Mortality under early access to antiretroviral therapy vs. Eswatini's national standard of care: the MaxART clustered randomized stepped-wedge trial

Chao, A.; Spiegelman, D.; Khan, S.; Walsh, F.; Mazibuko, S.; Pasipamire, M.; ... ; Okello, V.

DOI: 10.1111/hiv.12876

HIV Medicine (2020), **21**, 429–440

ORIGINAL RESEARCH

Mortality under early access to antiretroviral therapy *vs.* Eswatini's national standard of care: the MaxART clustered randomized stepped-wedge trial

A Chao,[1] D Spiegelman [1] S Khan,[2] F Walsh,[3] S Mazibuko,[4] M Pasipamire,[4] B Chai,[5] R Reis,[6,7,8] K Mlambo,[2] W Delva,[9,10,11,12] G Khumalo,[13] M Zwane,[14] Y Fleming,[15] E Mafara,[2] A Hettema,[2] C Lejeune,[2] T Bärnighausen[16] and V Okello[17]

[1]*Department of Biostatistics, Yale School of Public Health, Center for Methods in Implementation and Prevention Science (CMIPS), New Haven, CT, USA,* [2]*Clinton Health Access Initiative (CHAI), Mbabane, Eswatini,* [3]*Clinton Health Access Initiative (CHAI), Boston, MA, USA,* [4]*Eswatini National ART program (SNAP), Ministry of Health, Mbabane, Eswatini,* [5]*Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA,* [6]*Leiden University Medical Center, Leiden University, Leiden, Netherlands,* [7]*Amsterdam Institute for Social Science, University of Amsterdam, Amsterdam, Netherlands,* [8]*Children's Institute, University of Cape Town, Cape Town, South Africa,* [9]*The South African Department of Science and Technology – National Research Foundation (DST-NRF) Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa,* [10]*Center for Statistics, Hasselt University, Diepenbeek, Belgium,* [11]*International Centre for Reproductive Health, Ghent University, Gent, Belgium,* [12]*Rega Institute for Medical Research, KU Leuven, Leuven, Belgium,* [13]*Eswatini National Network of People Living with HIV (SWANNEPHA), Mbabane, Eswatini,* [14]*SAfAIDS, Manzini, Eswatini,* [15]*Aidsfonds, Amsterdam, Netherlands,* [16]*Heidelberg Institute of Public Health, University of Heidelberg, Heidelberg, Germany and* [17]*Directorate Office, Ministry of Health, Mbabane, Eswatini*

Objectives

Current WHO guidelines recommend the treatment of all HIV-infected individuals with antiretroviral therapy (ART) to improve survival and quality of life, and decrease infection of others. MaxART is the first implementation trial of this strategy embedded within a government-managed health system, and assesses mortality as a secondary outcome. Because primary findings strongly supported scale-up of the 'treat all' strategy (hereafter Treat All), this analysis examines mortality as an additional indicator of its impact.

Methods

MaxART was conducted in 14 Eswatinian health clinics through a clinic-based stepped-wedge design, by transitioning clinics from then-national standard of care (SoC) to the Treat All intervention. All-cause, disease-related, and HIV-related mortality were analysed using the Cox proportional hazards model, censoring SoC participants at clinic transition. Median follow-up time among study participants was 292 days. There were 36/2034 deaths in SoC (1.77%) and 49/1371 deaths in Treat All (3.57%).

Results

Between September 2014 and August 2017, 3405 participants were enrolled. In SoC and Treat All interventions, respectively, the multivariable-adjusted 12-month all-cause mortality rates were 1.42% [95% confidence interval (CI): 0.66–2.17] and 1.60% (95% CI: 0.78–2.40), disease-related mortality rates were 1.02% (95% CI: 0.40–1.64) and 1.10% (95% CI: 0.46–1.73), and HIV-related mortality rates were 1.03% (95% CI: 0.40–1.65) and 0.99% (95% CI: 0.40–1.58). Treat All had no impact on all-cause [hazard ratio (HR) = 1.12, 95% CI: 0.58–2.18, P = 0.73], disease-related (HR = 1.04, 95% CI: 0.52–2.11, P = 0.90), or HIV-related mortality (HR = 0.93, 95% CI: 0.46–1.87, P = 0.83).

Correspondence: Donna Spiegelman, Yale School of Public Health, 60 College Street, New Haven, CT, 06510, USA. Tel: 617 835 5119; fax: 203 764 4353; e-mail: donna.spiegelman@yale.edu

Conclusion

There was no immediate benefit of the Treat All strategy on mortality, nor evidence of harm. Longer follow-up of participants is needed to establish long-term consequences.

Keywords: antiretroviral therapy, Eswatini, HIV/AIDS, mortality, Treat All

Accepted 13 April 2020

Introduction

HIV and AIDS continue to be a major global public health issue. UNAIDS estimated there were 36.9 million people living with HIV in 2017 [1]. The vast majority of HIV infections burdens those located in low- and middle-income countries, with an estimated 66% of people living with HIV (PLHIV) residing in sub-Saharan Africa [2].

In 2017, 940 000 people died of AIDS-related illnesses globally. While this number has significantly reduced since the peak of 1.9 million in 2004 [2], HIV/AIDS remains as one of the leading causes of death in sub-Saharan Africa [3]. Eswatini, in particular, has the highest HIV prevalence in the world with 26% of adults (aged 15–49 years) living with HIV, and a weighted HIV incidence of 2.4% as of 2011, which is the highest national rate known [4]. In 2018, 2100 out of 190 000 adults living with HIV in Eswatini died as a result of AIDS [5], translating to approximately 11 deaths per 1000 adults living with HIV.

HIV-associated morbidity and mortality rates have reduced significantly globally through the introduction of antiretroviral therapy (ART), which suppresses viral replication and increases CD4 count, thereby decreasing opportunistic infections and malignancies associated with AIDS [6]. The timing of ART initiation also greatly influences survival outcomes among PLHIV, as studies have found that early ART access contributes to better survival [7,8]. However, methodologically, it would also be important to assess the benefits of early ART initiation by disease stage, as even in the absence of any benefit of early ART access, patients presenting at an earlier disease stage will have longer survival.

In 2016, WHO removed the threshold for ART participation, recommending that ART be initiated in all adults with HIV, regardless of WHO clinical stage and CD4 cell count. The goal was to implement a treat all approach (hereafter Treat All) for immediate ART initiation following HIV diagnosis [9]. The MaxART trial was thus implemented to determine the impact of the Treat All strategy on retention in care and viral suppression compared with that of the then-national standard of care (SoC) in Eswatini [10]. The trial was conducted in a public health sector setting and reflected strong support of the scale-up of the Treat All strategy in Eswatini and countries with similar HIV epidemics and health systems. However, even though there were increased retention and viral suppression results from the Treat All strategy [combined hazard ratio (HR) = 4.88, 95% confidence interval (CI): 2.96–8.05, $P < 0.001$], the relative mortality between SoC and Treat All participants in MaxART is not known. Moreover, of the four other community-based universal HIV testing and treatment trials implemented in sub-Saharan Africa [ANRS 12249 Treatment as Prevention (TasP) trial in South Africa, HPTN 071 (PopART) trial in South Africa and Zambia, BCPP/YaTsie in Botswana, and SEARCH in Uganda and Kenya], mortality as a secondary outcome has not yet been examined [11].

As MaxART is the first Treat All implementation trial embedded within a government-managed health system, this secondary analysis to MaxART investigates mortality rates associated with the Treat All strategy as compared with those with later ART initiation. The results on longevity in accordance with this strategy, which has become more commonly adapted especially in countries with high prevalence settings such as Eswatini, will serve as an additional indicator of its impact.

Methods

Trial background

The MaxART trial was conducted in 14 public sector health clinics in Eswatini. The trial was implemented using a clinic-based stepped-wedge design. Baseline data were collected for 4 months in all clinics, and then the Treat All intervention commenced with one pair of randomly assigned clinics transitioning from Eswatini's SoC of ART initiation to the intervention at pre-specified dates at each 4-month step.

The ART-naïve HIV-positive participants, aged 18 years or older, with no mental illness, and not pregnant or breastfeeding within 30 days of enrolment were eligible for the trial. Verbal informed consent was sought from eligible participants to ensure they were ready to start ART outside of national guidelines, regardless of whether the participant was initiated on the control or the intervention phase, and included a description of purpose of the study, the study procedures, and the anticipated risks and benefits of providing laboratory samples. An in-

country Community Advisory Board was established as a part of this study to ensure that the study was implemented in accordance with community values, culture, social practices, human rights and ethical standards. Patients incurred no penalties if they refused to participate in the study, and continued to receive the standard of care as described in the national HIV treatment guidelines. Those who declined to enrol in the study were still given the option to receive ART even if their CD4 count was above the current national HIV treatment guidelines, but were excluded from study.

In the SoC phase, participants meeting SoC ART eligibility criteria were referred for ART initiation, while those not eligible were enrolled in pre-ART care. During the course of the trial, the ongoing changes in the SoC ART eligibility guidelines were incorporated into the trial implementation. From 1 September 2014 to 1 December 2015, the ART initiation threshold was a CD4 count of $\leq$ 350 cells/μL and/or WHO Stage 3 or 4. On 1 December 2015, the threshold changed to a CD4 count of $\leq$ 500 cells/μL and/or WHO Stage 3 or 4, then on 1 October 2016, Eswatini adopted the Treat All strategy as SoC. Under Treat All, all HIV participants were eligible for ART initiation irrespective of their CD4 count or WHO stage.

The trial started on 1 September 2014. The last pair was transitioned on 1 October 2016 when Eswatini changed the SoC from a CD4 count of $\leq$ 500 cells/μL to the Treat All strategy. The total duration of the trial was 36 months.

Statistical analysis

Standard operating procedures for data management were implemented in the 14 clinics to transfer participant records in the clinics' usual paper-based files to an electronic database. Nurse mentors regularly reviewed the participant files, and provided mentorship to the clinic staff.

Three mortality endpoints – all-cause, disease-related, and HIV-related mortality – were analysed to observe the effect of the Treat All intervention on mortality patterns among PLHIV. Disease-related mortality refers to deaths caused by any kind of disease but not accidents, violence, or injury. HIV-related deaths are a subset of disease-related deaths plausibly caused by HIV infection. Deaths were primarily identified by following up with participants with missed appointments or were lost to follow-up. In very rare cases, relatives of the participants reported to the facilities that the participants had died. Once death has been established, the MaxART team reached out to the participants' relatives and collected data on events prior to the participants' deaths. This information was then reviewed by an MD and a decision was made on the classification of the cause of death.

All analyses described were additionally performed for two sub-groups. Those with CD4 counts $\geq$ 350 cells/μL (or 500 cells/μL after 1 December 2015) and not in WHO stage 3 or 4, were sub-grouped as 'SoC-ineligible' participants, as they were only eligible for ART under Treat All. The rest who were eligible for ART under SoC at the time of their enrolment were thus 'SoC-eligible' participants.

Under intent-to-treat analysis, survival curves were adjusted for step-time by a set of indicator variables, and the Breslow estimator was used to estimate cumulative incidence rates. Step-time-adjusted cumulative incidence rates were calculated at the mean step-time in the population follow-up experience, and multivariable-adjusted cumulative incidence rates were additionally calculated at the mean level of all covariates included in the Cox proportional hazards model. In addition, SoC participants were censored at the time of their clinic transition. In the multivariable-adjusted analyses, a wide range of known or suspected determinants of mortality were included – age, sex, marital status, education, CD4 count, WHO stage, body mass index (BMI), tuberculosis screening, and viral load at study enrolment, as well as baseline facility volume, level of facility, days between testing HIV-positive and study enrolment, and access to HIV treatment supporter. When the number of cases in a model was limited, a reduced set of covariates were fitted. A competing-risks approach was used to estimate disease-related and HIV-related mortality rates [12]. The missing indicator method was used to handle missing covariate data. Sensitivity analysis using inverse probability weighting was additionally performed to assess the potential for bias due to missing covariate data arising from the use of the missing covariate indicator method [13].

Each mortality endpoint was analysed using the Cox proportional hazards model censoring SoC participants at clinic transition. Because clustered models are numerically unstable when there is a very small amount of clustering and tend to underestimate the variance, the data were analysed as non-clustered because the between-facility intraclass correlations for all endpoints were < 1% [14]. To assess departure from the proportional hazards assumption, for each endpoint, a likelihood ratio test between the multivariate-adjusted model and the same model additionally containing a time-dependent interaction term between intervention status and time since enrolment was used.

Effect modification between intervention status and each of these covariates was evaluated. This analysis was not conducted for sub-groups with < 20 deaths because

the statistical power was unlikely to be sufficient to detect the effect modification. Heterogeneity tests were performed through likelihood ratio tests. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

MaxART is a stepped-wedge trial, with all clusters being in both the control and intervention groups, and no clusters were lost to follow-up. Between 1 September 2014 and 31 August 2017, there were 3485 potential participants in the 14 participating clinics. After further screening of study eligibility, 80 participants (2%) were excluded from the trial due to *a priori* exclusion criteria, leaving a total of 3405 study participants who were consented and enrolled in the trial (Fig. 1). Of these, 2034 (60%) were enrolled during the SoC phase of their clinics, and 1371 (40%) were enrolled during the intervention phase (Fig. 2). In all, 1225 participants were grouped as 'SoC-ineligible' participants, while 2180 participants were 'SoC-eligible'. There were 493 study participants lost to follow-up, of whom 327 were in SoC and 166 were in Treat All. After censoring SoC participants at clinic transition, 48 (15%) SoC participants were censored, leaving 279 participants in the SoC group lost to follow-up. The median follow-up time among all participants was 292 days.

Figure 2 shows the distribution of enrolment by clinic and step. In step 1, all pre-ART participants were enrolled into the trial. However, in later steps, only participants, including returning pre-ART participants, who were newly diagnosed or had previously disengaged from pre-ART were enrolled. As all sites started in the SoC stage, more participants were enrolled during the SoC phase than during Treat All.

Table 1 provides basic characteristics of MaxART study participants at study enrolment. Demographic characteristics did not significantly differ over the study period except for sex, where 34% and 44% of the participants enrolled under SoC and Treat All were male, respectively. However, clinical characteristics did change over time: 44% of participants in SoC, compared with 56% in Treat All, enrolled with baseline CD4 count < 350 cells/μL. Additionally, 59% of participants in SoC enrolled within a year of HIV diagnosis, whereas 79% of participants in Treat All did so. Even though there was a higher proportion of Treat All participants enrolled within a year of HIV diagnosis compared with SoC participants, there was also a higher proportion of Treat All participants with a

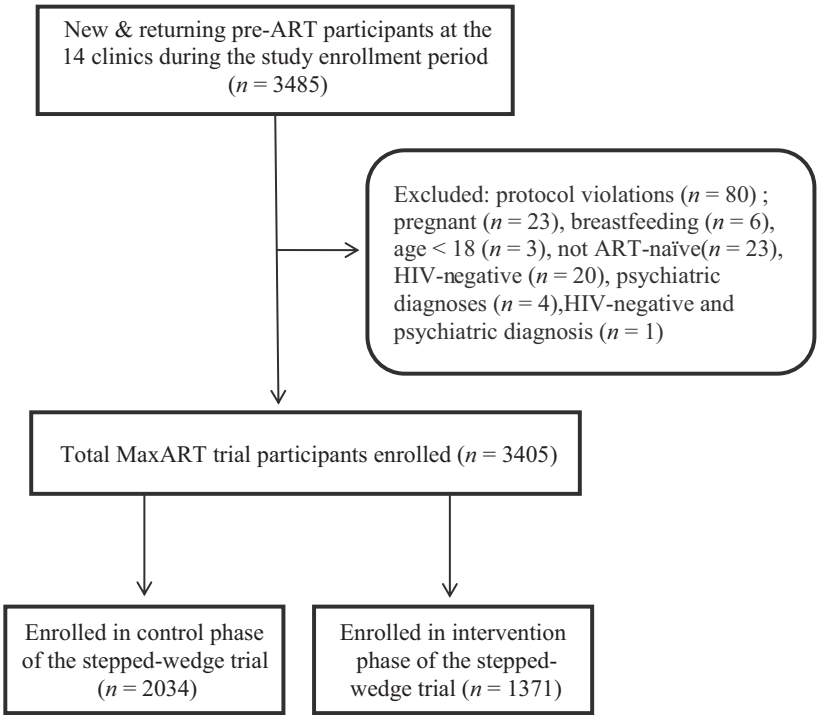

Fig. 1 Flow diagram of participants enrolled during the control [national standard of care (SoC)] and intervention (Treat All) phases in MaxART.

		Steps (4 month periods)									
Group	**Clinic**	**1**	**2**	**3**	**4‡**	**5**	**6**	**7§**	**8**	**9**	**Total**
1	**1**	67	58	34	14	20	20	13	15	4	**245**
	2	81	27	23	10	8	18	13	13	7	**200**
2	**3**	27	13	17	6	14	12	13	12	8	**122**
	4	37	12	56	14	19	16	8	5	5	**172**
3	**5**	27	13	10	13	14	9	15	5	1	**107**
	6	50	27	33	34	25	23	17	11	6	**226**
4	**7**	20	5	6	10	4	8	4	5	14	**76**
	8	163	87	83	116	109	78	43	57	62	**798**
5	**9**	93	45	30	17	22	18	6	19	22	**272**
	10	64	28	29	29	18	35	15	16	7	**241**
6	**11**	59	23	30	34	30	27	24	21	10	**258**
	12	54	16	34	20	9	26	23	16	13	**211**
7	**13**	16	18	18	22	12	7	17	6	4	**120**
	14	112	63	36	27	34	33	24	10	18	**357**
	Total	**870**	**435**	**439**	**366**	**338**	**330**	**235**	**211**	**181**	**3405**

Fig. 2 Clinic-based step-wedged trial diagram showing number of enrolled participants by clinic pair and steps. Calendar times for each step are as follows: 1, September 2014–December 2014; 2, January 2015–April 2015; 3, May 2015–August 2015; 4, September 2015–December 2015; 5, January 2016–April 2016; 6, May 2016–August 2016; 7, September 2016; 8, 9, October 2016–August 2017. ‡, Eswatini antiretroviral therapy (ART) guidelines for ART initiation changed from a CD4 count threshold of ≤ 350 cells/μL to ≤ 500 cells/μL on December 2015. §, Eswatini's national ART guidelines for ART initiation changed from a CD4 count threshold of ≤ 500 cells/μL to a universal test and treat approach on October 2016.

baseline CD4 count < 350 cells/μL. This may have been a result of randomization, or could have been due to Treat All being implemented in later calendar times, resulting in Treat All participants having waited longer to be diagnosed after being infected.

Table 2 provides step-time-adjusted mortality rates per person-year and HRs for all-cause, disease-related and HIV-related mortality. There were 36/2034 (1.8%) all-cause deaths in the SoC group over a median follow-up time of 268.50 years over 1665.65 person-years, and 49/1371 (3.6%) deaths in the Treat All group over a median follow-up time of 322.00 years over 1364.58 person-years. There were 34 and 47 diseases-related deaths, and 32 and 44 HIV-related deaths, in the SoC and Treat All groups, respectively. The Treat All strategy had no impact on all-cause mortality (HR = 1.12, 95% CI: 0.58–2.18, $P = 0.73$), disease-related mortality (HR = 1.12, 95% CI: 0.57–2.21, $P = 0.74$), or HIV-related mortality (HR = 0.93, 95% CI: 0.46–1.87, $P = 0.83$). There were no material differences between the multivariable-adjusted HRs which used the missing covariate indicator method and those obtained from the sensitivity analysis (missing covariate indicator method – all-cause mortality, HR = 1.12, 95% CI: 0.58–2.18, $P = 0.73$; disease-related mortality, HR = 1.04, 95% CI: 0.52–2.11, $P = 0.90$; HIV-related mortality, HR = 0.93, 95% CI: 0.46–1.87, $P = 0.83$; sensitivity analysis – all-cause mortality, HR = 1.15, 95% CI: 0.43–3.02, $P = 0.78$; disease-related mortality, HR = 0.85, 95% CI: 0.30–2.37, $P = 0.75$; HIV-related mortality, HR = 1.09, 95% CI: 0.39–3.09, $P = 0.87$).

Survival curves were compared between the SoC and Treat All groups. At 1 year, in SoC and Treat All, respectively, the all-cause mortality rates were 1.42% (95% CI: 0.66–2.17) and 1.60% (95% CI: 0.78–2.40) (Fig. 3), the disease-related mortality rates were 1.18% (95% CI: 0.51–1.84) and 1.36% (95% CI: 0.62–2.10) (Fig. 4), and the HIV-related mortality rates were 1.02% (95% CI: 0.40–1.64) and 1.00% (95% CI: 0.40–1.59) (Fig. 5).

In the SoC-ineligible group, the Treat All strategy had no impact on all-cause mortality (HR = 1.65, 95% CI:

Table 1 Basic characteristics of all antiretroviral therapy (ART)-naïve participants at the time of study enrolment

	Standard of care (n = 2034)	Treat All (n = 1371)	All ART-naïve (n = 3405)
Demographic characteristics			
Age at trial enrolment (year) median (q1, q3)	33 (28,42)	33 (27,40)	33 (27,41)
Age group (years) [n (%)]			
18 to < 20	40 (2%)	34 (2%)	74 (2%)
20 to < 30	679 (33%)	472 (34%)	1151 (34%)
30 to < 40	722 (35%)	500 (36%)	1222 (36%)
40 to < 50	354 (17%)	230 (17%)	584 (17%)
50 to < 60	156 (8%)	97 (7%)	253 (7%)
60+	83 (4%)	38 (3%)	121 (4%)
Sex n (%)			
Male	695 (34%)	603 (44%)	1298 (38%)
Female	1339 (66%)	768 (56%)	2107 (62%)
Marital status [n (%)]			
Married	1045 (52%)	634 (48%)	1679 (51%)
Divorced/widowed	127 (6%)	78 (6%)	205 (6%)
Single	825 (41%)	614 (46%)	1439 (43%)
Marital status missing [n (%)]	37 (2%)	45 (3%)	82 (2%)
Education, n (%)			
Illiterate/primary	589 (40%)	384 (38%)	973 (39%)
Secondary	438 (30%)	362 (36%)	800 (32%)
High school	401 (27%)	218 (22%)	619 (25%)
Tertiary	48 (3%)	37 (4%)	85 (3%)
Education missing [n (%)]	558 (27%)	370 (27%)	928 (27%)
Clinical characteristic[†]			
BMI (kg/m^2) [n (%)]			
< 18.5	82 (4%)	81 (6%)	163 (5%)
18.5 to < 25	971 (49%)	762 (57%)	1733 (52%)
25 to < 30	529 (27%)	281 (21%)	810 (25%)
≥ 30	387 (20%)	212 (16%)	599 (18%)
BMI missing [n (%)]	65 (3%)	35 (3%)	100 (3%)
CD4 count (cells/μL) [n (%)]			
< 350	804 (44%)	632 (56%)	1436 (49%)
350–500	441 (24%)	224 (20%)	665 (22%)
> 500	591 (32%)	266 (24%)	857 (29%)
CD4 missing n (%)	198 (10%)	249 (18%)	447 (13%)
WHO stage [n (%)]			
1	1074 (63%)	800 (63%)	1874 (63%)
2	357 (21%)	320 (25%)	677 (23%)
3 or 4	264 (16%)	146 (12%)	410 (14%)
WHO stage missing [n (%)]	339 (17%)	105 (8%)	444 (13%)
Screened for tuberculosis (TB) symptoms [n (%)]			
Positive	190 (10%)	100 (8%)	290 (9%)
Missing screening for TB symptoms [n (%)]	82 (4%)	66 (5%)	148 (4%)
Viral load (copies/mL) [n (%)]			
< 1000	229 (12%)	120 (10%)	349 (11%)
1000 to < 50 000	781 (41%)	479 (40%)	1260 (41%)
50 000 to < 100 000	213 (11%)	150 (13%)	363 (12%)
≥ 100 000	661 (35%)	438 (37%)	1099 (36%)
Viral load missing [n (%)]	150 (7%)	184 (13%)	334 (10%)
Time between testing HIV-positive to trial enrolment (years) [n (%)]			
≤ 1	1189 (59%)	1076 (79%)	2265 (67%)
1 to ≤ 3	421 (21%)	134 (10%)	555 (16%)
> 3	413 (20%)	144 (11%)	557 (16%)
Access to HIV treatment supporter [n (%)]			
Yes	1980 (97%)	1339 (98%)	3319 (97%)
Clinic characteristics			
Level of clinic [n (%)]			
Hospital	449 (22%)	349 (25%)	798 (23%)
Clinic with maternity ward	317 (16%)	181 (13%)	498 (15%)
Clinic without maternity ward	1268 (62%)	841 (61%)	2109 (62%)
Clinic volume by ART visits at baseline[‡] [n (%)]			
< Median (400 visits)	915 (45%)	385 (28%)	1300 (38%)
≥ Median (400 visits)	1119 (55%)	986 (72%)	2105 (62%)

[†]Values within 90 days of enrolment and before ART initiation.
[‡]ART participant visits received during the first quarter into trial. Median number of visits during this period is 400.

0.29–9.42, P = 0.57), disease-related mortality (HR = 4.40, 95% CI: 0.55–35.47, P = 0.16), and HIV-related mortality (HR = 1.77, 95% CI: 0.18–17.57, P = 0.63). In the SoC-eligible group, the Treat All strategy also did not influence all-cause mortality (HR = 0.85, 95% CI: 0.44–1.64, P = 0.62), disease-related mortality (HR = 1.15, 95% CI: 0.62–2.13, P = 0.65) and HIV-related mortality (HR = 1.17, 95% CI: 0.62–2.20, P = 0.62). As expected, the estimated HRs for the SoC-eligible group were closer to 1, compared with those from the main analyses and the SoC-ineligible group because everyone was able to receive ART at study enrolment in the SoC-eligible group, resulting in little distinction between SoC and Treat All participants. No significant effect modification of the intervention effect by any covariate was observed for any endpoint (Tables S1–S3). It is likely that these tests were underpowered because the trial was not designed to assess effect modification.

Discussion

Since 2002, WHO guidelines on ART access have been evolving in accordance with growing evidence of the benefit of earlier initiation of ART, including reduced mortality, morbidity, and HIV transmission. In 2016, the WHO strongly recommended that ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and CD4 cell count.

The MaxART study is the only trial to study retention and viral suppression as primary endpoints to assess the effectiveness of early ART access. The trial found strong causal evidence that the Treat All strategy increased viral suppression and retention, and demonstrated that this strategy can be successfully implemented in a public

Table 2 The effect of the Treat All strategy on all-cause mortality, disease-related mortality, and HIV-related mortality, censoring national standard of care (SoC) participants at clinic transition

	Control			Intervention			Intent to treat		Multivariable-adjusted	
Population	Number of deaths	Follow-up time (person-years)	Mortality rate per person-year	Number of deaths	Follow-up time (person-years)	Mortality rate per person-year	HR[†] (95%CI)	*P*-value	HR (95%CI)	*P*-value
All-cause mortality										
All	36	1665.65	0.022	49	1364.58	0.036	1.20 (0.65–2.20)	0.57	1.12 (0.58–2.18)[‡]	0.73
SoC-ineligible	4	851.70	0.005	5	399.63	0.013	1.83 (0.35–9.61)	0.48	1.65 (0.29–9.42)[§]	0.57
SoC-eligible	30	661.89	0.045	36	839.66	0.043	1.10 (0.60–2.02)	0.76	0.85 (0.44–1.64)[¶]	0.62
Disease-related mortality										
All	34	1665.65	0.020	47	1364.58	0.034	1.27 (0.68–2.37)	0.46	1.12 (0.57–2.21)[‡]	0.74
SoC-ineligible	2	851.70	0.002	4	399.63	0.010	4.28 (0.56–32.94)	0.16	4.40 (0.55–35.47)[‡]	0.16
SoC-eligible	30	661.89	0.045	35	839.66	0.042	1.08 (0.59–2.00)	0.80	1.15 (0.62–2.13)[‡]	0.65
HIV-related mortality										
All	32	1665.65	0.019	44	1364.58	0.032	1.10 (0.57–2.10)	0.78	0.93 (0.46–1.87)[‡]	0.83
SoC-ineligible	2	851.70	0.002	3	399.63	0.008	1.78 (0.18–17.88)	0.63	1.77 (0.18–17.57)[‡]	0.63
SoC-eligible	28	661.89	0.042	34	839.66	0.040	1.11 (0.59–2.07)	0.75	1.17 (0.62–2.20)[‡]	0.62

[†]Adjusted for step-time only, averaged over step-time at study enrolment.

[‡]Adjusted for step-time, age (18 to < 20, 20 to < 30, 30 to < 40, 40 to < 50, 50 to < 60, 60 + years), sex, marital status (married, divorced/widowed, single), education (illiterate/primary, secondary, high school, tertiary), CD4 (< 350, 350–500, > 500 cells/μL), WHO stage (stage 1, stage 2, stage 3 or 4), body mass index (BMI) (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), screened for tuberculosis (TB) symptoms (yes/no), viral load (< 5000, 5000–30 000, > 30 000 HIV-1 RNA copies/mL), access to HIV treatment supporter (yes/no), level of clinic (hospital, clinic with maternity, clinic without maternity), time from testing HIV-positive to enrolment (≤1, 1 to ≤ 3,>3 years), clinic volume (low, < median; high, ≥ median). All adjusted variables were derived at study enrolment. Missing data were treated as a separate group for each of the covariates in the models.

[§]Adjusted for step-time, sex, CD4 counts at study enrolment (< 350, 350–500, > 500 cells/μL), BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL). Due to the small number of events, only limited covariates can be fit. Missing data were treated as a separate group for each of the covariates in the models.

[¶]Adjusted for step-time, age at study enrolment (18–24, 25–39, ≥ 40 years), sex, marital status (married, divorced/widowed, single), WHO stage at 180 days post-ART initiation (stage 1, stage 2, stage 3 or 4), BMI at study enrolment (< 25, ≥ 25 kg/m^2), TB screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL), level of facility (hospital, clinic with maternity, clinic without maternity), study enrolment date [2 knots stepwise restricted cubic splines (SRCS)]. Missing data were treated as a separate group for each of the covariates in the models.

[††]Adjusted for step-time, sex, BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL). Due to the small number of events, only limited covariates can be fitted. Missing data were treated as a separate group for each of the covariates in the models.

[‡‡]Adjusted for step-time, age at study enrolment (18 to < 20, 20 to < 30, 30 to < 40, 40 to < 50, 50 to < 60, 60+ years), sex, marital status (married, divorced/widowed, single), WHO stage at 180 days post-ART initiation (stage 1, stage 2, stage 3 or 4), BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), TB screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL), level of facility (hospital, clinic with maternity, clinic without maternity). Missing data were treated as a separate group for each of the covariates in the models.

[§§]Adjusted for step-time, sex, BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2). Due to the small number of events, only limited covariates can be fitted. Missing data were treated as a separate group for each of the covariates in the models.

[¶¶]Adjusted for step-time, age at study enrolment (18 to < 20, 20 to < 30, 30 to < 40, 40 to < 50, 50 to < 60, 60+ years), sex, marital status (married, divorced/widowed, single), WHO stage at 180 days post-ART initiation (stage 1, stage 2, stage 3 or 4), BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), TB screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL), level of facility (hospital, clinic with maternity, clinic without maternity). Missing data were treated as a separate group for each of the covariates in the models.

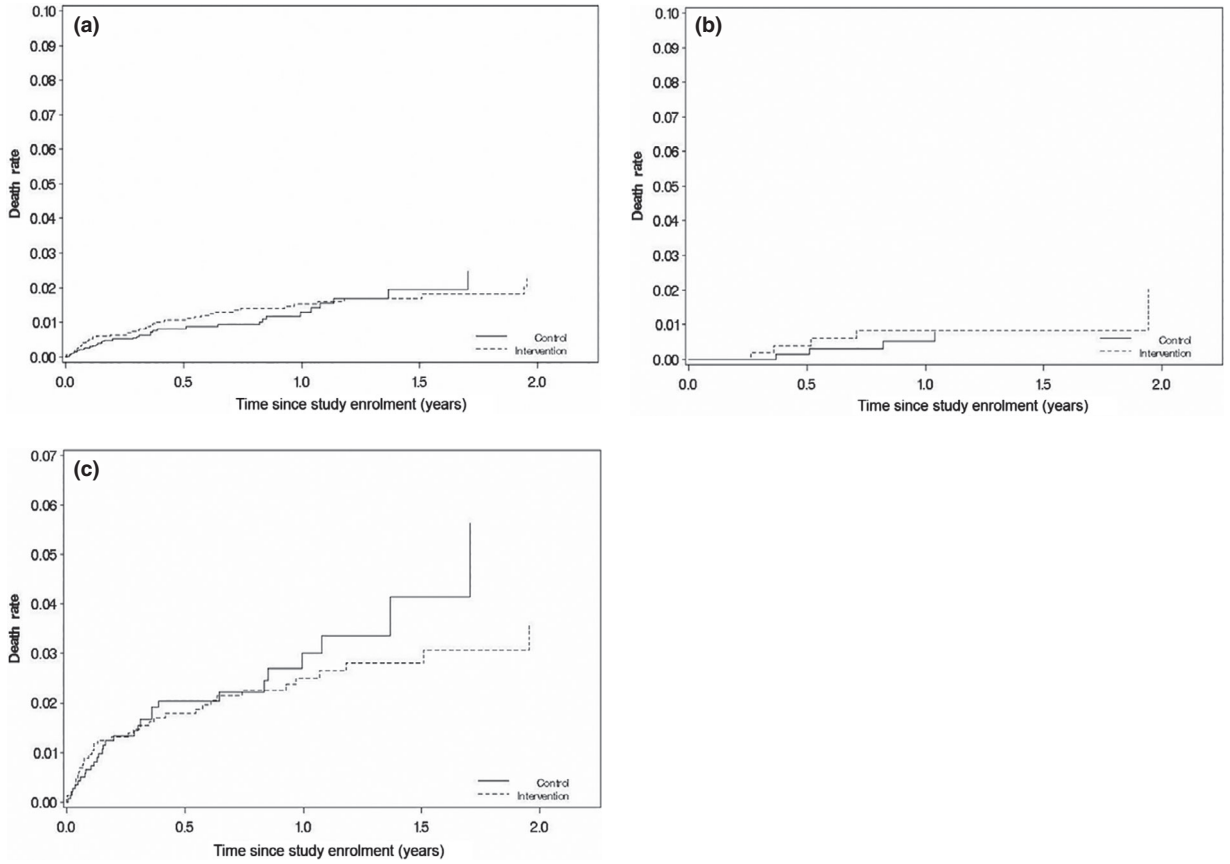

Fig. 3 Kaplan–Meier curves for all-cause mortality by treatment group. (a) All antiretroviral therapy (ART)-naïve participants; (b) national standard of care (SoC)-ineligible participants; (c) SoC-eligible participants. Mortality rates are evaluated by censoring SoC participants at clinic transition. Graphs reflect the cumulative incidence averaged over covariates. Time reflects years since study enrolment. (a) Adjusted for step-time, age at study enrolment (18 to < 20, 20 to < 30, 30 to < 40, 40 to < 50, 50 to < 60, 60+ years), sex, marital status (married, divorced/widowed, single), education (illiterate/primary, secondary, high school, tertiary), CD4 counts at study enrolment (< 350, 350–500, > 500 cells/μL), WHO stage at study enrolment (stage 1, stage 2, stage 3 or 4), body mass index (BMI) at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), tuberculosis (TB) screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 HIV-1 RNA copies/mL), treatment support (yes/no), level of facility (hospital, clinic with maternity, clinic without maternity), time from testing HIV-positive to enrolment (≤ 1, 1 to ≤ 3, > 3 years), facility volume at study enrolment (low, < median; high, ≥ median). Missing data were treated as a separate group for each of the covariates in the models. (b) Adjusted for step-time, sex, CD4 counts at study enrolment (< 350, 350–500, > 500 cells/μL), BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL). Due to the small number of events, only limited covariates can be fitted. Missing data were treated as a separate group for each of the covariates in the models. (c) Adjusted for step-time, age at study enrolment (18–24, 25–39, ≥ 40 years), sex, marital status (married, divorced/widowed, single), WHO stage at 180 days post-ART initiation (stage 1, stage 2, stage 3 or 4), BMI at study enrolment (< 25, ≥ 25 kg/m^2), TB screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL), level of facility (hospital, clinic with maternity, clinic without maternity), study enrolment date [2 knots stepwise restricted cubic splines (SRCS)]. Missing data were treated as a separate group for each of the covariates in the models.

sector health system, in particular, in sub-Saharan African countries with a high prevalence of HIV [15]. These primary findings are consistent with those obtained in the CASCADE trial implemented in Lesotho, which compared same-day home-based ART initiation with usual care, and found a significant increase in linkage to care at 3 months and in viral suppression at 12 months [16].

Although the primary analysis strongly supported the scaling-up of the Treat All strategy, this secondary mortality analysis is inconclusive about the impact of the strategy on longevity among PLHIV. The mortality rates under the Treat All strategy were not significantly lower compared with SoC, as had been hypothesized, whether for all ART-naïve participants, SoC-eligible participants,

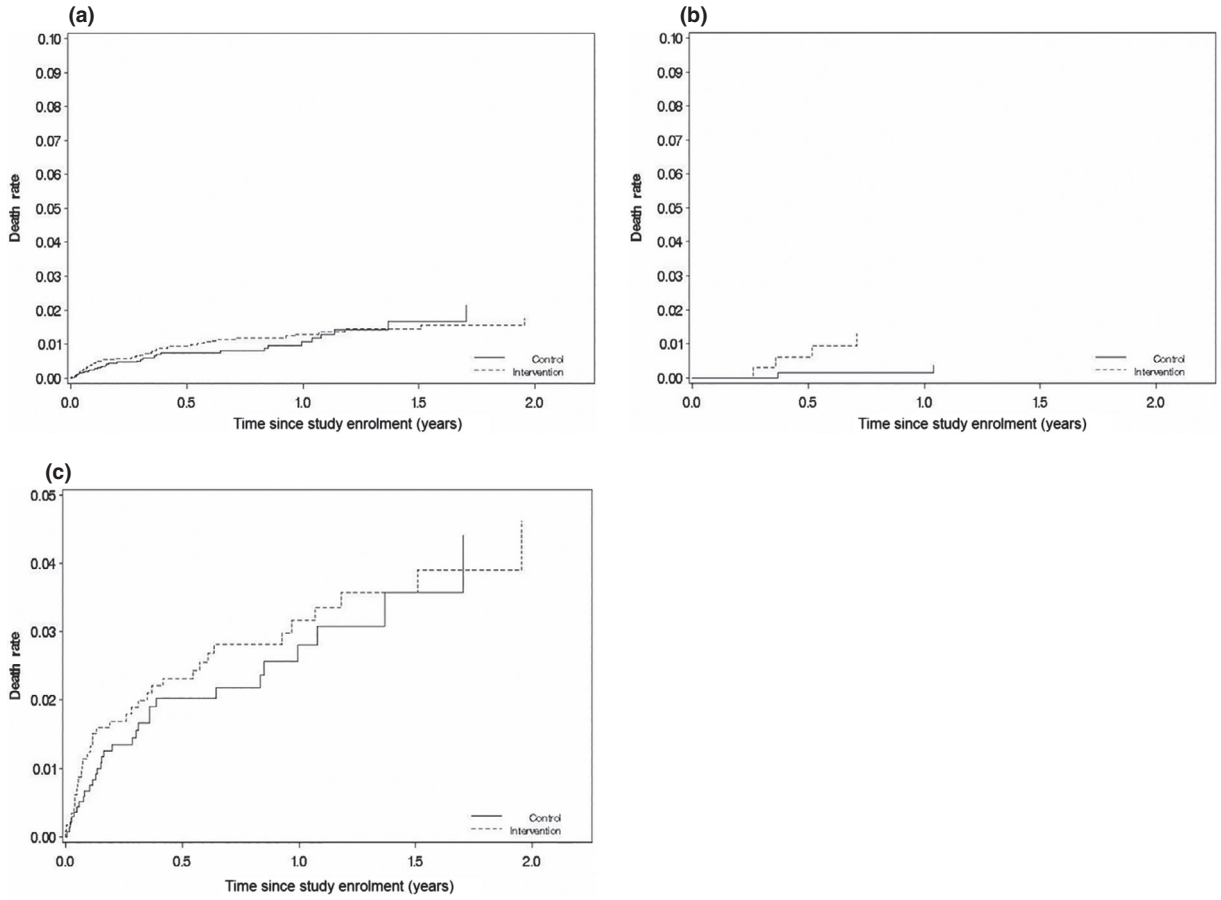

Fig. 4 Kaplan-Meier curves for disease-related mortality by treatment group. (a) All antiretroviral therapy (ART)-naïve participants; (b) national standard of care (SoC)-ineligible participants; (c) SoC-eligible participants. Mortality rates are evaluated by censoring SoC participants at clinic transition. Graphs reflect the cumulative incidence averaged over covariates under a competing-risks approach. Time reflects years since study enrolment. (a) Adjusted for step-time, age at study enrolment (18 to < 20, 20 to < 30, 30 to < 40, 40 to < 50, 50 to < 60, 60+ years), sex, marital status (married, divorced/widowed, single), education (illiterate/primary, secondary, high school, tertiary), CD4 counts at study enrolment (< 350, 350–500, > 500 cells/μL), WHO stage at study enrolment (stage 1, stage 2, stage 3 or 4), body mass index (BMI) at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), tuberculosis (TB) screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 HIV-1 RNA copies/mL), treatment support (yes/no), level of facility (hospital, clinic with maternity, clinic without maternity), time from testing HIV-positive to enrolment (≤ 1, 1 to ≤ 3, > 3 years), facility volume at study enrolment (low, < median; high, ≥ median). Missing data were treated as a separate group for each of the covariates in the models. (b) Adjusted for step-time, sex, BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL). Due to the small number of events, only limited covariates can be fit. Missing data were treated as a separate group for each of the covariates in the models. (c) Adjusted for step-time, age at study enrolment (18 to < 20, 20 to < 30, 30 to < 40, 40 to < 50, 50 to < 60, 60+ years), sex, marital status (married, divorced/widowed, single), WHO stage at 180 days post-ART initiation (stage 1, stage 2, stage 3 or 4), BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), TB screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL), level of facility (hospital, clinic with maternity, clinic without maternity). Missing data were treated as a separate group for each of the covariates in the models.

or SoC-ineligible participants. Larger studies with longer durations will be needed to ascertain whether this observation is spurious or indicative of a causal effect.

There were several limitations to this study. As the Eswatini national ART guidelines continued to evolve during the trial, the SoC offered in the trial was consequently required to provide the level of access to ART specified in the national guidelines. These changes resulted in SoC treatment increasingly resembling the Treat All strategy over time, and thereby reducing the statistical power to detect any impact of the intervention on mortality rates. Also, while in later steps of the trial, patients who had previously been disengaged from pre-ART were enrolled, these participants could not be

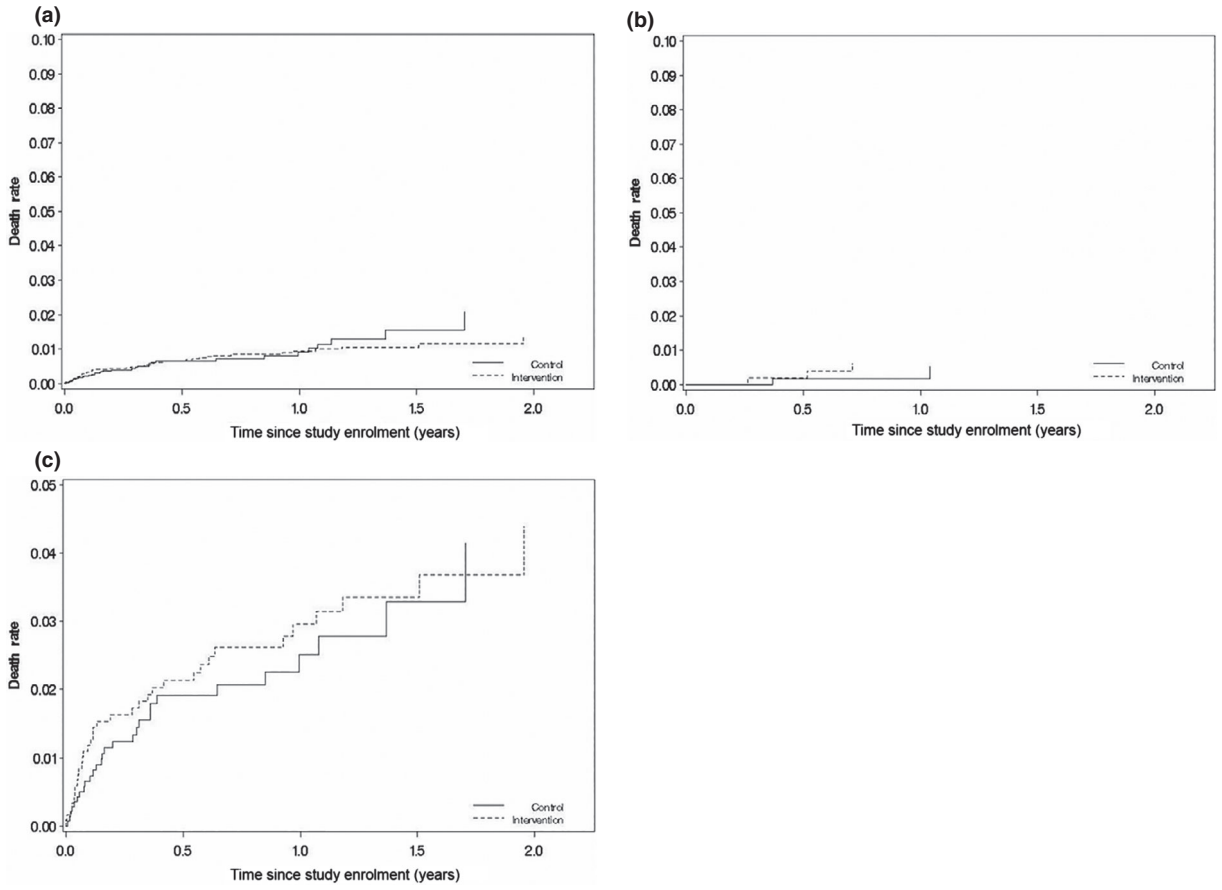

Fig. 5 Kaplan–Meier curves for HIV-related mortality by treatment group. (a) All antiretroviral therapy (ART)-naïve participants; (b) national standard of care (SoC)-ineligible participants; (c) SoC-eligible participants. Mortality rates are evaluated by censoring SoC participants at clinic transition. Graphs reflect the cumulative incidence averaged over covariates under a competing-risks approach. Time reflects years since study enrolment. (a) Adjusted for step-time, age at study enrolment (18 to < 20, 20 to < 30, 30 to < 40, 40 to < 50, 50 to < 60, 60+ years), sex, marital status (married, divorced/widowed, single), education (illiterate/primary, secondary, high school, tertiary), CD4 counts at study enrolment (< 350, 350–500, > 500 cells/μL), WHO stage at study enrolment (stage 1, stage 2, stage 3 or 4), body mass index (BMI) at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), tuberculosis (TB) screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 HIV-1 RNA copies/mL), treatment support (yes/no), level of facility (hospital, clinic with maternity, clinic without maternity), time from testing HIV-positive to enrolment (≤ 1, 1 to ≤ 3, > 3 years), facility volume at study enrolment (low, < median; high, ≥ median). Missing data were treated as a separate group for each of the covariates in the models. (b) Adjusted for step-time, sex, BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2). Due to the small number of events, only limited covariates can be fit. Missing data were treated as a separate group for each of the covariates in the models. (c) Adjusted for step-time, age at study enrolment (18 to < 20, 20 to < 30, 30 to < 40, 40 to < 50, 50 to < 60, 60+ years), sex, marital status (married, divorced/widowed, single), WHO stage at 180 days post-ART initiation (stage 1, stage 2, stage 3 or 4), BMI at study enrolment (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), TB screening positive at study enrolment (yes/no), viral load at study enrolment (< 5000, 5000–30 000, > 30 000 copies/mL), level of facility (hospital, clinic with maternity, clinic without maternity). Missing data were treated as a separate group for each of the covariates in the models.

identified as such, although it is possible that they may have had different outcomes from the rest of the study population.

With 36 deaths among 2034 in the SoC group (1.8%) and 49 deaths among 1371 in the intervention group (3.6%), there was limited statistical power to detect differences between the two groups and even less so for modification of intervention effects by baseline covariates. In comparison with the same study population from the primary MaxART analysis, 1311 participants in the SoC group (64.5%) and 855 in the Treat All group (62.4%) experienced the combined endpoint of retention and viral suppression, allowing for substantial power. The median follow-up time among all participants was also just 292 days, which may not have been a long enough follow-up period to observe mortality patterns. Although a

study conducted in China only followed patients for a maximum of 12 months, and the mortality rates per 100 person-years between the immediate and delayed ART initiation groups (1.04 and 2.25, respectively) were not drastically different, the study enrolled nearly 35,000 patients, allowing small differences to reach statistical significance [8]. While another study done in Lesotho also found that early ART initiation significantly reduced mortality, 'late initiation' was defined as initiating ART at CD4 count < 200 cells/μL [17]. Those with such low baseline CD4 count would probably have had a much greater risk of death regardless of ART treatment status. The START trial has also found significant benefits in immediate ART initiation at a CD4 count> 500 cells/μL compared with deferring until a CD4 count < 350 cell/μL in terms of a primary composite endpoint of any serious AIDS-related or non-AIDS-related event, including mortality [18]. However, it is difficult to assess whether mortality significantly decreased with early ART initiation from a composite endpoint.

Among all of this study's limitations, perhaps the most important is the insufficient follow-up time. A study that assessed mortality by CD4 count at ART initiation followed patients for up to 15 years to assess long-term survival, and found little evidence that baseline CD4 count was prognostic for mortality after 5 years of ART, as the mortality of patients who started ART with low baseline CD4 count (< 50 cells/μL) converged to that of patients with intermediate (200–349 cells/μL) to high (≥ 500 cells/μL) baseline CD4 count [19]. This suggests that differentiation of mortality rates between SoC and Treat All groups may require at least 5 years of follow-up.

An explanation of such a finding might be due to an initial adverse effect that crosses over to a longer-term benefit among the survivors. Some patients starting ART experience clinical worsening by immune reconstitution inflammatory syndrome, which in HIV is strongly associated with pre-existing clinical or subclinical opportunistic infections or diseases and severe immunodeficiency manifested by low CD4 counts [20]. Some patients on ART also fail to experience immune reconstitution despite viral suppression, putting them at higher risk for clinical events, including death. It is estimated that 50% of ART-treated patients may fail to reconstitute their CD4 counts to levels above 500 cells/μL, and up to 16% may not achieve a CD4 count > 200 cells/μl, even with long-term therapy. Therefore, longer follow-up of these participants will be necessary to establish long-term consequences of the Treat All strategy.

In summary, while the primary study found strong causal evidence of beneficial effects of the Treat All strategy on retention and viral suppression, supporting the benefit of scaling-up in Eswatini and other health systems with similar HIV epidemics, effects on mortality did not serve as an indicator of its success. However, as a major purpose of the Treat All strategy is to decrease infectiousness so that there are no new cases, it is also an important finding that there is no evidence of harm. Longer follow-up of these participants will be necessary to establish long-term consequences, particularly mortality, of the Treat All protocol.

Acknowledgements

Financial disclosure: This trial was funded by the Dutch Postcode Lottery in the Netherlands, and the Embassy of the Kingdom of the Netherlands in Mozambique, and supported by Mylan Laboratories Limited, which provided the antiretroviral drugs; Médecins Sans Frontières (with funding from UNITAID) for viral load testing; and British Columbia Centre for Excellence in HIV/AIDS for genotype testing. The MaxART Consortium thanks the many health workers and community members who actively participated in the MaxART study implementation. TB was supported by the Alexander von Humboldt Foundation through the Alexander von Humboldt Professor award, funded by the Federal Ministry of Education and Research; the Wellcome Trust; the European Commission; the Clinton Health Access Initiative; and NICHD of NIH (R01-HD084233), NIA of NIH (P01-AG041710), NIAID of NIH (R01-AI124389 and R01-AI112339) as well as FIC of NIH (D43-TW009775). DS was supported, in part, by NIH R01AI112339.

Conflict of interest: There are no conflicts of interest to declare.

Author contributions

FW, TB, DS, and VO designed the trial. SK, SM, MP, EM, AH, and CL implemented the trial. AC searched the literature and wrote the manuscript. DS and AC conducted the statistical analysis. All authors contributed to the interpretation and presentation of the findings, and approved the final version of the manuscript for submission.

References

1 UNAIDS. *Global HIV & AIDS statistics - 2019 fact sheet.* Geneva: UNAIDS, 2019.
2 Avert. *Global HIV and AIDS statistics.* Brighton: Avert, 2018.
3 Wang H, Wolock TM, Carter A, *et al.* Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015. *The lancet HIV* 2016; 3: e361–e387.

4 Justman J, Reed JB, Bicego G, *et al.* Swaziland HIV Incidence Measurement Survey (SHIMS): a prospective national cohort study. *The lancet HIV* 2017; **4**: e83–e92.
5 UNAIDS. *Eswatini.* Geneva: UNAIDS, 2018.
6 Odafe S, Idoko O, Badru T, *et al.* Patients' demographic and clinical characteristics and level of care associated with lost to follow-up and mortality in adult patients on first-line ART in Nigerian hospitals. *Journal of the International AIDS Society* 2012; **15**: 17424.
7 Farhan O, Achappa B, Bhaskaran U, *et al.* In-patient mortality among PLHIV: A 7-year hospital-based retrospective study in coastal South India. *Journal of the International Association of Providers of AIDS Care (JIAPAC)* 2017; **16**: 494–498.
8 Zhao Y, Wu Z, McGoogan JM, *et al.* Immediate antiretroviral therapy decreases mortality among patients with high CD4 counts in China: a nationwide, retrospective cohort study. *Clin Infect Dis* 2017; **66**: 727–734.
9 World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach.* Geneva: World Health Organization, 2016.
10 Walsh FJ, Barnighausen T, Delva W, *et al.* Impact of early initiation versus national standard of care of antiretroviral therapy in Swaziland's public sector health system: study protocol for a stepped-wedge randomized trial. *Trials* 2017; **18**: 383.
11 Perriat D, Balzer L, Hayes R, *et al.* Comparative assessment of five trials of universal HIV testing and treatment in sub-Saharan Africa. *Journal of the International AIDS Society* 2018; **21**: e25048.
12 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999; **94**: 496–509.
13 Little RJ, D'Agostino R, Cohen ML, *et al.* The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; **367**: 1355–1360.
14 Cook A. Small-sample robust variance correction for generalized estimating equations for use in cluster randomized clinical trials. *NIH Collaboratory*, 2015. https://www.nihcollaboratory.org/Products/Variance-correction-for-GEE_V1.2015
15 Khan S, Spiegelman D, Walsh F, *et al.* Universal test and treat (UTT) versus standard of care for access to antiretroviral therapy in HIV clients: the MaxART stepped-wedge randomized controlled health systems trial in Swaziland. *Journal of the International AIDS Society* 2018; **1** (21): 161–162.
16 Labhardt ND, Ringera I, Lejone TI, *et al.* Effect of offering same-day ART vs usual health facility referral during home-based HIV testing on linkage to care and viral suppression among adults with HIV in Lesotho: the CASCADE randomized clinical trial. *JAMA* 2018; **319**: 1103–1112.
17 Ford N, Kranzer K, Hilderbrand K, *et al.* Early initiation of antiretroviral therapy and associated reduction in mortality, morbidity and defaulting in a nurse-managed, community cohort in Lesotho. *Aids* 2010; **24**: 2645–2650.
18 Insight Start Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373**: 795–807.
19 May MT, Vehreschild JJ, Trickey A, *et al.* Mortality according to CD4 count at start of combination antiretroviral therapy among HIV-infected patients followed for up to 15 years after start of treatment: collaborative cohort study. *Clin Infect Dis* 2016; **62**: 1571–1577.
20 Wilson EM, Sereti I. Immune restoration after antiretroviral therapy: the pitfalls of hasty or incomplete repairs. *Immunol Rev* 2013; **254**: 343–354.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 (a) Effect of the intervention on all-cause mortality (censoring SoC participants at clinic transition) among SoC-eligible participants, by pre-specified subgroups. (b) Effect of the intervention on all-cause mortality (censoring SoC participants at clinic transition) among all ART-naïve participants, by pre-specified subgroups.

Table S2 (a) Effect of the intervention on disease-related mortality (censoring SOC participants at clinic transition) among SoC-eligible participants, by pre-specified subgroups. (b) Effect of the intervention on disease-related mortality (censoring SoC participants at clinic transition) among all ART-naïve participants, by pre-specified subgroups.

Table S3 (a) Effect of the intervention on HIV-related mortality (censoring SoC participants at clinic transition) among SoC-eligible participants, by pre-specified subgroups. (b) Effect of the intervention on HIV-related mortality (censoring SoC participants at clinic transition) among all ART-naïve participants, by pre-specified subgroups.