Longterm Antiretroviral Treatment Effects in a Multi-country Observational Cohort of Reproductive Age Women in Sub-Saharan Africa: The PEPFAR PROMOTE Study Findings

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Summary

Background.

We report the long-term impact of ART in reproductive age African women 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, multi-country, study known as the PEPFAR PROMise Ongoing Treatment Evaluation (PROMOTE), enrolled women who initiated ART in an earlier perinatal clinical trial known as Promoting Maternal and Infant Survival Everywhere (PROMISE). PROMISE continued from 2010/2011 to 2016 and PROMOTE follow-up started in 2016 and is on-going. The PROMOTE study is conducted 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). Following baseline enrollment, women and their children are followed every six months to collect information on medical history, ART use, adherence, health information, and to conduct physical examinations and laboratory tests. Obesity is defined as body-mass index >30 kg/m^2. Data analyses are restricted to summaries of the main long-term outcomes. We use descriptive and stratified analyses, and estimate rates using person-years of follow-up and compute probabilities based on Kaplan Meier methods.

Findings.

PROMOTE enrolled 1987 mothers and 2522 children. The median follow-up time for mothers was 41·8 months (IQR 35·8– 42·0) and for children 35·7 months (IQR 23·8–42·0). Overall retention rates for mothers and children, respectively, were 97% and 94% at 12 months, and 89% and 85% at 42 months. Undetectable viral load at 42 months was 89·1% among 1252 women and varied by site (81·7% to 93·8%). Reported maternal health improved over time; baseline vs 42 months, respectively: excellent/very good health 67·5% vs 86·9%; unwell and visited a health center 14·7% vs 2·8%; and admitted to hospital 1·5% vs 1·0%. Desire to have more children was consistently high at some sites (Uganda: 54·0%–64·0%). Obesity was high in South Africa and increased over time: 40·8% at baseline and 52·8% at 42 months. Overall, the pregnancy rate was 17·6 per 100 woman-years, and maternal and child (0–9 years) mortality rates were 2·4 and 3·4 per 1000 person-years, respectively.

Interpretation.

The findings from this multi-country study are re-assuring. It shows that African women can consistently use ART for a long period post initiation, and long-term benefits can be maintained. Services to support maternal HIV care and treatment and reproductive health should be strengthened.

Funding.

President's Emergency Plan for AIDS Relief (PEPFAR).

Introduction

The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial showed that antiretroviral treatment (ART) can substantially reduce perinatal transmission.[1–2] In the PROMISE randomized trial, pregnant women from 13 African sites and one non-African site were started on ART and followed for approximately five years (2011–2016). The PROMISE trial compared the relative efficacy and safety of various proven ART drugs for perinatal HIV prevention among asymptomatic women living with HIV with CD4 counts ≥350/mm^3 or country-specific threshold for treatment (see Appendix 1 for PROMISE randomizations and ART drugs used). Long-term data assessing safety and effectiveness of ART beyond the first few years of ART initiation remain limited among reproductive age African women. The difficulties of following large cohorts of women for an extended follow-up include logistics, cost, and retention challenges. Disruptions due to unanticipated events such as the current COVID-19 pandemic can also create further 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 PROMISE women with their children for another five more years from initiation of ART, from 2016 to the present.[6] In this analysis, we present summary outcome measures for women and children who enrolled in PROMOTE in 2016 and followed to this date. The overarching objective of this analysis is to present long-term multi-country 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 this paper's scope and will be provided separately.

Methods

Study settings 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 PROMISE mothers and children starting in 2016 from eight high enrolling African sites. These sites are in four African 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) are in urban/semi-urban settings. PROMOTE is currently in its fifth year of follow-up.

Study approval and provision of clinical care.

The PROMOTE study was approved by all relevant institutional review boards (IRBs) in the U.S. and collaborating African countries. All women signed a written informed consent form to enroll and be followed 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. All women are on ART regimens that conform with each country's national guidelines as the prevailing standard of care and are not provided by the study. The PROMOTE study offers laboratory testing at no cost and clinical management. Infants receive standard of care ART prophylaxis to prevent vertical transmission, and children who acquire HIV are started on ART per country-specific regimens and guidelines. Maternal counseling on ART adherence and other health issues are also provided.

Study enrollment and procedures.

Women living with HIV on life-long ART from the time of their enrollment in the PROMISE trial and who provided informed consent to enroll in the PROMOTE study and be followed with their index child (the infant born in the PROMISE trial) and their subsequently born children in the PROMOTE study, were eligible for enrollment.[6] There were no restrictions related to time of enrollment in PROMISE or having a subsequent child after the PROMISE child. The types of ART used were efavirenz (EFV)-based for all sites in 2016, except for the site in Kampala, Uganda, which was using protease-inhibitor (PI)-based ART. Per current WHO recommendations women are now being switched to dolutegravir (DTG); this process of switching started in 2019 and is at variable stages in each country.[8]

Post-enrollment visit, the PROMOTE study procedures included maternal follow-up evaluations every six months to collect data on medical history, ART use and adherence, physical examination (including weight and height), laboratory test results, and new events occurring between visits. The laboratory evaluations included viral load (HIV RNA PCR) testing every six months and complete blood count (CBC), CD4+ cell count, and serum chemistry (ALT, creatinine, and creatinine clearance) every 12 months. All laboratory tests were available when clinically indicated at unscheduled visits. Women who had new pregnancies in PROMOTE followed an eight-weekly schedule 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 at a six-week visit. Subsequently, information on children was collected every six months and included medical history, physical examination/anthropometry, child's HIV status, and survival status. Adverse events evaluations were collected at each scheduled and unscheduled visit based on the DAIDS toxicity table.[9]

Statistical analysis.

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

Baseline analyses were presented in an earlier report.[6] For the follow-up data, available to month 42 visit since enrollment, descriptive and

stratified analyses by research site and country are presented. These results are restricted to summaries of enrollment, follow-up, retention, ART use, adherence to ART, safety, survival, and health outcomes for mothers and children. Retention is defined as having neither missed at least two consecutive recent visits nor been terminated from the study. We focus on summary frequencies and percentages, median with interquartile ranges (IQRs), rates and trends, and intentionally do not analyze risk factors and associations with specific outcomes (these detailed analyses are underway and will be presented separately). The rates are estimated using person-time of follow-up as the denominator to the nearest time point available. Specifically, for pregnancy rates, pregnancy duration is subtracted from the person-time calculations and all the pregnancies for each participant are included in the analyses. Retention probabilities are estimated using Kaplan-Meier analyses and compared using the log-rank test. The 95% confidence intervals for the rates are calculated based on Poisson model with person-years as an offset. We use generalized estimating equations (GEE) for a repeated measure logistic regression to test whether odds (viral suppression and adherence) differed by site over time. We estimate body-mass index (BMI: height (kilogram)/height^2 (meter)) as an additional objective indicator of health and nutritional status, and summarize BMI as normal (<25), overweight (25–29·9), and obese (≥30).

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

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

Operational aspects of the cohort study conduct: In this PROMOTE study, 18152 scheduled and 4587 unscheduled visits for mothers and 16096 scheduled and 2005 unscheduled visits for children were conducted. A total of 2169 maternal and 2539 child visits were scheduled but unattended. Therefore, 89·3% (18152/20321) of the scheduled maternal visits and 86·4% (16096/18634) of the child visits were attended. During these visits, a total of 426924 sets of CRFs have been completed by site staff and transferred electronically to the DMC. Additionally, 10208 CBC for mothers and 8627 for children; 14934 viral loads for mothers and 1281 for children; 7904 CD4 cell counts for mothers and 101 for children; and 13715 ALT and 10055 creatinine tests for mothers were conducted.

Enrollment and retention: Table 1 shows that a total of 1987 mothers and 2522 children were enrolled in the PROMOTE study (1786 were index children born in the PROMISE trial, and 736 were born during PROMOTE follow-up). Overall, the mothers' current median age is 35 years (IQR 31–39 years). The children's current age distribution is variable: 13·0% are less than or equal to one year; 9·7% are two years old; 7·0% are three-five years, and 70·3% are six-nine years. At enrollment (baseline) 1588 (79·9%) women living with HIV reported having a partner (married, regular, or non-regular). During follow-up, 337 women (17·0% of 1987 who initially enrolled in the PROMOTE study) reported a change in partnership: 22·7% (80/352) in Kampala, Uganda; 9·6% (33/343) in Blantyre, Malawi; 10·6% (34/322) in Lilongwe, Malawi; 14·9% (14/94) in Harare, 10·1% (18/179) in Seke North, and 14·3% (25/175) in St. Mary's, Zimbabwe; 26·9% (67/249) in Durban and 24·2% (66/273) in Soweto, South Africa. At enrollment, 86·1% of 1588 women who had partners reported disclosing their HIV status to their partners. Overall retention has been high (≥ 85%) for both mothers and children (Table 1), and the retention rates across all sites were significantly different ($p<0·0001$).

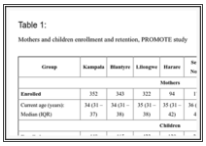
Table 1:
Mothers and children enrollment and retention, PROMOTE study
Group | Kampala | Blantyre | Lilongwe | Harare | Ha
Mothers
Enrolled | 352 | 343 | 322 | 94 | 1
Current age (years): Median (IQR) | 34 (31 – 37) | 34 (31 – 38) | 35 (31 – 38) | 35 (31 – 42) | 36 (
Children

Table 1:

Mothers and children enrollment and retention, PROMOTE study

Antiretroviral use and adherence to ART over time (undetectable viral load [VL], CD4 count, and reported use of ART): The last regimen used by 1984 women (99·8% of women originally enrolled in the PROMOTE study) is shown in Table 2 by site and country. Transitioning women to DTG is in progress, and in some countries such as Malawi >55% of the women have switched to DTG. In other countries such as South Africa, only a few women have switched to DTG. Overall, the proportions of women with undetectable VL (<20 or <40 copies per mL) showed a slight increase over time: 84·8% at enrollment; 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 VL >1000 copies per mL and varied by site. Among

the 218 mothers who were not retained in care, 158 (72·5%) had undetectable VL, and 60 (27·5%) had detectable VL with 45/60 (75%) above 1000 copies/mL. Of the1987 women enrolled, 420 (21·1%) were either not retained in care or had a last VL that was detectable. At month 42, women had viral suppression rate of 80% or more across sites. The lowest viral suppression rate was 76·9% from the Lilongwe site at baseline and the highest rate was 98·8% from the Harare site at month 42 visit. There were statistically significant differences in viral suppression ($p<0·002$) and reported adherence ($p<0·0001$) rates over time for all sites.

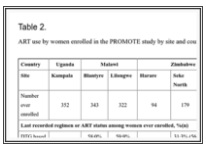

Table 2.

ART use by women enrolled in the PROMOTE study by site and country

The median CD4 count was also stable by site over time and varied between sites (Table 2). Self-reported adherence (number of ART doses taken correctly in the last 30 days) varied by site and between sites in the same country. For example, at 36 months reported adherence was 97·2% at the Kampala site, Uganda; 85·9% at the Blantyre site and 76·6% at the Lilongwe site, Malawi; 97·6% at the Harare site, 94·4% at the Seke North site, and 73·4% at the St. Mary's site, Zimbabwe; and 94·7% at the Soweto site and 88·1% at the Durban site, South Africa.

Maternal health status, fertility intentions and pregnancies over time: The overall frequencies of three indicators of maternal health over time in these women living with HIV on long-term ART are shown in Figure 1. Very high proportions of women reported excellent to very good health with an increasing trend at each follow-up visit compared to baseline. Consistent with the increasing frequency of better health status, there were declining trends in proportions of women reporting visiting a clinic for health problems and similarly decreasing proportions of reported admissions to hospitals during the last six months. There were few variabilities by site in reported health indicators; however, these were mostly limited to baseline and earlier visits. Mean BMI among ever non-pregnant women living with HIV and using ART (N=1123) remained relatively stable over time, and there was no decline from enrollment to last visit at all sites. Mean BMI was comparable in women from all sites, excluding women from the two South African sites where mean BMI was higher throughout the study. Figure 2 shows that a higher proportion of women from the South African sites were obese, starting from baseline (~40·0%) with increasing trend to the last visit at 42 months (~52%). There were no substantial changes in the obesity trend at other sites.

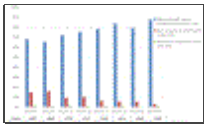

Figure 1:

Maternal health status over time, PROMOTE study – all sites combined

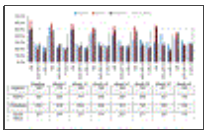

Figure 2:

Body-mass index of women who have never been pregnant by site over time, PROMOTE study

Fertility intentions (desire to have more children) at baseline and follow-up visits at each site are shown in Figure 3. Desire to have more children was consistently high in Uganda (range over time 54%−63%). Women at the Blantyre (Malawi) and Soweto (South Africa) sites consistently reported less desire to have more children than other sites. Variabilities between sites in the same country were noticeable (e.g., sites in Zimbabwe and South Africa).

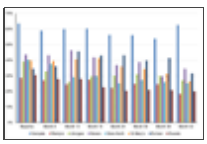

Figure 3:

Fertility intentions (desire to have more children) by research site over time, PROMOTE Study

In these reproductive-age women living with HIV and using ART, and consistent with the desire to have more children as shown in Figure 3, the frequencies and rates of pregnancies after enrollment in 2016 and onwards were high and comparable at all sites except for the two South African

sites which had slightly lower rates (10·6 per 100 women-years in Durban and 12·9 per 100 women-years in Soweto, Table 3). The pregnancy outcomes in the majority of these women using long-term ART were liveborn with normal birth weight (Table 3). The frequencies of low birth weight, preterm birth, and stillbirth were low among the women who became subsequently pregnant during the PROMOTE study. The commonest adverse pregnancy outcome was abortion/miscarriage <20 weeks and was highest in Uganda and the Soweto sites.

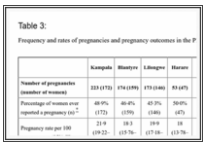

Table 3:

Frequency and rates of pregnancies and pregnancy outcomes in the PROMOTE study

Mortality and adverse events: There were 15 and 22 deaths observed over 6317·2 and 6565·1 person-years of follow-up for mothers and children (age range 0-nine years), resulting in mortality rate of 2·4 [95% confidence interval (CI) 1·4–3·9] and 3·4 [95% CI 2·2–5·1] per 1000 person-years, respectively. Mortality rates ranged from 0·7 to 3·7 for mothers and 2·1 to 5·7 for children. There were no significant differences in mortality rates by country neither for the mothers (p=0·11) nor for the children (p=0·30). Of the 22 children, only one was living with HIV before dying.

Ever-documented adverse events (AEs) for mothers and children are shown in Table 4. A total of 683 (34·4%) and 417 (16·5%) mothers and children have reported at least one adverse event. These AEs were assessed throughout the study and included events documented at scheduled and unscheduled visits based on reports, physical examinations, and laboratory testing. There were wide variabilities by site in frequency of maternal mild to severe AEs. Overall, there were 28 life-threatening AEs and 22 AEs that were related to the death of 15 mothers or neonatal deaths. The causes of deaths included four cases of efavirenz-induced liver toxicity (four cases: 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 both infectious and non-infectious diseases. Of all children born to these women living with HIV on long-term ART, 36 were children living 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 living with HIV born during the PROMOTE study (one each from Blantyre and Lilongwe in Malawi, and one from Harare in Zimbabwe) had consistently detectable viral loads throughout the study (VLs available for the last visits prior to childbirth were 36122; 39459; and 21097 copies per mL). All three mothers were using EFV+3TC+TDF.

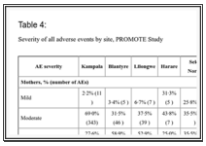

Table 4:

Severity of all adverse events by site, PROMOTE Study

Discussion

The findings we report here confirm that African women living with HIV are willing to continue using ART for years while maintaining high adherence. This longitudinal study shows that women and children have benefited from ART use, as demonstrated by improvements in health outcome indicators we monitored over time. From an implementation and policy perspective this study also shows that the six-monthly schedule 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 significant concerns that impeded study visits, collection of information, or study procedures. These women living with HIV may have become experienced, realized the study's health benefits, and developed a stronger incentive to continue participation. These gains are occurring despite persistent hurdles such as lack of full HIV disclosure to their partners and high partnership turnover at some sites. Therefore, it is encouraging that women have 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 VL, high CD4 count, and reported recent history of ART use. High adherence reflects confidence in these medications, and the effect of regular and consistent counseling by the study team. A prospective study monitoring long-term virological outcomes in women who started option B+ care during pregnancy for perinatal HIV transmission prevention in Tanzania recently reported comparable VL suppression of 88%.[10] These data are encouraging and similar to findings from countries in the region that conducted the Population-based HIV Impact Assessment (PHIA) surveys[11]; nonetheless, it is below the UNAIDS target of 95–95-95.[12] The improved maternal general health status shown by the self-reported indicators and the stable to increased mean BMI are

encouraging and confirm that consistent use of ART improves maternal health. A finding that needs further follow-up is the increasing proportion of women who are obese, especially at the South African sites; the dual epidemic of HIV and obesity in South Africa has been previously reported.[13] Obesity may be of heightened concern with the recent switching of ART regimens to DTG; potential adverse cardiovascular complications have been suggested with use of DTG.[14–19]

Another outcome related to improved maternal health among these women living with HIV on ART is the high fertility intentions and the high pregnancy rates at most sites in this study. It is noticeable that the desire to have more children has not declined among women living with HIV in Uganda; it appears the main driving force for high fertility in this setting remains cultural norms and determinants not influenced by HIV or ART use.[20—21] The pregnancy rates at the two South African sites were statistically lower than at the Uganda site, revealing the differences in underlying factors. Women at the two South African sites often lived in partnerships that appear to be unstable (partner change of ~59% at the Soweto site) and may be influenced by work in an urban setting.[22] We reported previously from a baseline analysis that women from these two sites had lower sex frequency and consistently used an effective contraceptive method (mostly injectables).[6] The long-term follow-up data in this study suggests 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 in this study are not different from those of uninfected women 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 likely 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 to background rates in most of these settings in populations with HIV and the general population (e.g., in sub-Saharan Africa the proportion of deaths among women of reproductive age that are due to maternal causes was 18·2% in 2017, and the probability of dying among children 5–9 years was 9·9 per 1000 in 2019).[25–27] An observation that deserves further monitoring and proper investigation is the relatively high frequency of abortions/miscarriage at some sites (e.g., in Uganda and Soweto) and also the low live birth percentage in Uganda despite the high pregnancy rate. We do not know if this relates to ART, prevailing biological or behavioral factors, or a reporting bias. We note the rates of pregnancy outcomes such as low birth weight and preterm birth were low in this study compared to the PROMISE study [1]; because these events sometimes were reported to the clinic after its occurrence, it is likely that there may have been under-reporting or misclassification. Most encouraging, however, is that 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 counseling during the PROMOTE study.

These data confirm 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 remain high as women switch to better regimens such as DTG. A potential limitation in our study relates to the definition of adherence based on only VL suppression without assessing resistance to antiretroviral drugs being used. Considering that approximately 11% of women had detectable VL at their last visit (and some women were also lost to follow-up) the potential consequences of suboptimal adherence (such as inflammation and related non-communicable disease) could be of concern. ART use has led to remarkable declines in child and maternal HIV related mortality, and substantially reduced perinatal HIV transmission and improved maternal health. This can be better appreciated when current rates are compared with historical rates in some of these settings.[28–29]

The strength of this large study is its multi-country design and extended follow-up of the same women for approximately 10 years. We were not able to enroll 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 biologic factors of those enrolled in PROMOTE and those not enrolled. Nonetheless, there could be differences influencing generalizability because this study had established clinics and dedicated personnel for several years. We have shown that a closed cohort can be maintained for extended period in diverse African settings. The PROMOTE study health outcome findings confirm that long-term use of maternal ART is safe and effective and improves overall long-term health and survival among women living with HIV and their HIV-exposed children. Reproductive services should be strengthened and integrated to meet the improving health and changing expectations of these women.

Research in context

Evidence before this study.

There is strong evidence that antiretroviral treatment (ART) for reproductive age women living with HIV can reduce perinatal HIV transmission. The multi-country randomized clinical trial "*Promoting Maternal and Infant Survival Everywhere (PROMISE)*" we conducted

during the period 2011–2016 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, reports on the long-term (five years or more) effects of ART in reproductive age women who started ART during an earlier pregnancy remain limited. The major constraint has been short duration of follow-up postpartum precluding long-term assessment of adherence (i.e., viral suppression) and longitudinal information on women's clinical outcomes, and reproductive intentions. Additionally, most studies were single-site or with limited sample size jeopardizing wider generalizability. We searched PubMed and other sources for reports showing the long-term effects of ART in African reproductive age women during the past 10 years, and despite the diversity of available data, the limitations we indicated especially the lack of multi-country investigations were still noticeable.

Added value of this study.

Our study enrolled women who were originally recruited as part of PROMISE multi-site trial and known as the "*PEPFAR PROMise Ongoing Treatment Evaluation (PROMOTE)*" study. PROMOTE started in 2016 (when the PROMISE follow-up was terminated). This observational study is continuing follow-up of women and their children at eight African sites from four countries in Uganda, Malawi, Zimbabwe and South Africa. The findings we report here are encouraging and show that African women are willing to be a part of a long follow-up period from 2010/2011 when they originally enrolled in PROMISE and continuing in the PROMOTE study to this date in 2021. Losses to follow-up are minimal, 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 is very low and similarly low child morbidity and mortality. Additionally, there were no major safety concerns associated with long-term use of antiretroviral drugs. These long-term evaluations demonstrating excellent ART effectiveness were conducted through a study schedule more typical of the standard of care in ART settings in these countries (every six months). Two major strengths of this study are the long-term follow-up period and inclusion of women from multiple countries.

Implications of all available evidence.

Long-term, multi-country studies can be conducted 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 confirms that ART benefits are continuing beyond the first five 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 non-HIV emerging diseases including the impact of the on-going pandemic of COVID-19 and its potential interventions.

Supplementary Material

Appendices

Click here to view.(243K, pdf)

Acknowledgements

We thank the women and children who are participating in the PROMOTE study at each of the research sites. We acknowledge the research teams at each of the following sites: MU-JHU, Kampala, Uganda; UNC Project Clinical Research Site, Lilongwe, Malawi; Johns Hopkins-College of Medicine Research Project, Blantyre, Malawi; University of Zimbabwe College of Health Sciences Clinical Trials Research Centre (UZCHS-CTRC) Zimbabwe; Perinatal HIV Research Unit (PHRU), Soweto, South Africa; Centre for the AIDS Programme of Research in South Africa (CAPRISA), uMlazi Clinical Research Site, Durban, South Africa. The PROMOTE study was funded by the President's Emergency Plan for AIDS Relief (PEPFAR) through DAIDS/NIAID/NIH grants to each of the participating Clinical Trials Units (Core grant # UM1 AI069530-11).

Footnotes

Declaration of interests

No competing interests declared.

Data sharing

De-identified participant data, including data dictionary, study protocol, and approvals will be made available one year after study closure upon submission of a data request form to the corresponding author (ttaha1@jhu.edu). All data sharing guidelines of the sponsors (PEPFAR and NIH) 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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TET and MGF conceptualized the PROMOTE study, wrote the protocol, prepared analysis plan, contributed to the analyses, interpretation of the data, prepared the final draft of the manuscript, and contributed to editing of the manuscript. NYZ and SSB conceptualized the analysis plan, performed the analyses, interpretation of the data, and writing/editing of the manuscript. LSC, LWO, SD, LC, MMN, SH, BM, TC, PA, and JA contributed to the conduct of the study, interpretation of the data, writing of the manuscript and editing. All authors participated in review of the final version. All authors had access to the data coordinated by CAPRISA (NYZ).

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