

1 **Rapid Antiretroviral Therapy Initiation in the Botswana Combination Prevention**  
2 **Project**

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28

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36 Netherlands, June 2018.

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40 **Abstract** (294 words)

41 *Background*

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

44 *Methods*

45 BCPP was a community-randomized HIV-prevention trial performed from 2013-2018. In June  
46 2016 universal HIV-treatment and rapid ART initiation with dolutegravir-based ART were  
47 introduced; same-day ART initiation was offered at the first clinic visit. We determined time  
48 to ART initiation, and rates of retention in care and viral suppression at one year.

49 *Findings*

50 1,717 eligible adults linked to study clinics prior to and 800 after rapid ART introduction.  
51 During the rapid ART period 57.1% (95% confidence interval [CI] 53.7-60.6%) of linked  
52 individuals initiated ART within 1 day of linkage, 73.7% (95%CI 70.6-76.7%) within 1 week  
53 of linkage, 84.9% (95%CI 82.4-87.3%) within 1 month, and 93.5% (95%CI 91.6-95.1%)  
54 within 1 year. Prior to the introduction of rapid ART 16.1% (95%CI 14.4-17.9%) of linked  
55 individuals initiated ART within 1 week of linkage, 48.9% (95%CI 46.5-51.3%) within 1  
56 month, and 89.2% (95%CI 87.7-90.6%) within 1 year. One year after ART initiation 90.5%  
57 (95%CI 87.4%-92.8%) of individuals who linked in the standard ART period were in care and  
58 had a viral load <400 copies/ml, compared to 91.6% (95%CI 88.1%-94.1%) in the rapid ART  
59 period (odds ratio 1.20, 95%CI 0.86-1.67, p=0.294). Median time from linkage to documented  
60 viral suppression was 99 days following introduction of rapid ART initiation (interquartile  
61 range [IQR] 86-166 days) compared to 186 days (IQR 116-323 days) prior to rapid ART  
62 (p<0.001).

63 *Interpretation*

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

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71

## 72 **Introduction**

73 Ensuring that individuals who are diagnosed with HIV infection rapidly initiate ART is a  
74 critical step in meeting the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-  
75 90 targets;<sup>1,2</sup> however, data from low- and middle-income (LMIC) settings have demonstrated  
76 high rates of loss from the care cascade between HIV testing and ART initiation, or substantial  
77 delays to initiation of treatment.<sup>2-8</sup> Many of these losses result from significant barriers to ART  
78 initiation including the need for multiple clinic visits, repeated pre-ART counselling sessions,  
79 and delays in receiving baseline blood test results.<sup>9-15</sup> A potential way to increase rates of ART  
80 initiation is to offer same-day ART to all individuals at their initial clinic visit - a strategy that  
81 became more feasible following the elimination of baseline CD4 testing to determine treatment  
82 eligibility as well as the transition to a dolutegravir (DTG)-containing first-line ART  
83 regimen.<sup>16,17</sup>

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

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

95

## 96 **METHODS**

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

105 **Study procedures.** Study interventions took place between October 2013 and March 2018. All  
106 16-64 year-old community residents identified through community testing activities were  
107 assessed through a standard intake questionnaire and asked if they were HIV-positive. Persons  
108 who did not know their status, did not have documentation of an HIV-positive status, or did  
109 not have documentation of a negative HIV test within the preceding 3 months were offered  
110 rapid HIV-testing using KHB (KHB, Shanghai Kehua Bio-Engineering Co Ltd, Shanghai,  
111 China) and Unigold (Trinity Biotech Plc, Bray, Ireland) parallel HIV tests. Discordant results  
112 were verified by laboratory testing using western blot. All participants provided verbal consent  
113 for HIV testing.

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

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

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

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

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

146 **Outcomes.** Primary outcome measures were (1) time from first eligible ART clinic visit to  
147 ART initiation, and (2) rates of retention in care and viral suppression (defined as a plasma VL  
148 <400 copies/ $\mu$ L) at 1 year post-ART initiation. Given the potential for patients to have viral  
149 load testing at either 9 months or 12 months depending on viral suppression status at month 3,  
150 and to allow for delays in clinic attendance, a 90-day window was placed around the 1 year VL  
151 timepoint. Patients were considered lost to follow-up if they had not attended any HIV-related  
152 clinic activity within 180 days of data censoring on 28<sup>th</sup> June 2018. Secondary outcomes  
153 included uptake of ART within 1 year of linkage, time from ART clinic linkage to HIV viral  
154 suppression, and mortality within 1 year of linkage.

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



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

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173 AIDS Relief. The funders had no direct role in study design, in the collection, analysis, and  
174 interpretation of data, in the writing of this report, or in the decision to submit it for publication.  
175 The corresponding author (JNJ) had full access to all the data in the study and had final  
176 responsibility for the decision to submit for publication.

177

## 178 **Results**

179 Between October 2013 and March 2018, BCPP research staff assessed HIV status in 61,655  
180 community residents, of whom 13,328 (22%) were HIV infected. Of these, 3,657 (27%) were  
181 not on ART; 3,282 (89.7% ) linked to care at an ART clinic a median of 6 days (IQR 3-35  
182 days) after community assessment. Three hundred and seventy four individuals linked to clinics  
183 outside the intervention communities and did not have reliably documented linkage or ART  
184 initiation dates and were excluded from further analysis. Of the remaining 2,908 individuals  
185 included in the final analysis 2,108 linked during the standard ART period of whom 1,717  
186 (81.5%) were eligible for ART initiation, and 800 linked after the introduction of rapid ART  
187 initiation when all HIV-positive individuals were eligible for ART (Figure 1). Baseline  
188 characteristics of study participants are shown in Table 1.

### 189 ***ART uptake and time to ART initiation following linkage***

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

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

201 Interrupted time series analysis using log-transformed monthly aggregate data showed  
202 a non-significant downwards trend in ART initiation timing during the standard ART initiation  
203 period ( $\beta$  coefficient  $-0.009 \log_{10}\text{days}$  per month, 95% CI  $-0.018-0.0004$ ,  $p=0.062$ ), and a  
204 significant decline during the rapid ART initiation period ( $\beta$  coefficient  $-0.023 \log_{10}\text{days}$  per  
205 month, 95% CI  $-0.034-0.011$ ,  $p<0.001$ ). There was a significant decrease in time from linkage  
206 to ART initiation in the month following introduction of rapid ART initiation guidelines ( $\Delta=-$   
207  $0.78 \log_{10}\text{days}$ , 95% CI  $-0.93- -0.63 \log_{10}\text{days}$ ,  $p<0.001$ )(Figure 2b).

### 208 ***Retention in care and viral suppression following ART initiation***

209 Retention in care at 1 year following ART initiation (limited to those individuals  
210 initiating ART at least 1 year prior to data censoring), and rates of viral suppression are shown  
211 in Figure 3. Retention in care was 98.4% (1601/1627) at 1 year among individuals who linked  
212 prior to introduction of rapid ART initiation guidelines and initiated ART, and 96.9% (610/631)  
213 among individuals linking to care and initiating ART following introduction of rapid ART.  
214 One-year VL results were available for 92.7% (1509/1627) of individuals who linked and  
215 initiated ART in the standard ART period and 93.8% (592/631) of patients initiating during the  
216 rapid ART period, with viral suppression rates of 97.5% and 97.6% respectively. Overall,  
217 90.5% (1472/1627, 95% CI 87.4% - 92.8%) of individuals who linked in the standard ART  
218 period and initiated ART were in care and had a documented VL  $<400$  copies/ml after 1 year

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

### 221 *Time from linkage to viral suppression*

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

### 230 *Safety of rapid ART initiation*

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

243 1.16% (20/1717) in the standard ART period, and 1.00% (8/800) in the rapid ART period  
244 (p=0.714).

245

## 246 **Discussion**

247 Simplified rapid ART initiation with the offer of same-day treatment at first ART clinic visit  
248 to all clinically-stable patients was acceptable and feasible in public ART clinics in Botswana,  
249 with over half of patients initiating ART within 1 day of ART clinic linkage and 74% initiating  
250 within 1 week. Following the introduction of rapid ART the proportion of patients established  
251 on ART increased from 49% to 85% at 1 month from clinic linkage, and from 89% to 94% at  
252 1 year. The median time from clinic linkage to viral suppression was significantly reduced,  
253 with potential contributions from both more rapid initiation of ART and the switch to DTG.  
254 Rates of retention in care and viral suppression were similarly high in individuals initiated on  
255 ART prior to the introduction of rapid ART and those initiated during the rapid ART period,  
256 with documented viral suppression after 1 year of ART in over 90% of individuals in both  
257 groups.

258 Our findings add to the accumulating evidence demonstrating the feasibility,  
259 acceptability, and safety of rapid ART initiation in LMIC settings, and provide some of the  
260 first evidence for the acceptability among patients with high CD4 counts.<sup>3</sup> Recent clinical trials  
261 from South Africa,<sup>18,27</sup> Lesotho,<sup>21</sup> Haiti,<sup>20</sup> and Uganda<sup>19</sup> have all shown the high uptake of  
262 same-day or rapid ART when offered to patients in clinic<sup>18-20,27</sup> or community<sup>21</sup> settings. In the  
263 RapIT trial in South Africa 72% of individuals offered rapid ART initiation initiated same-day,  
264 and 96% within one month.<sup>18</sup> Similar figures were reported by Amanyire et al. from a cluster-  
265 randomized trial in Uganda, where a clinic-level streamlined ART initiation intervention led to  
266 71% of individuals initiating on the day of eligibility, compared to 18% in the control arm.  
267 Even higher rates of 99% uptake of same day ART have been reported from a recent clinic

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

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

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

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

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

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

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

340

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465 **Tables**466 **Table 1.** Baseline characteristics of study participants

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

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.

<sup>†</sup>Patients diagnosed as HIV infected for the first time at study baseline testing.

<sup>‡</sup> 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 Kruskal-Wallis test).

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

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**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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu$ L	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/ $\mu\text{L}$  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/ $\mu\text{L}$  or CD4  $\geq 500$  cells/ $\mu\text{L}$  and viral load (VL)  $> 10,000$  copies/ $\mu\text{L}$ . \*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 ( $\Delta = -0.78$   $\log_{10}$ 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/ $\mu$ L); 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  $\leq$ 200 cells/ $\mu$ L were initiated on ART significantly more rapidly following linkage than those with CD4 counts >200 cells/ $\mu$ L. Although the introduction of rapid ART initiation guidelines led to significantly more rapid ART initiation in both the group with CD4 cell counts  $\leq$ 200 cells/ $\mu$ L and those with CD4 counts >200 cells/ $\mu$ L, 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.

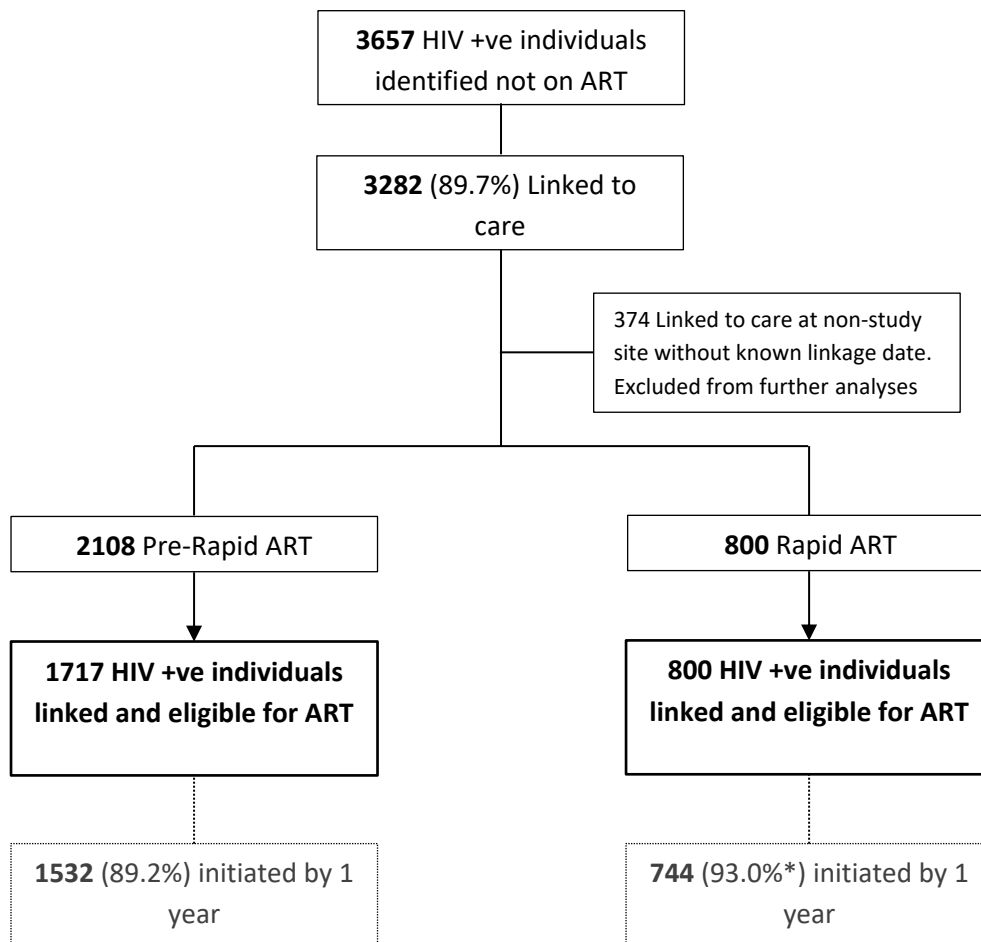
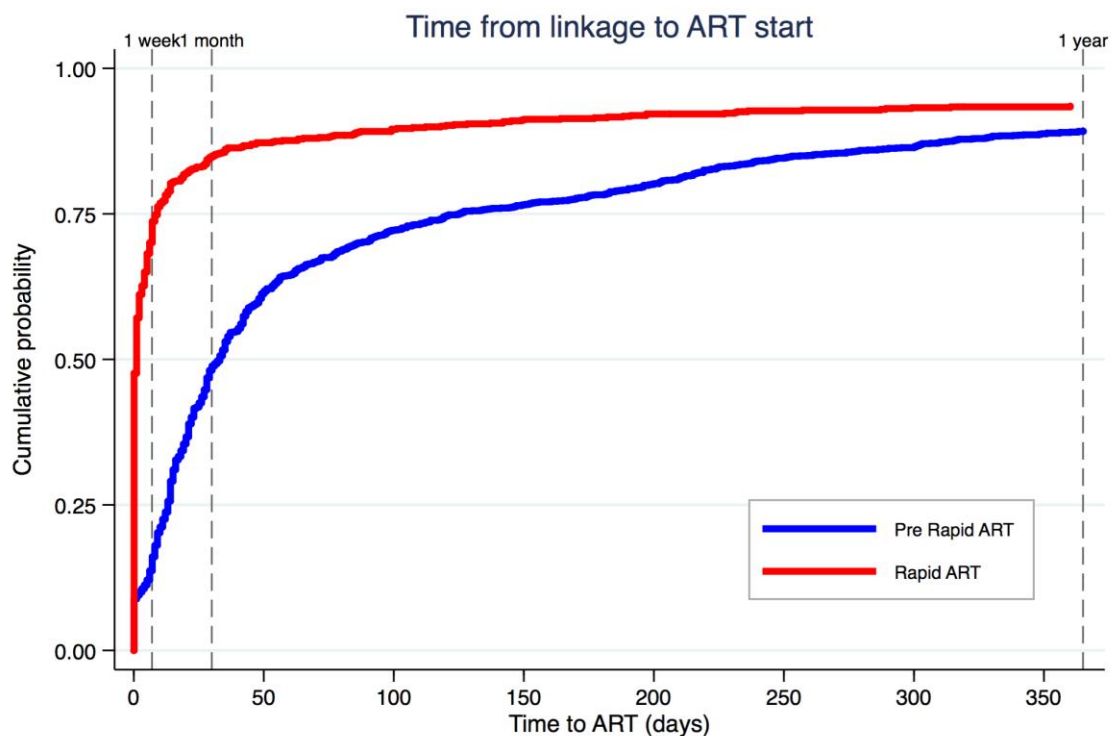


Figure 2.a.



No. at risk		Pre	1717	609	432	369	272	222	185
	Post	800	97	75	64	54	49	45	

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.

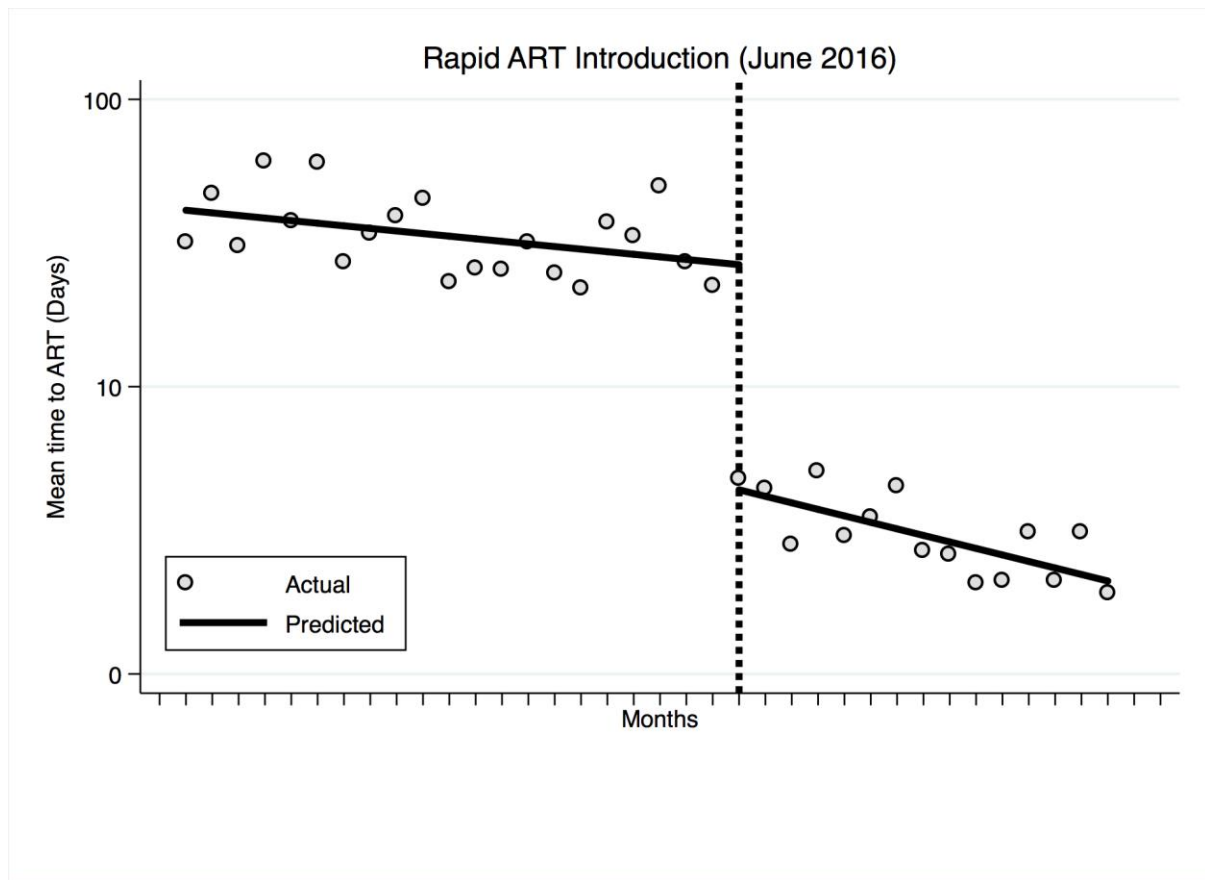
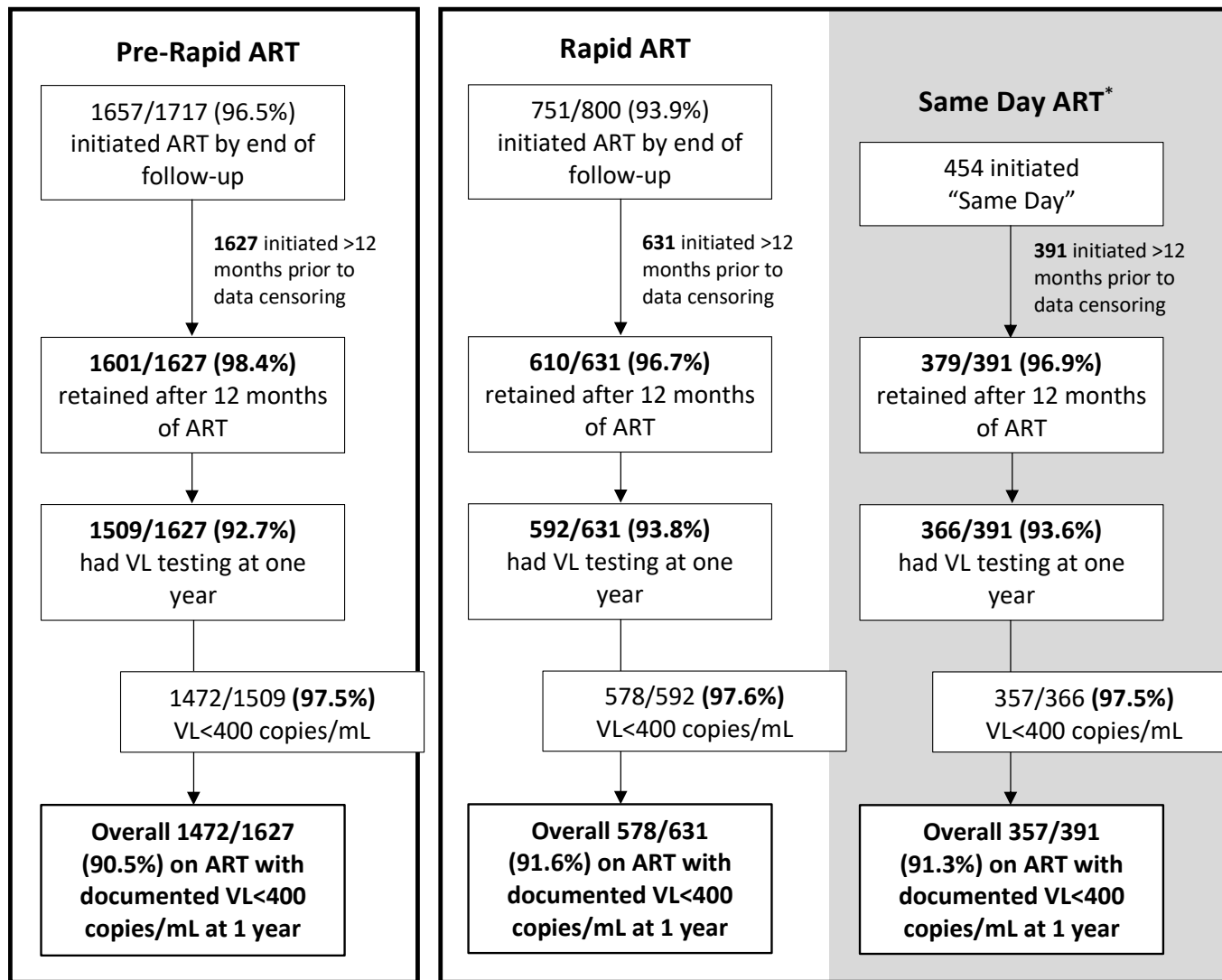
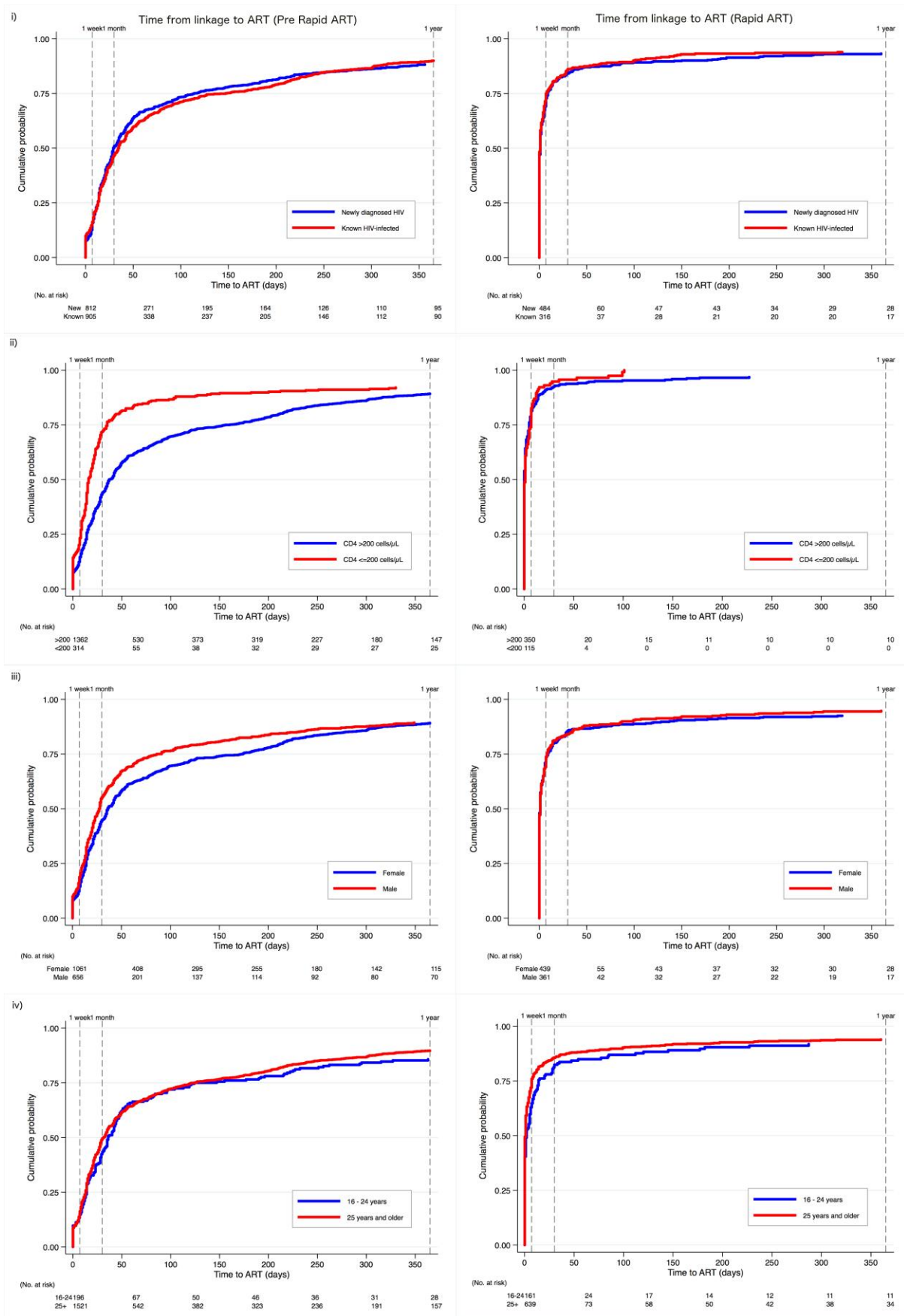


Figure 3.



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