Published in final edited form as:

Int J Gynaecol Obstet. 2016 March ; 132(3): 347–352. doi:10.1016/j.ijgo.2015.09.015.

Effect of subsequent pregnancies on HIV disease progression among women in the Mulago Hospital MTCT-Plus program in Uganda

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Abstract

Objective—To investigate the effect of subsequent pregnancies on HIV disease progression among HIV-infected women at Mulago Hospital, Uganda.

Methods—In a retrospective cohort study, data were analyzed from women enrolled in the Mother-To-Child Transmission Plus program from March 2003 to December 2011. The CD4 cell count, the development of new AIDS-defining opportunistic infections, and the AIDS-related mortality were compared between women with and without subsequent pregnancies.

Results—Overall, 409 women were enrolled and 195 (47.7%) had subsequent pregnancies. Antiretroviral therapy (ART) was initiated in 143 (73.3%) women with and 155 (72.4%) women without subsequent pregnancies. Kaplan–Meier analysis for women receiving ART showed no differences between women with and without subsequent pregnancies in the median times to clinical failure (62.7 vs 64.7 months; $P = 0.31$), immunological failure (68.8 vs 75.5 months; $P = 0.10$), and death (68.8 vs 75.5 months; $P = 0.53$). In a Cox regression analysis, subsequent pregnancies were not associated with immunological failure during follow-up (adjusted hazard ratio 1.13, 95% confidence interval 0.06–2.09).

Conclusion—Subsequent pregnancies could have no detrimental effect on HIV disease progression among HIV-infected women whose treatment is well managed.

Keywords

HIV progression; Maternal mortality; Mulago; Subsequent pregnancies; Uganda; Women

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Conflict of interest

The authors have no conflicts of interest.

1 Introduction

Considerable strides have been made globally in the provision of care to HIV-positive individuals, including the administration of antiretroviral therapy (ART). The provision of this care has led to a decrease in morbidity and mortality among HIV-positive patients [1]. It is therefore hypothesized that the improved quality of life could lead to increased fertility among HIV-positive women [2–6].

Many factors have been implicated as affecting the rate of HIV disease progression to AIDS, but no firm conclusions have been drawn regarding the role of pregnancy, with some studies reporting no effect and others reporting a detrimental effect. Most of the studies conducted in Sub-Saharan Africa were performed before the era of ART, and the considerable methodological differences between the studies made it difficult to assess the true effect of pregnancy on HIV disease progression [7–9]. In Uganda, a study conducted before the introduction of ART [9] found that the initial comparative immunological advantage possessed by fertile women before they became pregnant was lost again as a result of the pregnancy, whereas another small study [10] that examined the effect of only the first pregnancy while receiving ART showed no negative effect of pregnancy. There is therefore a need to conduct larger studies with a longer follow-up period that include women with multiple pregnancies in the era of improved HIV care and ART provision.

The present study was designed to evaluate the effect of subsequent pregnancies on HIV disease progression, particularly in terms of the CD4 cell count, the development of new AIDS-defining opportunistic infections, and AIDS-related mortality.

2 Materials and methods

In the present retrospective cohort study, the data of women who were enrolled in the Mother-to-Child Transmission (MTCT)-Plus program at Mulago Hospital, Kampala, Uganda, from March 1, 2003, to December 31, 2011, were analyzed. Mulago Hospital is the national referral hospital for Uganda and a teaching hospital for Makerere University. Ethics approval was obtained from the School of Medicine Research and Ethics Committee, Makerere University, and the Uganda National Council of Science and Technology. As a result of the retrospective nature of the study, informed consent was not necessary; however, strict confidentiality was maintained.

The MTCT-Plus care program is run by the Makerere University–John Hopkins University (MUJHU) Research Collaboration and is based at Mulago National Referral Hospital in Kampala, Uganda. The program started in 2003; it is a donor, not-for-profit, comprehensive family HIV care program offering free medical care, including ART and contraceptive counseling services, to HIV-infected women and their families. The point of entry of a woman into the program is during pregnancy or soon after delivery when she is diagnosed as HIV-positive through the Mulago Hospital Prevention of MTCT program.

Patient data were captured in source forms and an electronic database. At program entry, sociodemographic characteristics and the clinical status were documented. Follow-up information while on the program was captured in Follow-up and Laboratory Results forms.

Qualified and trained medical doctors, nurses, and counselors collected the various data. Each patient had a unique patient identity number that was used to link the data both in the source documents and in the electronic database. The information was then entered into an electronic database by trained data entry clerks. Access to the patient files was restricted to staff members at the MUJHU Research Collaboration and all electronic patient data were in a password-protected database that was managed by the data managers only.

The patients were routinely reviewed every 3 months, and at each visit, information on the medical history and pregnancy status was obtained and a clinical assessment (including clinical staging of HIV according to the WHO classification [11]) was performed. Patients receiving ART made monthly clinic visits to obtain drug refills. During the routine visits, the patients were seen by a physician, a counselor, and a nurse. The patients received treatment and prophylaxis for opportunistic infections. To avoid loss to follow-up, a health visitor traced patients who had missed an appointment using the available locator information. When a patient was not able to come as scheduled, she would contact her health visitor and come for the visit as soon as possible. In case of a patient death outside a hospital with no official death certificate indicating the cause of death, the health visitor would perform a verbal autopsy by interviewing the relatives.

At program entry, all patients were ART-naïve. Eligibility for ART was based on the clinical stage of the disease and the CD4 cell count (ART was started when <200 cells per mm^3).

Laboratory tests were performed by the MUJHU Core Laboratory, which is certified by the College of American Pathologists. The BD FACSCalibur (Becton Dickinson, Franklin Lakes, NJ, USA) instrument was used to determine the CD4 cell count at 6-month intervals.

Data in the electronic patient database were accessed and any missing information was extracted from the source documents. A form was used to guide the data retrieval process. All eligible women with complete data were included in the analysis to maximize the power of the study. Those with incomplete data were excluded.

The following data were retrieved for analysis in the present study: age, marital status, years of education, parity, CD4 cell count, WHO clinical stage, and number of pregnancies after enrollment. A pregnancy was recorded irrespective of whether it ended in an abortion, a stillbirth, or a live birth.

The outcome measures were clinical failure, immunological failure, and AIDS-related mortality. Clinical failure was defined as a new occurrence of any one of the medical conditions classified as WHO clinical stage III or IV—i.e. an AIDS-defining illness. Women were considered to have immunological failure when the CD4 cell count rose to a maximum and then dropped by 50% or more during follow-up, dropped to 100 cells per mm^3 or less, or returned to the baseline value at initiation of ART. AIDS-related mortality was defined as a death that was attributed to HIV/AIDS.

The statistical analyses were performed using Stata version 10 (StataCorp, College Station, TX, USA). The distribution of the study outcomes in women with subsequent pregnancies was compared with those in women who did not become pregnant again after being enrolled

into the program using the Wilcoxon rank-sum test. The women were further stratified by ART status.

In a second analysis that included only women receiving ART, survival analysis for the three outcomes was performed using the Kaplan–Meier method and the log-rank test was used to test the null hypothesis that the pattern of survival (i.e. the time to each study outcome) for women with and without pregnancies is the same. Cox proportional hazard ratios were computed to compare the risk of immunological failure between women with and without subsequent pregnancies. Crude and adjusted hazard ratios were reported with 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant.

In a third analysis that included all women in the program (women receiving ART and women not receiving ART), the CD4 cell counts over time were plotted separately to compare the trends.

3 Results

A total of 409 HIV-infected women were enrolled and followed up in the MTCT-Plus program. Of these, 195 (47.7%) women had one or more subsequent pregnancies after enrollment in the MTCT-Plus program (Fig. 1). Among the women with and without subsequent pregnancies, 143 (73.3%) and 155 (72.4%) began ART, respectively.

Among the 195 women who had subsequent pregnancies, 116 (59.5%) had one pregnancy, 61 (31.3%) had two pregnancy, 15 (7.7%) had three pregnancies, and 3 (1.5%) had four subsequent pregnancies during the study period.

At baseline, women with a subsequent pregnancy were younger than those with no subsequent pregnancy ($P = 0.017$) (Table 1). There were no significant differences between the two groups in terms of the baseline CD4 cell count and the baseline WHO clinical stage.

Among women receiving ART, there was no difference in the proportion of women with and without subsequent pregnancies ($P = 0.837$). Regarding the ART drug combination, 268 (89.9%) women received zidovudine, lamivudine, and nevirapine (ZDV + 3TC + NVP). The combinations of stavudine, lamivudine, and nevirapine (d4T + 3TC + NVP), zidovudine, lamivudine, and efavirenz (ZDV + 3TC + EFV), and stavudine, lamivudine, and efavirenz (d4T + 3TC + EFV) accounted for the remaining 11.1%.

Among the 155 women with no subsequent pregnancies, 13 (8.4%) had a new AIDS-defining illness and were classified as experiencing clinical failure, as opposed to 10 (7.0%) women among 143 women with subsequent pregnancies. Overall, the new AIDS-defining illnesses included: severe bacterial infection ($n = 9$ [39.1%]), pulmonary tuberculosis ($n = 5$ [21.7%]), grade IV wasting syndrome ($n = 3$ [13.0%]), Kaposi sarcoma ($n = 2$ [8.7%]), extrapulmonary tuberculosis ($n = 1$ [4.3%]), suspected disseminated candidiasis ($n = 1$ [4.3%]), *Pneumocystis jiroveci* pneumonia ($n = 1$ [4.3%]), and extrapulmonary cryptococcal infection ($n = 1$ [4.3%]).

Kaplan–Meier analysis among women receiving ART showed that there was no significant difference in the median time to clinical failure between those with and without subsequent pregnancies (62.7 months [95% CI 25.4–83.1] vs 64.7 months [95% CI 35.0–82.6]; $P=0.31$). The overall median time to clinical failure was 63.0 months (95% CI 28.0–82.9) (Fig. 2).

The overall median time to immunological failure among women receiving ART was 73.3 months (95% CI 41.2–85.8). The Kaplan–Meier analysis showed no significant difference in the median time to immunological failure for women with and without subsequent pregnancies (68.8 months [95% CI 37.1–85.4] vs 75.5 months [95% CI 43.9–86.6]; $P=0.10$) (Fig. 3).

In the Cox proportional hazard regression analysis, having subsequent pregnancies was not associated with immunological failure during follow-up, even after adjustment for age, parity, education, marital status, and WHO clinical stage (adjusted hazard ratio 1.13 [95% CI 0.06–2.09]). Baseline CD4 cell count, level of education, parity, age, and marital status were also not associated with the long-term immunological outcome. By contrast, WHO clinical stages 3 and 4 at baseline were independently associated with an increased risk of immunological failure (crude hazard ratio 1.45 [95% CI 1.02–2.06]; adjusted hazard ratio 1.60 [95% CI, 1.10–2.32]) (Table 2).

A total of nine women died; of these, four had no subsequent pregnancies whereas five had subsequent pregnancies. The overall median time to death was 73.3 months (95% CI 41.2–85.8). The Kaplan–Meier analysis showed no significant difference in the median time to death between women with subsequent pregnancies (68.8 months [95% CI 37.1–85.4]) and those without subsequent pregnancies (75.5 months [95% CI 43.9–86.6]; $P=0.53$).

A total of 111 women did not receive ART. Of these, 59 (53.1%) had no subsequent pregnancies and 52 (46.8%) had subsequent pregnancies. None of the women had immunological or clinical failure during follow-up. There were no AIDS-related deaths. When the CD4 count for women not receiving ART was plotted over time, there was no significant difference between women with and without subsequent pregnancies (Fig. 4).

There was an improvement in the immunological status of the study population overall irrespective of ART use. No difference in the CD4 count trend over time was observed between those who had a subsequent pregnancy and those who did not (Fig. 5).

4 Discussion

In the present study, there was no difference in HIV disease progression between women with subsequent pregnancies and those with no subsequent pregnancies. The results were the same even after stratification by ART use. Having a subsequent pregnancy was not associated with a faster CD4 cell count decline, the development of a new AIDS-defining illness, death, or time to disease progression.

The present findings are consistent with data for women in high-income countries [8,12–14], where pregnancy is not associated with a CD4 decline or a faster progression to AIDS. One

study [15] found that pregnancy was actually associated with a lower risk of HIV disease progression, probably because women who become pregnant are generally healthier.

However, the present results differ from the results of previous studies in low-income countries [7,10,16]; these studies examined the effect of one subsequent pregnancy and showed that pregnancy is associated with a detrimental immunological outcome. Two similar studies conducted in Uganda gave contradicting findings. Mayanja et al. [9], in a prospective study of HIV-infected women receiving highly active antiretroviral therapy, showed that pregnancy had no lasting negative effect on immunological and virological ART outcomes. The study examined the effect of the first pregnancy while using ART. It had the major limitation of a small sample size (88 women, 28 of whom became pregnant) and it did not examine the effect of multiple pregnancies. A retrospective analysis of a cohort in rural Uganda, conducted by Lieve et al. [10] before the era of ART, found that pregnancy worsened the immunological status. These authors analyzed the data of 139 women. The immune status was evaluated using CD4 cell counts. However, a low CD4 count does not necessarily translate into HIV disease progression. If the authors had evaluated disease progression using the same parameters as those used in the present study (death, AIDS-defining illness, and CD4 cell count combined), the findings might have been similar to the present results. It is also important to note that these earlier studies compared HIV-positive nonpregnant women with HIV-positive women who became pregnant, whereas the present study enrolled HIV-positive women who were already pregnant and assessed the effect of subsequent pregnancies on HIV disease progression. Despite this difference, the interpretation of the present study findings remains the same.

The finding in earlier studies that pregnancy had a detrimental effect is probably a true reflection of reality. The present study and a recent systematic review and meta-analysis [17] have both shown no detrimental effect. This could be attributable to improvements in HIV care, better knowledge about living with HIV, and changes in the biology of the HIV virus over time.

Conventionally, the assessment of disease progression includes an evaluation of the viral load. In the present study, viral load measurement was not included because this was not routinely done during the study period given that it is expensive. Indeed, to date, viral load measurement is still out of reach in most low-resource settings including Uganda.

The women in the MTCT-Plus program who conceived again were generally younger than those who did not conceive again. This was to be expected because younger women are more likely to be of lower parity than older women, and they are therefore more likely to have a subsequent pregnancy.

To support the present findings, viral load measurements need to be done in future studies. In addition, larger prospective cohorts with longer follow-up would eliminate the bias associated with the retrospective nature of the present study and allow for real-time evaluation of outcomes.

In conclusion, in settings where women receive appropriate HIV/AIDS care including ART, subsequent pregnancies have no detrimental effect on HIV disease progression. The present

study has demonstrated that when women are receiving appropriate HIV/AIDS care, including ART, their clinical and immunological status is not affected by subsequent pregnancies. These findings from a resource-limited setting are encouraging, because most women with HIV infection are of reproductive age and will want to have children. These women can be allowed to achieve their fertility desires, but emphasis should be placed on provision of care and treatment to all women with HIV infection in low-income settings.

Acknowledgments

This work was supported by Training Health Researchers into Vocational Excellence in East Africa (THRiVE), grant number 087540, funded by the Wellcome Trust. The content of the present article is solely the responsibility of the authors and does not necessarily represent the official views of the supporting offices.

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Fig. 1.

Patient flow chart Abbreviations: ADI, AIDS-defining illness; ART, antiretroviral therapy; MTCT-Plus, Mother-to-Child Transmission Plus program.

Fig. 2.

Kaplan–Meier analysis of time to clinical failure by pregnancy status Abbreviations: NoPreg, no subsequent pregnancies; SubPreg, subsequent pregnancies.

Fig. 3.

Kaplan–Meier analysis of time to immunological failure by pregnancy status. Abbreviations: NoPreg, no subsequent pregnancies; SubPreg, subsequent pregnancies.

Fig. 4. CD4 cell count trends for HIV-infected women not receiving antiretroviral therapy by subsequent pregnancy status. Abbreviations: NoPreg, no subsequent pregnancies; SubPreg, subsequent pregnancies.

Fig. 5.

CD4 cell count trends for the study population overall stratified by pregnancy status.

Abbreviations: NoPreg, no subsequent pregnancies; SubPreg, subsequent pregnancies.

Table 1Baseline characteristics of HIV-positive women at Mulago Hospital, Uganda, by pregnancy status (n = 409).^a

Baseline characteristics	Subsequent pregnancies (n = 195)	No subsequent pregnancies (n = 214)	Total (n = 409)	P value
Age, y	28 (25–31)	29 (25–33)	29 (25–32)	0.018
Mean age, y	28.5	30.0	29.3	
CD4 count at enrollment, cells/mm ³	348.5 (174–582)	313.5 (194–519)	329.2 (179–558)	0.411
WHO stage				0.390
I	60 (30.8)	69 (32.2)	129 (31.5)	
II	88 (45.1)	85 (39.7)	173 (42.3)	
III	42 (21.5)	48 (22.4)	90 (22.0)	
IV	5 (2.6)	12 (5.6)	17 (4.2)	
Parity	3 (2–4)	3 (2–4)	3 (2–4)	0.562
Marital status (n = 395)				0.314
Legally married	36 (19.0)	37 (18.1)	73 (18.5)	
Living together with a partner	93 (49.0)	84 (41.0)	177 (44.8)	
Not married/not living with partner	40 (21.1)	55 (26.8)	95 (24.1)	
Widowed	21 (11.1)	29 (14.2)	50 (12.7)	
Years of education	8 (6–12)	8 (6–11)	8 (6–11)	0.570

^aValues are given as median (interquartile range) or number (percentage), unless indicated otherwise.

Table 2

Cox regression analysis for effect of subsequent pregnancy and sociodemographic characteristics on immunological outcome among women receiving antiretroviral therapy (n = 298).

Variable	Total	Subsequent pregnancies ^a	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age						
<30 y	188	106 (56.4)	1			
30 y	110	37 (33.6)	0.99 (0.94–1.04)	0.584	0.96 (0.89–1.04)	0.349
Education level						
Primary	123	54 (43.9)	1			
Above primary	156	79 (50.6)	0.96 (0.89–1.04)	0.343	0.97 (0.88–1.06)	0.481
Pregnancy status						
No subsequent pregnancies	155	NA	1			
Had subsequent pregnancies	143	NA	1.05 (0.59–1.87)	0.856	1.13 (0.06–2.09)	0.704
Marital status						
Married	173	87 (50.3)	1			
Not married	120	53 (44.2)	1.01 (0.75–1.37)	0.936	0.91 (0.65–1.27)	0.578
Parity						
0–3	170	86 (50.6)	1			
>3	121	53 (43.8)	1.04 (0.89–1.22)	0.581	1.05 (0.85–1.31)	0.628
WHO clinical stage						
Stages 1 or 2	198	99 (50.0)	1			
Stages 3 or 4	99	44 (44.4)	1.45 (1.02–2.06)	0.034	1.60 (1.10–2.32)	0.014

Abbreviations: HR, hazard ratio; CI, confidence interval; NA, not applicable.

^aValues are given as number (percentage).