Effects of long-term antiretroviral therapy in reproductive-age women in sub-Saharan Africa (the PEPFAR PROMOTE study): a multi-country observational cohort study

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Summary

Background We report the long-term impact of ART in women of reproductive age (15–49 years) in Africa who have been using ART for up to 10 years. We assess outcomes of retention, adherence, maternal health, fertility intentions, and safety.

Methods This longitudinal, multicountry study (PROMOTE) enrolled women who initiated ART in an earlier perinatal clinical trial, PROMISE. PROMISE occurred from 2011 to 2016 and PROMOTE follow-up started in 2016 and is ongoing. The PROMOTE study was done at eight sites in four countries: Malawi (Blantyre and Lilongwe), South Africa (Durban and Soweto), Uganda (Kampala), and Zimbabwe (Harare, Seke North, and St Mary's). After baseline enrolment, women and their children are followed up every 6 months to collect information on medical history, antiretroviral therapy (ART) use, adherence, and health information, and to do physical examinations and laboratory tests. Obesity was defined as a body-mass index of 30 kg/m² or more. Data analyses were restricted to summaries of the main long-term outcomes (retention, adherence, maternal health, fertility intentions, and safety). We used descriptive and stratified analyses, and estimated rates using person-years of follow-up and computed probabilities based on Kaplan-Meier methods.

Findings PROMOTE enrolled 1987 mothers and 2522 children. The median follow-up time for mothers was 41·8 (IQR 35·8–42·0) months and for children was 35·7 (23·8–42·0) months. Overall retention rates were 96·5% for mothers and 94·3% for children at 12 months, and, at 42 months, were 88·9% for mothers and 85·4% for children. 1115 (89·1%) of 1252 women had an undetectable viral load at 42 months, which varied by site (81·7–93·8%). Reported maternal health improved over time, with the proportion of women with excellent to very good health increasing from 67·5% at baseline to 87·5% at 42 months, the proportion of unwell participants who visited a health centre declining from 14·7% to 2·8%, and the proportion of those admitted to hospital declining from 1·5% to 1·0%. The desire to have more children was consistently high at some sites. The proportion of women with obesity was high in South Africa and increased over time from 40·2% at baseline to 52·8% at 42 months. The overall pregnancy rate was 17·6 (95% CI 16·5–18·7) per 100 women-years, and mortality rates were 2·4 (1·4–3·9) per 1000 person-years for mothers and 3·4 (2·2–5·10) per 1000 person-years for children (0–9 years).

Interpretation The findings from this multicountry study are reassuring. These findings show that African women can consistently use ART for a long period after initiation, and long-term benefits can be maintained. Services to support maternal HIV care, treatment, and reproductive health should be strengthened.

Funding US President's Emergency Plan for AIDS Relief.

Introduction

The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial showed that antiretroviral therapy (ART) can substantially reduce perinatal transmission.[1,2] In the PROMISE randomised trial, pregnant women from 13 African sites and one non-African site were given ART and monitored for approximately 5 years (2011–16). The PROMISE trial compared the relative efficacy and safety of various ART drugs for perinatal HIV prevention among women living with asymptomatic HIV with CD4 counts of more than 350 cells per µL (or the country-specific threshold for treatment; see appendix [p 1] for PROMISE randomisation data and ART drugs used). There are sparse long-term data assessing the safety and effectiveness of ART beyond the first 3–5 years of ART initiation among African women of reproductive age (15–49 years). The difficulties of monitoring large cohorts of women for an extended follow-up period include logistical, cost, and retention challenges. Disruptions due to unanticipated events, such as the current COVID-19 pandemic, can also create additional difficulties to participants and providers.[3–5]

The PEPFAR PROMISE Ongoing Treatment Evaluation (PROMOTE) study succeeded the PROMISE trial and continued follow-up of the women in the PROMISE trial

Research in context

Evidence before this study

There is strong evidence that antiretroviral therapy (ART) for women of reproductive age (ie, aged 15–49 years) living with HIV can reduce perinatal HIV transmission. The multicountry randomised clinical trial, PROMISE, conducted during 2011–16 in 13 African sites and one non-African site showed very low rates of perinatal HIV transmission when pregnant women living with HIV, without advanced disease, received combination antiretroviral drugs. Consistent use of ART also improves maternal health and survival, and restores immunological status. However, there are few reports on the long-term (5 years or more) effects of ART in women of reproductive age who started ART during an earlier pregnancy. The major constraint has been the short duration of follow-up post partum, precluding long-term assessment of adherence (ie, viral suppression) and longitudinal information on women's clinical outcomes and reproductive intentions. Additionally, most studies were single-site studies or had a small sample size, jeopardising wider generalisability. We searched PubMed for reports in English showing the long-term effects of ART published between July 1, 2011, to July 1, 2021. We searched the databases using the terms "ART in African women", "antiretroviral therapy (including ART, HAART, cART)", "multi-country ART and perinatal transmission in Africa", "ART and MTCT", and "long-term effects of antiretroviral therapy in Africa". Despite the diversity of available data, the limitations we indicated, especially the scarcity of multicountry investigations, were noticeable.

Added value of this study

Our study (PROMOTE) enrolled women who were originally recruited as part of the PROMISE multisite trial. PROMOTE started in 2016 (when the PROMISE follow-up period was terminated). PROMOTE is continuing the follow-up of women and their children at eight African sites from four countries (Uganda, Malawi, Zimbabwe, and South Africa). The findings we report here are encouraging and show that African women are willing to be part of a long follow-up period from 2010 to 2021. Losses to follow-up have been small, adherence to ART remains high, and there is clear evidence that these women have benefited from ART use, as reflected in improving health indicators over time, high fertility, and excellent satisfaction with their own reported health. Perinatal transmission of HIV among women who had subsequent pregnancies was very low and, similarly, so was child morbidity and mortality. Additionally, there were no major safety concerns associated with long-term use of antiretroviral drugs. These long-term evaluations were done with a study schedule similar to the standard of care in ART settings in these countries (every 6 months). Two major strengths of this study are the long-term follow-up period and inclusion of women from multiple countries.

Implications of all the available evidence

Long-term, multicountry studies can be done in sub-Saharan Africa. The global initiatives that have supported HIV research and services on the continent during the past decades have provided reasonable infrastructure, expertise, and training opportunities for long-term assessment of novel interventions such as ART and others. Early HIV observational and intervention studies provided evidence of success; however, implementation and long-term assessment of safety and effectiveness of the earlier successes require longer follow-up. The findings of this study are reassuring and support that ART benefits continue beyond the first 5 years. The study also provides an important longitudinal approach that researchers and policy makers should consider when evaluating new regimens, such as dolutegravir and other emerging diseases, including COVID-19 and its potential interventions.

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See **Online** for appendix

with their children for another 5 years from initiation of ART, from 2016 to 2021.[6] In this analysis, we present summary outcome measures for women and children who enrolled in PROMOTE in 2016 and followed up on them until Jan 27, 2021. The overarching objective of this analysis was to present long-term multicountry outcome data in one source on women who have been in follow-up for up to 10 years. More in-depth specific outcomes analyses, such as adherence, safety, fertility intentions, pregnancies, and associated factors, are beyond the scope of this Article and will be published separately.

Methods

Study design and participants

Details of the PROMOTE study were provided in earlier reports.[6,7] Briefly, the PEPFAR PROMOTE study is a prospective observational cohort that enrolled mothers and children, starting in 2016, from the PROMISE trial from eight high enrolling African sites. These sites were in four countries in southern and eastern Africa: Kampala, Uganda; Blantyre and Lilongwe, Malawi; Harare, Seke North, and St Mary's, Zimbabwe; and Johannesburg and Durban, South Africa. All sites (clinics) were in urban or semiurban settings. PROMOTE is currently in its fifth year of follow-up.

The PROMOTE study was approved by all relevant institutional review boards in the USA and collaborating African countries. All women signed a written informed consent form to enrol and be followed up with their children for the study duration and to provide study samples. Children provided assent to continue study participation once reaching the appropriate age and maturity level per country guidelines. All women were on ART regimens that conformed with each country's national guidelines as the prevailing standard of care and were not provided by the study. The PROMOTE study offered laboratory testing at no cost and clinical management. Infants received standard of care ART

prophylaxis to prevent vertical transmission and children who acquire HIV were started on ART per country-specific regimens and guidelines. Maternal counselling on ART adherence and other health issues were also provided.

Procedures

African women living with HIV on lifelong ART from the time of their enrolment in the PROMISE trial and who provided informed consent to enrol in the PROMOTE study and be followed up with their child born in the PROMISE trial and, subsequently, their children born in the PROMOTE study, were eligible for enrolment.[6] There were no restrictions related to the time of enrolment in the PROMISE study or having a subsequent child after the child was born during the PROMISE study. The types of ART used were efavirenz-based for all sites in 2016, except for the site in Kampala, Uganda, which used protease inhibitor-based ART. As per current WHO recommendations, women are now being switched to dolutegravir. This process of switching started in 2019 and is at different stages in each country.[8]

After the enrolment visit, the PROMOTE study procedures included maternal follow-up evaluations every 6 months to collect data on medical history, ART use and adherence, physical characteristics (including weight and height), laboratory test results, and new events occurring between visits. The laboratory evaluations included viral load (HIV RNA PCR) testing every 6 months and complete blood count (CBC), CD4 cell count, and serum chemistry (alanine aminotransferase, creatinine, and creatinine clearance) every 12 months. All laboratory tests were available when clinically indicated at unscheduled visits. Women who had new pregnancies during the PROMOTE study followed a schedule every 8 weeks that included pregnancy registration, confirmation of pregnancy, medical history, physical examination, antenatal and delivery evaluations, and laboratory tests. Children born during the PROMOTE study were registered at birth and then followed up with a visit at 6 weeks. Subsequently, information on children was collected every 6 months and included medical history, physical examination and anthropometry, HIV status, and survival status. Adverse event evaluations were collected at each scheduled and unscheduled visit based on the Division of Acquired Immunodeficiency Syndrome toxicity table.[9]

Statistical analysis

The Data Management Center (DMC) at the Centre for the AIDS Programme of Research in South Africa in Durban, South Africa, electronically received, managed, and coordinated data collected at all study sites. At the sites, data were collected on designated case report forms by trained study workers who were regularly visited by the study monitors and DMC personnel to provide refresher training and to maintain quality control and quality assurance procedures. Data were collected locally by qualified and trained study staff and securely transferred to the DMC. Data were collected from Dec 2, 2016, to Jan 27, 2021.

Baseline analyses were presented in an earlier report.[6] For the follow-up data in this Article, available up to 42 months after enrolment, we present descriptive and stratified analyses by research site and country. These results are restricted to summaries of enrolment, follow-up, retention, ART use, adherence to ART, safety, survival, and health outcomes for mothers and children. Retention was defined as not having missed at least two consecutive visits and not having been terminated from the study. We focus on summary frequencies and proportions, medians, and rates and trends, and we intentionally did not analyse risk factors and associations with specific outcomes (these detailed analyses are being done and will be presented separately). The rates are estimated using person-time of follow-up as the denominator to the nearest timepoint available. Specifically, for pregnancy rates, pregnancy duration was subtracted from the person-time calculations and all the pregnancies for each participant are included in the analyses. Retention probabilities were estimated using Kaplan-Meier analyses and compared using the log-rank test. The 95% CIs for the rates were calculated using a Poisson model with person-years as an offset. The 95% CIs for adherence estimates were calculated using the score test method. We use generalised estimating equations for a repeated measure logistic regression to test whether odds (viral suppression and adherence) differed by site over time. We estimated body-mass index (BMI) as an additional objective indicator of health and nutritional status, and summarise BMI as healthy (<25 kg/m²), overweight (25–29·9 kg/m²), and obese (>30 kg/m²).

Role of the funding source

The sponsors of this study had no role in the design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

The number of PROMISE participants not considered in the PROMOTE study from the low-enrolling African sites was 469 (14·7%) of 3199 compared with 2730 (85·3%) of 3199 women considered from the high-enrolling sites (appendix p 2 shows a flowchart with distributions by site and reasons for non-enrolment). We compared maternal demographic and biological factors (median age, number of livebirths, weight, BMI, WHO HIV clinical disease stage, and screening CD4 cell count) among women enrolled and not enrolled in the PROMOTE study and there were no differences between these two groups.

In this PROMOTE study, there were 18 152 scheduled and 4587 unscheduled visits for mothers and 16 096 scheduled and 2005 unscheduled visits for

children. A total of 2169 maternal and 2539 child visits were scheduled but unattended. 18 152 (89·3%) of 20 321 scheduled maternal visits and 16 096 (86·4%) of 18 634 child visits were attended. During these visits, a total of 426 924 sets of case report forms had been completed by site staff and transferred electronically to the DMC. Additionally, 10 208 case report forms for mothers and 8627 for children; 14 934 viral load measurements for mothers and 1281 for children; 7904 CD4 cell counts for mothers and 101 for children; and 13 715 alanine aminotransferase tests and 10 055 creatinine tests for mothers were done. The median follow-up time was 41·8 (IQR 35·8–42·0) months for mothers and 35·7 (23·8–42·0) months for children. Overall retention rates were 96·5% for mothers and 94·3% for children at 12 months, and 88·9% for mothers and 85·4% for children at 42 months.

A total of 1987 mothers and 2522 children were enrolled in the PROMOTE study (1786 were originally enrolled and born in the PROMISE trial, and 736 were born during PROMOTE follow-up; table 1). Overall, the median age of mothers was 35 (IQR 31–39) years. The children's age distribution was variable: 13·0% were aged 1 year or younger; 9·7% were aged 2 years; 7·0% were aged 3–5 years, and 70·3% were aged 6–9 years. At enrolment (baseline), 1588 (79·9%) women living with HIV reported having a partner (married, or cohabiting with a male partner either regularly or non-regularly). During follow-up, 337 (17·0%) of 1987 women who initially enrolled in the PROMOTE study reported a change in partnership: 80 (22·7%) of 352 in Kampala, Uganda; 33 (9·6%) of 343 in Blantyre, Malawi; 34 (10·6%) of 322 in Lilongwe, Malawi; 14 (14·9%) of 94 in Harare, 18 (10·1%) of 179 in Seke North, and 25 (14·3%) of 175 in St Mary's, Zimbabwe; and 67 (26·9%) of 249 in Durban, and 66 (24·2%) of 273 in Soweto, South Africa. At enrolment, 1367 (86·1%) of 1588 women had partners reported disclosing their HIV status to their partners. Overall retention was high (≥85%) for both mothers and children (table 1), and the retention rates across all sites were significantly different from each other over time (p<0·0001).

The last recorded regimen used is shown in table 2 by site and country. Transitioning women to dolutegravir was still in progress and, in some countries (eg, Malawi),

	Kampala	Blantyre	Lilongwe	Harare	Seke North	St Mary's	Durban	Soweto	Total
Mothers									
Enrolled, n	352	343	322	94	179	175	249	273	1987
Median age (IQR), years	34 (31–37)	34 (31–38)	35 (31–38)	35 (31–42)	36 (33–40)	35 (31–39)	34 (30–38)	37 (32–40)	35 (31–39)
Children									
Enrolled, n	449	465	423	139	247	252	239	308	2522
Children enrolled in PROMISE, n	310	317	289	91	169	162	204	244	1786
Children enrolled in PROMOTE, n	139	148	134	48	78	90	35	64	736
Age, n (%)									
0–1 year	67 (14·9%)	64 (13·8%)	55 (13·0%)	28 (20·1%)	34 (13·8%)	51 (20·2%)	16 (6·7%)	14 (4·5%)	329 (13·0%)
2 years	37 (8·2%)	47 (10·1%)	49 (11·6%)	15 (10·8%)	30 (12·1%)	23 (9·1%)	14 (5·9%)	29 (9·4%)	244 (9·7%)
3–5 years	37 (8·2%)	38 (8·2%)	31 (7·3%)	9 (6·5%)	14 (5·7%)	17 (6·7%)	5 (2·1%)	26 (8·4%)	177 (7·0%)
6–9 years	308 (68·6%)	316 (68·0%)	288 (68·1%)	87 (62·6%)	169 (68·4%)	161 (63·9%)	204 (85·4%)	239 (77·6%)	1772 (70·3%)
Retention (number not retained; number at risk)*									
Month 12									
Mothers	99·4% (2; 350)	95·9% (14; 329)	94·7% (16; 306)	98·9% (1; 93)	97·8% (4; 175)	97·1% (5; 170)	95·2% (12; 237)	94·5% (15; 258)	96·5% (69; 1918)
Children	96·3% (16; 396)	96·2% (17; 409)	92·7% (30; 362)	97·6% (3; 118)	97·5% (6; 224)	95·8% (10; 217)	91·0% (21; 210)	88·5% (35; 268)	94·3% (138; 2204)
Month 24									
Mothers	97·4% (9; 343)	90·7% (32; 311)	90·7% (30; 292)	98·9% (1; 93)	96·6% (6; 173)	94·9% (9; 166)	86·7% (33; 216)	88·3% (32; 241)	92·4% (152; 1835)
Children	93·4% (27; 350)	91·7% (35; 354)	89·8% (41; 316)	96·0% (5; 103)	94·7% (12; 197)	92·9% (16; 182)	79·9% (46; 176)	78·0% (66; 222)	89·4% (248; 1900)
Month 36									
Mothers	95·7% (15; 315)	86·7% (45; 231)	86·0% (45; 236)	98·9% (1; 89)	95·5% (8; 160)	90·9% (16; 149)	82·7% (43; 182)	83·9% (44; 201)	89·1% (217; 1563)
Children	89·5% (41; 240)	86·9% (52; 220)	86·3% (53; 211)	96·0% (5; 86)	92·2% (17; 151)	90·3% (21; 149)	71·4% (64; 99)	75·2% (74; 153)	85·4% (327; 1309)
Month 42									
Mothers	95·7% (15; 116)	86·7% (45; 190)	86·0% (45; 130)	98·9% (1; 69)	95·5% (8; 141)	90·9% (16; 134)	82·7% (43; 156)	83·4% (45; 124)	88·9% (218; 1060)
Children	89·5% (41; 49)	86·9% (52; 164)	86·3% (53; 105)	96·0% (5; 57)	92·2% (17; 124)	90·3% (21; 127)	71·4% (64; 57)	75·2% (74; 96)	85·4% (327; 779)

Data cutoff was Jan 27, 2021. *Probabilities obtained from Kaplan-Meier analysis.

Table 1: **Mothers and children enrolment and retention in the PROMOTE study**

	Kampala	Blantyre	Lilongwe	Harare	Seke North	St Mary's	Durban	Soweto	Total
Ever enrolled, n	352	343	322	94	179	175	249	273	1987
Last recorded regimen or ART status among women ever enrolled, n (%)									
Dolutegravir based	159 (45·2%)	199 (58·0%)	193 (59·9%)	43 (45·7%)	56 (31·3%)	65 (37·1%)	26 (10·4%)	0	741 (37·3%)
Efavirenz or nevirapine based	78 (22·2%)	128 (37·3%)	118 (36·6%)	45 (47·9%)	116 (64·8%)	103 (58·9%)	217 (87·1%)	258 (94·5%)	1063 (53·5%)
Ritonavir-boosted lopinavir, ritonavir-boosted atazanavir based, or ritonavir based	111 (31·5%)	3 (0·9%)	3 (0·9%)	5 (5·3%)	7 (3·9%)	5 (2·9%)	5 (2·0%)	14 (5·1%)	153 (7·7%)
Lamivudine and tenofovir based	2 (0·6%)	2 (0·6%)	0	0	0	1 (0·6%)	0	0	5 (0·3%)
Stopped ART*	2 (0·6%)	11 (3·2%)	6 (1·9%)	0	0	1 (0·6%)	1 (0·4%)	1 (0·4%)	22 (1·1%)
Not on ART†	0	0	2 (0·6%)	1 (1·1%)	0	0	0	0	3 (0·2%)
Undetectable viral load, n (%)‡									
Baseline	293 (83·2%) of 352	276 (81·4%) of 339	248 (77·0%) of 322	80 (85·1%) of 94	162 (90·5%) of 179	151 (86·3%) of 175	220 (88·4%) of 249	251 (91·9%) of 273	1681 (84·8%) of 1983
Month 6	268 (79·3%) of 338	266 (82·9%) of 321	238 (82·6%) of 288	75 (84·3%) of 89	160 (92·0%) of 174	147 (88·0%) of 167	222 (90·2%) of 246	250 (95·4%) of 262	1626 (86·3%) of 1885
Month 12	257 (84·8%) of 303	267 (83·2%) of 321	223 (85·8%) of 260	77 (87·5%) of 88	157 (94·0%) of 167	137 (88·4%) of 155	206 (88·4%) of 233	238 (94·4%) of 252	1562 (87·8%) of 1779
Month 18	289 (88·9%) of 325	262 (84·2%) of 311	222 (83·1%) of 267	79 (89·8%) of 88	154 (92·2%) of 167	140 (90·3%) of 155	194 (90·7%) of 214	230 (94·7%) of 243	1570 (88·7%) of 1770
Month 24	280 (91·8%) of 305	254 (83·6%) of 304	212 (84·5%) of 251	75 (89·3%) of 84	144 (94·7%) of 152	125 (93·3%) of 134	172 (89·1%) of 193	217 (92·7%) of 234	1479 (89·3%) of 1657
Month 30	266 (88·4%) of 301	241 (84·3%) of 286	215 (85·7%) of 251	77 (88·5%) of 87	152 (96·2%) of 158	133 (92·4%) of 144	163 (90·1%) of 181	211 (93·8%) of 225	1458 (89·3%) of 1633
Month 36§	130 (93·5%) of 139	171 (90·5%) of 189	144 (83·7%) of 172	67 (84·8%) of 79	100 (94·3%) of 106	108 (88·5%) of 122	111 (82·2%) of 135	142 (93·4%) of 152	973 (88·9%) of 1094
Month 42	256 (93·8%) of 273	144 (87·3%) of 165	170 (81·7%) of 208	71 (85·5%) of 83	122 (93·8%) of 130	102 (90·3%) of 113	104 (83·9%) of 124	146 (93·6%) of 156	1115 (89·1%) of 1252
Median CD4 cell count (IQR; n), cells per μL									
Baseline	964 (747–1190; 352)	768 (596–969; 335)	727 (545–903; 322)	960 (779–1170; 94)	928 (761–1069; 179)	858 (646–1081; 175)	886 (721–1087; 249)	736 (608–880; 273)	826 (649–1036; 1979)
Month 12	1006 (825–1276; 269)	778 (614–934; 298)	731 (599–927; 242)	825 (703–1004; 88)	911 (741–1077; 160)	825 (643–993; 150)	895 (720–1104; 226)	763 (613–953; 240)	836 (667–1038; 1673)
Month 24	1021 (843–1279; 274)	746 (602–923; 265)	734 (575–892; 210)	842 (683–1057; 88)	901 (732–1109; 141)	834 (677–993; 128)	927 (745–1132; 184)	724 (545–926; 211)	836 (661–1045; 1501)
Month 36	1082 (813–1281; 115)	789 (642–995; 161)	683 (499–874; 145)	838 (699·5–1070·5; 80)	927 (752–1134; 95)	829 (678–1066; 99)	844 (658–1009; 129)	735 (573–881; 139)	818 (649–1046; 963)

ART=antiretroviral therapy. *Stopped ART for the following reasons: laboratory or clinical toxicity, participant decision, virological failure, or compliance issues. †Participant did not initiate ART in this study. ‡Undetectable viral load at <20 or <40 copies per mL (ie, lower limit of assay quantification). §Missing data due to COVID-19 pandemic lockdown at most sites.

Table 2: **ART use by women enrolled in the PROMOTE study by site and country**

58·9% of the women had switched to dolutegravir by Jan 27, 2021. In other countries (eg, South Africa), few women had switched to dolutegravir. Overall, the proportion of women with undetectable viral load (<20 or <40 copies per mL) showed a slight increase over time: 84·8% at enrolment; 86·3% at 6 months; 87·8% at 12 months; 88·7% at 18 months; 89·3% at 24 and 30 months; 88·9% at 36 months; and 89·1% at 42 months (table 2). At 42 months, 5·5% of women presented with a viral load of more than 1000 copies per mL and varied by site. Among the 218 mothers who were not retained in care (ie, did not attend follow-up visits), 158 (72·5%) had an undetectable viral load, and 60 (27·5%) had a detectable viral load with 45 (75%) of these having a viral load of more than 1000 copies per mL. Of the 1987 women enrolled, 420 (21·1%) were either not retained in care or had a last recorded viral load that was detectable. At month 42, the women had a viral suppression rate of 80% or more across sites. The lowest viral suppression rate was 77·0% from the Lilongwe site at baseline and the highest rate was 96·2% from Seke North at the month 30 visit.

Among all women enrolled in PROMOTE, the median CD4 cell count was stable by site over time and varied between sites (table 2). These results were also similar for data restricted to only women who attended all visits (appendix p 3). Self-reported adherence (number of ART doses taken correctly in the last 30 days) varied by site and between sites in the same country. At 36 months, reported adherence was 97·2% (95% CI 93·1–98·9) at the Kampala site, Uganda; 85·9% (80·2–90·1) at the Blantyre site and 76·6% (69·7–82·3) at the Lilongwe site, Malawi; 97·6% (91·5–99·3) at the Harare site, 94·4% (88·4–97·4) at the Seke North site, and 73·4% (65·0–80·4) at the St Mary's site, Zimbabwe; and 94·7% (89·9–97·3) at the Soweto site and 88·1% (81·6–92·6) at the Durban site, South Africa. There were statistically significant differences in viral suppression (p=0·0017) and reported adherence (p<0·0001) rates over time for all sites.

Very high proportions of women reported excellent to very good health, which increased at each follow-up visit compared with baseline (figure). Consistent with the increasing proportion of better health status, the proportions of women who reported visiting a clinic for health problems and who reported admissions to hospital during the last 6 months preceding the interview declined. There were a few differences by site in reported health indicators; however, these were mostly limited to baseline and earlier visits. This pattern was similar for data of women who had attended all follow-up visits (appendix p 4). Mean BMI among women who were never pregnant who were living with HIV and using ART (n=1123) remained stable over time, and there was no decline from enrolment to last visit at all sites. Mean BMI was similar in women from all sites, excluding women from the two South African sites, in whom mean BMI was higher than other sites throughout the study. A higher proportion of women from the South African sites were obese than in other sites, starting from baseline (40·2%) to the last visit at 42 months (52·8%; appendix p 5). There were no substantial changes in obesity at other sites.

Fertility intentions (desire to have more children) at baseline and follow-up visits at each site were consistently high in Uganda (range over time 53·8–63·6%; appendix p 6). Women at the Blantyre (Malawi) and Soweto (South Africa) sites consistently reported less desire to have more children than women in other sites. There were also differences between sites in the same country (eg, sites in Zimbabwe and South Africa).

In women of reproductive age living with HIV and using ART, and consistent with the desire to have more children, the frequencies and rates of pregnancies after enrolment in 2016 to 2021 were high and comparable at all sites except for the two South African sites, which had slightly lower rates (10·6 [95% CI 8·5–13·2] per 100 women-years in Durban and 12·9 [10·6–15·7] per 100 women-years in Soweto; table 3). The pregnancy outcomes in the majority of these women using long-term ART were liveborn with healthy birthweight (table 3). The frequencies of low birthweight, preterm birth, and stillbirth were low among the women who became subsequently pregnant during the PROMOTE study. The most common adverse pregnancy outcome was abortion or miscarriage less than 20 weeks after pregnancy and was highest in the Uganda and the Soweto sites.

15 deaths were recorded over 6317·2 person-years of follow-up for mothers and 22 deaths over 6565·1 person-years of follow-up for children (aged 0–9 years), resulting in a mortality rate of 2·4 (95% CI 1·4–3·9) per 1000 person-years for mothers and 3·4 (2·2–5·10) per 1000 person-years for children. Mortality rates ranged from 0·7 to

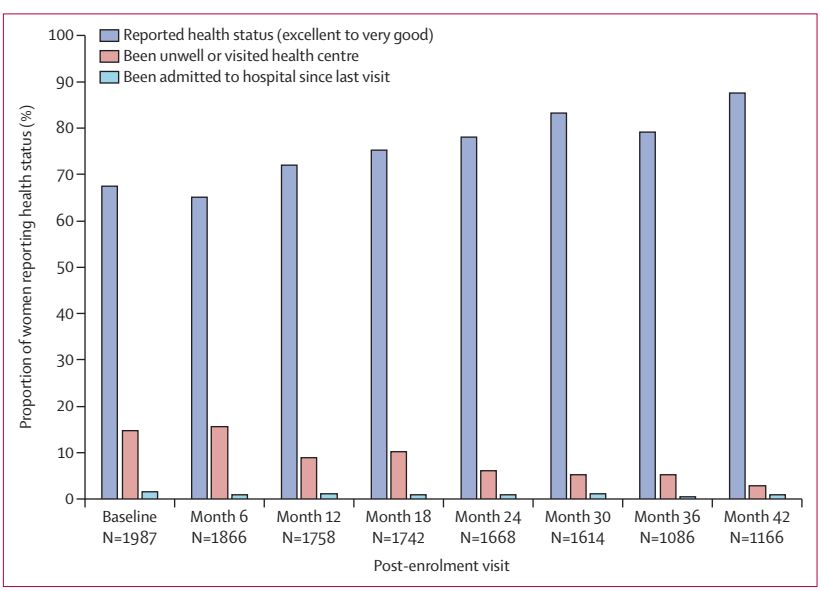

Figure: **Maternal health status over time in the PROMOTE study**

3·7 per 1000 person-years for mothers and from 2·1 to 5·7 per 1000 person-years for children. There were no significant differences in mortality rates by country for the mothers (p=0·11) or for the children (p=0·30). Of the 22 deaths in children, only one had HIV before dying.

A total of 683 (34·4%) and 417 (16·5%) mothers and children had at least one adverse event (table 4). These adverse events were assessed throughout the study and included events documented at scheduled and unscheduled visits on the basis of reports, physical examinations, and laboratory testing. There were wide variabilities by site in the frequency of maternal mild to severe adverse events. Overall, there were 28 life-threatening adverse events and 22 adverse events that were related to the death of 15 mothers or neonates. The causes of death included four cases of efavirenz-induced liver toxicity (three in Blantyre and one in Kampala). Among children, there were 16 life-threatening events and 19 events that were associated with the death of 22 children. The causes of death included infectious and non-infectious diseases. Of all children born to women with HIV on long-term ART, 36 were children with HIV (33 from the PROMISE trial conducted before 2016 and three born during the PROMOTE study [see table 1 for totals enrolled]). The mothers of the three children with HIV born during the PROMOTE study (one from Blantyre, one from Lilongwe, and one from Harare) had

	Kampala	Blantyre	Lilongwe	Harare	Seke North	St Mary's	Durban	Soweto	Total
Pregnancies during the PROMOTE study, n; women with pregnancies, n	223; 172	174; 159	173; 146	53; 47	94; 84	109; 89	78; 74	102; 93	1006; 864
Number of women ever reported a pregnancy*	172 (48·9%)	159 (46·4%)	146 (45·3%)	47 (50·0%)	84 (46·9%)	89 (50·9%)	74 (29·7%)	93 (34·1%)	864 (43·5%)
Pregnancy rate (95% CI), per 100 women-years	21·9 (19·2–25·0)	18·3 (15·8–21·2)	19·9 (17·2–23·1)	18 (13·8–23·6)	17·1 (13·9–20·9)	20·8 (17·3–25·1)	10·6 (8·5–13·2)	12·9 (10·6–15·7)	17·6 (16·5–18·7)
Pregnancy outcome or current state									
Livebirth	129 (57·8%)	144 (82·8%)	124 (71·7%)	43 (81·1%)	72 (76·6%)	83 (76·1%)	47 (60·3%)	62 (60·8%)	704 (70·0%)
Low birthweight (<2500 g)	4 (1·8%)	1 (0·6%)	6 (3·5%)	1 (1·9%)	4 (4·3%)	4 (3·7%)	0	5 (4·9%)	25 (2·5%)
Preterm delivery (<37 weeks)	7 (3·1%)	3 (1·7%)	4 (2·3%)	1 (1·9%)	2 (2·1%)	2 (1·8%)	5 (6·4%)	1 (1%)	25 (2·5%)
Stillbirth or intrauterine foetal death (≥20 weeks)	4 (1·8%)	3 (1·7%)	7 (4%)	0	1 (1·1%)	3 (2·8%)	2 (2·6%)	3 (2·9%)	23 (2·3%)
Abortion or miscarriage (<20 weeks)	52 (23·3%)	10 (5·7%)	15 (8·7%)	2 (3·8%)	5 (5·3%)	10 (9·2%)	6 (7·7%)	12 (11·8%)	112 (11·1%)
Outcome unknown	3 (1·3%)	2 (1·1%)	1 (0·6%)	0	0	0	0	0	6 (0·6%)
Other†	24 (10·8%)	11 (6·3%)	16 (9·2%)	6 (11·3%)	10 (10·6%)	7 (6·4%)	18 (23·1%)	19 (18·6%)	111 (11·0%)
Total, n	223	174	173	53	94	109	78	102	1006

Data are n (%) unless otherwise specified. Data cutoff was Jan 27, 2021. *Denominator is the number of women ever enrolled. †Other includes women who are currently pregnant (n=95), those who were terminated before delivery (n=4), those who missed visits and pregnancy outcome was not yet recorded (n=9), no outcome due to false pregnancy (n=2), and those with congenital anomalies (n=1).

Table 3: **Frequency and rates of pregnancies and pregnancy outcomes in the PROMOTE study**

	Kampala	Blantyre	Lilongwe	Harare	Seke North	St Mary's	Durban	Soweto	Total
Mothers									
Mild	11 (2·2%)	5 (3·4%)	7 (6·7%)	5 (31·3%)	8 (25·8%)	6 (7·9%)	1 (0·6%)	6 (4·0%)	49 (4·1%)
Moderate	343 (69·0%)	46 (31·5%)	39 (37·5%)	7 (43·8%)	11 (35·5%)	16 (21·1%)	115 (71·9%)	61 (40·4%)	638 (54·0%)
Severe	137 (27·6%)	86 (58·9%)	55 (52·9%)	4 (25·0%)	11 (35·5%)	45 (59·2%)	40 (25·0%)	66 (43·7%)	444 (37·6%)
Life threatening	5 (1·0%)	1 (0·7%)	0	0	1 (3·2%)	9 (11·8%)	2 (1·3%)	10 (6·6%)	28 (2·4%)
Adverse event associated deaths; deaths, n*	1 (0·2%); 1	8 (5·5%); 4	3 (2·9%); 3	0; 0	0; 0	0; 1	2 (1·3%); 0	8 (5·3%); 6	22 (1·9%); 15
Total events, n	497	146	104	16	31	76	160	151	1181
Children									
Mild	10 (2·4%)	4 (7·5%)	1 (3·3%)	3 (100·0%)	1 (6·3%)	4 (17·4%)	1 (2·0%)	5 (6·7%)	29 (4·4%)
Moderate	311 (75·5%)	15 (28·3%)	6 (20·0%)	0	8 (50·0%)	5 (21·7%)	30 (61·2%)	42 (56·0%)	417 (63·1%)
Severe	79 (19·2%)	31 (58·5%)	21 (70·0%)	0	3 (18·8%)	7 (30·4%)	15 (30·6%)	24 (32·0%)	180 (27·2%)
Life threatening	9 (2·2%)	0	0	0	1 (6·3%)	2 (8·7%)	2 (4·1%)	2 (2·7%)	16 (2·4%)
Adverse events associated deaths; deaths, n*	3 (0·7%); 3	3 (5·7%); 3	2 (6·7%); 3	0; 2	3 (18·8%); 4	5 (21·7%); 4	1 (2·0%); 1	2 (2·7%); 2	19 (2·9%); 22
Total events, n	412	53	30	3	16	23	49	75	661

Data are n (%) unless otherwise specified. *15 women and 22 children died, some died without reported adverse events; maternal adverse events without deaths represent an associated adverse outcome, such as neonatal death or stillbirth.

Table 4: **Severity of all adverse events by site in the PROMOTE study**

consistently detectable viral loads throughout the study (viral loads available for the last visits before childbirth were 36 122 copies per mL, 39 459 copies per mL, and 21 097 copies per mL). All three mothers were on efavirenz, lamivudine, and tenofovir.

Discussion

Our findings support that African women living with HIV are willing to continue using ART for years and maintain high adherence. The study shows that women and children have benefited from ART use, as demonstrated by the improvements in health outcome indicators we monitored over time. From an implementation and policy perspective, the study also shows that the schedule of visits every 6 months we used in PROMOTE, which is typical of standard of care ART services, did not lead to excessive losses to follow-up. Retention was high and participants did not show research exhaustion or raise substantial concerns that impeded study visits, collection of information, or study procedures. During the course of the study, the women living with HIV might have become experienced, realised the study's health benefits, and developed a stronger incentive to continue participation. These gains occurred despite persistent hurdles, such as little full HIV disclosure to their partners and a high partnership turnover at some sites. It is encouraging that the women had acquired a degree of autonomy to continue long-term follow-up despite local barriers, including the COVID-19 pandemic restrictions.

Adherence to ART use was excellent, as shown by the high rates of undetectable viral load, high CD4 count, and reported recent history of ART use. High adherence reflects the participants' confidence in these medications and the effect of regular and consistent counselling by the study team. A prospective study monitoring long-term virological outcomes in women who started option B+ care (ie, starting women with HIV who are pregnant or breastfeeding on lifelong ART as soon as diagnosed) during pregnancy for perinatal HIV transmission prevention in Tanzania reported comparable viral load suppression of 88%.[10] These data are encouraging and are similar to findings from countries in the region that conducted the Population-Based HIV Impact Assessment surveys;[11] nonetheless, this viral load suppression is below the UNAIDS 95–95–95 target.[12] The improved general health status in mothers, shown by the self-reported indicators and the stable-to-increased mean BMI, are encouraging and support that consistent use of ART improves maternal health. We did not observe differences in trends of viral load, CD4 cell count, or reported health status over time in data from women who attended all eight follow-up visits compared with all women who enrolled in the study from the outset. These findings suggest that missing data (due to losses to follow-up) were random. A finding that needs additional investigation is the increasing proportion of women who were obese, especially at the South African sites. This dual epidemic of HIV and obesity in South Africa has been previously reported.[13] Obesity might be of increased concern with the switching of ART regimens to dolutegravir. Potential adverse cardiovascular complications have been suggested with the use of dolutegravir.[14–19]

Another outcome related to improved maternal health among these women with HIV on ART is the high fertility intentions and the high pregnancy rates at most sites in this study. The desire to have more children had not declined among women with HIV in Uganda; it appears the main driving force for high fertility in this setting was cultural norms and other determinants not influenced by HIV or ART use.[20,21] The pregnancy rates of the women at the two South African sites were lower than at the Ugandan site, revealing the differences in underlying factors. Women at the two South African sites were often in partnerships that were unstable (eg, a partner change from baseline of about 24% at the two South African sites) and might be influenced by work in an urban setting.[22] We previously reported from a baseline analysis that women from these two sites had a lower sex frequency and consistently used an effective contraceptive method (mostly injectables).[6] The long-term follow-up data in this study suggest that women using ART can overcome the adverse effects of a chronic infection such as HIV, and therefore improve their biological capacity (fecundity) to have children. Although we do not have a concurrent cohort of women without HIV in this study, the fertility rates are not different from those of women without HIV previously studied in these settings.[23,24]

Monitoring of long-term safety outcomes did not reveal major concerns. Life-threatening events related to ART use were rare, and four of the maternal deaths were probably associated with efavirenz-induced liver toxicity. Similarly, life-threatening events were rare in children, and mortality rates for both mothers and children were low compared with background rates in most of these settings in populations with HIV and the general population. For example, the proportion of deaths among women of reproductive age that were due to maternal causes was 18·2% in 2017 in sub-Saharan Africa, and the probability of dying among children aged 5–9 years was 9·9 per 1000 children in 2019.[25–27] An observation that deserves additional monitoring and proper investigation is the relatively high frequency of abortions and miscarriage at some sites (eg, in Uganda and Soweto) and the low livebirth proportion in Uganda despite the high pregnancy rate. We do not know if these observations relate to ART, prevailing biological or behavioural factors, or a reporting bias. We note the rates of pregnancy outcomes, such as low birthweight and preterm birth, were low in this study compared with the PROMISE study.[1] Because these events were sometimes reported to the clinic after their occurrence, it is likely that there might have been under-reporting or misclassification. However, only three new HIV perinatal infections

occurred during this study follow-up. These perinatal transmissions were associated with inadequate adherence to ART despite repeated intensive counselling during the PROMOTE study.

These cohort data support that ART provided as the standard of care in these settings is highly effective when used consistently despite the high frequency of prolonged breastfeeding.[2] We expect adherence to treatment to remain high as women switch to better regimens, such as dolutegravir. A potential limitation in our study relates to the definition of adherence based on only viral load suppression without assessing resistance to antiretroviral drugs being used. Considering that approximately 11% of women had a detectable viral load at their final visit (and some women were also lost to follow-up), the potential consequences of suboptimal adherence (eg, inflammation and related non-communicable disease) could be of concern. ART use has led to remarkable declines in child and maternal HIV-related mortality, substantially reduced perinatal HIV transmission, and improved maternal health. This decline can be better appreciated when current data are compared with historical data in some of these settings.[28,29]

The strength of this large study is its multicountry design and extended follow-up of the same women for approximately 10 years. We were not able to enrol all women who previously enrolled in the PROMISE study in the PROMOTE follow-up. Although the number of women who were not enrolled from the low enrolling sites was small, selection bias cannot be ruled out. However, we did not observe differences in demographic and biological factors between those enrolled in PROMOTE and those not enrolled. Nonetheless, there could be differences influencing generalisability because this study had established clinics and dedicated personnel for several years. We have shown that a closed cohort can be maintained for an extended period in diverse African settings. The PROMOTE study's health outcome findings show that long-term use of maternal ART is safe and effective and improves overall long-term health and survival of women living with HIV and their children exposed to HIV. Reproductive services should be strengthened and integrated to meet the improving health and changing expectations of these women.

Contributors

TET and MGF conceptualised the PROMOTE study, wrote the protocol, prepared the analysis plan, contributed to the analyses and interpretation of the data, prepared the final draft of the manuscript, and contributed to the editing of the manuscript. NY-Z and SSB conceptualised the analysis plan, did the analyses and interpretation of the data, and contributed to the writing and editing of the manuscript. LS-C, LWO, SD, LC, MMN, SH, BM, TC, PA, and JA contributed to the study, interpretation of the data, writing and editing of the manuscript. All authors participated in the review of the final version. All authors had access to the data coordinated by Centre for the AIDS Programme of Research in South Africa. NYZ and TET accessed and verified the data.

Declaration of interests

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Data sharing

Deidentified participant data, including data dictionary, study protocol, and approvals will be made available 1 year after study closure on submission of a data request form to the corresponding author (TET). All data sharing guidelines of the sponsors (US President's Emergency Plan for AIDS Relief and US National Institutes of Health) will be followed. Approval of the data request form (provided by the corresponding author) and signing of a data access agreement form will be required.

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