior to rapid ART (p<0.001).

Interpretation

Simplified rapid ART initiation with the offer of same-day ART to individuals led to high rates of ART initiation, and significantly reduced time from linkage to starting ART and to virological suppression. Rates of retention in care and viral suppression after one-year of ART were high.

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Introduction

Ensuring that individuals who are diagnosed with HIV infection rapidly initiate ART is a critical step in meeting the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets;[1,2] however, data from low- and middle-income (LMIC) settings have demonstrated high rates of loss from the care cascade between HIV testing and ART initiation, or substantial delays to initiation of treatment.[2-8] Many of these losses result from significant barriers to ART initiation including the need for multiple clinic visits, repeated pre-ART counselling sessions, and delays in receiving baseline blood test results.[9-15] A potential way to increase rates of ART initiation is to offer same-day ART to all individuals at their initial clinic visit - a strategy that became more feasible following the elimination of baseline CD4 testing to determine treatment eligibility as well as the transition to a dolutegravir (DTG)-containing first-line ART regimen.[16,17]

Several randomized controlled trials from LMICs have shown that rapid ART initiation is acceptable and feasible, and can increase rates of ART initiation, retention in care, and virological suppression.[18-21] In 2017 the WHO updated treatment guidance to recommend rapid ART initiation (≤7 days) with the offer of same-day ART initiation in all individuals who were ready to start treatment.[16] However, prior trials included enhancements to care beyond changes to ART timing, and also included CD4-based eligibility criteria, potentially limiting their generalizability.[2,22,23] Concerns also exist about ongoing retention in care after rapid ART initiation in patients with high CD4.[22,24]

We were able to evaluate the acceptability, feasibility and outcomes of rapid ART initiation with the offer of ART at first clinic visit in public sector ART clinics in Botswana in the context of the cluster-randomized Botswana Combination Prevention Project (BCPP).[25]

METHODS

Study design and participants. BCPP was a cluster-randomized HIV prevention trial. A full description of the study design is available elsewhere.[25] Study interventions included intensive HIV-testing campaigns, linkage-to-care interventions, and expanded ART, including universal DTG-containing ART starting in 2016. The interventions were conducted in 15 rural or peri-urban community clusters, while 15 matched control community clusters received standard of care services. Average community population was approximately 6,000 individuals. This analysis is restricted to persons identified as HIV positive, not on ART, who were referred for treatment in the 15 study intervention communities.

Study procedures. Study interventions took place between October 2013 and March 2018. All 16-64 year-old community residents identified through community testing activities were assessed through a standard intake questionnaire and asked if they were HIV-positive. Persons who did not know their status, did not have documentation of an HIV-positive status, or did not have documentation of a negative HIV test within the preceding 3 months were offered rapid HIV-testing using KHB (KHB, Shanghai Kehua Bio-Engineering Co Ltd, Shanghai, China) and Unigold (Trinity Biotech Plc, Bray, Ireland) parallel HIV tests. Discordant reults were verified by laboratory testing using western blot. All participants provided verbal consent for HIV testing.

All newly-identified and known HIV-positive persons not on ART were referred to their local Ministry of Health community clinic for ART initiation and provided with linkage support services. Prior to the introduction of rapid ART initiation, all HIV-infected individuals not on ART had a point-of-care (POC) CD4 count (PIMA™ CD4, Alere, Inc. Waltham, MA, USA) at the initial community intake contact. ART was initiated (1) when an individual's CD4 was <350 cells/microliter (μL) or they met criteria for WHO clinical stage III or IV, based on Botswana's national guidelines; or (2) if they met the BCPP expanded ART eligibility criteria of CD4 <500 cells/μL or CD4 $\geq$500 cells/μL and viral load (VL) > 10,000 copies/μL (Abbott

RealTime HIV-1 assay on the automated m2000 system, Abbott Laboratories, Wiesbaden, Germany). Standard procedures for ART initiation required 3 adherence counselling visits and baseline laboratory tests to be drawn and reviewed, thus requiring at least three clinic visits before ART initiation occurred. First-line therapy consisted of tenofovir, emtricitabine, and efavirenz as a single combination tablet.

Starting in June 2016, all HIV-infected persons were eligible and referred for ART, regardless of CD4 count or disease stage. Baseline VL testing and POC CD4 testing were discontinued. The first-line regimen changed to tenofovir and emtricitabine as a combination tablet, plus DTG. In the intervention arm we concurrently introduced rapid ART initiation, aiming to start ART within 7 days of HIV testing (or 7 days of referral to the clinic, for persons who already knew their positive HIV status), with the offer of same-day ART initiation at first clinic visit. Baseline blood tests including CD4 counts were taken at the initial clinic visit, but providers were not required to await results prior to ART initiation. No additional changes to baseline clinical assessment or opportunistic infection screening algorithms were made.

For the duration of the study patients were seen 2 weeks following ART initiation for clinical review, then 3 months after ART initiation for VL testing. Clinic appointments with VL testing were then performed 6-monthly thereafter, unless the initial VL was not suppressed in which case patients would undergo repeat VL testing 3 months later. CD4 testing was performed at baseline then annually unless the initial CD4 count was <200 cells/μL, in which case it was repeated after 6 months.

The study was approved by the Centers for Disease Control and Prevention Institutional Review Board (Protocol #6475) and the Botswana Health Research and Development Committee. The study was monitored by an Independent Data and Safety Monitoring Board, and prospectively registered at ClinicalTrials.gov, number NCT01965470.

Outcomes. Primary outcome measures were (1) time from first eligible ART clinic visit to ART initiation, and (2) rates of retention in care and viral suppression (defined as a plasma VL <400 copies/μL) at 1 year post-ART initiation. Given the potential for patients to have viral load testing at either 9 months or 12 months depending on viral suppression status at month 3, and to allow for delays in clinic attendance, a 90-day window was placed around the 1 year VL timepoint. Patients were considered lost to follow-up if they had not attended any HIV-related clinic activity within 180 days of data censoring on 28th June 2018. Secondary outcomes included uptake of ART within 1 year of linkage, time from ART clinic linkage to HIV viral suppression, and mortality within 1 year of linkage.

Statistical analysis. Analysis was restricted to study participants in the 15 intervention clusters linking to care at a Ministry of Health facility. Data were analysed using Stata version 14 (StataCorp, College Station, TX). The standard ART care cohort included any individual eligible for ART and linking to a clinic prior to June 1st 2016. The rapid ART start cohort included all individuals linking a clinic from June 1st 2016 onwards following introduction of universal ART and rapid ART initiation guidelines. Data were summarised using frequencies and proportions with robust 95% confidence intervals (CI) adjusted for clustering by community, and medians and interquartile ranges (IQRs). Rates of ART initiation were compared between groups using a hierarchical Cox proportional hazards model accounting for clustering by community through inclusion of a random-effects term. Adjusted analyses were performed stratified by age, sex, CD4 count, and whether individuals were newly diagnosed with HIV or had a previously known diagnosis. An interrupted time series analysis using monthly aggregated ART timing data was performed using the "itsa" function in Stata[26]. Rates of retention in care and virological suppression at 1 year were summarized using proportions with robust 95% CIs adjusted for clustering by community, and compared between groups

using a hierarchical mixed effects regression model incorporating a random effects term for community. P-values of <0.05 were considered to be statistically significant.

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Results

Between October 2013 and March 2018, BCPP research staff assessed HIV status in 61,655 community residents, of whom 13,328 (22%) were HIV infected. Of these, 3,657 (27%) were not on ART; 3,282 (89.7%) linked to care at an ART clinic a median of 6 days (IQR 3-35 days) after community assessment. Three hundred and seventy four individuals linked to clinics outside the intervention communities and did not have reliably documented linkage or ART initiation dates and were excluded from further analysis. Of the remaining 2,908 individuals included in the final analysis 2,108 linked during the standard ART period of whom 1,717 (81.5%) were eligible for ART initiation, and 800 linked after the introduction of rapid ART initiation when all HIV-positive individuals were eligible for ART (Figure 1). Baseline characteristics of study participants are shown in Table 1.

ART uptake and time to ART initiation following linkage

ART initiation occurred significantly more rapidly following the introduction of rapid ART guidelines in June 2016 (Figure 2a, p<0.001 in unadjusted and adjusted hierarchical Cox proportional hazards model). During the rapid ART period 57.1% (457) of linked individuals initiated ART within 1 day of linkage, 73.7% (589) initiated within 1 week of linkage, 80.3% (641) within 2 weeks, and 84.9% (678) within 1 month; overall, 93.5% (744) of individuals

had initiated ART within the first year following linkage during the rapid ART period. Prior to the introduction of rapid ART initiation guidelines 16.1% (276) of linked individuals initiated ART within 1 week of linkage, 29.1% (499) within 2 weeks, and 48.9% (839) within 1 month; Overall, 89.2% (1,532) of individuals had initiated ART within the first year following linkage. Analyses stratified by prior HIV status (new or known), sex, age, and baseline CD4 count are shown is supplementary figure S1.

Interrupted time series analysis using log-transformed monthly aggregate data showed a non-significant downwards trend in ART initiation timing during the standard ART initiation period (ß coefficient -0.009 log_{10}days per month, 95% CI -0.018-0.0004, p=0.062), and a significant decline during the rapid ART initiation period (ß coefficient -0.023 log_{10}days per month, 95% CI -0.034-0.011, p<0.001). There was a significant decrease in time from linkage to ART initiation in the month following introduction of rapid ART initiation guidelines (Δ=-0.78 log_{10}days, 95% CI -0.93- -0.63 log_{10}days, p<0.001)(Figure 2b).

Retention in care and viral suppression following ART initiation

Retention in care at 1 year following ART initiation (limited to those individuals initiating ART at least 1 year prior to data censoring), and rates of viral suppression are shown in Figure 3. Retention in care was 98.4% (1601/1627) at 1 year among individuals who linked prior to introduction of rapid ART initiation guidelines and initiated ART, and 96.9% (610/631) among individuals linking to care and initiating ART following introduction of rapid ART. One-year VL results were available for 92.7% (1509/1627) of individuals who linked and initiated ART in the standard ART period and 93.8% (592/631) of patients initiating during the rapid ART period, with viral suppression rates of 97.5% and 97.6% respectively. Overall, 90.5% (1472/1627, 95% CI 87.4% - 92.8%) of individuals who linked in the standard ART period and initiated ART were in care and had a documented VL <400 copies/ml after 1 year

of ART, compared to 91.6% (578/631, 95% CI 88.1% - 94.1%) of individuals who linked in the rapid ART period and initiated ART (odds ratio[OR] 1.20, 95%CI 0.86-1.67, p=0.294).

Time from linkage to viral suppression

Median time from linkage to documented viral suppression was significantly shorter following the introduction of rapid ART initiation guidelines, at 99 days (IQR 86-166 days) compared to 186 days (IQR 116-323 days) prior to rapid ART (p<0.001). In the group linking prior to the introduction of rapid ART 74.3% (1,276/1,717) had achieved virological suppression within a year of linkage, compared to 82.9% (663/800) following the introduction of rapid ART (p<0.001). Median time from ART initiation to documented viral suppression was 112 days (IQR 84-194) during the standard ART period, and 93 days (IQR 82-139 during the rapid ART period, p<0.001.

Safety of rapid ART initiation

Twelve patients (1.5%) who initiated ART following the introduction of rapid ART guidelines were found to have pre-ART creatinine clearance <60mL/minute (Supplementary Table S1). Of these, 9 initiated ART within the first two weeks, 7 of whom started ART on the same-day (i.e. prior to availability of creatinine clearance results). Two of these 9 patients had been started on non-tenofovir-containing regimens (abacavir) due to a known history of renal impairment, three were switched to non-tenofovir containing regimens (abacavir) on receipt of renal function results, and four remained on tenofovir-based regimens with stable renal function. Two of the nine patients died during the first year of follow-up. One had been started on an abacavir-based regimen, and died of cervical carcinoma after 46 weeks of ART. The second started a tenofovir based regimen. Serum creatinine remained stable at 91 mmol/L at week 2, and the attending clinicians opted to maintain the patient on tenofovir. The patient died after 20 weeks of ART of unknown causes. Overall mortality in the year following linkage was

1.16% (20/1717) in the standard ART period, and 1.00% (8/800) in the rapid ART period (p=0.714).

Discussion

Simplified rapid ART initiation with the offer of same-day treatment at first ART clinic visit to all clinically-stable patients was acceptable and feasible in public ART clinics in Botswana, with over half of patients initiating ART within 1 day of ART clinic linkage and 74% initiating within 1 week. Following the introduction of rapid ART the proportion of patients established on ART increased from 49% to 85% at 1 month from clinic linkage, and from 89% to 94% at 1 year. The median time from clinic linkage to viral suppression was significantly reduced, with potential contributions from both more rapid intiation of ART and the switch to DTG. Rates of retention in care and viral suppression were similarly high in individuals initiated on ART prior to the introduction of rapid ART and those initiated during the rapid ART period, with documented viral suppression after 1 year of ART in over 90% of individuals in both groups.

Our findings add to the accumulating evidence demonstrating the feasibility, acceptability, and safety of rapid ART initiation in LMIC settings, and provide some of the first evidence for the acceptability among patients with high CD4 counts.[3] Recent clinical trials from South Africa,[18,27] Lesotho,[21] Haiti,[20] and Uganda[19] have all shown the high uptake of same-day or rapid ART when offered to patients in clinic[18-20,27] or community[21] settings. In the RapIT trial in South Africa 72% of individuals offered rapid ART initiation initiated same-day, and 96% within one month.[18] Similar figures were reported by Amanyire et al. from a cluster-randomized trial in Uganda, where a clinic-level streamlined ART initiation intervention led to 71% of individuals initiating on the day of eligibility, compared to 18% in the control arm. Even higher rates of 99% uptake of same day ART have been reported from a recent clinic

based rapid ART initiation trial in Haiti,[20] and 98% of participants in a community-based trial in Lesotho indicated readiness for same-day ART.[21] These very high rates of same-day initiation (compared to 57% in our study) are generally in the context of selected populations; for example 21% (225/1054) patients in the South African study were deemed too sick to participate; the Ugandan study only included patients once they had had CD4 testing and clinical assessment and been deemed eligible for ART;[19] and the Haitian study was also restricted to patients meeting clinical and CD4-based eligibility criteria.[20]

Importantly, given potential concerns about attrition from care with rapid ART initiation, particularly in individuals with high CD4 counts who may not perceive the need for treatment such as those in PMTCT Option B-plus programs,[22,24] our data also support the findings from these studies indicating that benefits of rapid ART initiation are sustained over time. Findings from the prior rapid ART studies in South Africa, Haiti Uganda, and Lesotho have all indicated either equivalent or increased retention in care and viral suppression with rapid ART when compared to standard models of ART delivery.[18-21] Our finding of 90% documented retention and virological suppression at 1 year following ART initiation closely matches data from the recent SEARCH trial in Uganda and Kenya, showing 89% retention in care among patients newly linked to care and rapidly initiated on ART.[28]

To the best of our knowledge, these are the first data reporting the outcomes of rapid ART initiation in a routine LMIC care setting, without baseline screening blood tests, POC CD4 counts, or additional assessment of asymptomtic patients. Although the safety of initiating ART whilst awaiting laboratory results has understandably been of concern to many clinicians[2], we did not document adverse patient outcomes arising from either initiation of tenofovir-based therapy in the absence of a serum creatinine result, or the development of immune reconstitution inflammatory syndromes in patients with low CD4 counts. Mortality within 1 year of linkage was low at 1% during both the standard ART and rapid ART periods.

The more rapid ART initiation and shorter time from linkage to viral suppression observed following implemetation of rapid DTG-based ART initiation in our study are likely to have both individual- and population-level benefits. HIV transmission risk is highly dependent on viral load,[29] with convincing evidence for marked reductions in transmission to sexual partners in individuals on effective ART.[30,31] It is also probable that rapid ART can confer individual-level health benefits, particularly among individuals with low CD4 cell counts (<200 cells/μL) who are at extremely high risk of mortality if ART is delayed for even a few weeks.[32-34] We did not find a mortality reduction following rapid ART initiation in our setting, probably in part due to the relatively high median CD4 count at ART initiation. A further potential reason for the lack of an observed mortality benefit in our study is the fact that during the standard ART period individuals with low CD4 counts were identified with POC CD4 counts, which would not be the case in routine care, and rapidly initiated on ART, lessening the impact of the introduction of rapid ART initiation guidelines in our study.

Our study had several limitations. Firstly, as a sub-analysis planned after initial protocol development we were unable to randomize patients to the rapid ART intervention. The group initiating rapid ART were more likely to be newly diagnosed with HIV, more likely to be men, and more likely to be younger; factors previously associated with worse uptake of HIV services.[6,9,35-40] The before and after design also leads to the possibility of temporal confounding. Although there were no major changes in ART initiation procedures other than introduction of rapid ART during the study it is possible that clinic staff became more proficient at initiating patients as the study progressed; or that other study-specific or external factors influenced ART timing. The interrupted time series analysis, performed to examine this possibility, revealed no significant temporal trends in time to ART pre-rapid ART implementation. Additionally, as rapid ART was implemented during the latter half of the trial, participants in the rapid ART group did not have the same length of time as those in the standard

ART group to cycle back into care and be classified as on treatment after missing appointments, potentially leading to an underestimation of retention in care in the rapid ART period. Secondly, a change that was implemented contemporaneously with rapid ART was the switch to DTG-based ART. This is unlikely to influence ART timing but is likely to have contributed to the more rapid viral suppression in the later cohort. Median time from ART initiation to viral suppression was slightly shorter in the rapid ART period when DTG was the standard ART regimen but did not account for the major difference in time from linkage to viral suppression. Finally, results may not be directly generalizable to all African or LMIC settings. Our study sites were rural or peri-urban, and the study population 60% women with a median age of almost 35 years and a relatively high median baseline CD4 count of 350 cells/μL. Although the study was conducted in public facilities, extra trained staff was placed by the Ministry of Health (with support from the study team) to deal with congestion at the clinics. Additional staff trainings were provided, and a higher level of monitoring and supervision was performed than is standard in the Government sector in Botswana. Most HIV testing was community based, with testing staff receiving specific training on delivering counselling messages facilitating rapid ART initiation.

In conclusion, we have shown that offering same day ART to individuals presenting for HIV care in public sector clinics in Botswana leads to high rates of ART initiation, significantly reduced time from linkage to starting ART, and significantly reduced time to virological suppression. Rapid ART initiation was safe, even in the absence of baseline blood test results, and the benefits were sustained, with comparable rates of retention in care and viral suppression after 1 year of ART to those achieved with traditional models of care.

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Tables

Table 1. Baseline characteristics of study participants

	Pre-Rapid ART (1,717)	**Rapid ART (800)**	***p-value***
Age (years, median, IQR)	37 (29-45)	33 (26-41)	*<0.001*
Sex (% male, n)	38.2% (656)	45.1% (361)	*0.001*
Weight* (kg, median, IQR)	61 (54-71)	61 (54-69)	*0.990*
New HIV+ve diagnosis† (% newly diagnosed HIV, n)	47.3% (812)	60.5% (484)	*<0.001*
Prior ART default (% ART experienced, n)	6.3% (108)	6.8% (54)	*0.020*
Baseline CD4 cell count‡ (cells/µL, median, IQR)	342 (232-472)	344 (202-504)	*0.647*
Baseline creatinine (mmol/L, median, IQR)	67 (55-80)	66 (55-77)	*0.523*
Baseline haemoglobin (g/dL, median, IQR)	13.1 (11.8-14.3)	13.4 (12.1-14.8)	*0.001*
Baseline alanine transaminase (IU, median, IQR)	17 (13-23)	17 (12-24)	*0.777*

Restricted to patients eligible for ART initiation (see methods section).

*Weights were missing in 342/1,717 participants in the pre-Rapid ART group and 232/800 participants in the Rapid ART group.

†Patients diagnosed as HIV infected for the first time at study baseline testing.

‡ Baseline CD4 counts were missing in 41/1,717 participants in the pre-Rapid ART group and 335/800 participants in the Rapid ART group.

P-values for comparisons of proportions were derived from a hierarchical mixed effects regression model incorporating a random effects term for community. P-values for comparisons of medians were derived from ranked testing (F-testing) of Somers' D parameter estimates accounting for clustering by site (comparable to a Kruskall-Wallis test).

ART: antiretroviral therapy. IQR: interquartile range. n: number. IU: International Units.

Supplementary Table 1. Outcomes in study participants initiated on ART with abnormal creatinine clearance.

	Age	Sex	CD4 Count	ART Regimen	ART Initiation Day	Creatinine Clearance	Creatinine Result	Follow-up	1 Year Outcome	1 Year Viral Load
1.	60 years	Male	84 cells/µL	TDF/FTC, DTG	0	50 mL/min	82 mmol/L	Remained on TDF. Stable on ART. Alive and well at 1 year.	Alive	< 400 copies/ml
2.	45 years	Male	478 cells/µL	TDF/FTC, DTG	0	46 mL/min	120 mmol/L	Remained on TDF. Repeat creatinine=69 mmol/L at week 10. Stable on ART. Alive and well at 1 year.	Alive	< 400 copies/ml
3.	28 years	Male	615 cells/µL	TDF/FTC, DTG	0	59 mL/min	129 mmol/L	Remained on TDF. Repeat creatinine=70 mmol/L at week 4. Stable on ART. Alive and well at 1 year.	Alive	< 400 copies/ml
4.	61 years	Male	94 cells/µL	TDF/FTC, DTG	0	49 mL/min	91 mmol/L	Remained on TDF. Repeat creatinine=91mmol/L at week 2. Died week 20. Cause of death unknown.	Died	NA
5.	32 years	Male	17 cells/µL	TDF/FTC, DTG	0	20 mL/min	369 mmol/L	Switched to non TDF containing regimen (Abacavir) day 12. Repeat creatinine=98 mmol/L at week 2 and 65 mmol/L week 12. Stable on ART. Alive and well at 1 year.	Alive	<400 copies/ml
6.	41 years	Female	213 cells/µL	ABC, 3TC, DTG	0	56 mL/min	113 mmol/L	Started on non TDF containing regimen (Abacavir) as history of abnormal renal function. Died week 46 due to Cervical cancer	Died	NA
7.	33 years	Female	154 cells/µL	ABC, 3TC, DTG	0	32 mL/min	137 mmol/L	Started on non TDF containing regimen (Abacavir) as history of abnormal renal function. Stable on ART. Alive and well at 1 year.	Alive	< 400 copies/ml
8.	54 years	Male	9 cells/µL	TDF/FTC, DTG	7	51 mL/min	91 mmol/L	Switched to non TDF containing regimen (Abacavir) month 4. Stable on ART. Alive and well at 1 year.	Alive	< 400 copies/ml
9.	57 years	Female	448 cells/µL	TDF/FTC, DTG	9	51 mL/min	68 mmol/L	Switched to non TDF containing regimen (Abacavir) month 4. Stable on ART. Alive and well at 1 year. 77 week 4 58 week 8	Alive	< 400 copies/ml
10.	63 years	Female	480 cells/µL	TDF/FTC, DTG	65	46 mL/min	132 mmol/L	109.4 week 8. Switched to non TDF containing regimen (Abacavir) month 3. Stable on ART. Alive and well at 1 year.	Alive	< 400 copies/ml
11.	53 years	Male	151 cells/µL	TDF/FTC, DTG	53	34 mL/min	137 mmol/L	214 week 8. Switched to non TDF containing regimen (Abacavir) week 7. Stable on ART. Alive and well at 1 year.	Alive	< 400 copies/ml
12.	41 years	Female	85 cells/µL	ABC, 3TC, DTG	487	40 mL/min	86 mmol/L	Started on non TDF containing regimen (Abacavir) due to abnormal renal function. Stable on ART. Alive and well at 1 year.	Alive	Unknown

ART:Antiretroviral therapy. TDF: tenofovir. FTC: emtricitabine. DTG: dolutegravir. ABC: abacavir. NA: not applicable.

Figure Legend

Figure 1. Patient flow diagram. Prior to the introduction of universal antiretroviral therapy (ART) in June 2016 an individual was eligible for ART when (1) CD4 was <350 cells/μL or they met criteria for WHO clinical stage III or IV, based on Botswana's national guidelines; or (2) if they met the BCPP expanded ART eligibility criteria of CD4 <500 cells/μL or CD4 ≥500 cells/μL and viral load (VL) > 10,000 copies/μL. *The cumulative proportion on ART (as in Figure 2) was 93.5% as not all individuals in the Rapid ART group had completed 1 year of follow-up by the time of data censoring.

Figure 2. Time from linkage (first ART clinic visit) to ART initiation. Figure 2.a. shows cumulative time to ART during the pre-Rapid ART cohort (in blue), and following the introduction of Rapid ART (in red), with cumulative probabilities at 1 day, 1 week, 2 weeks, 1 month, 3 month, and 1 year in the table below. The hazards of ART initiation derived from the hierarchical Cox proportional hazards model accounting for clustering by community and adjusted for age, sex, CD4 count, and whether individuals were newly diagnosed with HIV or had a previously known diagnosis was 3.83 (95% confidence interval [CI] 3.41-4.32), p<0.001. Figure 2.b. shows the results of an interrupted time series analysis using log transformed monthly aggregate data. There was a significant decrease in time from linkage to ART initiation in the month following introduction of rapid ART initiation guidelines (Δ=-0.78 $\log_{10}$days, 95% CI -0.93 to -0.63 $\log_{10}$days, p<0.001). Months with less than 15 ART initiations in total were excluded from analysis to prevent any possible influence of statistical outliers due to small samples.

Figure 3. Retention in care and virological suppression at 12 months following standard or rapid ART initiation. (ART: antiretroviral therapy. VL: viral load). In an analysis restricted just to those who initiated ART within 1 day of linkage ("same day") during the rapid ART period, 96.9% (379/391) of individuals were retained at 1 year; 1 year VLs were recorded in 93.6% (366/391) of individuals initiating same day, with a 97.5% viral suppression rate in those with a VL result, and 91.3% (357/391) individuals overall in care and with a documented VL <400 copies/ml after 1 year of ART.

Supplementary Figure S1. Time from linkage (first ART clinic visit) to ART initiation pre and post the introduction of Rapid ART stratified by i) prior HIV status (new or previously known diagnosis at study entry); ii) baseline CD4 cell count (dichotomized at 200 cells/μL); iii) sex; and iv) age (16-24 years or 25 years and older). Introduction of Rapid ART guidelines led to significantly faster rates of ART initiation in all strata. The stratified analyses of ART timing showed no significant interactions between rapid ART introduction and prior HIV status (new or known), sex, or age (less than 25 years or 25 years and older); however very weak evidence for an interaction was found between the effect of rapid ART introduction on ART timing and baseline CD4 count (panel 2). Prior to rapid ART introduction individuals with CD4 cell counts ≤200 cells/μL were initiated on ART significantly more rapidly following linkage than those with CD4 counts >200 cells/μL. Although the introduction of rapid ART initiation guidelines led to significantly more rapid ART initiation in both the group with CD4 cell counts ≤200 cells/μL and those with CD4 counts >200 cells/μL, the impact was less marked in the low CD4 count group due to the already more rapid ART initiation rates during the standard ART period in this group (hazard ratio 0.81, 95%CI 0.63-1.04, p=0.10).

Figure 1.

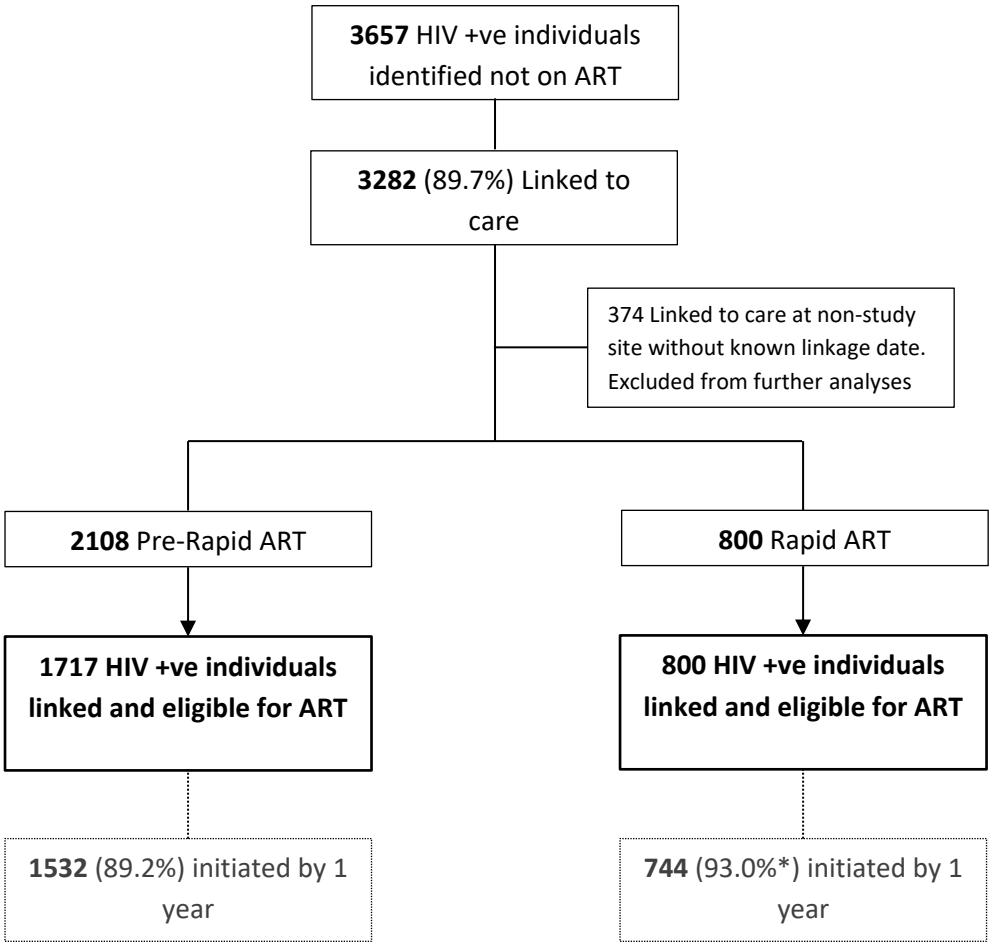
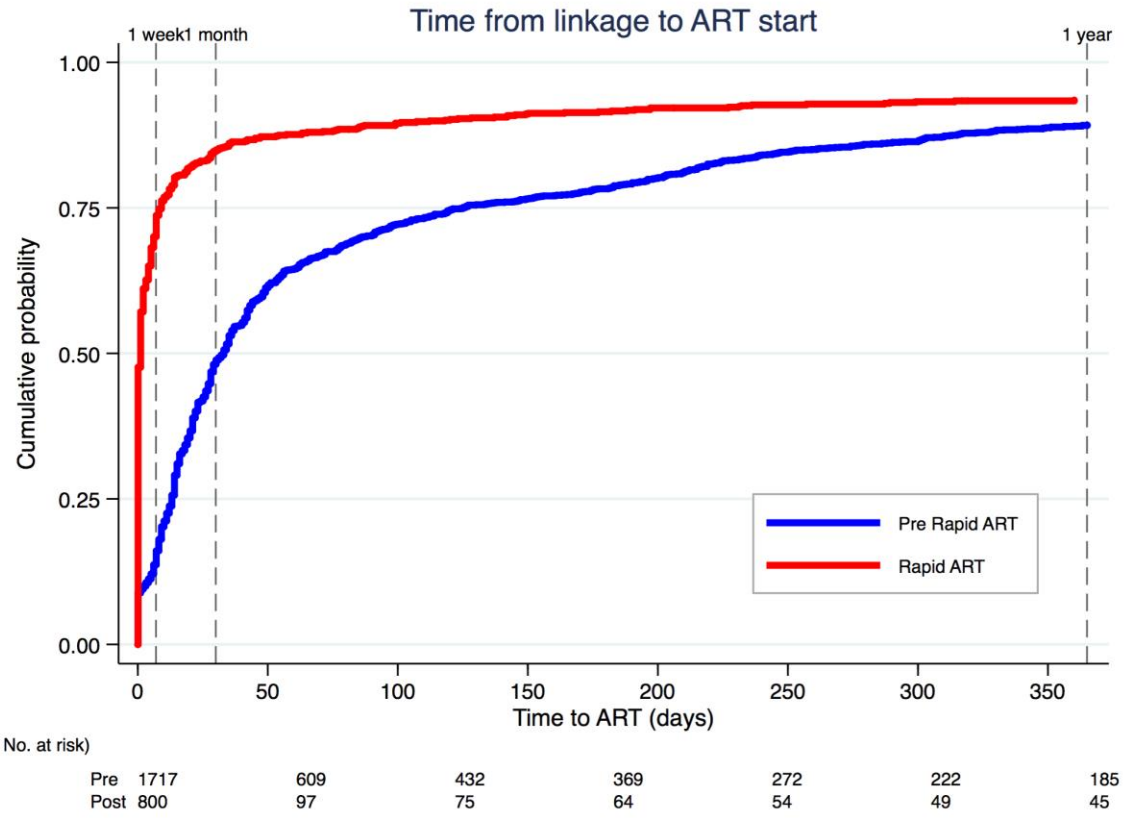

3657 HIV +ve individuals identified not on ART
3282 (89.7%) Linked to care
374 Linked to care at non-study site without known linkage date. Excluded from further analyses
2108 Pre-Rapid ART
800 Rapid ART
1717 HIV +ve individuals linked and eligible for ART
800 HIV +ve individuals linked and eligible for ART
1532 (89.2%) initiated by 1 year
744 (93.0%*) initiated by 1 year

Figure 2.a.



Time from linkage	Pre Rapid ART (1717)		Post Rapid ART (800)	
	Number	Cumulative probability of ART initiation (95% CI)	Number	Cumulative probability of ART initiation (95% CI)
1 day	163	9.5% (8.2-11.0)	457	57.1% (53.7-60.6)
1 week	276	16.1% (14.4-17.9)	589	73.7% (70.6-76.7)
2 weeks	499	29.1% (27.0-31.3)	641	80.3% (77.4-83.0)
1 month	839	48.9% (46.5-51.3)	678	84.9% (82.4-87.3)
3 months	1208	70.4% (68.2-72.5)	711	89.2% (86.9-91.2)
1 year	1532	89.2% (87.7-90.6)	744	93.5% (91.6-95.1)

Figure 2.b.

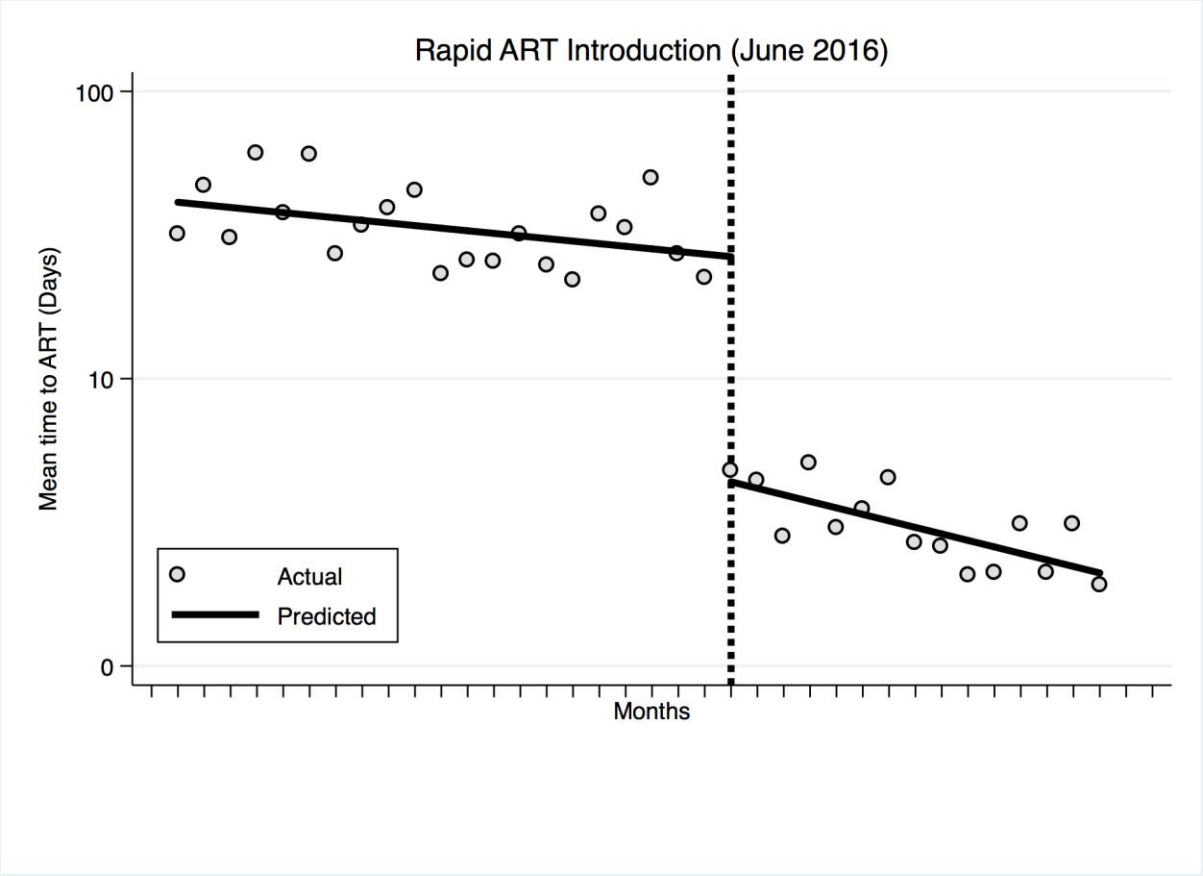
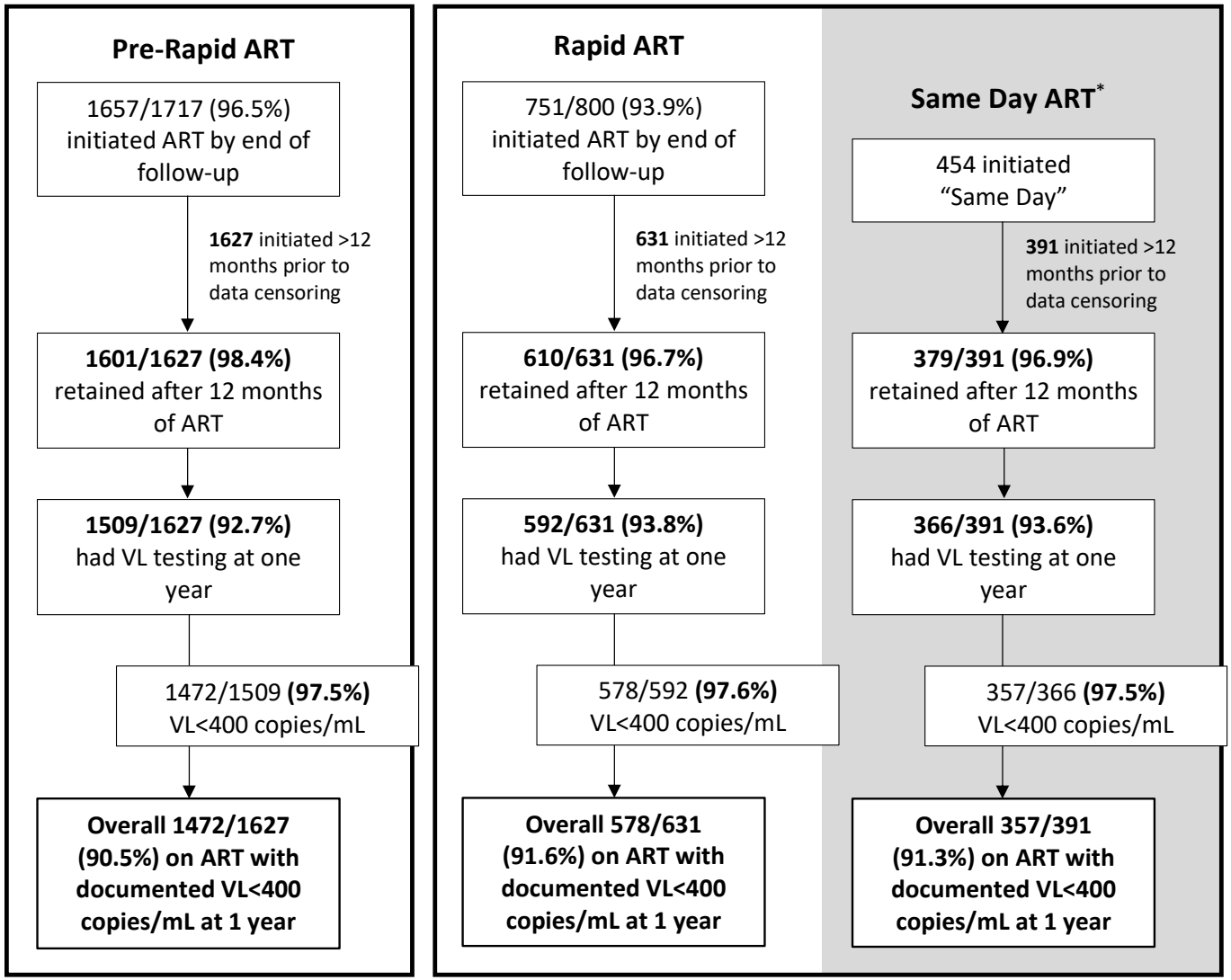
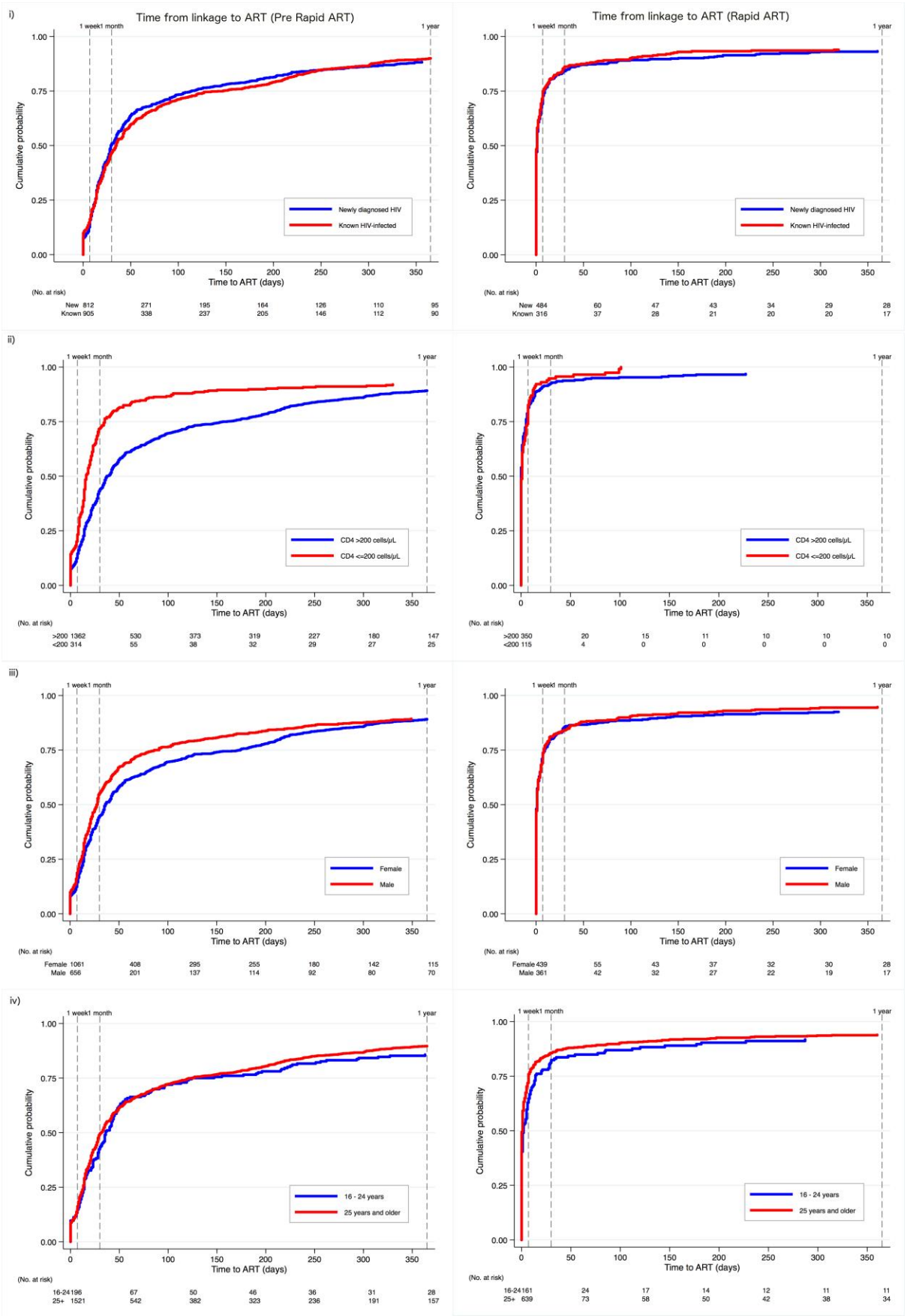

Rapid ART Introduction (June 2016)
100
10
0
Mean time to ART (Days)
Actual
Predicted
Months

Figure 3.


Pre-Rapid ART
1657/1717 (96.5%) initiated ART by end of follow-up
1627 initiated >12 months prior to data censoring
1601/1627 (98.4%) retained after 12 months of ART
1509/1627 (92.7%) had VL testing at one year
1472/1509 (97.5%) VL<400 copies/mL
Overall 1472/1627 (90.5%) on ART with documented VL<400 copies/mL at 1 year
Rapid ART
751/800 (93.9%) initiated ART by end of follow-up
631 initiated >12 months prior to data censoring
610/631 (96.7%) retained after 12 months of ART
592/631 (93.8%) had VL testing at one year
578/592 (97.6%) VL<400 copies/mL
Overall 578/631 (91.6%) on ART with documented VL<400 copies/mL at 1 year
Same Day ART*
454 initiated "Same Day"
391 initiated >12 months prior to data censoring
379/391 (96.9%) retained after 12 months of ART
366/391 (93.6%) had VL testing at one year
357/366 (97.5%) VL<400 copies/mL
Overall 357/391 (91.3%) on ART with documented VL<400 copies/mL at 1 year

Supplementary Figure S1.



Research in context

Evidence before this study

There is strong evidence for both the patient-level health benefits of ART and public health benefits of ART resulting from reduced HIV transmission. To fully realise these benefits, it is critical that individuals who are diagnosed with HIV infection rapidly initiate ART. However, data from low- and middle-income (LMIC) settings has demonstrated high rates of loss from the care cascade between HIV testing and ART initiation, or substantial delays to initiation of treatment. A potential way to increase rates of ART initiation is to offer same-day ART to all individuals at their initial clinic visit. We searched PubMed, EMBASE, and PubMed Central for studies published between Jan 1, 2000, and July 31, 2019, investigating the acceptability, feasibility, safety, and outcomes of rapid or same-day antiretroviral therapy (ART) initiation in HIV-infected individuals presenting to treatment services. Several randomized controlled trials from LMIC settings have shown that rapid ART initiation, including treatment initiation at the first clinic visit, is acceptable and feasible, and can increase rates of ART initiation, retention in care, and virological suppression. However, prior trials included enhancements to care beyond changes to ART timing, and also included CD4-based eligibility criteria, potentially limiting their generalizability to more routine care settings in the test and treat era.

Added value of this study

We were able to evaluate the acceptability, feasibility and outcomes of rapid ART initiation with the offer of ART at first clinic visit in the context of the cluster-randomized Botswana Combination Prevention Project (BCPP). Simplified rapid ART initiation with the offer of same day treatment at first ART clinic visit was acceptable and feasible in public ART clinics in Botswana. Following the introduction of rapid ART guidelines, the proportion of patients established on ART within 1 month from clinic linkage increased from 49% to 85%, and from

89% to 94% at 1 year. The median time from clinic linkage to viral suppression was significantly reduced. Rates of retention in care and viral suppression were similarly high in individuals initiated on ART prior to the introduction of rapid ART and those initiated during the rapid ART period, with documented viral suppression after 1 year of ART in over 90% of individuals in both groups. To the best of our knowledge, these are the first data reporting the outcomes of rapid ART initiation in a routine LMIC care setting, without baseline screening blood tests, point-of-care CD4 counts, or additional clinical assessments. Our findings add to the accumulating evidence demonstrating the feasibility, acceptability, and safety of rapid ART initiation in LMIC settings, and indicate that benefits of rapid ART initiation are sustained over time.

Implications of all the available evidence

The more rapid ART initiation and shorter time from clinic linkage to viral suppression observed following implementation of rapid ART initiation guidelines are likely to have both individual- and population-level benefits. The findings support recent World Health Organisation guidance recommending rapid ART initiation and could help HIV-treatment programmes in Africa and globally reach the ambitious UNAIDS 90-90-90 targets.

END