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DISSERTATION

Prävention der vertikalen Übertragung von HIV in der Option B+ Ära unter besonderer Berücksichtigung der Adhärenz während der Schwangerschaft

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Zusammenfassung

Einleitung: Zur Vermeidung einer HIV-Übertragung von Mutter zu Kind während Schwangerschaft und Stillzeit empfahl die WHO in ihren Leitlinien seit 2012 die Einleitung einer lebenslangen antiretroviralen Therapie für alle HIV-positiven Schwangeren (Option B+). Bislang wurden sowohl die Durchführbarkeit der Strategie hinsichtlich der mütterlichen Therapieadhärenz als auch Einflüsse auf das Geburtsergebnis kaum untersucht.

Methoden: Zur Untersuchung der Durchführbarkeit von Option B+ im Sinne einer konstanten Therapieadhärenz führten wir eine longitudinale, prospektive Beobachtungsstudie in Uganda durch. HIV-positive Frauen wurden in der Schwangerenvorsorge zweier Kliniken rekrutiert und bis 18 Monate nach Entbindung nachverfolgt. Die Therapieadhärenz wurde während und nach der Schwangerschaft in regelmäßigen Abständen evaluiert. Parallel wurden in einer Querschnittsstudie mögliche Einflüsse der antiretroviralen Medikation auf das Geburtsergebnis untersucht. Für diese Studie wurden entbindende Frauen rekrutiert, die Häufigkeit von Komplikationen erfasst und auf einen möglichen Zusammenhang mit der Einnahme antiretroviraler Medikamente untersucht.

Ergebnisse: In die longitudinale Beobachtungsstudie wurden 124 HIV-positive schwangere Frauen eingeschlossen. Hiervon kehrten 45 (36.3%) nach ihrer ersten Vorstellung nicht mehr in die Schwangerschaftsvorsorge zurück. Der Verbleib in der PMTCT-Maßnahme korrelierte signifikant mit vorheriger Kenntnis sowie Offenlegung des HIV-Status. In der Gruppe der Frauen, die bis zur Geburt nachverfolgt wurden zeigte sich die Therapieadhärenz stabil und auf hohem Niveau (Median 95.7% eingenommene Tabletten). Nach der Geburt jedoch erreichte keine der Frauen längerfristig eine adäquate Adhärenz. Es zeigte sich eine Abnahme der medianen Adhärenz auf 49% nach 6 Monaten und auf 20% nach 18 Monaten. Inadäquate Therapieadhärenz korrelierte signifikant mit einer höheren Anzahl an vorausgegangenen Schwangerschaften, einem höheren Alter der Frau sowie hohen Transportkosten. Eine HIV-Übertragung von Mutter zu Kind trat bis 18 Monate nach Geburt nicht auf.

Im Rahmen der Querschnittsstudie wurden 412 Gebärende untersucht. 110 Frauen (26.7%) waren HIV positiv, von diesen hatten 88.1% eine antiretrovirale Therapie bereits vor (34.5%), oder während der Schwangerschaft (53.6%) begonnen. In der Gesamtkohorte zeigte sich eine hohe Rate an Komplikationen: 40.6% der Frauen waren von Totgeburt, Frühgeburt oder niedrigem Geburtsgewicht des Babys betroffen. Ein Zusammenhang mit der Einnahme

antiretroviraler Medikamente konnte jedoch unabhängig von Art und Einnahmedauer nicht festgestellt werden.

Diskussion: Zusammenfassend zeigt sich Option B+ während der Schwangerschaft als prinzipiell realisierbare und effektive Strategie mit hoher und konstanter Therapieadhärenz, und ohne Anhaltspunkte für einen negativen Einfluss auf das Geburtsergebnis. Die hohe Rate an Drop-outs zu Beginn der Schwangerschaft, sowie die deutlich nachlassende Adhärenz nach Geburt, sind jedoch alarmierend. An diesen beiden kritischen Punkten der Therapie erscheint eine nachhaltigere Betreuung der Frauen unerlässlich.

Abstract

Introduction: For the prevention of mother to child transmission (PMTCT) of HIV, the WHO guidelines of 2012 stipulated the initiation of a lifelong antiretroviral treatment for all HIV-positive pregnant women (Option B+). Yet, feasibility in terms of treatment adherence as well as influences of this regimen on birth outcomes have barely been evaluated.

Methods: In order to describe feasibility of Option B+, we conducted a longitudinal, observational study in Uganda. HIV-positive women were recruited on their first antenatal care (ANC) visit in two clinics and were followed-up until 18 months after delivery. Adherence was evaluated at regular intervals during and after pregancy. At the same time, we conducted a cross-sectional study to determine possible influences of antiretroviral drug intake on birth outcomes. Delivering women were recruted, and adverse birth outcomes were determined and assessed for possible correlations with antiretroviral drug intake.

Results: In total, 124 HIV-positive women were enrolled into the longitudinal study. Among these, 45 clients (36.3%) were lost to follow-up immediately after their first ANC visit. Retention in care was significantly associated with prior knowledge and disclosure of HIV status. Among followed-up clients, the median pill count adherence remained on a high and stable level (median 95.7% pill intake) until delivery. However, no client achieved adequate adherence for a longer term period postpartum. Adherence levels decreased to a median of 49% after 6 months and 20% after 18 months. Inadequate adherence was associated with higher numbers of previous deliveries, older age of the mother and higher transport costs. HIV transmission from mother to child did not occur until 18 months postpartum.

Within our cross-sectional study, 412 delivering women were included into the evaluation. Within this cohort, 110 women (26.7%) were HIV positive, most of these (88.1%) had started ART either before, (34.5%), or as Option B+ during pregnancy (53.6%). Overall, we found high rates of adverse birth outcomes: 40.6% of women were affected by stillbirth, preterm delivery or small for gestational age. However, we found no evidence of any correlation with antiretroviral drug intake.

Discussion: In conclusion, we found encouraging evidence on effectiveness and adherence to Option B+ during pregnancy, without implications for adverse birth outcomes. However, the high rate of immediate loss to care on uptake, as well as the decrease of adherence after delivery, are alarming results. Substantial support at these critical points of the intervention seems to be of crucial importance.

Einleitung

Trotz umfangreicher Bemühungen in der Vergangenheit stellt die Entwicklung einer effektiven Strategie zur Vermeidung der HIV-Übertragung von Mutter zu Kind während Schwangerschaft und Stillzeit („Prevention of Mother-to-Child Transmission“, PMTCT) auch heutzutage noch eine Herausforderung dar. Das Übertragungsrisiko kann mittels eines effektiven antiretroviralen Regimes von 25-45% auf weniger als 5% gesenkt werden[1-3], dennoch infizierten sich 2015 weltweit weiterhin etwa 150 000 Kinder neu mit HIV[4].

Die WHO empfahl in ihren Leitlinien seit 2012 die Einleitung einer lebenslangen antiretroviralen Therapie für alle HIV-positiven Schwangeren (Option B+)[5]. Im Unterschied zu bisherigen Ansätzen (Option A und Option B) bedeutet dies eine einheitliche Therapiestrategie für alle Frauen, unabhängig von klinischem Status, CD4-Zellzahl und Gestationswoche. Ein potentieller Vorteil dieser Strategie liegt in der deutlichen Vereinfachung des Regimes, wodurch eine flächendeckendere Versorgung von Frauen auch in ressourcenlimitierten, ländlichen Regionen gewährleistet werden kann. Des Weiteren bietet Option B+ einen kontinuierlichen und effektiven Schutz durch dauerhafte Suppression der Viruslast auch über die Dauer der bestehenden Schwangerschaft hinaus, was in Regionen mit hohen Geburtenraten ebenfalls einen bedeutenden Faktor darstellt. Hierbei kann sowohl das Übertragungsrisiko in nachfolgenden Schwangerschaften minimiert[6], als auch das Risiko der Resistenzbildung durch wiederholte Therapiepausen zwischen den Schwangerschaften gemindert werden. Auch für die Gesundheit der Frauen selbst stellt eine rechtzeitig begonnene antiretrovirale Therapie einen Vorteil dar, da die Krankheitsprogression verlangsamt und durch eine gesenkte Viruslast das Risiko opportunistischer Infektionen gemindert wird[7, 8]. Potentiell HIV-negative Partner profitieren ebenfalls bei niedrigerer Viruslast ihrer Partnerinnen von einem geringeren Übertragungsrisiko[9-11].

Bislang jedoch wurden längerfristige Ergebnisse dieser Strategie kaum untersucht. Studien bisheriger Strategien konnten wiederholt suboptimale Therapieadhärenz während der Schwangerschaft als einen wichtigen limitierenden Faktor nachweisen[3, 12-15]. Auch für die Adhärenz nach Geburt des Kindes ergaben bisherige Untersuchungen keine zufriedenstellenden Ergebnisse[12, 14, 16]. Angesichts der Einführung einer lebenslang fortzuführenden Therapie gewann die Aufrechterhaltung einer konstanten Therapieadhärenz in den vergangenen Jahren nun

zusätzlich an Bedeutung. Suboptimale Adhärenz senkt nicht nur die Effektivität der Strategie hinsichtlich einer erfolgreichen Vermeidung der HIV-Übertragung von Mutter zu Kind, sondern birgt auch das Risiko der Resistenzbildung gegen die eingesetzten Medikamente[17, 18].

Zudem ist über die Sicherheit einer kontinuierlichen Einnahme antiretroviraler Medikamente während der Schwangerschaft bislang wenig bekannt. Auf der einen Seite kann eine mütterliche HIV-Infektion das Risiko für ungünstige Geburtsergebnisse wie Früh- oder Totgeburten oder niedriges Geburtsgewicht erhöhen[19, 20], sowohl durch das Virus selbst, als auch durch virusassoziierte Komlikationen (mütterliches Untergewicht, Anämie, opportunistische Infektionen, Tuberkulose etc.). Eine Senkung der Viruslast könnte somit über eine Verbesserung des allgemeinen Gesundheitszustandes der Frauen zu positiven Schwangerschaftsverläufen beitragen[21]. Andererseits besteht die Möglichkeit, dass die antiretrovirale Medikation an sich ein Risiko für perinatale Morbidität und Mortalität darstellen könnte[22, 23]. Bisherige Untersuchungen vermuten ein erhöhtes Risiko für perinatale Mortalität insbesondere unter Einnahme von Proteaseninhibitoren[24-26], jedoch wurde auch nukleosidischen und nicht-nukleosidischen Reverse-Transkriptase-Inhibitoren, wie sie in Option B+ zum Einsatz kommen, ein möglicher negativer Einfluss auf die Gesundheit der Neugeborenen unterstellt[23, 27].

In diesem Kontext führten wir im Zeitraum Januar 2013 bis April 2015 eine Beobachtungsstudie in Fort Portal in West Uganda durch. Ziel der Studie war die Untersuchung der Durchführbarkeit von Option B+ im Sinne einer anhaltenden Therapieadhärenz während und nach der Schwangerschaft im Rahmen eines longitudinalen Studienarms. Parallel hierzu untersuchten wir in einer Querschnittsstudie mögliche Einflüsse der antiretroviralen Medikation auf Geburtsergebnisse.

Methoden

Studienumfeld

Die Durchführung der Studie erfolgte in Fort Portal, der Hauptstadt des Kabarole District in West Uganda. Im September 2012 führte Uganda als eines der ersten Länder Option B+ als landesweite PMTCT-Leitlinie ein. Die HIV-Prävalenz wurde zum Zeitpunkt der Studie (2013) auf etwa 7.4% geschätzt[28]. Gleichzeitig weist Uganda eine der weltweit höchsten Geburtenraten mit durchschnittlich 5.9 Geburten pro Frau auf[28]. Die neonatale Mortalität ist mit 23 pro 1000 Geburten (2015) weiterhin hoch, ebenso die maternale Mortalität (440/100 000 Lebendgeburten)[28].

Datenerhebung:

1. Longitudinale Studie (Publikation 1 und 2):

Für die longitudinale Studie wurden Patientinnen aus der Schwangerenvorsorge zweier verschiedener Kliniken rekrutiert: Dem privaten, katholischen Holy Family Virika Hospital, sowie dem öffentlichen Fort Portal Regional Referral Hospital. In beiden Häusern werden die Leistungen der Schwangerschaftsvorsorge und die HIV-Behandlung für die Patientinnen kostenfrei angeboten. Frauen, die sich erstmalig in der Schwangerenvorsorge vorstellten, wurden nach folgenden Einschlusskriterien in den longitudinalen Studienarm eingeschlossen: schriftliches Einverständnis, Alter über 18 Jahre, nachgewiesene Schwangerschaft, positives HIV- Testergebnis, keine bisherige HIV-Therapie. Nach Diagnosestellung erfolgten Aufklärung und Beginn der Option B+ entsprechend den nationalen Leitlinien. Entsprechend der WHO-Leitlinien wurde den Frauen ausschließliches Stillen bis 6 Monate nach Geburt, und Stillen mit Beikost bis 12 Monate nach Geburt empfohlen. Zudem ist für neugeborene Kinder HIV-positiver Mütter eine Nevirapin-Einnahme für 6 Wochen postpartal vorgesehen.

Bei Studieneinschluss wurden soziodemographische und medizinische Daten über einen Fragebogen erhoben. Zusätzlich erfolgten eine klinische Untersuchung und eine Blutentnahme zur Bestimmung von Hämoglobinwert und CD4-Zellzahl sowie ein Malariatest.

Bis zur Geburt waren unabhängig von der Studie monatliche Vorstellungen in der Schwangerenvorsorge zum Routine-Checkup und zur Medikamentenausgabe vorgesehen. Bei jedem Besuch wurden mittels eines Follow-up-Fragebogens Daten zum Verlauf der

Schwangerschaft und zur Einnahme der ART erhoben und die Adhärenz mittels „pill count adherence“ determiniert. Die Berechnung erfolgte aus der Differenz zwischen ausgehändigten und zurückgebrachten Tabletten, geteilt durch die Anzahl der Tage seit der letzten Vorstellung. Die Adhärenz wurde sowohl für die einzelnen Zeitabstände zwischen den Vorstellungsterminen, als auch für die Gesamtdauer der Schwangerschaft bestimmt. Frauen, die nach ihrem ersten Besuch nicht mehr in die Schwangerenvorsorge zurückkehrten, wurden als “Lost to follow-up” (LTFU) definiert. Nach der Geburt waren weitere Vorstellungstermine jeweils nach 6 Wochen, 6 Monaten, 12 Monaten und 18 Monaten vorgesehen.

Die Therapieadhärenz nach der Geburt wurde aus Angaben der Frauen und anhand regelmäßiger Medikamentenabholung bestimmt. Die Angaben der Frauen zur Regelmäßigkeit der Medikamenteneinnahme wurden in 5 Kategorien erfasst (von 1: „alle Tabletten eingenommen“, bis 5: „keine Tabletten eingenommen“). Zur Beurteilung regelmäßiger Medikamentenabholung wurde die Angabe der Frauen zur Anzahl der wahrgenommenen Abholungstermine mit der Anzahl notwendigen Abholungstermine verglichen. Frauen wurden als adhärent eingestuft, wenn sie sowohl über eine tägliche Einnahme berichteten, als auch in ausreichender Häufigkeit zur Medikamentenabholung erschienen waren. Die Neugeborenen wurden bei jedem Vorstellungstermin mittels PCR auf eine HIV-Infektion getestet.

2. Querschnittstudie (Publikation 3):

Im Rahmen der Querschnittsstudie wurden im Zeitraum Februar bis Dezember 2013 Frauen unter Geburt im Kreißsaal des Virika Hospital nach folgenden Einschlusskriterien rekrutiert: Alter >18 Jahre, keine Mehrlingsschwangerschaft, schriftliche Einwilligung, nachgewiesener HIV-Status unter Geburt. Hierfür war peripartal eine erneute Testung/Bestätigung des HIV Status mittels Antikörperschnelltest vorgesehen. Sofern bislang keine dauerhafte Einnahme antiretroviraler Medikamente (ART) bestand, wurde bei Geburt mit Option B+ begonnen. Mittels eines Fragebogens wurden soziodemographische und medizinische Daten erhoben. Des Weiteren erfolgten eine klinische Untersuchung sowie eine Blutentnahme zur Testung von Malaria und Hämoglobin. Zur Bewertung des Geburtsoutcomes wurden Schwangerschaftswoche bei Geburt sowie Gewicht und Apgar-Score des Neugeborenen bestimmt. Ergänzend wurde der mophologische Reifestatus des Neugeborenen mittels Finnström Score festgestellt. Als Frühgeburt wurden Neugeborene vor der 37. Schwangerschaftswoche oder einem entsprechend niedrigeren Reifescore nach Finnström klassifiziert. Als „small for gestational age“ (SGA, i.S. mangelnder Reife) wurde ein Gewicht unter der 10. Perzentile der Wachstumskurve eingestuft.

Für die Bewertung eines möglichen Einflusses antiretroviraler Medikamente wurde eine Einnahme von mindestens 90 Tagen vor Geburt vorausgesetzt.

Statistik

Die erhobenen Daten wurden in elektronischen Datenbanken (Microsoft Excel) gesichert und für die statistische Auswertung in IBM SPSS (Version 22.0) übertragen.

1. Longitudinale Studie (Publikation 1 und 2):
Es erfolgte eine deskriptive Analyse der Basisdaten. Für die Analyse der Adhärenz vor Geburt wurden Adherenzniveaus einzelner Frauen sowie der Gesamtkohorte jeweils für die einzelnen Vorstellungstermine und den Gesamtzeitraum bestimmt. Für den Zeitraum nach der Geburt wurden Medikamentenversorgung und Adhärenz für die jeweiligen Zeiträume zwischen den Vorstellungsterminen bestimmt. In einer bivariaten Analyse wurde der Einfluss einzelner soziodemographischer Parameter auf Adhärenz und LTFU geprüft. Zur Analyse kategorialer Variablen wurden je nach Anwendbarkeit der exakte Test nach Fisher oder der Pearson Chi-Quadrat Test verwendet. Die Analyse nicht-normalverteilter metrischer Parameter erfolgte mittels Mann-Whitney-U-Test. Für den Vergleich zwischen stattgehabten und notwendigen Vorstellungen zur Medikamentenabholung wurde der Wilcoxon Test verwendet. Zur Prüfung möglicher Einflussfaktoren wurden Odds Ratio (OR) und 95% Konfidenzintervalle berechnet. Voraussetzung für statistische Signifikanz war ein P-Wert <0.05.

2. Querschnittstudie (Publikation 3):
Auch hier erfolgte eine deskriptive Analyse der Basisdaten sowie der Geburtsergebnisse. In beiden Fällen wurden die Daten HIV-positiver mit denen HIV-negativer Mütter verglichen. Für univariate Analysen wurden bei kategorialen Variablen der exakte Test nach Fisher oder der Pearson Chi-Quadrat Test angewandt, während kontinuierliche Variablen mittels Mann-Whitney-U-Test oder Kruskal-Wallis-Test analysiert wurden. Bei der Testung möglicher Einflussfaktoren auf Geburtskomplikationen wurde die OR berechnet. Variablen, die hierbei einen signifikanten Einfluss hatten, wurden in eine multivariate Analyse eingeschlossen zur Ermittlung der Adjusted Odds Ratio (AOR). Wie in der longitudinalen Studie war ein P-Wert <0.05 Voraussetzung für statistische Signifikanz.

Ergebnisse

1. Longitudinale Studie (Publikation 1 und 2):

Insgesamt wurden 124 HIV-positive Frauen bei ihrer ersten Vorstellung in der Schwangerenvorsorge rekrutiert. Vor ihrem ersten Besuch in der Schwangerenvorsorge hatte die Mehrheit der Frauen (80.8%) keine Kenntnis ihres positiven HIV-Status. Die mediane CD4-Zellzahl der getesteten Frauen lag bei 486/µl, wobei 22.4% (15/67) der Frauen eine CD4-Zellzahl von <350/µl aufwiesen, und sich somit auch unabhängig von ihrer Schwangerschaft für eine ART qualifiziert hätten.

Von den 124 rekrutierten Schwangeren kehrten 45 (36.3%) nach ihrer ersten Vorstellung nicht mehr in die Schwangerenvorsorge zurück, und wurden als LTFU definiert. Der Verbleib in der PMTCT-Maßnahme korrelierte signifikant mit vorheriger Kenntnis (p=0.049) und Offenlegung des HIV-Status gegenüber Angehörigen vor oder während des ersten Besuchs in der Schwangerenvorsorge (p=0.019). Auch ein höherer Bildungsgrad (secondary education) konnte als protektiver Faktor nachgewiesen werden (p=0.031).

In der Gruppe der Frauen, die regelmäßig zu den Vorsorgeuntersuchungen zurückkehrten, ergab sich bis zur Geburt eine hohe Therapieadhärenz mit einer Medikamenteneinnahme von 95.7% im Median. Mehr als die Hälfte der Schwangeren (51.3%) erreichte eine mediane pill count adherence von >95%. Für 40.8% aller der Frauen ergab sich eine vollständige Therapieadhärenz (100% pill count adherence). Die Frauen stellten sich im Median zu 4 Terminen vor, in einem medianen Intervall von 29 Tagen. Über die Dauer der Schwangerschaft hinweg zeigten sich Adhärenz sowie Anzahl der Tage zwischen den Vorstellungen stabil. Die mediane Einnahmedauer der ART während der Schwangerschaft betrug 129 Tage.

Nach der Geburt wurden 8 Frauen (6.5%) aufgrund von Totgeburt oder frühkindlichem Tod aus der weiteren Nachbeobachtung ausgeschlossen. Von den übrigen 166 Studienteilnehmerinnen kehrten 67 (58.0%) planmäßig 6 Wochen nach Geburt in die betreuende Einrichtung zurück und wurden in die Nachbeobachtung eingeschlossen. Jüngeres Alter erwies sich als Risikofaktor für ein vorzeitiges Ausscheiden aus der Maßnahme zu Beginn (p=0.006), während eine Offenbarung des HIV-Status dem Partner gegenüber als protektiver Faktor identifiziert werden konnte (p=0.029).

In der Nachbeobachtung erschienen 61 Frauen (91%) zu mindestens einem weiteren Termin, 53 Frauen (79.1%) erschienen zu 3 oder mehr Vorstellungsterminen. Keine der Frauen erfüllte über den Nachbeobachtungszeitraum von 18 Monaten die festgelegten Adhärenzkriterien. Im Verlauf zeigte sich die Anzahl an Frauen die als adhärent eingestuft wurden deutlich rückläufig. Während 6 Monate postpartal noch knapp die Hälfte der Frauen (49.0%, 25/51) als adhärent eingestuft wurden, galt dies nur noch für etwa ein Fünftel der Frauen nach 12 und 18 Monaten (19.0%, 8/42; bzw. 20.5%, 9/44).

Unzureichende Adhärenz nach 6 Monaten korrelierte signifikant mit einer höheren Anzahl an vorherigen Geburten (p=0.015) sowie mit einem höheren Kostenaufwand für die Anreise zur betreuenden Einrichtung (p=0.024). 12 Monate postpartal zeigten sich hingegen ein höheres Alter der Mutter als Risikofaktor für unzureichende Adhärenz (p=0.001), sowie weiterhin eine höhere Anzahl an vorherigen Geburten (p=0.039). 18 Monate postpartal zeigte keiner der erwähnten Faktoren noch einen signifikanten Einfluss. Eine HIV-Übertragung auf das Kind konnte in keinem der Fälle nachgewiesen werden.

2. Querschnittsstudie (Publikation3):

Im genannten Studienzeitraum fanden im Kreissaal des Virika Hospital 912 Geburten statt. 445 Frauen (48.8%) konnten aufgrund eines nicht durchgeführten peripartalen HIV-Testes nicht in die Studienkohorte eingeschlossen werden, 55 Frauen wurden aus anderen Gründen ausgeschlossen (z.B. Alter unter 18 Jahre oder Mehrlingsgeburt). 412 Frauen erfüllten alle Einschlusskriterien und wurden für die Studie rekrutiert. In der Studienkohorte hatten 302 Frauen (73.3%) einen nachweislich negativen HIV-Status; 110 Frauen (26.7%) wurden positiv getestet. Unter den HIV-positiven Studienteilnehmerinnen hatten 38 (34.5%) bereits vor der Schwangerschaft mit der Einnahme antiretroviraler Medikamente begonnen, während 59 (53.6%) während der Schwangerschaft im Rahmen von Option B+ mit der Einnahme begonnen hatten. Die Einnahme erfolgte in der Mehrzahl der Fälle (84.4%) über einen Zeitraum von mehr als 90 Tagen vor der Geburt.

Komplikationen im Geburtsverlauf wurden in 40.3% der Fälle beobachtet. 26 der 412 Frauen waren von einer Totgeburt betroffen (6.3%), wobei als Risikofaktoren arterielle Hypertonie und eine Anreisezeit von mehr als 90 Minuten als Risikofaktoren nachgewiesen werden konnten (jeweils $p<0.001$). In 116 von 410 Fällen (28.3%) lag eine Frühgeburt vor, hierbei konnten als Risikofaktoren Anämie (p=0.049) und eine Malariaepisode innerhalb von 2 Wochen vor Geburt

als Risikofaktoren identifiziert werden (p=0.044). Geburtsgewicht und Schwangerschaftswoche bei Geburt wurden für 399 Neugeborene dokumentiert, hierbei ergab sich für 47 Kinder (11.8%) ein mangelnder Reifestatus im Sinne einer SGA-Geburt. Mütterliches Alter von mehr als 30 Jahren und eine Malariaepisode im letzten Trimester der Schwangerschaft konnten als Risikofaktoren nachgewiesen werden.

Ein signifikanter Zusammenhang zwischen dem HIV-Status der Frauen, beziehungsweise der Einnahme antiretroviraler Medikamente wie bei Option B+ über einen Zeitraum von mehr als 90 Tagen, und der Häufigkeit von Geburtskomplikationen ließ sich nicht belegen.

Diskussion

Hinsichtlich der Effektivität von Option B+ als Methode zur Vermeidung der HIV-Übertragung von Mutter zu Kind liefern die hier erhobenen Daten grundsätzlich positive Ergebnisse: So konnte in unserer Kohorte kein einziger Fall einer HIV-Übertragung von Mutter zu Kind beobachtet werden, und es ergibt sich kein Anhalt für einen nachteiligen Effekt der Medikation auf das Geburtsergebnis. Insbesondere die Therapieadhärenz während der Schwangerschaft zeigt sich auf einem hohen und konstanten Niveau, was im Vergleich zu der in Studien erhobenen Ergebnissen früherer Strategien (Option A und Option B) eine bedeutende Verbesserung darstellt[29-31]. Hieraus lässt sich schließen, dass mit der Vereinfachung des Medikamentenregimes im Rahmen von Option B+ (z.B. mit dem Verzicht auf unterschiedliche Therapieprotokolle in Abhängigkeit von der CD4-Zahl) im Kontext ressourcenlimitierter Regionen eine höhere Adhärenz während der Schwangerschaft erreicht werden kann.

Jedoch zeigen sich bei der Durchführung von Option B+ in unserer Studienkohorte zwei kritische Punkte: Zum einen schied rund ein Drittel aller rekrutierten Frauen bereits unmittelbar nach Diagnose der HIV-Infektion im Rahmen der Schwangerenvorsorge aus der PMTCT-Maßnahme aus. Die hohe Rate an Therapieabbrüchen zu Beginn stellt in der Durchführung von PMTCT-Programmen ein bekanntes Problem dar[13, 14, 32-35]. Ein erhöhtes Risiko bestand in unserer Studie vor allem für diejenigen Frauen, die von ihrer HIV-Infektion zuvor keinerlei Kenntnis hatten[14]. Die Kenntnis des HIV-Status ist hierbei nicht nur im Rahmen von PMTCT von Bedeutung: Immerhin 22.4% der getesteten Frauen in unserer Kohorte wiesen eine CD4-Zellzahl von <350µl auf, womit auch unabhängig von der Schwangerschaft die Indikation zur Einleitung einer HAART bestanden hätte. Die Ausweitung flächendeckender HIV-Tests in der Bevölkerung, und die frühzeitige Aufklärung über die Möglichkeit effektiver PMTCT-Programme könnten hier einen entscheidenden Faktor darstellen. Bisherige Erhebungen diesbezüglich bestätigen die unzureichende Diagnostik und Aufklärung in der Gesamtbevölkerung: So wurden laut Uganda Demographic and Health Survey 2016 lediglich 54.6% der Frauen im Alter von 15-49 Jahren innerhalb eines Jahres auf HIV getestet, und nur 45.7% der Frauen im Alter von 15-24 Jahren weisen ausreichendes Wissen über Präventionsmaßnahmen auf[36, 37]. Die Tatsache, dass auch in der Kohorte unserer Querschnittsstudie bei fast der Hälfte der Frauen unter Geburt kein HIV-Status erhoben wurde, unterstreicht diese Problematik zusätzlich.

Den zweiten kritischen Punkt in der Durchführung von Option B+ stellt die Therapieadhärenz nach der Geburt des Kindes dar. Hier bestätigen unsere Ergebnisse die bereits in vorherigen Studien erhobenen Befürchtungen einer deutlich nachlassenden Adhärenz nach der Geburt des Kindes[14, 16, 38]. Die Gründe hierfür sind vermutlich multifaktoriell. So lässt sich vermuten, dass der Schutz des ungeborenen Kindes für die Mütter die entscheidende Motivation zur Einnahme der Medikation darstellt, während die eigene Gesundheit – insbesondere bei Abwesenheit klinischer Symptome – nachrangig erscheint.[16] Hier könnte eine vermehrte Aufklärung der Frauen über das weiterhin bestehende Übertragungsrisiko während der Stillperiode womöglich zu einer Verbesserung führen. Zudem konnten wir in unserer Studie höhere Transportkosten sowie eine höhere Anzahl an vorherigen Geburten als Risikofaktoren nachweisen, so dass nahe liegt, dass die zusätzliche Belastung der Frau durch die Versorgung des Neugeborenen ebenfalls eine Rolle spielt. In diesem Zusammenhang könnten Modelle zur intensiverer Betreuung und Motivation der Frauen beispielsweise im Rahmen regelmäßiger Anrufe, Textnachrichten oder gemeindebasierten Unterstützungsprogrammen einen vielversprechenden Ansatz zu der längerfristigen Adhärenz bieten [39-41].

Nicht zuletzt stellt jedoch die Offenbarung des HIV-Status einen entscheidenden Faktor dar. Die Einbeziehung der Angehörigen, und insbesondere des Partners, hat sich bereits in vielfachen Erhebungen als protektiver Faktor erwiesen, und zeigt auch in unserer Studie einen positiven Einfluss[29, 30, 42-45]. Hierdurch erklärt sich möglicherweise auch die nachlassende Adhärenz nach der Geburt: Während der Schwangerschaft sind regelmäßige Vorstellungen in den Kliniken ohnehin vorgesehen. Eine Offenlegung des HIV-Status ist für die Frauen nicht zwingend notwendig, da sich die Klinikbesuche auch alleine durch die Schwangerschaft rechtfertigen lassen. Dies ändert sich nach der Geburt des Kindes. Letzten Endes stellt somit die Einbeziehung der Angehörigen die Grundvoraussetzung für die Aufrechterhaltung einer lebenslangen Therapieadhärenz dar, da sich eine kontinuierliche Einnahme antiretroviraler Medikamente und regelmäßige Vorstellungen in den betreuenden Einrichtungen langfristig nicht vor Partner und Familie verbergen lassen. So lange jedoch die Angst vor einer Stigmatisierung und vor dem Verlassenwerden durch den Partner größer ist als die Sorge um den eigenen Gesundheitszustand, ist eine langfristige Adhärenz kaum zu erreichen.[37, 43]

Schlussfolgerung

In der Zusammenschau der Befunde liefern unsere Daten zwar ermutigende Ergebnisse zur Effektivität und Durchführbarkeit von Option B+ während der Schwangerschaft, zeigen aber auch Herausforderungen auf. Sowohl zu Beginn der Maßnahme, als auch im weiteren Verlauf sind inhaltliche und strukturelle Verbesserungen (wie etwa die konsequente und regelmäßige Bestimmung des HIV-Status) notwendig, um den Erfolg von Option B+ zu gewährleisten. Hierbei ist hinsichtlich der Gewährleistung einer Langzeitadhärenz insbesondere eine bessere Integration von Familie und Partner von essentieller Bedeutung.

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Eidesstattliche Versicherung

„Ich, Alexandra Schnack, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Prävention der vertikalen Übertragung von HIV in der Option B+ Ära unter besonderer Berücksichtigung der Adhärenz während der Schwangerschaft“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Alexandra Schnack hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1:

Schnack A, Rempis E, Decker S, Braun V, Rubaihayo J, Busingye P, Tumwesigye NM, Harms G, Theuring S. Prevention of Mother-to-Child Transmission of HIV in Option B+ Era: Uptake and Adherence During Pregnancy in Western Uganda. *AIDS Patient Care and STDs*. 2016

Beitrag:

- Koordination der Datenerhebung vor Ort im Zeitraum März 2013- August 2013 (Zeitraum der Datensammlung insgesamt: Januar 2013 – April 2015), dabei insbesondere:
    - Überprüfung und Archivierung der ausgefüllten Fragebögen
    - Eingabe, Sicherung und Überprüfung der innerhalb dieses Zeitraums erhobenen Daten in Excel
    - Problembehandlung im täglichen Ablauf der Datensammlung
    - Koordination der Ausweitung der Studie auf einen zweiten Standort
- Bereinigung/Aufbereitung des für diese Publikation benötigten Datensatzes
- Eigenverantwortliche statistische Analyse mittels SPSS
- Ausarbeitung aller Tabellen und Grafiken dieser Publikation
- Durchführung der Literaturrecherche und Auswahl der relevanten Literatur
- Interpretation und Diskussion der Daten in Zusammenarbeit mit den Koautoren
- Federführung bei dem Verfassen der Publikation

Publikation 2:

Decker S, Rempis E, **Schnack A**, Braun V, Rubaihayo J, Busingye P, Tumwesigye NM, Harms G, Theuring,S. Prevention of Mother-to-Child Transmission of HIV: Postpartum adherence to Option B+ until 18 months in Western Uganda*., PLoS One.* 2017; Jun 29; 12(6): e0179448.

Beitrag:

- Koordination der Datenerhebung vor Ort im Zeitraum März 2013- August 2013, dabei insbesondere:
    - Überprüfung und Archivierung der ausgefüllten Fragebögen
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    - Problembehandlung im täglichen Ablauf der Datensammlung
    - Koordination der Ausweitung der Studie auf einen zweiten Standort
    - Lagerung und Versand von Laborproben
- Teilnahme an Interpretation und Diskussion der Ergebnisse in Zusammenarbeit mit der Erstautorin (z.B. Überarbeitung Literaturverzeichnis, inhaltliche Diskussion)
- Korrekturlesen des fertigen Manuskriptes

Publikation 3:

Rempis, E, **Schnack A**, Decker S, Braun V, Rubaihayo J, Busingye P, Tumwesigye, NM, Harm G, Theuring, S. Option B+ for prevention of vertical HIV transmission has no influence on adverse birth outcomes in a cross-sectional cohort in Western Uganda. *BMC Pregnancy and Childbirth.* 2017

Beitrag:

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    - Überprüfung und Archivierung der ausgefüllten Fragebögen
    - Eingabe, Sicherung und Überprüfung der innerhalb dieses Zeitraums erhobenen Daten in Excel
    - Problembehandlung im täglichen Ablauf der Datensammlung
    - Koordination der Ausweitung der Studie auf einen zweiten Standort
    - Lagerung und Versand von Laborproben
- Teilnahme an Interpretation und Diskussion der Ergebnisse in Zusammenarbeit mit der Erstautorin
- Korrekturlesen des fertigen Manuskriptes

Unterschrift des Doktoranden/der Doktorandin

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Publikation 1:

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Prevention of Mother-to-Child Transmission of HIV in Option B+ Era: Uptake and Adherence During Pregnancy in Western Uganda.
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PLOS ONE

RESEARCH ARTICLE

Prevention of mother-to-child transmission of HIV: Postpartum adherence to Option B+ until 18 months in Western Uganda

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Data Availability Statement: Data cannot be shared publicly, as participants were assured anonymity and confidentiality in the consent procedure, and the data contain identifying information. Data can be requested from Prof. Dr. Frank Mockenhaupt (frank.mockenhaupt@charite.de) as well as the Corresponding Author, or from the Institute of Tropical Medicine and International Health, Charité- Universitätsmedizin, Augustenburger Platz 1, 13353 Berlin, Germany.

Abstract

Since 2012, the WHO recommends Option B+ for the prevention of mother-to-child transmission of HIV. This approach entails the initiation of lifelong antiretroviral therapy in all HIV-positive pregnant women, also implying protection during breastfeeding for 12 months or longer. Research on long-term adherence to Option B+ throughout breastfeeding is scarce to date. Therefore, we conducted a prospective observational cohort study in Fort Portal, Western Uganda, to assess adherence to Option B+ until 18 months postpartum. In 2013, we recruited 67 HIV-positive, Option B+ enrolled women six weeks after giving birth and scheduled them for follow-up study visits after six, twelve and 18 months. Two adherence measures, self-reported drug intake and amount of drug refill visits, were combined to define adherence, and were assessed together with feeding information at all study visits. At six months postpartum, 51% of the enrolled women were considered to be adherent. Until twelve and 18 months postpartum, adherence for the respective follow-up interval decreased to 19% and 20.5% respectively. No woman was completely adherent until 18 months. At the same time, 76.5% of the women breastfed for ≥12 months. Drug adherence was associated with younger age ($p<0.01$), lower travel costs ($p = 0.02$), and lower number of previous deliveries ($p = 0.04$). Long-term adherence to Option B+ seems to be challenging. Considering that in our cohort, prolonged breastfeeding until ≥12 months was widely applied while postpartum adherence until the end of breastfeeding was poor, a potential risk of postpartum vertical transmission needs to be taken seriously into account for Option B+ implementation.

Introduction

In 2014, about 1.2 million HIV-positive women were giving birth in the 21 priority countries for prevention of mother-to-child transmission of HIV (PMTCT) in Sub-Saharan Africa, and the number of children newly infected with HIV was still as high as 170.000.[1] Yet, it is

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beyond doubt that considerable progress has been achieved in PMTCT during the last five years, and UNAIDS has just announced the goal to reach less than 20.000 new infections among children by 2020. [2] The Global Plan towards the elimination of new HIV infections among children targeted a reduction of the final mother-to-child transmission (MTCT) rate to 5% or less among breastfeeding populations, and 2% or less among non-breastfeeding populations. [3] By 2014, the 21 Sub-Saharan African priority countries for PMTCT had in fact achieved an overall transmission rate of 5% after six weeks, but this increased to a final rate of 14% at the end of the breastfeeding period.[1] Hence, breastfeeding still represents the major weakness for successful PMTCT, even though its benefit for the infant´s health in resource-poor settings is uncontroversial. [3–6]

Since 2013, WHO recommends lifelong triple antiretroviral therapy (ART) for all pregnant and breastfeeding women living with HIV regardless of their CD4-cell count and clinical stage, the so-called Option B+, as PMTCT approach wherever this is feasible to implement. [7] According to WHO, when ARVs are taken throughout the breastfeeding period as in Option B+, countries should opt to recommend breastfeeding for the first six months of life, followed by mixing suitable complementary food and continued breastfeeding from month 7–12. [8,9]

When drugs are taken as required, Option B+ allows for achieving lasting viral suppression and reducing emergence of drug resistant viral strains, and the simplified procedures and harmonization of Option B+ with general ART care are assumed to facilitate uptake and long-term adherence. [7] Yet, experiences with this approach have shown that ARV adherence and continuity of care during pregnancy and the early postpartum period are major challenges in the implementation of Option B+. [10–13] Research on later postpartum stages has been limited so far, and there is concern that ARV adherence could even more decline in the later breastfeeding period. A systematic review and meta-analysis studying perinatal adherence before the Option B+ era suggests that sufficient adherence was higher during pregnancy compared to the postpartum period [14], and barriers after delivery, such as the mother´s belief that she is cured or fear of disclosure have been described. [15,16]

Uganda faces an HIV prevalence of 7.4% [17], with a fertility rate of 5.9 births per woman [18] and an estimated number of 120.000 HIV positive pregnant women in 2013 [17]; hence, the country requires continuous engagement in effective implementation of a PMTCT approach. Uganda adopted WHO's Option B+ strategy as one of the first sub-Saharan African countries. The roll-out began in 2012 and had reached all PMTCT facilities by March 2014. [19] After the fairly rapid nationwide introduction of Option B+, research accompanying the implementation of Option B+ in the postpartum period is rare to date, and to our knowledge, studies on feasibility during an extended breastfeeding period for up to 18 months in Uganda are entirely lacking so far. Therefore, we conducted a longitudinal study in a rural high-prevalence setting in Western Uganda to examine longer-term adherence to Option B+ and associated influencing factors until 18 months postpartum, i.e. until the end of the breastfeeding period.

Methods

Study setting and cohort

Within the scope of a larger PMTCT research project [11], we conducted a prospective observational follow-up study in Fort Portal, the capital of Kabarole district in Western Uganda. As of 2014, Uganda had a final MTCT rate of 8%. [1] The two major hospitals in Fort Portal, Fort Portal Regional Referral Hospital (FPRRH) and The Holy Family Virika Hospital (VH), were included in the study. Both provide standard antenatal care (ANC), post-natal care (PNC), HIV testing and treatment on-site as well as other primary healthcare and counselling services free of charge and were described in detail in a recent publication. [11]

The prospective study cohort consisted of women having been already enrolled into a larger PMTCT study at their first ANC visit [11]. Pregnant women were initially recruited and enrolled if they provided informed written consent, were above the age of 18 years, and had a positive HIV status without being on ART prior to recruitment. HIV status was determined in a routine testing sequence utilizing rapid HIV antibody test equipment (e.g., Statpack, Determine, and Unigold). ANC clients tested HIV positive between January and December 2013, were enrolled on Option B+ for PMTCT according to the national guidelines based on a single-pill fixed-dose combination of tenofovir/lamivudine/efavirenz. Drug dispensation was based on a one-month pill supply, hence requesting women to come back for drug collection monthly.

Procedures

Participants from the larger study were enrolled into this sub-study if they returned for routine PNC at six weeks postpartum. This PNC visit at six weeks served as the first study visit for our investigation. Follow-up visits for the study were scheduled at six, twelve, and 18 months postpartum and took place until December 2015. They were aligned with routine visits for ARV drug collection, which are scheduled every four weeks in this healthcare setting. Regarding our study visits, deviation of several weeks from the scheduled date was tolerated in order to achieve a sufficiently large cohort showing three follow-up visits until the end of breastfeeding. At all four study visits, the participants were interviewed by ANC clinic staff using structured questionnaires, without interfering with routine procedures. Dried blood spots of infants were collected at all postpartum visits to determine HIV status. Standard counselling on exclusive breastfeeding for the first six months and continued complementary feeding along with breastmilk until twelve months was given in line with national recommendations. At each study visit, the appointment for the upcoming visit was scheduled. Participants not returning after the first or second study visit were defined as lost to follow up (LTFU). Data on the following socio-demographic and health care related factors had been collected at baseline in the larger PMTCT study[11] and could be examined for our sub-cohort as potential influencing factors on drug and breastfeeding adherence: age, marital status, education, occupation, obstetric history, number of members and children in the household, travel distance, travel cost, ANC attendance, and disclosure of HIV status to partner. A social status scale was established containing information on availability of electricity, tap water, radio, television, fridge, car, and a shelf in the household (scale ranging from 0–8).

Breastfeeding status and history was captured at every study visit. At the first visit, the mother´s intended feeding strategy and the infant´s drug regimen were determined. Exclusive breastfeeding (EBF) was defined as breastmilk only (plus drugs and/or vitamins as prescribed). If supplementary food, non-solid or solid, was given along with breastmilk, this was referred to as mixed feeding (MF) in infants $\leq$6 months, and as complementary feeding (CF) in infants >6 months. [20] Infant's health status was determined by the study nurse and categorized as alive and well, alive with minor problems, alive with major problems, or dead.

Measures of adherence

Drug adherence to Option B+ was assessed with two distinct measuring instruments. First, a self-rating scale for participant's pill intake during the past month with five response categories (ranging from 1 = "took all pills" to 5 = "took no pills") was applied. *Self reported pill intake during the last month* was assessed at every study visit. Secondly, women were asked to report the number of their drug restock visits since the last study visit. In routine PNC these were scheduled once per month. The number of restock visits was compared to the number of visits

required to cover a woman´s drug supply for the particular time period. The resulting variable *difference of reported and requested drug restock visits* was created for the three intervals between the four study visits. Out of those two measures, one overall adherence category was created. A woman was defined as being fully adherent if she reported drug intake of "all" drugs during the last month, *and* if the number of her drug restock visits was in accordance with or even exceeding the required visits during the particular time span. Women not fulfilling one of these two criteria were considered as not adherent.

Data analysis

Questionnaire data was crosschecked and entered into a Microsoft Excel database. Statistical analyses were carried out in IBM SPSS (Version 22). Descriptive statistics were performed to assess participants' baseline information, including feeding status, duration, and infant medication. Clients LTFU were compared to returning women using t-test for continuous variables or Mann-Whitney U-test when variables were not normally distributed. Categorical data was compared using the χ^2 -test. Associated factors to overall adherence were analyzed using non-parametric tests due to small sample size and non- normally distributed variables. Pearson´s χ^2 or, Mann- Whitney U- test were applied for categorial or continuous data, respectively. Wilcoxon signed rank test was used to compare the two dependent variables "self-rated number of drug restock visits" and "required number of restock visits". P-values $\leq$0.05 were regarded as statistically significant.

Compliance with ethical standards

Data was used anonymously and was treated strictly confidential throughout study conduction. Informed consent was obtained from all individual participants included in the study. Women could withdraw their participation from the study at all times without explanation and without any negative consequences for their continued healthcare. The study was ethically approved by the Committee of Higher Degrees, Research and Ethics, College of Health Sciences, Makerere University, Kampala, and by the Ugandan National Council for Science and Technology.

Results

Out of 124 HIV-positive women recruited during ANC, eight women (6.5%) were excluded due to abortion, stillbirth or early infant death. Of the remaining 116 women, 67 (58.0%) returned to the involved health facilities after delivery for their 6 weeks-visit and hence formed the cohort of this sub-study. The 67 women had given birth to 68 babies (66 singletons and one set of twins). Out of all enrolled women, 61 (91%) returned at least once in the follow-up period until 18 months postpartum, and 53 (79.1%) attended three or four visits. The number of returning clients and LTFU per visit are displayed in Fig 1.

Baseline characteristics

Sociodemographic and clinical characteristics of the study cohort are shown in Table 1. Fourteen women (20.9%) were LTFU within the first six months. Comparing them to participants retained in care for twelve months or longer (n = 53; 79.1%) revealed a significant age difference with women LTFU being significantly younger (mean 22.1 years) than followed-up clients (mean 26.7 years; p = 0.006). Among clients LTFU, 9/14 (64.3%) had disclosed their HIV status to their spouse whereas among the followed-up clients 47/52 (90.4%) had done so (p = 0.029).

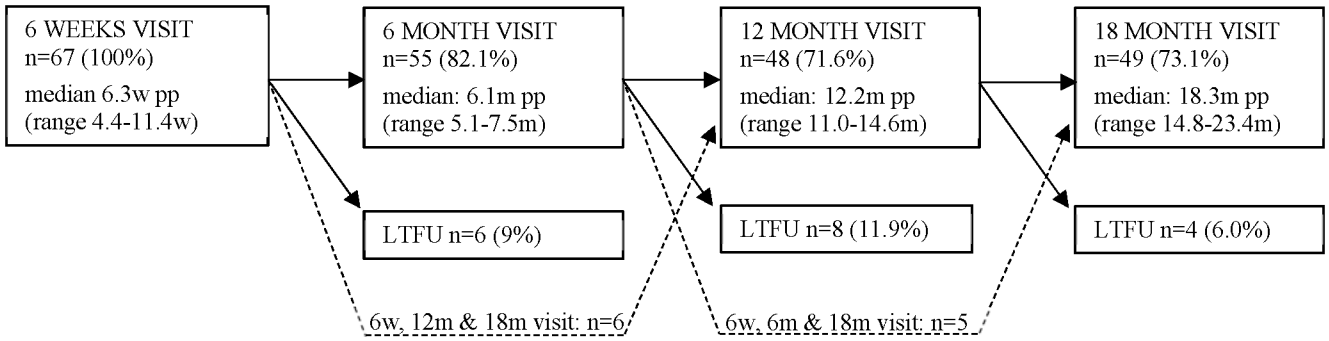

Fig 1. Option B+ enrolled women attending postpartum study visits.

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Maternal drug adherence

According to the study´s definition of full adherence, three participants (4.5% of all) were adherent until 12 months i.e. during the 6 weeks-6 months interval and during the following 6 months-12 months interval. However, no single client was fulfilling the criteria during the entire follow-up period until 18 months. Analyzing overall adherence and associated factors for every follow-up visit separately, our definition of full adherence applied to 26/51 participants (51.0%) at the 6 weeks-6 months interval, to 8/42 participants (19.0%) at the 6–12 months interval, and to 9/44 participants (20.5%) at the 12–18 months interval (Table 2).

We also analysed the two scales separately that determined our "full adherence" category. Self-rated adherence was high throughout all four study intervals with ≥95% of clients claiming that they had taken all pills. However, drug restock visits, which were part of the PNC routine, were performed less frequently than required: There was no difference between reported drug collection visits and required amount of visits at six months postpartum, but a median of two restock visits was missing for the preceeding time periods at twelve and 18 months postpartum (Table 2). Throughout all study visits, clients median number of drug collections was 11.0 compared to a median of 15.0 required drug collection visits (p = 0.01).

Mothers non-adherent at six months postpartum had a higher median number of previous deliveries (p = 0.015) and higher travel costs to hospital (p = 0.024). Longer intended duration of complementary breastfeeding was associated with full adherence (p = 0.035). However, there was no significant link between actual breastfeeding duration and postpartum adherence. Comparing adherent and non-adherent mothers one year after delivery revealed significantly older age (p = 0.001) and higher number of previous deliveries (p = 0.039) in non-adherent mothers (Table 3). At eighteen months postpartum, none of these differences were found to be significant between the adherent and the non-adherent participants.

Breastfeeding duration and infant health

Most participants (91%, n = 61) were lactating exclusively for the first six months, while five women did so for four months or less (1 missing data). The median breastfeeding duration was 12.0 months (range 2–18 months). The WHO- recommended breastfeeding period of at least 12 months was realized by 76.5% of the participants followed-up (12 months, n = 38; 18 month, n = 1), while at the first visit, 55/67 women (83.6% of all) had expressed their intention to do so. A shorter breastfeeding period of 10 month was reported by two (3.9%) of the followed-up women. Two participants failed to give retrospective information on feeding duration.

Table 1. Sociodemographic and clinical characteristics of the study cohort.

Variable	
Enrolled postpartum clients	67
VH	38 (56.7%)
FPRRH	29 (43.3%)
Number of antenatal care visits (n = 67)	
Median (range)	4.0 (1–7)
Number of postpartum study visits (n = 67)	
Median (range)	3.0 (1–4)
Age (n = 67)	
Median (range)	25.0 (18–39)
Educational degree (n = 67)	
None or primary education only	39 (58.2%)
Higher than primary	28 (41.8%)
Marital status (n = 67)	
Married	44 (65.7%)
Single/unmarried/widowed/divorced	23 (34.4%)
Occupation (n = 63)	
No income-generating activity	31 (49.2%)
Income-generating activity	32 (49.8%)
Social Status Index (0–8, n = 67)	
median (range)	3.0 (0–8)
Number of household members[a] (n = 61)	
median (range)	3.0 (1–10)
Number of children in the household[a] (n = 59)	
median (range)	1.0 (0–7)
Travel distance (minutes, n = 59)	
median (range)	30.0 (0–180)
Travel cost (UGX, n = 62)	
median (range)	2000 (0–10000)
Previous deliveries[a] (n = 65)	
median (range)	1.0 (0–7)
Delivery mode (n = 67)	
Spontaneous delivery	61 (91.0%)
Cesarean section	6 (9%)

[a] data collected antepartum

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ARV coverage for infants (nevirapine for six weeks postpartum) exceeded 90%. At the first study visit, 62 infants (91.2%) had been receiving ARVs since delivery. Among those six infants who had not received ARV prophylaxis immediately after delivery, four had received Nevirapine until the second study visit, and two were LTFU. At all four study visits, $\geq$95% of infants were considered as being well, and no child had major health issues at any visit. All infants were HIV negative during their first PCR at six weeks, and remained seronegative throughout the entire breastfeeding period. Until 18 months postpartum, there was no case of HIV transmission observed in the study cohort.

Table 2. Maternal adherence at different study visits.

Maternal Adherence Variables		6 months postpartum	12 months postpartum	18 months postpartum
Self-reported complete pill intake during last month	n (%)	53 (96.4%)	48 (100.0%)	47 (95.9%)
Difference of reported and requested drug restock visits[a]	median (range)	0 (-5–3)	-2 (-5–5)	-2 (-9–12)[b]
Overall adherence category[c]				
Adherent	n (%)	25 (49.0%)	8 (19.0%)	9 (20.5%)
Non-adherent	n (%)	26 (51.0%)	34 (81.0%)	35 (79.5%)

[a] Number of reported drug restock visits compared to the number of visits required to cover the woman´s drug supply for the particular time interval, with negative values indicating missing drug restock visits for the time interval

[b] More than 6 requested visits were noted for women where follow-up time intervals deviated from the 6-months interval, according to the length of their interval.

[c] Created out of the first two variables, i.e. self-reported pill intake and sufficient drug restock visits

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Table 3. Sociodemographic and clinical characteristics by adherence category.

Variables	n	Adherent 12 months Postpartum	Non-adherent 12 months postpartum	p-value[a]
	42	(n = 8)	(n = 34)	
Age at first ANC visit				
Median (range)		20 (20–25)	28 (18–38)	**.001**
Educational degree *n (%)*	**42**			
None or primary	25	6 (24.0)	19 (76.0)	.282
Higher than primary	17	2 (11.8)	15 (88.2)	
Marital status *n (%)*	**42**			
Married	25	3 (12.0)	22 (88.0)	.156
Single/widowed/divorced	17	5 (29.4)	12 (70.6)	
Occupation *n (%)*	**40**			
No income-generating activity	23	4 (17.4)	19 (82.6)	.489
Income-generating activity	17	2 (11.8)	15 (88.2)	
Disclosure of HIV status *n (%)*	**41**			
Status disclosed	38	8 (21.1)	30 (78.9)	.512
Status not disclosed	3	0 (0)	3 (100)	
Social Status Index	**42**			
median (range)		2.5 (1–8)	3 (1–8)	.210
Travel distance (in minutes)	**34**			
median (range)		20 (10–60)	30.0 (0–180)	.741
Travel costs (in UGX)	**40**			
median (range)		3000 (1000–7000)	2000 (0–10000)	.263
Number of household members	**38**			
median (range)		2.5 (1–7)	3.5 (1–10)	.368
Number of children in the household	**38**			
median (range)		0 (0–3)	2 (0–7)	.050
Previous deliveries	**40**			
median (range)		0.5 (0–2)	2 (0–7)	**.039**

[a] Pearsons Chi^2 or Mann-Whitney U-Test

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Discussion

Our longitudinal study in rural Uganda is among the first to observe adherence to Option B+, breastfeeding duration, and MTCT rates from delivery until 18 months postpartum. Overall, we found that despite the relative convenience of simplified procedures in Option B+, no mother from our cohort managed to fully adhere to it until 18 months postpartum. At the six-month postpartum visit, half of all clients fulfilled our definition of adherence, declining to only three clients fully adherent throughout 12 months.

Our finding of suboptimal postpartum adherence coincides with other studies based in sub-Saharan countries. In a recent study conducted in Zambia, Okawa et al. found self-reported adherence to Option B+ in 80% of clients from pregnancy to six weeks postpartum, and a decrease to 70% at 24 weeks postpartum. [13] This is comparable to our finding of high self-reported adherence. Moreover, among previous studies focusing on postpartum Option B + adherence, follow-up periods are shorter and adherence is often defined as retention in care. Studies conducted before the Option B+ era found comparably low postpartum adherence to PMTCT care. In rural Tanzania, adherence in terms of correct dispensation of drugs after delivery was seen in 78% of participating mother-infant pairs. [21] In a cross-sectional study conducted in South Africa, 86% of participating women who were asked about their postnatal adherence to regular azidothymidine intake reported that they were adherent the last four days prior to the interview. [22] Another study from Uganda found a 38% adherence rate for meeting a scheduled appointment six-weeks postpartum. [23] The design, adherence definition and recommended drug regimens in these studies differed from the conditions in our study, thus, respective adherence levels are not comparable. This represents a general problem in adherence-related research, and further investigations targeting the comparability and also the reliability of various adherence measures would be extremely helpful.

Research on Option B+ adherence during pregnancy usually found better adherence. In an Ethiopian study, 87.1% of participants were reported to be adherent in self-reported drug intake. [10] A Kenyan study revealed predelivery adherence rates of 84% [24], and in Uganda, a median pill count adherence level of 95% was found throughout pregnancy. [11] As a matter of a fact, the relatively high adherence to Option B+ in ANC seems to decline in the postpartum period, particularly in the later breastfeeding stage, as observed in our cohort. We found that from the clients having been enrolled in the larger PMTCT study, only 58% returned after delivery for postnatal care. As our study visits were scheduled in line with routine PNC/drug refill services, LTFU corresponds to poor retention in care in the postpartum period. Future research should focus on how to retain women in PMTCT services at this point of the PMTCT cascade.

Our findings also raise the question how barriers for adherence to Option B+ might be different in the postpartum period compared to the antenatal period. [16] A factor previously suggested, and presumably specific to the postnatal period, is the belief that HIV care for the mother´s own health is irrelevant once the infant is born, especially after a baby is proven to be HIV-negative. [15] Moreover, mothers who do not suffer from clinical symptoms might not feel a strong need to adhere to health care appointments and daily drug intake. Previous research suggests that mothers who initiated ART for PMTCT are more likely to drop out of care after delivery than women starting ART for their own health [12, 25].

According to our findings, adherence was higher in the first six pospartal months compared to later observation periods. This implies that particularly the later part of the breastfeeding period should be in the focus of attention of health care providers regarding adherence motivation to avoid late stage transmission. Phone calls or SMS text messaging have proven to be effective in increasing retention in several studies. [26–28] Furthermore, assignment of

community health workers [29], as well as adherence counselling training for health care staff [30] were previously used to increase adherence in pregnancy and early infant diagnosis; these strategies should be adapted to the breastfeeding period. For health service implementers, it is highly relevant to understand in which time interval after delivery it could be especially difficult for mothers to adhere to drug regimens or pick up their drugs from the health facility. This knowledge could lead to specific support activities for specific time intervals e.g., repeated adherence counselling in the later postpartum stage, rendered to Option B+ clients by the health facilities.

Socioeconomic determinants to adherence and retention during the entire PMTCT cascade have been summarized in previous reviews. [16,31,32] We found that postpartum non-adherence until six months after delivery was associated with higher travel costs. Previous research similarly identified structural barriers such as long travel distance to the health facility, often linked with higher travel expenses. [33,34] Another significant influencing factor was found in higher number of previous deliveries, serving as a proxy for the number of children a woman already has at home, hence for the burden of workload she is facing regarding child care. To overcome structural barriers like distance, time and travel funds, health policy makers and governmental institutions should take into consideration how these could be targeted on a lasting basis. Home-based care [35] for those who cannot leave their homes due to child care duties or travel costs might also be an option worthwhile debating.

In our study, three quarters of our participants adhered to the recommended 12-month breastfeeding period with six months of exclusive breastfeeding, demonstrating a broad acceptance of the paradigm shift from abrupt weaning after six months towards a recommended 12-month breastfeeding period for women living with HIV. This is in accordance with findings from Ngoma et al., in which mothers reported a high adherence to breastfeeding recommendations. [36] Mothers' strong commitment to having a healthy, well-nourished baby [37] could explain the high compliance with breastfeeding recommendations, and represents a factor that interventions for increased PMTCT adherence should focus on. However, continued breastfeeding for 12 months as recommended by WHO is strongly and inevitably linked to the precondition that the mother is under ART/Option B+. [7,8] Without sufficient viral suppression, prolonged breastfeeding could lead to high postnatal vertical transmission rates [38], as in the early times of short-term PMTCT regimens. Our finding that in the Option B+ era, HIV-positive mothers widely apply the recommendation for longer breastfeeding on the one hand, but on the other hand do not adhere to continuous drug intake throughout infant exposure to breastmilk is therefore rather alarming. Health authorities urgently need to focus on strengthening postpartum adherence when deciding that health services should counsel in favor of prolonged breastfeeding, in order to avoid a setback in MTCT rates.

We found no case of vertical transmission in our study cohort. While possibly pointing to a high effectiveness of Option B+ despite suboptimal adherence, such conclusions should be drawn with caution in the light of our relatively small sample size. Apart from that, it is possible that HIV-infected infants were among the cases LTFU, possibly having deceased within the first 18 months of life, and results from our followed-up group could be underestimating true transmission rates. For conclusive appraisals on HIV transmission after 18 months under Option B+, larger cohorts are urgently needed, and following-up the dropout cases would be highly elucidating.

The rather small sample size was also a limitation for our study in terms of not permitting multivariate analysis, which would have strengthened our assessment of factors influencing adherence. Yet, considering the immense scale-up of HIV testing and ART programs in the past years, it has become challenging to obtain large PMTCT cohorts, and related research will have to focus on multicenter studies in order to achieve high patient volumes [11]. At the same

time, longitudinal cohorts over a period of 18 months are prone to LTFU, further decreasing the final sample size. The problem of high drop-out rates during follow-up are a common limitation in PMTCT-related research in general [34,39,40]. We tried to mitigate this problem by aligning study visits with routine healthcare visits; yet, dropout rates in the course of the postpartum period were high, and actively following-up on these dropouts was beyond the scope of our study. However, given the scarcity of respective longitudinal studies, we believe that we can still provide meaningful insights in terms of adherence to Option B+ in the postpartum period.

Another limitation of this research is found in the fact that self-reported adherence is prone to social desirability and recall bias and hence to an overestimation of adherence. In our study, we aimed at mitigating those biases by not only relying on self-reported adherence, but combining it with measuring sufficiency of drug restock visits, as well as by creating a nonjudgemental interview setting within the study to facilitate honest reporting. Beyond that, it would give helpful insight on adherence measurement to triangulate self-reported adherence with pill count and plasma drug levels in future research. Finally, we acknowledge that adherence to drug dispensary visits does not necessarily equal drug intake, again underlining the potential risk of overestimating adherence. Still, if true, this only would reinforce our finding of suboptimal adherence.

In conclusion, we identified long-term drug adherence to Option B+ until 18 months postpartum to be suboptimal, pointing at enduring challenges in the implementation of this strategy. Meanwhile, the WHO recommendation for continuous breastfeeding until 12 months and beyond was widely applied by HIV-positive women under Option B+. Low drug adherence clearly compromises the effectiveness of Option B+, and it should be stressed that especially women who prolong the breastfeeding duration for their baby while at the same time not adhering to ARV intake put their infant at high risk for infection. Our findings emphasize a need for postpartum interventions encouraging drug adherence among women taking Option B+, especially in later stages of breastfeeding.

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Option B+ for prevention of vertical HIV transmission has no influence on adverse birth outcomes in a cross-sectional cohort in Western Uganda

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Abstract

Background: While most Sub-Saharan African countries are now implementing the WHO-recommended Option B+ protocol for prevention of vertical HIV transmission, there is a lack of knowledge regarding the influence of Option B+ exposure on adverse birth outcomes (ABOs). Against this background, we assessed ABOs among delivering women in Western Uganda.

Methods: A cross-sectional, observational study was performed within a cohort of 412 mother-newborn-pairs in Virika Hospital, Fort Portal in 2013. The occurrence of stillbirth, pre-term delivery, and small size for gestational age (SGA) was analysed, looking for influencing factors related to HIV-status, antiretroviral drug exposure and duration, and other sociodemographic and clinical parameters.

Results: Among 302 HIV-negative and 110 HIV-positive women, ABOs occurred in 40.5%, with stillbirth in 6.3%, pre-term delivery in 28.6%, and SGA in 12.2% of deliveries. For Option B+ intake ($n = 59$), no significant association was found with stillbirth (OR 0.48, $p = 0.55$), pre-term delivery (OR 0.97, $p = 0.92$) and SGA (OR 1.5, $p = 0.3$) compared to seronegative women. Women enrolled on antiretroviral therapy (ART) before conception ($n = 38$) had no different risk for ABOs than women on Option B+ or HIV-negative women. Identified risk factors for stillbirth included lack of formal education, poor socio-economic status, long travel distance, hypertension and anaemia. Pre-term delivery risk was increased with poor socio-economic status, primiparity, Malaria and anaemia. The occurrence of SGA was influenced by older age and Malaria.

Conclusion: In our study, women on Option B+ showed no difference in ABOs compared to HIV-negative women and to women on ART. We identified several non-HIV/ART-related influencing factors, suggesting an urgent need for improving early risk assessment mechanisms in antenatal care through better screening and triage systems. Our results are encouraging with regard to continued universal scale-up of Option B+ and ART programmes.

Keywords: Human immunodeficiency virus type 1 (HIV-1), Antiretroviral therapy (ART), Prevention of mother-to-child-transmission (PMTCT), Option B+, Adverse pregnancy (birth) outcomes, Stillbirth, Preterm delivery, Small for gestational age, Uganda

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Background

Maternal HIV infection can increase the occurrence of adverse birth outcomes (ABOs), such as pre- term delivery (PTD), stillbirth (SB), or newborns too small for gestational age (SGA) [1–3]. Not only HIV infection itself, but also HIV- associated conditions like lower maternal body weight, anaemia, sexually transmitted infections, Malaria, or Tuberculosis [4–7] are associated with higher rates of ABO. Prophylactic antiretroviral (ARV) drug regimens during pregnancy are not only an instrument for prevention of mother-to-child-transmission of HIV (PMTCT), but can also improve the mother's health and positively influence conditions associated with ABO occurrence [8]. Since 2012, the WHO has recommended "Option B+" for PMTCT [9], which stands for initiation of life-long antiretroviral therapy (ART) among all HIV- positive pregnant women. This approach has since then been further strengthened by the trend to lower thresholds for ART initiation, particularly by the recent WHO release of "treat all"- recommendations, pursuing ART for all HIV-positive individuals including pregnant women. Consequently, the vast majority of PMTCT clients in the near future will be exposed to lifelong ART [8].

However, ARV drugs themselves may also negatively influence the occurrence of ABOs, and thus increase perinatal morbidity and mortality. Research has shown higher rates for SB [10, 11], PTD [12–15] and SGA [11, 16, 17] for infants of women who take ARVs for treatment or prevention. SGA and PTD do not only have an immediate influence on perinatal mortality, but have repercussions on the under-1-year and even under-five year infant morbidity and mortality [18, 19]. While it seems that ARV regimens containing protease inhibitors (PI) have a higher influence on the occurrence of ABOs [17, 20–23], possible relations were also discovered for Nucleotide/Nucleoside reverse transcriptase inhibiting (N(t)RTI) and non- NRTI (NNRTI) drugs now recommended as Option B+ regimen [10, 12–14]. There also seems to be an association between ABOs and the duration of drug intake and time of drug initiation, with pre-conception drug intake linked with higher odds for ABOs than initiation during pregnancy [10, 24, 25].

HIV serostatus and different ARV drug regimens for HIV seropositive women may thus both negatively influence birth outcome. Increasing numbers of women and infants will benefit from the therapeutic and preventive effects of ARV intake during pregnancy. In this light, more information about possible adverse effects of ARV exposure is required. Since ABOs have substantial impact on the overall morbidity and mortality of infants, we aimed to understand their association with different types and duration of ARV exposure (ART or Option B +) in pregnancy.

In Uganda, an estimated 1.6 million people are living with HIV/AIDS, of which around 170 thousand are children [26]. While the nation-wide prevalence of HIV in pregnant women is 6.1% [27], the prevalence of 13.4% in Kabarole district, Western Uganda, is among the highest in the country [28]. The total fertility rate of Ugandan women is 6.0 children. The neonatal mortality rate is estimated at 23/1000, and the SB rate at 25/1000 births. Low birth weight incidence was 14% in 2011 [29]. As of 2011, 57.4% of women delivered in a health facility [29]. The implementation of Option B+ in Uganda for PMTCT started at the end of 2012. Our study aimed at assessing ABOs among women and their newborns in Fort Portal, Uganda, under consideration of ARV exposure during pregnancy.

Methods

We conducted a cross-sectional study to investigate the occurrence of birth outcomes like SB, PTD and SGA among a cohort of delivering women in Fort Portal, Uganda. The primary objective was to assess possible influence of HIV serostatus and ARV exposure duration and type (ART or Option B+). Furthermore, we assessed associations of non-HIV related factors to the occurrence of ABO.

Study site

Virika Hospital, a private catholic hospital representing one of two referral hospitals of Kabarole District, offers standard antenatal, delivery and HIV care and contains a 32-bed obstetric department. Around 10% of delivering women are HIV-infected in this setting. For women identified HIV-positive during pregnancy, Option B+ for PMTCT is applied since September 2012. For assumed seronegative delivering women, HIV status is reassessed peripartumly as a routine procedure. In accordance with the Ugandan PMTCT protocol, all tested women receive pre- and post-test counselling, and those who test positive are counselled and immediately enrolled in Option B+ drug regimen. All women receive adequate standard obstetrical care.

Data collection

From February until December 2013, women who came to Virika Hospital for delivery were recruited into the study. Eligibility criteria included age 18 years or older, singleton pregnancy, informed written consent, and known HIV serostatus (as confirmed in routine peripartum testing). Upon recruitment, we obtained sociodemographic, obstetric, and medical data by using an interviewer-administered, structured questionnaire based on women's self-report. Medical data involved history of Malaria infection and HIV-related data, which included prophylactic and therapeutic measures during the

current and former pregnancies. Women were examined clinically and obstetrically, and a venous blood sample was taken. Malaria status at delivery was determined by microscopy and a rapid test device. Haemoglobin (HB) level was determined using photometer technique. The newborn' s birth outcome and weight were documented. Gestational age in weeks (GW) of the newborns was assessed using the Finnstroem scoring system [30].

The outcome variables were defined as follows: SB was determined as a newborn above 28 GW, delivered with an APGAR score of 0 in the first and after five minutes. PTD was specified as a newborn with an equivalent score of 37 GW or less according to the Finnstroem score assessment. We defined infants to be SGA if they had a birth weight below the 10^{th} percentile of a foetal growth chart. Since to date no growth chart is available for Uganda, we used a chart developed for Tanzania [31]. Due to cultural reasons, stillborn infants were often taken away by the family before they could be assessed and weighed. Some SB babies were therefore missing in the PTD and SGA analysis, but all were included in the SB analysis.

The explanatory variable "HIV-negative" was defined as having had a negative bedside peripartum test; "ART pre-conception" (ARTpc) was specified as having commenced a highly active ARV treatment (Tenofovir, Lamivudine and Efavirenz as recommended first-line regimen) before conception of the current pregnancy. The definition of "Option B+" was the intake of the ARV combination Tenofovir, Lamivudine and Efavirenz, initiated during the current pregnancy. Date of treatment/PMTCT start was extracted from the ANC card, or self- reported if ANC card was missing.

Since it was shown that a protective effect of PMTCT due to viral load reduction requires a minimum of 90 days of ARV intake [32–34], we used this as cut-off point for analysing influence of ARV intake duration before delivery. A second cut-off point was set at 14 GW, as ARV exposure early in pregnancy is particularly suspected to influence ABO occurrence [10, 12, 24, 35, 36].

Six women referred from external facilities were still enrolled on the "Option A" regimen (Zidovudine after GW 14 and Co-trimoxazole) at the time of delivery. For two women, the PMTCT regimen was not specified. These were included in analyses concerning serostatus and non- HIV related explanatory factors for ABO, but excluded from ARV-related analysis. All women on Option A were changed on Option B+ regimen after delivery and referred to chronic HIV care. Only five HIV-positive women were not on ARVs, with two of them not being aware of their seropositivity. They were included in descriptive baseline analysis, but excluded from analysis of HIV/ARV related parameters.

As non-HIV related explanatory variables for ABO, haemoglobin level of 11.5 g/dl and less was defined as anaemia, using the WHO definition of 11 g/dl, adding 0.5 g/dl to adjust for the study site's altitude of 1550 m [37]. The occurrence and gestational week of Malaria in pregnancy (MIP) were either extracted from the ANC card or self- reported by the women. Where the last normal menstrual period date was available, MIP was classified as having occurred in the first trimester, or after start of the second trimester. Women whose laboratory examination confirmed Malaria infection upon delivery were included into the variable "Malaria within two weeks prior delivery". The variable "any obstetric risk history" consisted of self-reported obstetric history of abortion, stillbirth, preterm delivery and preterm labour and clinical findings during this current pregnancy, including hypertension, pre-eclampsia, or sexually transmitted diseases.

Socio-economic status (SES) was classified by using a scale of self-reported availability of resources in the woman's household as proxies, such as tap water, electricity, refrigerator, motorbike/car, cattle, cupboard, and television. Lowest SES was defined as having none of the proxy assets available in the household. We also assessed whether the women benefitted from transport and delivery cost coverage through support organisations (e.g., Baylor Uganda).

Data analysis

Data was entered into Excel (Microsoft) data sheets and checked for consistency. Data analysis was carried out using IBM SPSS Statistics, version 22.0. We performed descriptive analysis of the sociodemographic, economic and clinical background of clients and tested for differences between HIV-positive and negative women. Clinical outcomes of newborns were described and equally tested for differences according to HIV-exposure. For univariate analysis, Mann- Whitney or Kruskal-Wallis test was used for continuous data, and Pearson's Chi Square and Fisher's exact test (as appropriate) for categorical data. We looked for factors influencing the outcome variables SB, PTD, SGA calculating odds ratios (OR). Explanatory variables which were significant in univariate analysis were included into multivariate logistic regression to calculate adjusted odds ratios (AOR). A significant p-value ≤0.05 and a confidence interval of 95% was used for all analyses.

Results

Socio-demographic characteristics

From 912 deliveries in the recruitment period, 412 mother-newborn-pairs fulfilled eligibility criteria for inclusion into the study; 445 (48.8%) had to be excluded

from the cohort because of missing peripartum serostatus determination, 55 due to other non- eligibility criteria.

Within our cohort 302 women were confirmed seronegative, and 110 were confirmed seropositive. Among HIV-positive women, 38 (34.5%) had already been on ART before conception, and 59 (53.6%) were enrolled in the Option B+ PMTCT programme (five women untreated, eight women on other PMTCT regimens). Of the women taking ARTpc or Option B+, 81 (84.4%) commenced drug intake a minimum of 90 days before delivery, while 15 (15.6%) received Option B+ for less than 90 days (one missing data on intake duration). The median intake of Option B+ was 131 days prior to delivery. The five untreated seropositive participants showed no clinical signs of advanced disease, anaemia was documented in two cases.

Basic sociodemographic data are shown in Table 1. Participants were most frequently from Kabarole district and Batooro ethnicity. Travel distance to Virika Hospital was on average 60 min. While 168 (41.1%) women were referred for deliveries from lower level healthcare services, free of charge transport and delivery cost coverage was provided for 72 (18.7%). Almost all women (97.5%) had presented at least once to ANC services, with an average of 4 visits during the pregnancy. The majority (90.4%) of women had received Malaria prophylaxis.

HIV-infected women were significantly less often in a partner relationship compared to non-infected women ($p = 0.005$). The risk of HIV infection was negatively correlated with school education on a significant level ($p = 0.021$), and increased with parity ($p = 0.008$), and, by trend, with age ($p = 0.052$).

Obstetric and newborn data

Of the 412 women, 32.4% were primiparae, and 11.7% grand multiparae (five or more deliveries). According to their clinical history, 30.4% of women had an obstetric risk or pathologies within the current pregnancy. HIV-positive women showed increased odds for having an obstetric risk history, especially for previous SB (OR 2.5, CI 1.09–5.77, $p = 0.027$) or preterm labour (OR 5.66 CI 1.02–31.34, $p = 0.046$). 27.4% reported MIP, of which 15.8% occurred within the 3rd trimester, and 6.1% within the last 2 weeks prior to delivery. A positive peripartum bedside Malaria test was found in 13 (3.4%) cases. Average haemoglobin level was 12.23 g/dl (SD 1.98), anaemia was found in 117 (31.4%) of women at delivery.

In our study cohort, 209 male and 201 female singletons were delivered (sex not reported in two cases). Birth weight was significantly lower for female infants ($p = 0.01$). 157 newborns were delivered by caesarean

Table 1 Sociodemographic and clinical baseline data, difference by HIV status

Variables	Overall	HIV negative	HIV positive	OR[a]	CI 95%	*P* value[b]
N total (%)	412 (100)	302 (73.3)	110 (26.7)			
Age (years)[c]	25 (18–42)	25 (18–42)	26 (18–42)			0.052[d]
No. of persons in household[c]	4 (1–22)	4 (1–22)	3.5 (1–10)			0.08[d]
Single/widowed/divorced [e]	67/410 (16.3)	40 (13.3)	27 (24.8)	2.15	1.24–3.72	*0.005*
Education: primary and less[e]	242/405 (59.8)	168 (56.4)	74 (69.2)	1.74	1.09–2.78	*0.021*
Income generating activity[e]	101/394 (25.6)	69 (24.0)	32 (30.2)	1.37	0.84–2.25	0.21
Socioeconomic status: lowest category[e]	92/411 (22.4)	74 (24.6)	18 (16.4)	0.6	0.34–1.06	0.08
Travel distance to hospital ≥90 min[e]	74/374 (19.8)	61 (21.8)	13 (13.8)	0.58	0.3–1.11	0.094
Referral from other health facility[e]	168/409 (41.1)	123 (41.1)	45 (40.9)	0.99	0.64–1.55	0.97
Cost coverage grant for transport/delivery[e]	103/397 (25.9)	60 (20.3)	43 (42.2)	2.9	1.76–4.63	*<0.001*
Primiparity[e]	131/409 (32.4)	107 (35.5)	24 (21.8)	0.51	0.3–0.84	*0.008*
Grand multiparity (≥5 deliveries)[e]	48/411 (11.7)	35 (11.6)	13 (11.8)	1.02	0.52–2.01	0.96
Any obstetric risk history[e]	122/401 (30.4)	71 (24.1)	51 (48.1)	2.93	1.84–4.66	*<0.001*
Hypertension[e]	10/412 (2.4)	8 (2.6)	2 (1.8)	0.68	0.14–3.26	0.63
MIP reported[e]	110/402 (27.4)	84 (28.3)	26 (24.8)	0.84	0.5–1.39	0.49
Anaemia ≤11.5 mg/dl[e]	117/373 (31.4)	84 (29.9)	33 (35.9)	1.31	0.8–2.2	0.28
ANC attendance: yes[e]	387/397 (97.5)	286 (97.6)	101 (97.1)	0.82	0.21–3.25	0.78
No. of ANC visits[c]	4 (0–9)	4 (0–9)	4 (0–9)			0.16[d]

[a]All dichotomous variables consist of the respective attribute compared to the converse attribute and were cross tabulated against the women's serostatus. The results of the converse attribute is not displayed
[b]Bivariate, Pearson's X2 asymptotic two-sided *p*-value, if not indicated otherwise. *P*-values in italics indicate statistically significant differences between the groups
[c]median (range)
[d]Mann–Whitney-U-Test
[e]n/total n with available data (%)

section (38.6%), four (1%) by obstetric operative methods and 246 (60.4%) as spontaneous vaginal delivery (5 missing data). Basic infant data differentiated for maternal HIV serostatus is shown in Table 2.

Adverse birth outcomes

ABOs were observed in 165 (40.3%) of women (n= 409, 3 missing data for SGA), with no significant difference (p = 0.57) between male (n = 86, 41.5%) and female (n = 78, 39%) newborns. ABOs occurred in 119 (39.7%) of seronegative and 46 (42.2%) of seropositive women (p = 0.64). The difference in occurrence of SB (OR 0.81, p = 0.67), PTD (OR 1.01, p = 0.97) and SGA (OR 1.18, p = 0.63) was not significant according to serostatus (Table 3).

There was also no difference in the occurrence of ABOs between the groups of exposure to ARVs. Among the 5 HIV-positive unexposed women, there was no ABO reported apart from one woman, who had anaemia and PTD at 37 GW. Compared to seronegative women, women on ARTpc did not have a significantly elevated risk for ABO occurrence (OR 0.82, CI 0.4–1.68, p = 0.59). The same was found for women on Option B+ (OR 1.2, CI 0.68–2.11, p = 0.53). When comparing the two groups of ARV exposure, ARTpc and Option B+, to each other, there was also no significance (OR 1.46, CI 0.62-3.4, p = 0.39) in ABO risk difference. No differing ABO risk could be reported for women who took ARV drugs longer or shorter than 90 days (OR 0.55, CI 0.18–1.68, p = 0.29) as well as among ARV-exposed and HIV-negative women during first trimester (OR 0.82, CI 0.36–1.87, p = 0.64).

Stillbirth

In our cohort, 26/412 (6.3%) mothers delivered a stillborn infant. Women who had no formal education, were of poor SES, had hypertension, and who had anaemia were more likely to experience SB. SB occurred also more often to women who were referred to Virika Hospital from a distance of more than 90 min of travel time. In multivariate logistic regression, hypertension in pregnancy (AOR 18.03, CI 3.31–98.1, p = 0.001) and a travel distance to Virika Hospital of > 90 min (AOR 5.83, CI 2.21–15.42, p < 0.001) remained highly significant risk factors for SB (Table 4).

Pre-term delivery

In 116 of 410 deliveries (missing gestational age in two cases), newborns were born pre-term (28.3%). PTD was more frequent in women of poor SES, lower education, primiparity, MIP in the last 2 weeks before delivery and anaemia (Table 5). Blood haemoglobin was on average 11.9 g/dl (5.9–15.9 g/dl, SD 1.87). Protective factors against PTD were tertiary education (OR 0.39, CI 0.16–0.96, p = 0.034), and higher SES (OR 0.47, CI 0.25–0.88, p = 0.008). After logistic regression, only anaemia (AOR 1.69, CI 1.01–2.84, p = 0.047) and MIP within the last 2 weeks before delivery (AOR 2.58, CI 1.03–6.46, p = 0.044) remained risk factors for PTD.

Small for gestational age

Of 399 newborns with documented gestational duration and birth weight, 47 (11.8%) were SGA (Table 6). Comparing SGA occurrence among women with ARV intake >90 days to HIV-negative, ARV unexposed women, SGA risk was not different (Table 2). No significant correlations were found when assessing marital status, occupation, obstetric risk history, or haemoglobin level (Median 12.6 g/dl, SD 1.86, p = 0.89) for risk of SGA. In univariate analysis, women over the age of 30 years were more prone to deliver an SGA infant. If women experienced MIP, those with an SGA baby had the episode

Table 2 Basic Infant data

Variables	Overalll[a]	No HIV exposure N (%)	HIV exposure N (%)	OR	CI 95%	*P* value[b]
N total	412	302	110			
Gestational week (Finnstroem score)[c]	38 (28–42)	39 (28–42)	38 (30–42)			0.5[d]
Birth weight[c]	3095 (500–4500)	3100 (500–4500)	3040 (1200–4500)			0.821[d]
APGAR score[c]	10 (0–10)	10 (0–10)	10 (0–10)			0.34[d]
Newborn sex						
Male	209/410 (51.0)	156 (52.0)	53 (48.2)	1		
Female	201/410 (49.0)	144 (48.0)	57 (51.8)	1.17	0.75–1.8	0.49
Stillbirth	26/412 (6.3)	20 (6.6)	6 (5.5)	0.81	0.32–2.08	0.67
Preterm delivery	116/410 (28.3)	85 (28.2)	31 (28.4)	1.01	0.62–1.64	0.97
Small for gestational age	47/399 (11.8)	33 (11.3)	14 (13.1)	1.18	0.61–2.31	0.63
Any adverse birth outcome	165/409 (40.3)	119 (39.7)	46 (42.2)	1.11	0.71–1.73	0.64

[a]All data n/total n with available respective data (%), if not indicated otherwise
[b]Bivariate, Pearson's X^2 asymptotic two- sided p- value
[c]Median (range)
[d]Mann–Whitney-U-Tes

Table 3 Comparing different ARV exposure groups and adverse birth outcomes (ABOs)

Variables	Still-birth N (%) [a]	OR	CI 95%	*P* value[b]	Preterm Delivery N (%)[c]	OR	CI 95%	*P* value[b]	Small for gest. age N (%)[d]	OR	CI 95%	*P* value[b]	Any ABO N (%)	OR	CI 95%	*P* value[b]
Drug exposure	25				112				44				158			
HIV negative	20 (6.6)	1			85 (28.2)	1			33 (11.3)	1			119 (39.7)	1		
ART pre-conception	3 (7.9)	1.21	0.34–4.28	0.73[e]	11 (28.9)	1.04	0.49–2.18	0.93	3 (8.3)	0.71	0.21–2.46	0.78[e]	13 (35.1)	0.82	0.4–1.68	0.59
Option B+	2 (3.4)	0.5	0.11–2.18	0.55[e]	16 (27.6)	0.97	0.52–1.81	0.92	8 (13.8)	1.3	0.55–2.88	0.59	26 (44.1)	1.2	0.68–2.11	0.53
ARV regimens	5				27				11				39			
ART pre-conception	3 (7.9)	1			11 (28.9)	1			3 (8.3)	1			13 (35.1)	1		
Option B+	2 (3.4)	0.41	0.07–2.57	0.38[e]	16 (27.6)	0.94	0.38–2.32	0.89	8 (13.8)	1.76	0.44–7.12	0.52[e]	26 (44.1)	1.46	0.62–3.4	0.39
Drug initiation[f]	5				27				11				39			
ARV exposure after GW 14	2 (4.3)	1			12 (26.7)	1			6 (13.3)	1			20 (43.5)	1		
ARV exposure before GW 14	3 (6.0)	1.4	0.22–8.81	1[e]	15 (30.0)	1.18	0.48–2.89	0.72	5 (10.4)	0.76	0.21–2.67	0.66	19 (38.8)	0,82	0.36–1.87	0.64
Any ARV intake ≥90 days prior delivery	5 (6.2)	1			21 (26.3)	1			8 (10.3)	1			8 (53.5)	1		
Any ARV intake <90 days prior delivery	0 (0)	0.84	0.76–0.92	1[e]	6 (40.0)	1.87	0.6–5.9	0.35[e]	3 (20.0)	0.46	0.11–1.97	0.38[e]	31 (38.8)	0.55	0.18–1.68	0.29
Exposure time	25				112				44				158			
HIV negative	20 (6.6)	1			85 (28.2)	1			33 (11.3)	1			119 (39.7)	1		
ARV exposure before GW 14	3 (6.0)	0.9	0.26–3.15	1[e]	15 (30.0)	1.09	0.57–2.1	0.8	5 (10.4)	0.91	0.34–2.47	0.86	19 (38.8)	0.96	0.52-1.79	0.91
Any ARV intake ≥90 days prior delivery	5 (5.2)	0.78	0.28–2.12	0.62	27 (28.4)	1.01	0.61–1.68	0.97	11 (11.8)	1.05	0.51–2.18	0.89	39 (41.1)	1.06	0.66–1.69	0.81
PMTCT intake prior delivery in days, Median (range)	135 (126–144)			0.86[g]	113,5 (14–278)			0.6[g]	125 (19–232)			0.73[g]	129 (14–278)			0.71[g]

[a]Total SB: 26; number excludes one woman who was on Option A at the time of delivery
[b]all data are bivariate, Pearson's X^2 asymptotic two- sided *p*- value, apart from where indicated differently
[c]Total PTD: 116; number excludes three women on Option A and one HIV positive woman without ARV treatment
[d]Total SGA: 47; number excludes two women on Option A and one woman with undocumented PMTCT regimen
[e]Bivariate Fisher's Exact test two- sided *p*- value
[f]One woman on Option B+ excluded due to missing drug initiation date
[g]Mann–Whitney-U Test

Table 4 Adverse birth outcome: Stillbirth (SB)

Variables	SB[a,b]	OR	CI 95%	P- value[c]	AOR	CI 95%	*P*- value
N Total	26						
Age	26						
<30 year	19 (6.2)	1					
≥30 year	7 (6.7)	1.08	0.44–2.65	0.86			
Education	26						
Primary and higher	21 (5.5)	1					
No formal education	5 (21.7)	4.78	1.62–14.12	*0.011*[d]	1.12	0.22–5.67	0.89
Occupation	26						
Income generation	5 (5.0)	1					
No income generation	21 (7.2)	1.48	0.54–4.04	0.44			
Socioeconomic status (SES)	26						
Higher SES (≥1 assets)	15 (4.7)	1					
Lowest SES (0 assets)	11 (12.0)	2.75	1.22–6.22	*0.012*	1.89	0.69–5.17	0.21
Parity	26						
Primiparity	7 (5.3)	1					
Multiparity (≥2 deliveries)	19 (6.8)	1.29	0.53–3.15	0.58			
Travel distance	24						
<90 min	11 (3.7)	1					
≥90 min	13 (17.6)	5.6	2.4–13.1	*<0.001*[d]	5.83	2.21–15.42	*<0.001*
Hypertension	26						
No hypertension	22 (5.5)	1					
Hypertension	4 (40)	11.52	3.03–43.81	*0.002*	18.03	3.31–98.1	*0.001*
Malaria in pregnancy	26						
No MIP detected peri-partum	24 (6.4)	1					
MIP detected peri-partum	2 (15.4)	2.64	0.55–12.61	0.22[d]			
MIP >3rd trimester	3 (4.6)	1					
MIP ≤2nd trimester or no MIP	23 (6.6)	1.47	0.43–5.04	0.78[d]			
Anaemia ≤11.5 mg/l	24						
No	12 (4.7)	1					
Yes	12 (10.3)	2.32	1.01–5.34	*0.042*	2.26	0.88–5.84	0.09

[a]All data N (%)
[b]Percentages refer to the number of participants with available data on respective variable
[c]Bivariate, Pearson's X^2 asymptotic two-sided *p*-value if not indicated otherwise. *P*-values in italics indicate statistically significant differences between the groups
[d]Bivariate, Fisher's Exact test two- sided *p*- value

significantly later in pregnancy (Median 34.0 GW versus 28 GW, $p = 0.02$). After logistic regression, MIP in the third trimester was still a significant risk factor for SGA (Table 6).

Discussion

This cross-sectional, observational study assessed the occurrence of ABOs and their associations with maternal HIV status, ARV exposure and other influencing factors in a Western Ugandan health facility. PMTCT- Option B + had recently been introduced here, and this is the first study to investigate possible associations between ABOs and Option B+ in this region.

In our cohort, the overall rate of ABOs was alarmingly high, and only few other studies, albeit also conducted in referral institutions, have reported similarly high rates [38–41].

Maternal ARV intake and maternal HIV infection have both been known to be potential risk factors for ABOs. While increased ABO risk is frequently reported for seropositive untreated women compared to HIV-negative women [42–44], we did not find a significant difference among seropositive women receiving ARVs and seronegative women. These results are in line with other publications [17, 39, 45–49]. The majority of HIV-positive women in our study had reported ARV

Table 5 Adverse birth outcome: Pre- term delivery (PTD)

Variables	PTD[a,b]	OR	CI 95%	P-value[c]	AOR	CI 95%	*P*- value
N total	116						
Age	116						
<30 year	84 (27.5)	1					
≥30 year	32 (30.8)	1.18	0.72–1.91	0.52			
Education	114						
Tertiary	6 (14.3)	1					
Secondary and less	108 (29.8)	2.55	1.04–6.23	*0.034*	1.67	0.63–4.4	0.3
Socioeconomic status (SES)	115						
Higher SES (≥1 assets)	79 (24.9)	1					
Lowest SES (0 assets)	36 (39.1)	1.94	1.19–3.16	*0.008*	1.48	0.72–3.06	0.29
ANC attendance	111						
Yes	106 (27.4)	1					
No	5 (62.5)	4.42	1.04–18.81	*0.043*[d]	5.42	0.88–33.54	0.07
Parity	115						
Multiparity (≥2 deliveries)	68 (24.5)	1					
Primiparity	47 (35.9)	1.73	1.1–2.71	*0.017*	1.61	0.96–2.69	0.07
Malaria in pregnancy							
No MIP detected peri-partum	102 (27.5)/108	1					
MIP detected peri-partum	6 (46.2)	2.26	0.74–6.89	0.2			
MIP >2 weeks prior deliv. or no MIP	98 (26.1)/110	1					
≤2 weeks prior delivery	12 (48.0)	2.61	1.15–5.91	*0.018*	2.58	1.03–6.46	*0.044*
MIP >3rd trimester	17 (26.2)/116	1					
MIP ≤2nd trimester or no MIP	99 (28.7)	1.14	0.62–2.07	0.68			
Anaemia ≤11.5 mg/l	99						
No	60 (23.5)	1					
Yes	39 (33.6)	1.65	1.02–2.67	*0.04*	1.69	1.01–2.84	*0.047*

[a]All data N (%)
[b]Percentages refer to the number of participants with available data on respective variable
[c]Bivariate, Pearson's X^2 asymptotic two-sided *p*- value if not indicated otherwise. *P*-values in italics indicate statistically significant differences between the groups
[d]Bivariate, Fisher's Exact test two- sided *p*- value

exposure (ART or Option B+) exceeding 90 days, with presumably favourable effect on viral load and immunologic response by the time of delivery. Hence, our findings suggest a levelling-out effect of ARVs with respect to HIV infection as a risk factor for ABOs.

Among HIV-positive study participants, having started drug intake before conception (ARTpc) did not lead to a difference in ABO risk compared to having started only in pregnancy (Option B+). This is in accordance with findings from other studies, e.g. regarding PTD [22, 50] and SGA [17, 21, 48, 49]. For SB, our finding contradicts previous research, where higher risk for SB was reported among ARV-exposed women when intake started prior conception or early in pregnancy [11–13, 24, 40]. However, Cotter et al. [17] also did not observe risk differences for SB in relation to pre-conception ARV exposure. Among those initiating drug intake during pregnancy, length of Option B+ intake prior delivery did not play a significant role in our cohort.

In line with other studies, no difference was found for SGA risk among women taking ARV drugs and their seronegative counterparts. Several studies observed increased risks for PTD for women exposed to ARTpc containing PIs, probably caused by altered maternal progesterone levels [21, 24, 51, 52]. In our observational setting, apart from one woman, none took a regimen comprising PIs. The exposure to ARV combinations used in this study (N(t)RTIs and NNRTIS) did not have an increased risk for PTD and SB when compared to HIV-negative women, even if taken very early or throughout pregnancy. This confirms the result of other studies [17, 20, 34, 40, 53, 54]. At the same time, Marazzi et al. [34] could show a dramatic decrease of SB rate in women on ARV therapy compared to non-treated

Table 6 Adverse birth outcome: Small for Gestational Age (SGA)

Variables	SGA[a,b]	OR	CI 95%	P- value[c]	AOR	CI 95%	*P*- value
N total SGA	47						
Age	47						
≥30 year	7 (6.9)	1					
<30 year	40 (13.5)	2.11	0.92–4.88	*0.049*	2.09	0.9–4.85	0.085
Education	47						
No formal education	2 (9.1)	1					
Primary and higher	45 (12.1)	1.38	0.31–6.09	1.0[d]			
Socioeconomic status (SES)	47						
Higher SES (≥1 asset)	37 (12.0)	1					
Lowest SES (0 assets)	10 (11.1)	0.92	0.44–1.93	0.82			
Parity	47						
Grand multiparity ≥5 deliveries	2 (4.2)	1					
Parity ≤4 deliveries	45 (12.7)	3.21	0.75–13.72	0.1			
Malaria in pregnancy	47						
MIP detected peri-partum	1 (7.7)	1					
No MIP detected peri-partum	44 (12.2)	1.67	0.21–13.12	1.0[d]			
MIP ≤2nd trimester or no MIP	34 (10.6)	1					
MIP >3rd trimester	13 (20.3)	2.26	1.12–4.57	*0.02*	2.24	1.1–4.54	*0.026*
Anaemia ≤11.5 mg/l	46						
Yes	13 (11.8)	1					
No	31 (12.4)	1.06	0.53–2.11	0.88			

[a]All data N (%)
[b]Percentages refer to the number of participants with available data on respective variable
[c]Bivariate, Pearson's X^2 asymptotic two-sided *p*- value if not indicated otherwise. *P*-values in italics indicate statistically significant differences between the groups
[d]Bivariate, Fisher's Exact test two- sided *p*- value

seropositive women. Hence, the potential toxicity of ARVs might be counterbalanced by the positive effect of the drugs on maternal HIV infection. ART programmes are being extensively scaled-up in most HIV-endemic countries, and therefore constantly increasing numbers of women in reproductive age will be enrolled in ART in the near future, while at the same time, more and more women will continue ART lifelong in the course of Option B+. Therefore it is an encouraging finding that ARV exposure does not seem to increase the risk for ABOs, even if taken for a long time.

In our study, ABO risk was negatively correlated to educational level and SES, a finding that has been well described in other settings [38, 55, 56]. We identified a number of clinical preconditions significantly linked with ABOs. A history of ABO was a predictor for repeated occurrence of the same event, which confirms previous research in other similar settings [38, 39, 43, 55, 57]. An increased risk of SB for women in our study with hypertension was accordingly reported in other studies [38, 56]. We also found that primigravid women were more prone to deliver a pre-term infant, supporting findings from Taha et al. [58]. Maternal anaemia was strongly correlated with SB and PTD in our study, also described by Watson-Jones et al. and Turner [55, 59]. Even though ANC at Virika Hospital routinely provides ferrous sulphate and folic acid, this does not seem to be enough to tackle the problem of anaemia. Laboratory haemoglobin testing during the antenatal period could help to filter out anaemic women and treat them according to the cause of anaemia. In general, our findings suggest that ANC surveillance to identify women with risk parameters needs to be strengthened, including assessment of the socio-economic situation and thorough history taking. Adequate blood pressure monitoring and early treatment of these women will contribute to lower the risk for ABOs. SB occurred to many women who were referred due to obstetrical complications. In line with other research [56], women with higher distance to the referral site and thus increased danger of foetal distress experienced SB more frequently. This implies that there is still need to improve the triage system for warning signs of ABO at the smaller health centres. Women with risk factors need to be referred already at ANC level, or early after their arrival for delivery. Also, better access, financially and transport-wise, needs to be reinforced to

reach women in urgent need for adequate handling of risk pregnancies/deliveries. In our study setting, transport and cost coverage were provided to a part of the women, but these programs need to be expanded, and further research evaluating strategies for increasing accessibility is urgently required.

MIP turned out to be an important predictor of ABO occurrence. There was a strong correlation between MIP occurring later in pregnancy and SGA (3rd trimester) as confirmed by Schmiegelow et al. [60], who found that sonographically assessed foetal growth was altered by MIP especially in the last trimester, even if women consequently received antimalarial treatment. Rijken et al. [61] found that a single or even asymptomatic MIP episode could cause foetal growth alteration. Landis et al. [62] observed high rates of SGA (29%) confirmed by ultrasound, equally linked with MIP. Similarly, we observed a higher occurrence of PTD for women with MIP within the last 2 weeks prior delivery, congruent with findings of other authors [63, 64]. MIP remains a crucial risk factor for ABO until late pregnancy [65, 66]. This implies a revision of strategies to prevent MIP for all women. Other research focussing on MIP in our study setting found that intermittent preventive treatment in pregnancy recommended for the region might no longer be adequate. High resistance of *Plasmodium falciparum* towards intermittent preventive treatment with sulfadoxine/pyrimethamine was detected, as reported in detail elsewhere [37]. Thus, immediate action is required to provide effective prophylaxis against MIP also with respect to ABO reduction in this setting.

Partly explained by the nature of our observational study setting, this research had some limitations. Since the number of ARV-unexposed seropositive women was very low, "HIV status" as an isolated risk factor as opposed to "ARV exposure" could not be assessed in this cohort. However, since the subgroup of HIV-infected while ARV-unexposed pregnant women will in general gradually disappear thanks to the universal scale-up of ART and Option B+, we believe that in the context of implementation research, it is not any longer a highly relevant comparison group. As another limitation, hospital staff often omitted peripartum HIV tests among presumably seronegative women, and we had to exclude numerous delivering women due to unconfirmed serostatus. Participants were also excluded due to missing newborn data. Infants who were stillborn or highly unstable after delivery were in some cases not assessed and weighed. However, the overall sample size is still considered large enough to provide valid findings with regard to our study question. We acknowledge that there might be other co- factors and conditions which were not assessed in our study, but which may also have played a role in influencing ABOs, like gestational diabetes or sexually transmitted infections, and these should be considered in future studies. Furthermore, we assessed gestational age with the Finnstroem score method. Finnstroem et al. describe a possibility of variation of up to 3 weeks in estimation of the GW through their method [30], so some misclassification is possible, especially in the transition zone of pre-term and term delivery. Lastly, regarding MIP as an important predictor for ABO, retrospective self-reported occurrence, timing and frequency of MIP need to be seen in the light of potential reporting bias. The same applies for the timing and intake of ARVs, antimalarial treatment and prophylaxis, as far as not noted on the ANC cards, as well as for obstetric and clinical history.

Conclusions

While observed rates for ABOs in our study setting were overall considerably high, we did not find an adverse effect on birth outcomes for infants exposed to ARVs including both ARTpc and Option B+, independently from maternal intake duration. This is a promising result in the light of further roll- out of Option B+ and ART programmes in Subsaharan-African settings, especially considering the most recent "test and treat"- approach intending immediate treatment start for all HIV- infected individuals including pregnant women pursued by the WHO as well as by the Ugandan Ministry of Health after 2014 [8, 67]. Some other identified risk factors for ABOs, like hypertension, anaemia or delayed care caused by long travel distance might be avoided by improvement of ANC services, including better clinical screening and triage systems for timely referral. Also, effective preventive measures against MIP are urgently required to protect newborns from undesirable birth outcomes.

Abbreviations

3TC: Lamivudine; ABO: Adverse birth outcome; ANC: Ante natal care; APGAR: Vigilance score for newborns developed by Victoria APGAR; APO: Adverse pregnancy outcome; ART: Anti-retroviral therapy; ARTpc: Highly active antiretroviral therapy, commenced prior conception of the pregnancy; ARV: Anti-retroviral; AZT: Zidovudine; EFV: Efavirenz; GW: Gestational week; HB: Haemoglobin; HIV: Human immunodeficiency virus (Type 1); IPTp: Intermittent preventive treatment in pregnancy (against Malaria); MIP: Malaria in pregnancy; N(t)RTI: Nucleoside (Nucleotide) reverse transcriptase inhibitor; NNRTI: Non- nucleoside reverse transcriptase inhibitor; Option A: ARV regimen to prevent vertical transmission of HIV, using AZT and Co- trimoxazole after GW 14 for PMTCT; OPTION B+: Regimen used to prevent vertical transmission of HIV, comprising TDF, 3TC and EFV; PMTCT: Prevention of mother-to-child-transmission of HIV; PTD: Preterm delivery; SB: Stillbirth; SES: Socioeconomic status; SGA: Small for gestational age; TDF: Tenofovir; WHO: World Health Organisation

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Availability of data and materials
Our original dataset is not presented within the manuscript or publicly deposited, because despite strictly confidential data collection, women might be identifiable on the basis of the information. However, the dataset and all materials are available upon reasonable request from the corresponding author.

Authors' contributions
Study design: JR, NMT, PB, GH, ST. Patient recruitment, data collection: ER, AS, SD, VB. Data analysis and paper draft: ER and ST. Contributions to writing and approval of the final manuscript: ER, AS, SD, VB, JR, NMT, PB, GH, ST.

Competing interests
The authors declare that they have no competing interest.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The present study was approved by the Higher Degrees, Research, and Ethics Committee, College of Health Sciences, Makerere University, Kampala as well as by the Uganda National Council for Science and Technology (protocol number HDREC 193). Participation in the study was voluntary, and women were enrolled after informed and written consent. All data was strictly confidentially collected and stored, and processed anonymously.

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Komplette Publikationsliste

1. **Schnack A**, Rempis E, Decker S, Braun V, Rubaihayo J, Busingye P, Tumwesigye NM, Harms G, Theuring S. Prevention of Mother-to-Child Transmission of HIV in Option B+ Era: Uptake and Adherence During Pregnancy in Western Uganda. *AIDS Patient Care and STDs*. 2016; Mar 30; 110-8. Impact Factor: 3.578

2. Decker S, Rempis E, **Schnack A**, Braun V, Rubaihayo J, Busingye P, Tumwesigye NM, Harms G, Theuring,S. Prevention of Mother-to-Child Transmission of HIV: Postpartum adherence to Option B+ until 18 months in Western Uganda*., PLoS One.* 2017; Jun 29; 12(6): e0179448. Impact Factor: 3.54.

3. Rempis, E, **Schnack A**, Decker S, Braun V, Rubaihayo J, Busingye P, Tumwesigye, NM, Harm G, Theuring, S. Option B+ for prevention of vertical HIV transmission has no influence on adverse birth outcomes in a cross-sectional cohort in Western Uganda. *BMC Pregnancy and Childbirth*. 2017; Mar 7;17(1):82. Impact Factor: 2.263.

4. Braun V, Rempis E, **Schnack A**, Decker S, Rubaihayo J, Tumwesigye NM, Theuring S, Harms G, Busingye P, Mockenhaupt FP. Lack of effect of intermittent preventive treatment for malaria in pregnancy and intense drug resistance in western Uganda *Malaria Journal*. 2015; Sep 26;14:372. Impact Factor: 2.715.

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