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Habilitationsschrift

Herausforderungen in der Implementierung von Präventionsmaßnahmen für die Mutter-Kind-Übertragung von HIV in Ostafrika

zur Erlangung der Lehrbefähigung für das Fach Experimentelle Tropenmedizin
vorgelegt dem Fakultätsrat der Medizinischen Fakultät
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Abkürzungen

3TC	Lamivudin
ANC	*Antenatal Care*; Schwangerschaftsvorsorge
ART	Antiretrovirale Therapie
ARV	antiretroviral
AZT	Zidovudin
CTC	*Care and Treatment Center*; ART-Behandlungszentren
CVCT	*Couple Voluntary Counselling and Testing*; Gemeinsame Paarberatung und HIV-Testung
HIV	Humanes Immundefizienz-Virus
NVP	Nevirapin
PMTCT	*Prevention of mother-to-child transmission of HIV*; Prävention der Mutter-Kind-Übertragung von HIV
SGA	*Small for gestational age;* In der Reifeentwicklung verzögert
LTFU	*Lost to follow up;* Vorzeitig aus der Nachverfolgung ausgeschieden
UNAIDS	*Joint United Nations Programme on HIV/AIDS*
WHO	*World Health Organisation*

1. Einleitung

Weltweit lebten im Jahr 2016 knapp 37 Millionen Menschen mit dem Humanen Immundefizienz-Virus (HIV). Die Hauptlast der globalen HIV-Epidemie trägt die Region Subsahara-Afrika; dort leben zwar nur 12% der globalen Bevölkerung, jedoch 70% aller Menschen, die mit HIV infiziert sind (Kharsany et al. 2016; UNAIDS 2017).

Frauen sind mit knapp 60% aller Infektionen in Subsahara-Afrika überproportional von HIV betroffen (UNAIDS 2017). Der Hauptübertragungsweg in dieser Region mit einer generalisierten, nicht auf spezifische vulnerable Bevölkerungsgruppen konzentrierten Epidemie ist der heterosexuelle Geschlechtsverkehr. Gleichzeitig geht damit jedoch eine HIV-Epidemie bei Kindern einher, welche sich bei ihren Müttern durch vertikale Übertragung während Schwangerschaft, Geburt oder Stillzeit durch mütterliches Blut, Vaginalsekret oder Muttermilch infiziert haben (Kharsany et al. 2016). So lebten im Jahr 2016 weltweit über 2 Millionen Kinder unter 15 Jahren mit HIV, von denen ca. 98% vertikal mit dem Virus infiziert wurden (UNAIDS 2017). Ohne präventive Intervention liegt das Übertragungsrisiko von Mutter zu Kind in Abhängigkeit von vielfältigen Faktoren, wie z.B. der Viruslast der Mutter, dem Geburtsverlauf oder der Stilldauer, bei 20-45%. Dieses Übertragungsrisiko kann auch in ressourcenlimitierten Ländern auf unter 2-5% reduziert werden, wenn die mütterliche Viruslast während Schwangerschaft, Geburt und Stillzeit durch die Einnahme antiretroviraler (ARV) Medikamente adäquat gesenkt wird. (WHO 2010)

1.1. Hintergrund zur Prävention der Mutter-Kind-Übertragung von HIV

Die Prävention der Mutter-Kind-Übertragung von HIV (*prevention of mother to child transmission of HIV,* PMTCT) durch ARV-Medikamente durchlief in den letzten beiden Jahrzehnten mehrfache, die Wirksamkeit stetig steigernde Entwicklungen, und stellt in dem bis heute erreichten Maß an Effektivität und Zugänglichkeit der Medikamente einen der größten Public-Health-Erfolge der jüngeren Geschichte dar (Kellermann et al. 2013). Der deutliche Rückgang von HIV-Neuinfektionen im Kindesalter, von ca. 500.000 Fällen im Jahr 2000 auf ca. 300.000 jährliche Fälle zehn Jahre später, veranlasste führende internationale Gesundheitsbehörden wie UNAIDS und WHO bereits im Jahr 2011 zum Postulat einer „*AIDS-free generation*“, die faktisch durch die weltweite Eliminierung der Mutter-Kind-Übertragung von HIV geschaffen werden soll (UNAIDS 2011; WHO 2014; UNAIDS 2017).

1.1.1. Chronologische Übersicht früherer PMTCT-Regime

Die Entwicklung hin zu einem hocheffektiven PMTCT-Medikamentenregime, wie es heute angewendet wird, begann zu einem frühen Zeitpunkt der globalen HIV-Epidemie um die Jahrtausendwende zunächst mit einer einmaligen Gabe des nichtnukleosidischen Reverse-Transkriptase-Inhibitors Nevirapin (NVP) während der Geburt. Diese Einmaldosis für die Mutter zu Beginn der Wehen, sowie für das Neugeborene direkt nach Geburt, hatte den Vorteil, sehr preisgünstig und einfach in der Verabreichung zu sein. Sie senkte jedoch das vertikale Transmissionsrisiko nur um etwa 40%, ohne Schutz vor Übertragung während der Schwangerschaft oder der Stillzeit. Gleichzeitig bestand die hohe Gefahr einer Resistenzbildung gegen NVP, welche zu Komplikationen für die Behandlung der Mutter bei progredientem Verlauf der Infektion führen kann. (Stringer et al. 2003; Hauser et al. 2013)

Die Effektivität des NVP-Einfachregimes konnte durch Ergänzung der nukleosidischen Reverse-Transkriptase-Inhibitoren Zidovudin (AZT) und Lamivudin (3TC) verbessert werden (Dabis et al. 2005). Dieses Kombinationsregime zur Einnahme während Schwangerschaft und Geburt wurde seit 2006 als PMTCT-Standardmaßnahme ab der 28. Schwangerschaftswoche, seit 2010 bereits ab der 14. Schwangerschaftswoche empfohlen (WHO 2006; WHO 2010a). Trotz einer deutlich niedrigeren Transmissionsrate im Vergleich zur Einmaldosis NVP, bei gleichzeitig verringertem Risiko der Resistenzbildung, beinhaltete dieses Behandlungsschema weiterhin keinen Schutz des Säuglings vor Infektion während der Stillzeit. Des Weiteren erwies sich das Regime in der Anwendung als höchst komplex, da es die Einnahme unterschiedlicher Medikamente zu verschiedenen Zeitpunkten erforderte und bei mehreren Schwangerschaften wiederholt durchgeführt und wieder abgesetzt werden musste. Operationale Studien zur Umsetzbarkeit des Ansatzes zeigten, dass dies häufig nicht praktikabel für schwangere Frauen in ressourcenlimitierten, insbesondere ländlichen Regionen war (Kirsten et al. 2011). Entsprechend ließ sich die angenommene Transmissionsreduktion auf <5% in einem *real life*-Szenario in Tansania nicht bestätigen; dort lag die Übertragungsrate mit 14% weitaus höher (Hauser et al. 2012).

Um den Schutz des Neugeborenen vor einer vertikalen Transmission auf den gesamten Zeitraum des Stillens auszuweiten, veröffentlichte die WHO im Jahr 2010 eine Neuerung der PMTCT-Empfehlungen. Hierbei wurde zwischen den weiterhin nur zur Transmissionsprophylaxe vorgesehenen, aber die Stillzeit mitumfassenden

Optionen A und B unterschieden. Während Option A die bis dahin empfohlene mütterliche Kombinationsprophylaxe aus AZT, NVP und 3TC mit einer anschließenden täglichen Gabe von NVP-Sirup an den Säugling während der gesamten Stilldauer verband, beinhaltete Option B im Gegensatz dazu, dass die Mutter eine dreifache Kombinationsprophylaxe von der Schwangerschaft bis in die Stillzeit fortführen und nach dem Abstillen absetzen sollte (WHO 2010a).

Alle im vorherigen Teil beschriebenen, zeitlich begrenzten PMTCT-Regime wurden in die allgemeine Schwangerenvorsorge (*antenatal care*, ANC) integriert angeboten und richteten sich lediglich an HIV-positive schwangere Frauen, die keine Indikation für eine antiretrovirale Therapie (ART) aufwiesen, da sie über eine CD4-Zellzahl von >350 Zellen/µl verfügten (WHO 2006). Schwangere mit einem CD4-Wert ≤350 Zellen/µl wurden hingegen nicht als temporäre PMTCT-Klientinnen behandelt, sondern aufgrund dieser Indikation in allgemeine ART-Behandlungszentren überwiesen, um dort unabhängig von ihrer Schwangerschaft eine lebenslange Therapie zu beginnen. Dies bedeutete in der Praxis, dass schwangere Frauen mit einem positiven HIV-Testergebnis erst eine Laboruntersuchung zur Ermittlung der CD4-Zellzahl abwarten mussten, bevor sie in eines der beiden Schemata, temporäre Prophylaxe oder lebenslange ART, übernommen wurden. In ländlichen Gebieten Subsahara-Afrikas stellte diese Laboruntersuchung häufig eine unrealistische Anforderung an die primären Gesundheitseinrichtungen dar, und verursachte durch damit verbundene Wartezeiten in Kombination mit mangelhaften Transportmöglichkeiten der Patientinnen vielfach ein Ausscheiden aus der Versorgung noch vor Beginn der Behandlung.

Um diesem Missstand entgegenzuwirken, beinhaltete die WHO-Empfehlung von 2010 über Option A und B hinaus auch das nicht zeitlich begrenzte PMTCT-Regime Option B+, welches im folgenden Abschnitt näher erläutert wird.

1.1.2. Die Einführung von Option B+: *Test and treat*

Option B+ gilt seit 2010 als internationale PMTCT-Standardempfehlung und steht für eine Vereinheitlichung von PMTCT-Maßnahme und ART. Option B+ sieht bei allen schwangeren Frauen den unmittelbaren Beginn einer lebenslangen ART vor, sobald sie HIV-positiv getestet wurden (WHO 2010a). Hierdurch entfällt die Labordiagnostik zur Unterscheidung in Frauen mit Therapieindikation und Frauen mit vorübergehendem Prophylaxebedarf, da alle HIV-positiven schwangeren Frauen in

gleicher Weise weiterbetreut werden. Diese Vereinfachung des Prozedere ermöglicht den Zugang zu ART auch an kleineren, peripheren Gesundheitszentren ohne Laborausstattung, und trägt dadurch dazu bei, möglichst viele Frauen mit der PMTCT-Intervention zu erreichen (Schouten et al. 2011). Gleichzeitig erhöht der sofortige Beginn der ARV-Behandlung ohne Zeitverlust nach HIV-Diagnose die Effektivität der Maßnahme, da für die notwendige Senkung der mütterlichen Viruslast eine mindestens 13-wöchige pränatale Medikamenteneinnahme erforderlich ist (Chibwesha et al. 2011). Des Weiteren wird unter bestehender ART eine fetale HIV-Exposition bereits ab dem Zeitpunkt der Konzeption verhindert. Option B+ bietet damit auch in Hinsicht auf Multiparität, die in den Ländern Subsahara-Afrikas mit überwiegend hohen Fertilitätsraten der Regelfall ist, kontinuierlich hohen Schutz vor Übertragung für alle folgenden Schwangerschaften (Gopalappa et al. 2014; Etoori et al. 2018). Durch die fortdauernde Einnahme einer Kombinationstherapie werden Medikamentenresistenzen, die die Wirksamkeit des Schutzes beeinträchtigen können, zudem langfristig vermieden (Hauser et al. 2012; Machnowska et al. 2017). Ein zusätzlicher Vorteil des Option B+-Regimes ist der Schutz vor Virustransmission auf sexuelle Partner HIV-positiver Frauen im Falle von serodiskordanter Partnerschaft. Während eine Untersuchung in Lesotho zeigte, dass ca. 15% aller heterosexuellen Partnerschaften von diskordantem HIV-Status betroffen sind (MoH Lesotho 2014), kann durch ART beim HIV-positiven Partner die HIV-Transmission innerhalb der Partnerschaft weitgehend verhindert werden (Schouten et al. 2011; Gopalappa et al. 2014). Option B+ bietet also nicht nur die bestmögliche Maßnahme gegen die durch vertikale Transmission verursachte HIV-Epidemie bei Kindern in Subsahara-Afrika, sondern gleichzeitig auch ein wirkungsvolles präventives Instrument für die allgemeine Bevölkerung, und stellt damit eine Schlüsselkomponente der *„Treatment as Prevention*“- Strategie im Kampf gegen die globale HIV-Epidemie dar (Hull et al. 2014).

1.1.3. Umsetzung von PMTCT in *real life*-Settings

Trotz der beschriebenen medikamentösen Möglichkeiten zur Verhinderung der Mutter-Kind-Transmission ging die Anzahl der pädiatrischen Neuinfektionen in den letzten Jahren nicht so stark zurück wie erwartet. Im Jahr 2016 wurden weltweit noch immer 160.000 Kinder neu mit dem Virus infiziert, davon 86% in Subsahara-Afrika (UNAIDS 2017). Diese Zahl erscheint angesichts der Tatsache, dass hocheffektive Medikamente für PMTCT existieren und in Ländern Subsahara-Afrikas durch Generikahersteller billig verfügbar sind, inakzeptabel hoch (Hill et al. 2016). In

Hochprävalenzländern wie Uganda lag die Anzahl der pädiatrischen Neuinfektionen im Jahr 2013 mit einer Transmissionsrate von weiterhin etwa 11% bei ca. 13.000 Fällen (UNAIDS 2016). Dies traf zu, obwohl Option B+ im Jahr 2012 landesweit eingeführt worden war, und obwohl zu diesem Zeitpunkt der Großteil der schwangeren Frauen des Landes Zugang zu HIV-Testung und ARV-Medikamenten hatte.

Die Vermutung liegt damit nahe, dass klinische Studien, in denen sich PMTCT-Maßnahmen seit der Einführung von Kombinationsregimes zumeist als hocheffektiv erwiesen, häufig nicht die Realität tatsächlicher Implementierungsbedingungen reflektieren, und dass der wirksamen Umsetzung in *real life*-Settings oftmals strukturelle, logistische und persönliche Handlungsbarrieren entgegenstehen (O´hIarlaithe et al. 2014). Die Besonderheit einer PMTCT-Intervention im Vergleich zu anderen präventiven Gesundheitsmaßnahmen begründet sich, so legen frühere Untersuchungen nahe, zum einen in der grundsätzlichen sozialen und ökonomischen Vulnerabilität schwangerer Frauen, zum anderen in der gleichzeitigen Komplexität der Maßnahme, welche auf zahlreichen sequentiellen Entscheidungsschritten über den langandauernden Zeitraum zwischen Beginn der Schwangerschaft und Ende der Stillzeit hinweg aufbaut (Theuring et al. 2009; Gimbel et al. 2014). Dies führt zu einem hohen Risiko bei PMTCT-Klientinnen, mit der Intervention von vorneherein gar nicht zu beginnen, oder sie im späteren Verlauf abzubrechen.

1.1.4. Einflussfaktoren auf die erfolgreiche PMTCT-Durchführung

Intrinsische und extrinsische Einflussfaktoren auf die erfolgreiche Durchführung einer PMTCT-Maßnahme wirken multifaktoriell, und sind häufig untereinander eng verflochten. Gleichzeitig sind sie kulturell und geographisch hochvariabel und unterscheiden sich oftmals schon innerhalb verschiedener Gemeinden einer Region (Anigilaje et al. 2016). Als extrinsische Faktoren gelten neben der Erreichbarkeit von Gesundheitseinrichtungen vor allem auch durch das Gesundheitssystem selbst bedingte Barrieren. Hierzu zählen unter anderem schlecht ausgebildetes oder zu wenig dauerhaft angestelltes Personal, Mangel an HIV-Testkits oder ARV-Medikamenten in Krankenhäusern, oder mangelhaft koordinierte/verzögerte Abläufe (Kirsten et al. 2011, Gourlay et al. 2013). Darüber hinaus stellt aber auch das soziale Umfeld aus Partnerschaft, Familie oder Gemeinde eine hocheinflussreiche äußere Komponente für Entscheidungsprozesse einer schwangeren Frau dar. Dies kann sich zum Teil positiv auswirken, beispielsweise durch Unterstützung des Partners oder

Selbsthilfegruppen innerhalb einer Gemeinde; aber auch negative Beeinflussung ist möglich, z.B. durch gesellschaftliche Diskriminierung (Gourlay et al. 2013). Intrinsische PMTCT-Handlungsbarrieren hingegen lassen sich nach O´hlarlaithe et al. (2014) vor allem in folgende Untergruppen aufteilen:

- Soziale Normen und Wissensstand (z.B. mangelnde Entscheidungsautorität der Frau, fehlende Kenntnis des HIV-Status)
- Sozioökonomischer Status (z.B. hohe Anzahl von Kindern, hohe Arbeitsbelastung, mangelnde finanzielle Mittel für Transport)
- Klinischer Status (z.B. das Fehlen von Krankheitssymptomen)
- Psychologische Verfassung (z.B. Angst vor negativen Reaktionen, Verdrängung)

Zahlreiche der hier genannten Einflussfaktoren verhinderten bisher auch in Ländern wie Tansania oder Uganda trotz flächendeckender Einführung von PMTCT-Maßnahmen die dauerhafte Eliminierung von pädiatrischer HIV-Infektion. Gleichzeitig war zum Durchführungszeitpunkt der hier vorgestellten Arbeiten über die konkreten Herausforderungen einer erfolgreichen Umsetzung von PMTCT in diesen Ländern noch wenig bekannt. Der Einfluss und die Unterstützung männlicher Partner wurde beispielsweise in früheren Studien eines übergeordneten PMTCT-Forschungsprojektes am Institut für Tropenmedizin und Internationale Gesundheit als wichtiger Faktor für den Beginn und die Einhaltung einer PMTCT-Intervention in Tansania identifiziert (Theuring et al. 2009; Kirsten et al. 2011). Gleichzeitig erwiesen männliche Partner sich in den meisten Untersuchungen zu dem Thema als nicht engagiert, aber nur wenige Maßnahmen für eine Erhöhung der Partnerbeteiligung an HIV-Testung und PMTCT-Beratung wurden bisher evaluiert (Theuring et al. 2009; Theuring et al. 2010; Biratu et al. 2006; Ditekemena et al. 2012). Insbesondere für die neu eingeführte Option B+ stellt die langfristig erforderliche regelmäßige Abholung von Tabletten in Gesundheitseinrichtungen und das strikte Einnahmeschema ein häufig beschriebenes Implementierungsproblem dar, welches sich speziell für Frauen in abgelegenen, ruralen Gebieten als Barriere auswirkt (Nachega et al. 2012; Ngoma et al. 2015). In Uganda gab es zum Zeitpunkt der hier vorgestellten Studien kaum Untersuchungen zu Akzeptanz und Adhärenz von Option B+; ebenso lagen keine längerfristigen Ergebnisse zur Sicherheit des Regimes in Bezug auf negative Geburtsergebnisse vor.

1.2. Zielsetzung der Arbeit

PMTCT-Maßnahmen, bei denen durch mütterliche Medikamenteneinnahme die Mutter-Kind-Übertragung von HIV verhindert werden kann, sind seit beinahe zwei Jahrzehnten auch in Subsahara-Afrika weithin etabliert. Gleichzeitig sind internationale PMTCT-Empfehlungen in stark ressourcenlimitierten, ländlichen Regionen in der Praxis oftmals nicht optimal umsetzbar. Barrieren für die wirksame Implementierung von PMTCT-Maßnahmen bedürfen einer kontext- und länderspezifischen Analyse, um gesundheitspolitischen Handlungsbedarf ableiten zu können und langfristig die Eliminierung der Mutter-Kind-Übertragung von HIV und damit eine angestrebte „*AIDS-free Generation*“ herbeizuführen.

Die vorgelegte Arbeit hatte zum Ziel, die Implementierung von PMTCT-Maßnahmen in Ostafrika durch operationale Forschung zu begleiten und ihre Umsetzbarkeit zu untersuchen, spezifische Herausforderungen in der Umsetzung von PMTCT innerhalb des jeweiligen zeitlichen Kontextes zu identifizieren, und Strategien abzuleiten, die die Effektivität von PMTCT-Maßnahmen steigern können. Die enthaltenen eigenen Forschungsarbeiten umfassten folgende Einzelziele:

- Evaluierung des Überweisungsprozedere zwischen ANC/PMTCT und ART-Diensten bei HIV-positiven schwangeren Frauen mit Indikation für lebenslange ART in Tansania
- Untersuchung der Akzeptanz einer Maßnahme zur erhöhten Partnerbeteiligung an HIV-Testung in der Schwangerschaft in Tansania
- Identifizierung eines möglichen Einflusses des Option B+-Regimes auf Geburtsoutcomes in Uganda
- Untersuchung der Umsetzbarkeit von Option B+ hinsichtlich Akzeptanz und Adhärenz in der Schwangerschaft in Uganda
- Analyse der Umsetzbarkeit von Option B+ hinsichtlich Langzeit-Adhärenz bis 18 Monate nach Geburt in Uganda

2. Eigene Arbeiten

2.1. Effektivität der Vernetzung zwischen PMTCT und ART-Diensten

Theuring S, Sewangi J, Nchimbi P, Harms G & Mbezi P. The challenge of referring HIV-positive pregnant women with treatment indication from PMTCT to ART services: a retrospective follow-up study in Mbeya, Tanzania. AIDS Care: Psychological and Socio-medical Aspects of AIDS/HIV, 2014. 26:7.

http://doi.org/10.1080/09540121.2013.869535

Vor der Einführung einer universalen ART-Strategie für HIV-positive Schwangere galt die Ermittlung einer Indikation für lebenslange ART im Gegensatz zu einer zeitlich begrenzten Prophylaxe als erster Schritt innerhalb der PMTCT-Behandlungskaskade. Diese Indikation war in Ländern wie Tansania auf eine CD4-Zellzahl ≤350 Zellen/µl festgelegt (WHO 2006). HIV-positive schwangere Frauen mit Behandlungsindikation wurden von der Schwangerenvorsorge in die allgemeine HIV-Abteilung (*Care and Treatment Center*, CTC) innerhalb der Gesundheitseinrichtungen überwiesen, um dort eine lebenslange ART zu beginnen. Da die Daten von Patientinnen nicht über mehrere Abteilungen hinweg vernetzt wurden, gab es kaum Information zur Effektivität des Überweisungsvorganges, d.h. zu tatsächlichem Behandlungsbeginn und Fortführung der ART bei diesen bereits immunkompromittierten Frauen.

Ziel der Untersuchung war die retrospektive Datennachverfolgung einer Kohorte von schwangeren Frauen mit Behandlungsindikation in vier Gesundheitseinrichtungen in *Mbeya Region*, Tansania. Anhand eines Extraktionsformulars wurden für 60 Frauen jeweils verfügbare Informationen aus Schwangerschaftsvorsorge, CTC sowie der postpartalen Versorgung zusammengefügt. Über ein Drittel (35%) der Frauen mit Behandlungsindikation war nach CTC-Überweisung während der Schwangerschaft gänzlich ohne ARV-Einnahme verblieben. Bei den übrigen Frauen betrug die mediane pränatale ART-Einnahmedauer 57 Tage, lediglich acht Frauen erreichten die zur ausreichenden Senkung der Viruslast empfohlenen ≥90 Tage. Die von den Gesundheitseinrichtungen verschuldete Zeitlücke zwischen ART-Beratung und tatsächlichem ART-Beginn führten zu signifikant kürzerer pränataler Einnahmedauer. Bis sechs Monate nach Geburt nahmen die Frauen nur die Hälfte der vorgegebenen CTC-Besuche wahr. Diese Ergebnisse machen deutlich, dass die Überweisung von Schwangeren mit Behandlungsindikation in eine allgemeine HIV-Abteilung eine Hürde darstellen kann, um ART in dieser Hochrisikogruppe für vertikale Transmission effektiv

durchzuführen. Die Integration der ART-Dienste für diese Gruppe in die Schwangerschaftsvorsorge könnte diesem Problem entgegenwirken.

2.2. Erhöhung der Partnerbeteiligung an ANC und CVCT

Jefferys LF, Nchimbi P, Mbezi P, Sewangi J, Theuring S. Official invitation letters to promote partner attendance and couple voluntary counselling and testing in antenatal care through official invitation letters: An implementation study in Mbeya Region, Tanzania. Reproductive Health, 2015. 12:95. doi: 10.1186/s12978-015-0084-x.

Mangelnde Adhärenz in PMTCT-Maßnahmen wurden in zahlreichen Untersuchungen auf die oftmals schwache Entscheidungsautorität in Gesundheitsfragen bei Frauen in Subsahara-Afrika zurückgeführt. Die gemeinsame HIV-Testung von Paaren (*Couple voluntary counselling and testing*, CVCT) zu Beginn der Schwangerschaft wurde hingegen als positiver Einflussfaktor auf die Aufnahme von PMTCT-Maßnahmen und die folgende Programmadhärenz beschrieben. Die Beteiligung männlicher Partner an Schwangerschaftsvorsorge und CVCT ist jedoch in Settings wie dem ländlichen Tansania traditionell sehr gering (Theuring et al. 2009).
Diese Studie untersuchte die Akzeptanz und Wirkung von offiziellen Einladungsbriefen für männliche Partner zum Besuch der Schwangerschaftsvorsorge als Maßnahme zur Erhöhung von CVCT. An den Studienstandorten, drei Gesundheitseinrichtungen in *Mbeya Region,* Tansania, lag die CVCT-Rate vor Implementierung der Maßnahme bei 2-19%. Frauen, die die Schwangerschaftsvorsorge erstmalig aufsuchten und dabei nicht von ihrem Partner begleitet wurden, erhielten ein offizielles Schreiben, das ihren Partner einlud, die Frau beim folgenden Termin der Schwangerschaftsvorsorge zu begleiten. Partnerteilnahmeraten wurden bei den zwei folgenden Besuchen der Schwangerschaftsvorsorge erhoben. Von 318 Schwangeren wurden 54% bei einem Folgebesuch von Ihrem Partner begleitet, von diesen willigten >80% in CVCT ein. Frauen, die bei ihrem ersten ANC-Termin von einem positiven HIV-Serostatus berichteten, wurden bei den folgenden ANC-Besuchen seltener von ihrem Partner begleitet. Die Teilnahmerate der Partner variierte stark zwischen ländlichen (76%) und urbanen (31%) Studienstandorten. Die Mehrzahl der Frauen beurteilte die Maßnahme als positiv und hilfreich für die Paarkommunikation sowie die Entscheidungsfindung in Bezug auf reproduktive Gesundheit und HIV. Zusammenfassend erscheint diese niedrigschwellige und kostengünstige Maßnahme als eine weithin akzeptierte und praktikable Form, die Partnerbeteiligung an Schwangerschaftsvorsorge und HIV-Testung zu erhöhen.

Jefferys et al. Reproductive Health (2015) 12:95
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REPRODUCTIVE HEALTH

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Official invitation letters to promote male partner attendance and couple voluntary HIV counselling and testing in antenatal care: an implementation study in Mbeya Region, Tanzania

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Abstract

Background: The benefits of male partner involvement in antenatal care (ANC) and prevention of mother-to-child transmission of HIV (PMTCT) for maternal and infant health outcomes have been well recognised. However, in many
sub-Saharan African settings, male involvement in these services remains low. Previous research has suggested written invitation letters as a way to promote male partner involvement.

Methods: In this implementation study conducted at three study sites in southwest Tanzania, acceptability of written invitation letters for male partners was assessed. Pre-study CVCT rates of 2–19 % had been recorded at the study sites. Pregnant women approaching ANC without a male partner were given an official letter, inviting the partner to attend a joint ANC and couple voluntary counselling and testing (CVCT) session. Partner attendance was recorded at subsequent antenatal visits, and the invitation was repeated if the partner did not attend. Analysis of socio-demographic indices associated with male partner attendance at ANC was also performed.

Results: Out of 318 women who received an invitation letter for their partner, 53.5 % returned with their partners for a joint ANC session; of these, 81 % proceeded to CVCT. Self-reported HIV-positive status at baseline was negatively associated with partner return ($p = 0.033$). Male attendance varied significantly between the rural and urban study sites ($p < 0.001$) with rates as high as 76 % at the rural site compared to 31 % at the urban health centre. The majority of women assessed the joint ANC session as a favourable experience, however 7 (75 %) of women in HIV-positive discordant or concordant relationships reported problems during mutual disclosure. Beneficial outcomes reported one month after the session included improved client- provider relationship, improved intra-couple communication and enhanced sexual and reproductive health decision-making.

Conclusion: Official invitation letters are a feasible intervention in a resource limited sub-Saharan African context, they are highly accepted by couple members, and are an effective way to encourage men to attend ANC and CVCT. Pre-intervention CVCT rates were improved in all sites. However, urban settings might require extra emphasis to reach high rates of partner attendance compared to smaller rural health centres.

Keywords: Invitation letters, Male involvement, ANC, CVCT, HIV, PMTCT, Tanzania

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Background

Although much progress has been made towards reaching the United Nations Millennium Development Goals 4,5 and 6, many Sub-Saharan African countries still have high HIV incidence, high maternal and infant mortality, high attrition from prevention of mother-to-child transmission of HIV (PMTCT) services and suboptimal use of health facilities for delivery [1–3]. Male involvement in antenatal care (ANC) is seen as an increasingly valuable way to improve a number of these health indicators [4–6].

Encouraging results from male involvement in ANC have been shown in a number of studies. Male partner involvement (MPI) has been associated with more women delivering with a skilled birthing assistant [7, 8], and increased condom use is seen when couple voluntary counselling and HIV testing (CVCT) is included as part of the ANC visit [9, 10]. Furthermore, evidence from qualitative research has shown that the absence of male partner involvement in ANC and PMTCT can create a barrier for women to access these services [11].

Involving men in ANC is the gateway to their involvement in PMTCT [3, 5]. Studies have shown that MPI, in PMTCT, is associated with improved maternal adherence to antiretroviral therapy (ART) [10], infant feeding as per medical advice [12, 13] and retention in PMTCT programmes [2, 14]. Additionally, a study in Kenya showed an association between MPI and reduced HIV incidence in infants born to HIV positive women [15].

In many settings, HIV related health outcomes have been described as poorer for men than for women, with fewer men testing for HIV and more men initiating ART at a more advanced disease stage [16, 17]. Creating a channel for men to gain improved access to health education, VCT, and links to ART could impact on their health outcomes. A shift in perspective of PMTCT from the mother and infant to the family as a complete unit has been shown to improve ART adherence [18], and is recommended as a way for policy makers to encourage the inclusion of more men in HIV programmes [5].

Qualitative research has revealed that although men are generally interested in participating in ANC and PMTCT, in practice, numerous barriers prevent their involvement. Social norms can prevent women from asking their partners to attend ANC or for men to concede to attending [19]. ANC has been considered an arena for women, with predominately female staff, and reports of hostile reactions towards male partners if they attend [20]. Clinic opening hours and long waiting time conflict with male partner work commitments and, for some, the pressure to earn an income is greater than that of attending ANC [20, 21]. Formative research from different sub-Saharan African countries has recommended interventions to increase male partner attendance or involvement, such as opening clinics at evenings or weekends, peer-to-peer ANC/PMTCT education led by men, or home based CVCT during pregnancy [14, 22, 23]. Official written letters of invitation requesting male partner attendance ANC has been reported by both men and women as a good way to encourage male participation. Invitations are easy and cheap to implement and can overcome social normative barriers by removing the need for women to directly ask their partners to attend ANC, and the official nature of the invite invokes a certain authority which is reported to be respected by male partners [20, 21-24, 25]. However, further research is still needed to evaluate the effectiveness of written invitations in different settings [26].

In Tanzania, the national HIV prevalence is 5.3 %, while in our study area of Mbeya Region, it is higher at 9 % [27]. An estimated 43,000 new paediatric HIV infections annually contribute to almost a fifth of all new infections in the country [27]. Seventy per cent of Tanzanian women who tested HIV-positive during pregnancy received some form of ART regimen during their pregnancy and 50 % of HIV-exposed infants received ART prophylaxis. Although this is higher than the average for women receiving ART during pregnancy in the African priority countries (65 %), it represents a 20 % gap from the global 2015 target of 90 % [28, 29]. Furthermore, this perspective on the data does not take into account the estimated 65 % of women in lower and middle-income countries who are not tested for HIV during their pregnancy at all [28]. The lack of male participation in ANC and PMTCT has been identified in the National Strategic Plan as a key barrier to achieving PMTCT in Tanzania [27]. In Tanzania 21 % of male partners reportedly tested for HIV during their partner's pregnancy in 2010, and strategies are being implemented to promote CVCT alongside family planning for both men and women, with the aim to increase male partner testing during pregnancy to 50 % by 2015 [27, 29]. Given the low rates of MPI and CVCT combined with the increasing need to find effective strategies to improve them, we designed an implementation study to assess the acceptability and effectiveness of written invitations for male partners to attend joint ANC and CVCT in Tanzania. Secondary objectives of the study include analysis of socio-demographic indices associated with male partner attendance and evaluation of the repercussions of MPI for the women.

Methods

This implementation study was conducted in Mbeya Region, southwest Tanzania. Data was collected from a prospective, longitudinal cohort at three health centres at different locations in Mbeya Region. The centres were selected purposively and based on a maximum variation sampling approach to evaluate male involvement in

urban, rural and border town settings, in order to encompass a wide range of socio-demographic indices according to these different settings (respectively: Ruanda health centre, Mbeya City, Makongolosi dispensary, Chunya District, Tunduma health centre, Mbozi District). All three centres are free of charge, primary health care facilities, offering HIV treatment for the general population, pregnant and breastfeeding women. Early infant diagnosis by PCR is done at the tertiary referral hospital in Mbeya. Study enrolment was conducted between March 2013 and June 2013, during this time 1492 women presented for ANC at Ruanda, 697 at Tunduma and 122 at Makongolosi. Prior to the study period few male partners joined their partner for CVCT. Available data from the clinic registers reported that over the preceding three-month period 1.7 % of partners of all new ANC clients at Ruanda health centre had received CVCT, and 2.2 % at Tunduma health centre. Data from Makongolosi was accessible for male attendance from 2012 and showed a rate of 18.5 %.

Women attending ANC for the first time during their current pregnancy were recruited into the study, after written informed consent had been obtained. Eligibility criteria included a confirmed pregnancy and general accessibility of the partner, which was assessed by asking the women if their partner was permanently living away from the area or in a health condition that would not allow him accompany her to ANC services. Women were excluded if their partner attended the first ANC visit with them. Three separate questionnaires were developed for the interviews; these had been pre-tested on clinic attendees and adjusted accordingly by the investigators. Research assistants were recruited and received training from the principle investigator. In order to prevent the study procedures from interfering with running of the clinic, the research assistants were not routine clinic staff. Interviews were conducted after routine ANC sessions in a separate room and not in the presence of the ANC nursing staff or the male partner. During the routine ANC sessions, women were offered opt-out HIV testing as a standard ANC procedure.

After attending the first ANC visit, a baseline questionnaire was filled out by a research assistant to gather socio-demographic information about the study participant and their partner, including information about intimate partner violence (IPV) and knowledge of HIV status. Formal employment was defined as receiving a salary from another body or company. IPV included any physical, emotional or financial abuse reported by the woman. Results of HIV tests performed within the study sites were not known to the research team, therefore data on participant and partner HIV status' were self-reported by participants.

At the end of the baseline interview, women were given a written invitation letter for their male partner requesting their presence at the next routine ANC visit. This letter explained that information on pregnancy and parenthood and other important health issues would be given. It did not state that an HIV test would be offered. The letter was signed by the regional medical officer and was courteous and formal.

If the partner attended the next visit as requested, a joint antenatal session would take place during which CVCT was provided, if agreed to, by the couple. After this joint session the research assistant would interview the woman, collecting information about the partner's reaction on receiving an invitation letter and information about the session itself. If either of the couple did not want to take part in CVCT, VCT would be offered individually as part of standard procedures. CVCT included intensive pre- and post- test counselling of both partners and support in case of any problems during mutual status disclosure.

If the partner had not accompanied the woman to this second ANC visit, information was obtained regarding the reasons for his non-attendance and a further letter of invitation was given with a new appointment for a partner session.

After the third ANC visit recruited women were again interviewed by the research assistant. Those who had already been accompanied by their partner at the second visit gave information pertaining to any positive or negative repercussions and longer-term outcomes of the joint session. Women whose partners had not attended the second visit were asked if they attended at this third visit, and were then interviewed either regarding their opinion on the joint ANC and CVCT session, or regarding reasons for the partner to reject participation. No additional invitation letter was handed out for non-attending partners after the third visit.

During the study period intermittent community sensitisation on HIV and PMTCT occurred as part of routine government public health initiatives, which included community leader involvement and radio broadcasts encouraging VCT. This was the case for all the three study site areas. HIV-positive ANC clients lost to follow-up were routinely traced in community outreach programs in our study setting.

Statistical methods

Data analysis was performed using STATA version 13.1. To compare the socio-demographic indices across three different health centres, Kruskal-Wallis one-way analysis of variance was used for non-parametric continuous outcomes, and Fisher's exact test was used for categorical outcomes due to low cell values in the contingency table (<5 in one cell). To compare data between the women and their partners, two-sample Wilcoxon rank-sum test was used for medians, as the data was non-parametric,

and two-sample test of proportion was used for proportions.

For the bivariate analysis of socio-demographic indices on partner attendance variables, chi-square or Fishers exact test was used depending on the cell value.

A multiple logistic regression model was used for the multivariate analysis of factors associated with partner attendance and included the variables self-reported baseline HIV status, age, marital status, health facility, media exposure, IPV, partner employment and travel time to clinic. These variables were of interest as they were either significant or close to significant ($p < 0.06$) in the bivariate analysis. Questionnaire responses from Makongolosi for the variable 'previous partner involvement in ANC' was 100 % uniform and considered to have been collected incorrectly and was therefore not included in the regression model.

A significance level of <0.05 and a 95 % confidence interval (CI) was used throughout.

In addition to quantitative data, qualitative free-text was recorded to allow participants to expand on events that may have occurred after the joint session. These open-ended responses were categorised into relevant groups to allow for quantitative assessment.

Ethical considerations

The Mbeya Medical Research and Ethics Committee in Tanzania provided ethical approval for the time period of recruitment, data collection, and follow up. All participants gave informed written consent. The research assistant's training included participant confidentiality, and all data was recorded anonymously. Potential adverse outcomes connected to male involvement CVCT, like increased IPV, were closely screened during our study in order to respond appropriately if needed, and ANC staff was routinely trained in mediation and conflict management during CVCT in these healthcare settings.

Results

Between March and June 2013, 318 women were recruited into the study: 97 at Ruanda health centre, 101 at Tunduma health centre and 120 at Makongolosi dispensary. In total 237 (74.5 %) of the women had at least two visits and 143 (45 %) had three. The total male return rate during the study period was 170 (53.5 %).

Baseline socio-demographic indices of all study participants

The women were aged between 14 and 44 years (median 23) and presented at a median gestational week of 22. Many of the socio-demographic indices varied significantly between the health centres (Table 1). Women were oldest in Ruanda with a median age of 24 years at the urban setting Ruanda, and youngest at 22 years in the rural setting of Makongolosi ($p = 0.004$). Median travel time to clinic was highest at 30 min for Ruanda, lowest at ten minutes for Tunduma ($p < 0.001$).

The majority of the women were literate (86 %), achieved at least primary education (85 %) and were of Christian religion (91 %). Forty six per cent of the women reported having no children at home and 74 % were married. Around 25 % reported some form of IPV, of this abuse 80 % was emotional, 11 % physical and 8 % financial.

Twenty nine per cent of women reported that they did not know their HIV status, and 72 % said that they did not know their partners´ HIV status. Knowledge of partner HIV status varied between the health centres; knowledge of a partner's HIV status was highest in Tunduma (51 %) and lowest in Makongolosi (10 %) ($p < 0.001$).

The partners of the study participants were aged between 19 and 55 years (median 28), with a median age difference within the couple of four years and relationship duration of three years (Table 2). Almost all the partners had received at least primary education (97 %), were literate (96 %) and self-employed (89 %). The men were, on average, 5 years older than the women, and had a higher literacy rate: 96 % of the men compared to 86 % of the women (both $p < 0.001$), 30 % of the men had received secondary education, as had 21 % of the women ($p = 0.007$). The partners with a secondary education were more likely to be in formal employment (p <0.001). Between the study sites partner age, literacy, education and employment differed significantly.

Bivariate analysis of socio-demographic indices associated with partner attendance

Bivariate analysis (Table 3) was performed to assess the association of socio-demographic indices with partner attendance, Partner attendance was associated with a number of characteristics: women under 26 years of age and married women had significantly higher odds ratios (OR) of partner attendance (respectively: OR 1.72 $p = 0.022$ & OR 3.13 $p < 0.001$). Travel time to clinic was associated with borderline significance (OR 1.56 $p = 0.051$).

Formal sector employment of the partner was associated significantly with non-attendance (OR 0.33 $p = 0.041$), and previous partner attendance at ANC was associated with their re-attendance (OR 4.17 $p = 0.002$).

The different health facilities had a profound effect on partner attendance, the odds of partner attendance at Makongolosi being 7 times higher than at Ruanda ($p < 0.001$).

Having a radio at home, rather than any other combination of media exposure, and the absence of previous IPV were both significantly associated with partner attendance (respectively OR 2.87 $p = 0.042$ and OR 2.26 $p = 0.003$).

Table 1 Comparison of study participant characteristics by health centre

Characteristics of study participants	Sub-categories	Total	Makongolosi	Tunduma	Ruanda	*P* value
Total n		318	120	101	97	-
Age (years) median (Range)		23 (14–44)	22 (14–38)	23 (16–42)	24 (18–44)	0.004[c]
Gestation (wks) median (Range)		22 (4–36)	20 (4–36)	28 (16–36)	20 (7–34)	<0.001[c]
Travel time to clinic (minutes) median (range)		15 (1–360)	13.5 (1–120)	10 (5–20)	30 (5–360)	<0.001[c]
Travel cost (Shillings) median (range)		800 (0–4000)	[a]	300 (0–1000)	800 (0–4000)	<0.001[c]
Literate n (%)		270 (86)	89 (76)	91 (90)	90 (93)	0.001[d]
Marital status n (%)	Married	236 (74.2)	113 (94.2)	95 (95)	28 (28.9)	<0.001[d]
	Partnership	82 (25.8)	7 (5.8)	6 (5.9)	69 (71.1)	-
Religion n (%)	Christian	284 (90.5)	101 (86.3)	92 (91.1)	91 (94.8)	0.116[d]
	Muslim & Other	30 (9.6)	16 (13.7)	9 (8.9)	5 (5.2)	-
Education n (%)	None	49 (15.4)	30 (25)	10 (9.9)	9 (9.3)	0.001[d]
	Primary	203 (63.8)	74 (61.7)	71 (70.3)	58 (59.8)	-
	Secondary	66 (20.8)	16 (13.3)	20 (19.8)	30 (30.9)	-
Employment n (%)	None	59 (18.9)	10 (8.5)	27 (27.6)	22 (22.7)	<0.001[d]
	Formal	8 (2.6)	-	1 (1.0)	7 (7.2)	-
	Self-employed	245 (78.3)	107 (91.5)	70 (71.4)	68 (70.1)	-
Children at home N (%)	None	131 (46.2)	32 (37.2)	43 (43.4)	56 (58.3)	0.065[d]
	1_2	110 (39.2)	39 (45.4)	41 (41.4)	31 (31.3)	-
	>2	40 (14.2)	15 (17.4)	15 (15.2)	10 (10.4)	-
Media exposure at home n (%)	None	6 (1.9)	1 (0.8)	1 (1)	4 (4.1)	<0.001[d]
	Radio	190 (59.8)	95 (79.1)	51 (50.5)	44 (45.4)	-
	Media plus[b]	122 (38.4)	24 (20)	49 (48.5)	49 (50.5)	-

[a]Data not available
[b]Media plus: radio + TV +/− Newspaper, or TV or Newspaper only, or TV + Newspaper without radio
P values calculated using: [c]Kruskal-Wallis one-way analysis of variance. [d]Fishers Exact Test

Analysis of the association between HIV status and partner attendance

At baseline, 8 women (2.6 %) reported that they were HIV positive and 5 (1.6 %) reported that their partners were HIV positive. A self-reported positive HIV status by the woman at baseline decreased chances for attendance of the woman at subsequent ANC visits (OR= 0.28, $p = 0.061$), and significantly decreased chances for partner attendance (OR= 0.11, $p = 0.025$).

Multivariate analysis of factors associated with partner attendance

Multivariate analysis revealed that partner attendance remained independently associated with being enrolled

Table 2 Comparison of partner characteristics of study participants by health centre

Partner/Relationship characteristics	Sub-categories	Total	Makongolosi	Tunduma	Ruanda	*P* value
Partner's age (years) median (range)		28 (19–55)	26 (19–55)	28 (19–50)	29 (20–49)	0.020[a]
Age difference (years) median (range)		4 (0–21)	5 (1–21)	4 (1–21)	4.5(0–20)	0.254[a]
Duration of relationship (years) median (range)		3 (0–23)	2 (0.25–23)	3 (0.25–23)	4 (0.25–17)	0.103[a]
Partner literate n (%)		301 (95.9)	109 (91.6)	96 (98)	96 (99)	0.012[b]
Partner's education n (%)	None	11 (3.5)	9 (7.6)	1 (1.0)	1 (1)	<0.001[b]
	Primary	208 (66.5)	89 (74.8)	69 (70.4)	50 (52.1)	-
	Secondary	94 (30)	21 (17.6)	28 (28.6)	45 (46.9)	-
Partner's employment n (%)	None	10 (3.2)	1 (0.8)	1 (1.0)	8 (8.3)	<0.001[b]
	Formal	24 (7.7)	1 (0.8)	4 (4.1)	19 (29.8)	-
	Self	278 (89.1)	117 (98.4)	92 (94.9)	69 (71.9)	-

P values calculated using: [a]Kruskal-Wallis one-way analysis of variance. [b]Fishers Exact Test

Table 3 Bivariate analysis of factors effecting partner attendance at ANC

Variable	Categories	Study participants N/%	Partner attended N/%	OR	95 % CI	*P* value
Health facility	Makongolosi	120/37.7	91/75.8	7.01	3.57–13.74	<0.001[c]
	Tunduma	101/31.8	49/48.5	2.1	1.16–3.8	0.012[c]
	Ruanda	97/30.5	30/30.9	1	-	-
Age	<26 years	218/68.6	126/57.8	1.74	1.08–2.8	0.022[c]
	≥26 years	100/31.5	44/44	1	-	-
Travel time to clinic	≤15 min	186/58.5	108/58.1	1.56	0.99–2.46	0.051[c]
	>15 min	132/41.5	62/47	1	-	-
Literate	Literate	301/95.9	157/52.2	0.33	0.088–1.22	0.08[c]
	Illiterate	13/4.1	10/76.9	1	-	-
Marital status	Married	236/74.2	143/60.1	3.13	1.81–5.41	<0.001[c]
	Partnership	82/25.8	27/32.9	1	-	-
Religion	Christian	284/90.5	149/52.5	1	-	-
	Muslim + Others	30/9.5	19/63.3	1.07	0.5–2.32	0.86[d]
Partners age	≤26 years	117/38	69/59	1.45	0.91–2.32	0.115[c]
	>26 years	191/62	95/49.7	1	-	-
Partner employment	None	10/3.6	5/50	0.81	0.23–2.85	0.041[e]
	Formal	24/7.7	7/29.2	0.33	0.13–0.834	-
	Self-employed	278/89.1	154/55.4	1	-	-
Number of children at home	None	131/46.6	67/51.2	1	-	-
	1–2	110/39.2	50/45.6	0.79	0.48–1.32	-
	>2	40/14.2	22/55	1.17	0.57–2.38	0.51[e]
IPV	IPV reported	75/24.4	28/37.3	1	-	-
	Not reported	232 75.6	133/57.3	2.26	1.31–3.39	0.003[d]
Media	None	6/1.9	2/33.3	1		0.042[e]
	Radio	190/59.8	112/59	2.87	0.51–16.25	-
	Media plus[a]	122/38.4	56/45.9	1.7	0.297–9.7	-
Previous partner attendance at ANC[b]	Yes	27/13.9	19.4/70.4	4.17	1.63–10.67	0.002[d]
Self-reported HIV status (baseline)	Positive	8/2.6	1/12.5	0.11	0.01–0.92	0.025[e]
	Negative	212/68.6	121/57.1	1	-	-
	Unknown	89/28.8	43/48.3	0.7	0.43–1.16	-

[a]Media plus = radio + TV +/− Newspaper, or TV or Newspaper only, or TV + Newspaper without radio
[b]Data from Tunduma & Ruanda health centres
P value calculated using : [c]Chi-squared test. [d] Fishers exact test. [e]Fishers exact test (homogeneity/equal odds)

at the rural health centre Makongolosi (adjusted odds ratio [AOR] 7.5, $p < 0.001$). Self-reported positive HIV status at baseline also remained associated with partner non-attendance (AOR 11.12, $p = 0.033$). All other variables lost significance at this stage of the analysis (Table 4).

Acceptability and effectiveness of invitation letters

The letters were well accepted, 98 % of women who returned to clinic reported they had handed the letter to their partners. Male partners were supportive after having received a written invitation.

Across the three study sites the partner attendance rate was 53.5 %. Women attending ANC in Makongolosi showed the highest response, with 75.8 % returning with partners, while in Tunduma, the partner return rate was 48.5 %. Partner attendance was lowest in the urban setting of Ruanda health centre 31 % (Table 3).

When the partner attended a joint ANC session, 81 % of the couples received CVCT, while in the remaining 19 % only the women tested. Immediately after the session 95 % of women reported that the counsellor was helpful, 91 % stated the experience was good and (90 %) stated that there were no difficulties during mutual disclosure of HIV status.

Table 4 Multivariate analysis of factors effecting partner attendance at ANC

Variable	Categories	AOR for partner attendance	95 % CI	*P* value*
Health facility	Makongolosi	7.55	2.8–20.4	<0.001
	Tunduma	2.67	0.3–39.6	0.06
	Ruanda	1	-	-
Age	<26 years	1.5	0.86–2.6	0.15
	≥26 years	1	-	-
Travel time to clinic	≤15 min	1	-	-
	>15 min	1.004	0.99–1.01	0.406
Marital status	Married	1.09	0.47–2.55	0.84
	Partnership	1	-	-
Partner employment	None	1.8	0.45–7.4	0.396
	Formal	0.83	0.28–2.5	0.74
	Self-employment	1	-	-
Media	None	1	-	-
	Radio	3.72	0.33–42.5	0.289
	Media plus[a]	3.44	0.3–39.6	0.322
IPV	IPV reported	1.22	0.63–2.35	0.552
	Not reported	1	-	-
Self-reported HIV status (baseline)	Positive	0.09	0.01–0.82	0.033
	Negative	1	-	-
	Unkown	1.17	0.57–2.38	0.67

[a]Media plus = radio + TV +/− Newspaper, or TV or Newspaper only, or TV + Newspaper without radio
**P* values calculated using a multiple logistic regression model

Of women who had had a partner in attendance at the second visit, 115 attended a follow-up session roughly one month later. Seventy-five (71 %) reported positive events resulting from the joint ANC session whilst only nine (8 %) reported negative events. Positive events related to an improved relationship between the partner or the couple and the health services (40 %), improved communication and support between the couple (28 %) and an exposure to health education for the couple (23 %). Around 95 % of women stated that the joint session helped to improve their role in decision-making regarding ANC, family planning and sexual and reproductive health.

Of the negative events reported, five (56 %) occurred after one or both of the couple tested positive for HIV. These negative events included separation, blame and problems with negotiating safe sex. The majority of IPV was also reported after a couple had received a positive HIV result (4; 67 %), two reported emotional abuse and two reported financial abuse. Three of these couples were discordant, with a positive male partner in two cases, and one was a concordant couple.

The expected future events cited by the women were reduced anxiety about HIV testing and disclosure, improved communication within the couple, and improved relationship between the partner and the service providers.

Eighty-eight per cent of women thought they would have future joint ANC sessions and 95 % would recommend others to participate in joint ANC sessions. Fifty-five per cent of women shared with either family or friends that they had attended a joint session.

Of the 170 male partners attending ANC, 79 % of them did so after the first invite and 21 % attended after the second invitation. The most commonly stated reason for male non-attendance was visiting un-well relatives or attending a funeral (42 %), followed by work commitments (33.3 %). Those who stated work commitments as a reason for non-attendance had higher of odds of being in formal employment compared to self-employment (OR 3.13 $p = 0.097$). Marital conflict was also given as a reason for non-attendance (14 %).

Self-reported HIV results post-CVCT

After having attended CVCT during a joint ANC session, six women reported HIV positive results and eight stated that their partner tested positive; this corresponds to a prevalence of 4.3 % for the women and 7.8 % for the men for the study participants who underwent CVCT. Five couples were reported as concordant and three couples discordant, with two of these having a positive male partner. Seven (75 %) of the women in a HIV positive concordant or discordant relationship stated that there was a difficulty such as disappointment with results or conflict during mutual disclosure, despite this 38 % of them stated that the joint ANC session had been overall a good experience.

Discussion

Our study assessed male partner attendance at joint ANC sessions after providing women attending ANC a written invitation for their partners. Half of the women in our study returned to ANC with their male partner, and of these 81 % received CVCT. Data available from the pre-study period showed between 2 and 19 % of partners received CVCT at ANC. Although we cannot make a direct comparison between this historical data and the existing study results, the vastly higher numbers of male partners attending ANC after invitation is encouraging.

Our results also show higher partner attendance at ANC than some of the previous studies assessing written invitations. For example reported male attendance at ANC following invitation letters was 16 % in Uganda

[30], 26–35 % in South Africa [26], 33 % in Tanzania [31] and 36 % in Kenya [22]. In studies where women were encouraged to verbally invite their partner, male attendance at ANC was lower: 11 % in Kenya [12] and 12 % in Tanzania [10]. Outside of the context of ANC, the effectiveness of invitation letters for CVCT has also been assessed: results from a multi-centre study in Zambia and Ruanda showed 14 % of couples attended for CVCT after written invitation was given to either the couple together or to an individual couple member [23].

Our study showed high levels of acceptability of the invitations by the women, with almost 100 % giving the letter to their partner. Although reporting bias must be taken into account, this is an important finding, because high acceptance of the intervention among women is a precondition for its success. The majority of women reported that joint ANC sessions were a good experience and that positive events occurred afterwards. Discussing difficult topics together with a counsellor during the joint ANC session can be a useful platform to aid future discussions in the home and almost all the women in our study reported they felt that their role in sexual and reproductive decision-making had improved after the session. Over half had told family or friends that they had attended a joint ANC session, this should facilitate the normalisation of partner attendance at ANC.

Three quarters of the women who reported an HIV positive result after CVCT reported problems during disclosure, with some reports of negative events after the session such as IPV and separation. This highlights the on-going difficulties with disclosure of a positive HIV result despite receiving counselling from trained health professionals. The fears that have been described in qualitative research regarding positive HIV result disclosure to partners, especially during a vulnerable time such as pregnancy, are not necessarily removed by CVCT, and therefore more time and support for women, or their partners, who test positive should be available when offering CVCT services [32].

Our written invitations did not include information about receiving an HIV test, as this has been reported as a deterrent to attending joint ANC sessions [24, 31]. Contradicting this, other studies have shown that receiving an HIV test can encourage men to attend ANC, and a study from South Africa that included information about CVCT in their invitation letter showed improved partner attendance rates when compared to a letter without information about CVCT [26, 33]. Increased levels of community knowledge through sensitisation strategies and acceptance of routine CVCT at ANC should decrease any fear of HIV testing that could maintain barriers against men attending ANC. This is necessary to avoid men feeling coerced into testing during ANC, which has been reported during ANC in Zambia [34].

We found significant variation in partner attendance across our study sites: the lowest (31 %) in the urban health clinic and the highest (76 %) the rural clinic. This difference remained independently significant in the multiple regression model. The socio-demographic indices of the women varied significantly between the health centres: women in the urban clinic were older, had a longer travel time to clinic, higher level of secondary education and were more likely to have partners in formal employment. The rural clinic providing health care to a smaller community had the highest partner attendance in our study. It is likely in the smaller community that the participants, and perhaps also their partners, knew the ANC staff. This could have contributed to the higher rates of partner attendance seen in this rural setting as it has been reported that written invitations are more effective if given by someone that the couple knew personally, rather than a stranger [23]. Although few studies in this subject area stratify results by residence, one cross-sectional study retrospectively evaluating male participation in PMTCT found no difference in male attendance between men residing in rural or urban areas [25]. Still, many of the invitation studies have been based in urban areas, with results that correlate with the lower rates from our urban setting [22, 26, 30, 31]. Given that over half the women in sub-Saharan Africa live in rural areas, care may need to be taken when generalising the level of effectiveness of invitations from urban studies to rural populations [35].

Analysis of socio-demographic indices showed that many variables were associated with partner attendance and include the following: younger women, those who were married, not reporting IPV, having a partner who previously attended ANC and a partner in non-formal employment. These variables lost significance in the multivariate analysis. However being enrolled in the rural health centre remained significantly associated with male attendance in the multivariate analysis, and baseline self-reported positive HIV status remained associated with male non-attendance.

High attrition rates after a diagnosis of HIV and before receiving HIV care has been clearly acknowledged in other studies [36, 37]. By documenting self-reported HIV status in this study, we could observe the association between self-reported HIV positivity at baseline and non-return to ANC, either alone or with a partner. These women, unless they presented to alternative ANC services, represent missed opportunities for PMTCT and HIV care. Fear of disclosure during CVCT could have acted as a barrier for these women to return to ANC.

Self-reported HIV positive status was lower than regional HIV prevalence data, this may have been due to under-reporting by study participants and could reflect participants' fear of disclosure and concerns over

confidentiality. At baseline, 29 % of women stated they did not know their own HIV status and 72 % did not know their partners status. This knowledge gap represents a potential risk for both horizontal and vertical HIV infection. Therefore CVCT during ANC is clearly a valuable intervention for our study population, confirming similar insights from other settings: a South African study from 2014 showed that 40 % of recently pregnant women did not know their partners' HIV status, even after the pregnancy [38].

We suggest that there is value in repeating the invitation to partners, as 21 % of ANC-attending male partners had come only after a second invitation. Work commitments were cited by one third of the women as the reason why her partner did not attend ANC, and 42 % of partners were visiting un-well relatives or attending a funeral. Irrespective to barriers of male attendance being related to their physical absence from the home or to social normative behaviour, there seems to be a benefit in further motivation by health staff, thus providing partners with multiple opportunities to attend.

Strengths and limitations

By evaluating the acceptability of official invitation letters in three different healthcare scenarios, our study provides a long-needed addition to the current understanding of methods to improve male participation in ANC, and for their systematic implementation. Yet, some limitations were faced during this research.

We were unable to follow up the women who did not continue in the study, while information as to whether they continued ANC at another facility, or not at all, would be valuable to understand the magnitude of loss to follow up. However, the initially recruited overall cohort was sufficiently large to encounter loss-to-follow up with respect to valid study outcomes.

HIV results were self-reported by study participants, and under- or over-reporting may have occurred. This limits the conclusions that can be made regarding associations with HIV status and male partner attendance, and while this was not one of our outcome parameters, we accept that the prevalence of HIV in the cohort is unlikely to be accurate.

Uniformity of data collected for one variable at Makongolosi study site meant that we could not include this variable in the multivariate analysis. This site would have benefitted from more supervision throughout the study period to prevent any data errors occurring.

As this study was not conducted as a randomised controlled trial, we cannot draw conclusions about effectiveness. Nonetheless, given the large effect of the intervention compared to historical data, our findings are still assumed to be highly important for developing strategies to increase partner involvement.

Conclusions

This study demonstrated that written invitations for male partners to attend joint ANC and CVCT were well accepted by women attending ANC in Mbeya Region, Tanzania, and resulted in more than half of the women returning with their partner at a subsequent ANC visit.

We found significant differences in male attendance between our urban and rural settings, with potential implications for interventions aimed at increasing male attendance at ANC in different settings. Additional approaches maybe required to achieve higher partner attendance in areas with lower response rates to invitations, such as flexible opening hours or targeted community sensitization. The strongly improved partner return rates in all sites when compared to pre-study partner return rates imply that invitation letters are a valuable measure that can be implemented in a sub-Saharan African ANC/PMTCT setting to improve male participation in these services.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LJ entered the data, performed statistical analysis, interpreted the data and drafted the manuscript. PN, PM and JS contributed to study design, data acquisition and manuscript revision. ST was involved in the conceptual design of the study, data acquisition, and manuscript drafting and revision. All authors read and approved the final manuscript.

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2.3. Geburtsoutcomes unter Anwendung von PMTCT-Option B+

Rempis E, Schnack A, Decker S, Braun V, Rubaihayo J, Tumwesigye N, Busingye P, Harms 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. 17:82. doi: 10.1186/s12884-017-1263-2

In zahlreichen Ländern Subsahara-Afrikas, wie auch in Uganda, wurde im Jahr 2012 das Option B+-Regime, gleichbedeutend mit dem unmittelbaren Beginn einer lebenslangen ART für alle HIV-positiv getesteten Schwangeren, als PMTCT-Standardmaßnahme flächendeckend eingeführt (MoH Uganda 2012). Gleichzeitig waren mögliche negative Auswirkungen von Option B+ auf Geburtsoutcomes zu diesem Zeitpunkt weitgehend unerforscht. Aus diesem Grund führten wir in einem Krankenhaus in Fort Portal, West-Uganda, eine Querschnittsstudie durch, in welcher das Auftreten von negativen Geburtsergebnissen wie Totgeburt, Frühgeburt, sowie Unreife des Neugeborenen (*Small for gestational age*, SGA) unter Berücksichtigung des HIV-Status sowie des ARV-Behandlungsstatus an 412 Mutter-Neugeborenen-Paaren untersucht wurde.

Insgesamt wurden 110 HIV-positive Frauen sowie 302 HIV-negative Frauen während ihrer Entbindung in *Virika Hospital* rekrutiert. Daten wurden hinsichtlich der untersuchten Geburtsparameter sowie bezüglich soziodemographischer und klinischer Einflussfaktoren erfasst. Unsere Studie zeigte keinen Einfluss von Option B+ oder Langzeit-ART auf diese Geburtsparameter im Vergleich zu seronegativen Frauen. Als HIV-statusunabhängige signifikante mütterliche Risikofaktoren für Totgeburt wurden ein niedriger sozioökonomischer Status, weite Anreisestrecke zum Krankenhaus, Hypertonie und Anämie festgestellt. Frühgeburtlichkeit war ebenfalls mit einem niedrigen sozioökonomischen Status, Anämie, sowie Malaria in der Schwangerschaft assoziiert. Frauen in fortgeschrittenerem Alter und Frauen mit Malaria in der Schwangerschaft entbanden signifikant häufiger SGA-Neugeborene. Diese innerhalb unserer Kohorte identifizierten sozioökonomischen und klinischen Geburtsrisikofaktoren zeigen einen Verbesserungsbedarf bei pränatalem Screening und bei der Folgebetreuung deutlich auf. Gleichzeitig weist das Ergebnis hinsichtlich der Implementierung von Option B+ auf die Unbedenklichkeit der erweiterten ARV-Medikation bei schwangeren Frauen in Bezug auf negative Geburtsergebnisse hin.

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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 facilityl[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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2.4. Adhärenz in der pränatalen Phase von Option B+

Schnack A, Rempis E, Decker S, Braun V, Rubaihayo J, Tumwesigye N, Busingye P, Harms G, Theuring S. Prevention of mother-to-child-transmission of HIV in the Option B+ era: Uptake and adherence during pregnancy in Western Uganda. Journal of AIDS Patient Care and STIs, 2016. 30:3.

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Um die Umsetzbarkeit des neu eingeführten Option B+-Regimes unter realen Bedingungen in einem ressourcenschwachen, ländlichen Umfeld zu untersuchen, wurde innerhalb des unter 2.3. beschriebenen Studiensettings in Fort Portal, West-Uganda auch eine longitudinale Beobachtungsstudie durchgeführt. Hierfür wurden schwangere Frauen rekrutiert, die beim ersten Besuch der Schwangerschaftsvorsorge seropositiv getestet wurden, ART-naiv waren und bei denen daraufhin das Option B+-Regime initiiert wurde. In dieser Studie wurden die Frauen unter Erhebung der Adhärenz bis zum Zeitpunkt der Geburt nachverfolgt und Einflussfaktoren untersucht. Adhärenz wurde durch das Zählen der nicht eingenommenen Tabletten im vergangenen Monat (*pill count*), und die damit einhergehende Erstellung einer monatlichen Adhärenzrate bezüglich eingenommener Tabletten erhoben.

Von den insgesamt 124 rekrutierten Studienteilnehmerinnen war 81% ihr positiver HIV-Status bis zum Erstbesuch der Schwangerenvorsorge nicht bekannt gewesen. Mehr als ein Drittel der Frauen (n=45) kamen nach dem Erstbesuch nicht wieder in die Einrichtung zurück, um mit Option B+ zu beginnen, und fielen damit unmittelbar aus der Beobachtung heraus. Hiervon waren besonders solche Frauen betroffen, die von ihrem HIV-Status erst beim ANC-Erstbesuch erfahren hatten, oder Frauen, die ihren HIV-Status zwar bereits kannten, aber diesen ihrem persönlichen Umfeld bisher verheimlicht hatten. Unter denjenigen Frauen, die bis zur Geburt nachverfolgt werden konnten, stellten wir eine monatliche mediane Adhärenz von >95% Medikamenteneinnahme fest; dieser hohe Adhärenzwert blieb im Verlauf der Schwangerschaft durchgehend stabil. Die monatlichen Medikamentenrationen wurden von den meisten Frauen in regelmäßigen Abständen abgeholt. Die Studie zeigt, dass für Option B+ der Beginn der Maßnahme als hochgradig kritischer Punkt gelten muss, an dem Frauen intensive Beratung angesichts einer lebenslangen Medikamenteneinnahme benötigen, insbesondere, wenn sie ihren HIV-Status vor dem ersten ANC-Besuch noch nicht kannten. Wurde mit dem Regime jedoch einmal

begonnen, wurde dieses während der Schwangerschaft mit hoher und stabiler Adhärenz eingenommen.

2.5. Adhärenz in der postpartalen Phase von Option B+

Decker S, Rempis E, Schnack A, Braun V, Rubaihayo J, Busingye P, Tumwesigye N, 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. 12:6. e0179448. doi: 10.1371/journal.pone.0179448

Die unter 2.4. beschriebene Studie wurde in dieser Arbeit über den Zeitpunkt der Geburt hinaus fortgesetzt und untersuchte, auf derselben Kohorte aufbauend, die Umsetzbarkeit des Option B+-Regimes in der Stillzeit bis 18 Monate postpartal. Auch hier handelte es sich um eine longitudinale Beobachtungsstudie, für die zu vier Zeitpunkten nach Geburt Daten erhoben wurden: nach sechs Wochen sowie nach sechs, 12 und 18 Monaten. Die Messung der Adhärenz erfolgte durch selbstberichtete Medikamenteneinnahme der Frauen für den vergangenen Monat und der Rate der erfolgten monatlichen Besuche zur Medikamentenabholung; aus diesen beiden Messwerten wurde eine dichotome Adhärenzkategorie gebildet.
Siebenundsechzig der 124 pränatal rekrutierten Frauen wurden sechs Wochen nach Geburt in *Virika Hospital* wieder vorstellig und bildeten damit die postpartale Kohorte. Im Zeitraum bis sechs Monate nach Entbindung erfüllte etwa die Hälfte der Frauen die Kategorie „adhärent“. Dieser Anteil sank bis zu den Zeitpunkten 12 und 18 Monate auf ca. 20%. Keine einzige Frau nahm durchgehend bis 18 Monate nach Geburt alle Medikamente ein; gleichzeitig stillten jedoch 77% der Frauen ihr Kind für ein Jahr oder länger. Ein höheres mütterliches Alter, weiter Transportweg zum Krankenhaus, sowie eine höhere Anzahl vorausgegangener Geburten wurden als signifikante Risikofaktoren für die postpartale Medikamentenadhärenz ermittelt. In Anbetracht der Tatsache, dass die WHO in Verbindung mit dem Option B+-Regime für HIV-positive Frauen grundsätzlich eine Stilldauer von mindestens 12 Monaten empfiehlt, sollten unsere Ergebnisse als Warnung interpretiert werden, Frauen unter Option B+ ohne adäquate Adhärenzberatung und Betreuung zu dieser langen Stillzeit zu raten. Gleichzeitig wurde in unserer Kohorte trotz der suboptimalen Adhärenz keine vertikale Transmission bis zum Zeitpunkt 18 Monate festgestellt; diese Übertragungsrate bedarf jedoch einer Verifizierung anhand von größeren Stichproben.

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).

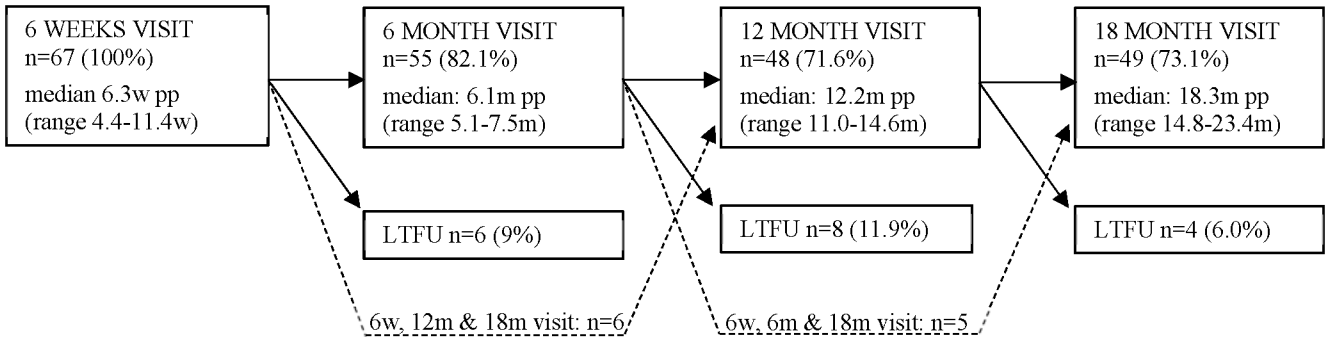

Fig 1. Option B+ enrolled women attending postpartum study visits.

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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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3. Diskussion

3.1. Vernetzung von HIV-Versorgungsdiensten

Bis zur Einführung einer universalen Behandlungsstrategie für alle HIV-positiven schwangeren Frauen, unabhängig von ihrer immunologischen Konstitution hinsichtlich des CD4-Zellwertes, stellte die Überweisung zwischen verschiedenen HIV-bezogenen Diensten eine wichtige Schnittstelle in der Versorgungskaskade für Schwangere mit ART-Indikation dar. Diese Vernetzung von ANC, PMTCT und CTC erwies sich in der unter 2.1. vorgestellten Arbeit in *Mbeya Region*, Tansania als äußerst unzureichend. Für jede dritte Frau aus der untersuchten Kohorte bedeutete der Überweisungsvorgang faktisch das Ausscheiden aus der medikamentösen HIV-Versorgung. Die Frauen mit Behandlungsindikation, also einem CD4-Zellwert ≤350 Zellen/µl, zählten durch das fortgeschrittene Krankheitsstadium zur Hauptrisikogruppe für die Mutter-Kind-Übertragungen von HIV; schätzungsweise 75%-88% aller vertikalen Infektionen sind dieser Patientinnengruppe zuzuordnen (Becquet et al. 2009). Für ausgerechnet diese Gruppe die HIV-bezogene Versorgung und Betreuung nicht lückenlos sicherzustellen, stellt ein eklatantes Versäumnis im Gesundheitssystem in Ländern wie Tansania dar.

Der Anteil an Frauen, die in unserer Studie nach CTC-Überweisung mit einer ART begannen, stimmt mit Ergebnissen anderer Studien in vergleichbaren Settings größtenteils überein (Kranzer et al. 2010; Stinson et al. 2010). Soziodemographische oder ökonomische Einflussfaktoren auf die Aufnahme von ART wurden nicht festgestellt; jedoch verfügten diejenigen Frauen, die nicht während der Schwangerschaft mit der ART begonnen hatten, trotz vorhandener Behandlungsindikation über signifikant höhere CD4-Werte. Die damit möglicherweise einhergehende Abwesenheit von Krankheitssymptomen könnte bei dieser Gruppe von Frauen zu einer Unterschätzung des Übertragungsrisikos auf ihr Kind geführt und dadurch einen unmittelbaren Therapiebeginn verhindert haben. Aus anderen Studien ist bekannt, dass die Abwesenheit von Krankheitssymptomen sich mitunter negativ auf gesundheitsbezogenes Verhalten bei Patienten auswirken kann (Ahoua et al. 2010).

Bei den Schwangeren, die in CTCs mit einer ART begonnen hatten, betrug der pränatale Behandlungszeitraum bis zur Geburt des Kindes im Durchschnitt lediglich acht Wochen, was anderen Studien entspricht (Stinson et al. 2010), jedoch für eine effektive Viruslastsenkung bis zur Geburt und damit als wirksame PMTCT-Maßnahme

als deutlich zu kurz gilt (Myer 2011). Hierbei zeigte sich, dass es oftmals durch die Gesundheitseinrichtung verschuldet zu Verzögerungen im Versorgungsablauf kam, beispielsweise zwischen dem vorgeschriebenen Beratungsgespräch zu ART-Adhärenz und dem tatsächlichen ART-Einnahmebeginn. Als Grund werden logistische Einschränkungen wie Personalmangel oder Medikamentenknappheit vermutet, welche in ressourcenlimitierten Ländern häufig auftreten (Chen et al. 2010; Stinson et al. 2010). Solcherlei Mängel müssen auf institutioneller und gesundheitspolitischer Ebene behoben werden, um wichtige Versorgungsabläufe nicht zu behindern und den für PMTCT erforderlichen pränatalen Behandlungszeitraum nicht zu beeinträchtigen.

Unsere Studie bestärkt Erkenntnisse vergleichbarer Untersuchungen in der Folgerung, dass die Integration von ART-Diensten in die Schwangerschaftsvorsorge den Therapiebeginn für Frauen mit Behandlungsindikation durch die Überwindung sowohl organisatorischer als auch soziokultureller Barrieren, wie dem potentiell stigmatisierenden Aufsuchen eines CTC, erheblich vereinfachen könnte (Myer et al. 2012; Killam et al. 2010). Hierbei ist vor allem die nähere und engmaschigere Betreuung der Frauen in der Schwangerschaftsvorsorge ein zentraler Faktor, welcher sich positiv auf die ART-Durchführung auswirken kann (Muchedzi et al. 2010).

Stärken und Schwächen der Arbeit

Im Studiensetting in *Mbeya Region*, Tansania stellte die vorgestellte Arbeit die erste Untersuchung zur Effektivität der Überweisung innerhalb der HIV-Versorgungsdienste für Schwangere dar. Die Untersuchung erbrachte wertvolle und neue Erkenntnisse über die Vernetzung der einzelnen Abteilungen innerhalb der Gesundheitszentren, welche im routinemäßigen Monitoring der Einrichtungen nicht erfasst wurden. Da die Patientinneninformationen aus verschiedenen Abteilungen jeweils manuell extrahiert und verknüpft werden mussten, war der Prozess der retrospektiven Datenerhebung äußerst aufwendig und komplex; er wurde durch unzuverlässige Dateneinträge zusätzlich erschwert, insbesondere in Bezug auf die zur Zuordnung über drei unterschiedliche Gesundheitsdienste hinweg unerlässlichen Identifikationsnummern der Klientinnen. Dies führte zu einer insgesamt eher kleinen Kohorte. Eine größere untersuchte Stichprobe hätte die Ergebnisse möglicherweise noch besser untermauern können. Patientinnendaten konnten zudem jeweils nur innerhalb einer Gesundheitseinrichtung verknüpft werden, so dass nicht ausgeschlossen werden kann, dass manche Klientinnen an eine andere Einrichtung wechselten und dort mit

einer ART begannen. Gleichzeitig ist dies in unserem Studiensetting grundsätzlich eher unwahrscheinlich, da es sich um eine ländliche Region mit vereinzelten Gesundheitszentren handelt und die lokale Bevölkerung zumeist ihrer nächstliegenden Einrichtung treu bleibt.

3.2. Einladungsbriefe zur Erhöhung männlicher Beteiligung an ANC/CVCT

Die Einbeziehung männlicher Partner in die Schwangerschaftsvorsorge wird mittlerweile weithin als wirkungsvolle Strategie zur Erhöhung der Effektivität von PMTCT-Maßnahmen anerkannt (WHO 2012; Jennings et al. 2014). Zahlreiche Studien ergaben, dass eine Partnerbeteiligung mit verbesserter Adhärenz der Frauen und höherem Verbleib im PMTCT-Programm assoziiert ist (Msuya et al. 2008; Chinkonde et al. 2009). Obwohl immer wieder konstatiert wurde, dass es dringend neuer Strategien bedürfe, um die im ländlichen Raum Subsahara-Afrikas niedrige Bereitschaft zur männlichen Teilnahme an der Schwangerschaftsvorsorge zu erhöhen (Msuya et al. 2008; Theuring et al. 2009), wurden nur wenige solche Strategien bis zum Durchführungszeitpunkt der unter 2.2. vorgestellten Arbeit systematisch umgesetzt und evaluiert. Gleichzeitig galten offizielle Einladungsschreiben der Gesundheitseinrichtungen an die Partner stets als vielversprechender Ansatz, der die männliche Anteilnahme am Wohlergehen des ungeborenen Kindes nicht als individuelle Überzeugungsleistung den betroffenen Frauen aufbürdet, sondern sie formell als gesellschaftliche Verantwortung festlegt (Allen et al. 2007; Mohlala et al. 2011; Nyondo et al. 2013).

In unserem Studiensetting fand die Maßnahme eine äußerst hohe Akzeptanz; beinahe 100% der Frauen gaben den Brief an ihren Partner weiter. Über die Hälfte der Partner besuchten nach Erhalt des Einladungsschreibens mit ihrer Frau den nächsten oder übernächsten Termin zur Schwangerschaftsvorsorge; der Großteil (>80%) von ihnen willigte dort in einen gemeinsamen HIV-Test ein. Unsere Ergebnisse lagen deutlich über denen anderer Studien im vergleichbaren Kontext, bei denen nur 16-35% der Männer nach schriftlicher Einladung ihre Partnerinnen begleiteten (Mohlala et al. 2011; Byamugisha et al. 2011; Osoti et al. 2014). Jedoch variierten die Rückkehrquoten der Partner in unserer Studie signifikant zwischen ländlichem und urbanem Raum. Die höchste Rate von 76% erreichte ein kleines Gesundheitszentrum in einer abgelegenen, bergigen Gemeinde, im Vergleich zu nur 31% männlichen Rückkehrern in einer großen Klinik in Mbeya-Stadt. Es ist davon auszugehen, dass in dem

ländlichen Studienstandort die Bewohner durch schlechte strukturelle Anbindung stärker auf ihr lokales Gesundheitszentrum angewiesen sind, und KlientInnen und Mitarbeiterinnen dort oftmals miteinander bekannt oder vertraut sind. Dies führt möglicherweise zu einem höheren sozialen Druck für Männer innerhalb der Gemeinde, dem Schreiben zu folgen, als in einer anonymen Umgebung wie dem urbanen Krankenhaus. Eine Studie von Allen et al. (2007) bestätigt diese Vermutung. Während Byamugisha et al. (2010) keinen Unterschied in der Partnerbeteiligung zwischen ruraler und urbaner Bevölkerung feststellten, wurden weitere Studien zu Einladungsschreiben an Partner meist lediglich in urbanem Raum durchgeführt (Mohlala et al. 2011; Osoti et al. 2014). In Anbetracht der Tatsache, dass über die Hälfte der Frauen in Subsahara-Afrika in ländlichen Gebieten lebt (IFAD 2012), sollte die möglicherweise höhere Effektivität der Maßnahme dort verifiziert und genutzt werden.

Frauen, die bei ANC-Erstbesuch einen HIV-positiven Serostatus angegeben hatten, erschienen seltener mit ihrem Partner zum Folgebesuch. Gleichzeitig berichtete die Mehrzahl der HIV-positiven Frauen nach CVCT mit erfolgter Statusoffenbarung gegenüber dem Partner von Problemen wie Schuldzuweisungen oder Trennung. Dies deutet darauf hin, dass die Ängste von Frauen vor negativen Konsequenzen bei Statusoffenbarung nicht automatisch dadurch beseitigt werden, dass ein HIV-Testergebnis im Rahmen von CVCT und der damit verbundenen institutionellen Begleitung der Paarkommunikation bekannt gegeben wird (Allen et al. 2007). Beratungspersonal in den Gesundheitseinrichtungen muss diesbezüglich adäquat geschult und äußerst sozialkompetent sein, um in einer Konfliktsituation als Mediator wirken und negative Konsequenzen auffangen zu können (Rujumba et al. 2012).

Stärken und Schwächen der Arbeit

Unsere Implementierungsstudie leistete einen wichtigen Beitrag im Diskurs um die verstärkte Beteiligung von Partnern an Gesundheitsleistungen für Frauen, indem sie die systematische Anwendung einer Strategie in verschiedenen geographischen Szenarien untersuchte. Die ermutigenden Ergebnisse der Studie wurden mit den lokalen Gesundheitsbehörden geteilt und zum Teil in Handlungsleitfäden der Einrichtungen übernommen.

Als Schwäche der Studie muss angesehen werden, dass es sich nicht um eine randomisierte klinische Studie handelte, durch die die Effektivität der Maßnahme im

Vergleich zu einer Kontrollgruppe gemessen werden konnte. Als Vergleich dienten uns Daten der Einrichtungen aus der Zeit vor Studienbeginn; veränderliche Faktoren wie klimatische Bedingungen zum Studienzeitpunkt oder aktuelle Maßnahmen zur öffentlichen Information können die Vergleichbarkeit solcher Daten beeinträchtigen. Da die Rückkehrraten nach Erhalt der Einladungsbriefe jedoch sehr deutlich über der Partnerbeteiligung vor Studienbeginn lagen, halten wir unsere Erkenntnisse dennoch für aussagekräftig. Weiterhin wurde der HIV-Status der Studienteilnehmerinnen lediglich aufgrund der Selbstauskunft der Frauen erfasst. Schlussfolgerungen, die bezüglich des HIV-Status im Zusammenhang mit der Partnerbeteiligung gemacht wurden, müssen daher mit Vorsicht betrachtet werden und sollten in weiteren Studien verifiziert werden.

3.3. Die Umsetzung von PMTCT-Option B+ in Uganda

Seit der offiziellen WHO-Empfehlung von Option B+ als PMTCT-Goldstandard im Jahr 2012 herrschte international weitgehender Konsens darüber, dass universelle ART für alle schwangeren, HIV-positiven Frauen die effektivste Strategie zur Prävention der vertikalen HIV-Übertragung darstellt (UNICEF 2012; WHO 2012a; Kamuyango et al. 2014). Gleichzeitig gab es in Anbetracht des Mangels an Langzeitstudien aber auch Bedenken an der flächendeckenden Implementierung des Regimes, beispielsweise bezüglich der Auswirkungen der verlängerten Medikamentenexposition auf das Kind oder der technischen Umsetzbarkeit in extrem strukturschwachen Regionen und Armutsmilieus, wie sie in vielen Ländern Subsahara-Afrikas vorherrschen (Coutsoudis et al. 2012). Die unter 2.3., 2.4. und 2.5. vorgestellten Arbeiten entstanden innerhalb eines der ersten operationalen Forschungsvorhaben zu Option B+ in Uganda, welches die Umsetzung des 2012 dort national eingeführten Regimes umfassend begleitete.

In unserer Untersuchung zum möglichen Einfluss von Option B+ auf Geburtsergebnisse und Gesundheit der Neugeborenen (2.3.) stellte sich heraus, dass bei Frauen unter Option B+ Vorkommnisse wie Frühgeburten, Totgeburten oder Unreife des Neugeborenen bei Geburt nicht häufiger waren als bei HIV-negativen Frauen. Dasselbe galt auch für Frauen, die mit einer ART bereits vor Konzeption begonnen hatten. Studien aus der Zeit vor Einführung von Option B+ zeigten, dass ein negativer Einfluss von ARV-Medikamenten auf Geburtsergebnisse hauptsächlich mit Proteaseinhibitoren assoziiert ist (Tuomala et al. 2002; Cotter et al. 2006), welche in unserem Setting nicht Bestandteil des Regimes waren. Grundsätzlich können jedoch

sowohl eine HIV-Infektion als auch ARV-Einnahme unabhängig voneinander negative Geburtsergebnisse bewirken (Brocklehurst et al. 1998). Die Frauen in unserer Kohorte wiesen mehrheitlich eine ART-Exposition von >90 Tagen auf; dieser Zeitraum gilt als entscheidend für eine signifikante Senkung der Viruslast zum Schutz des Kindes (Myer 2011). Es kann davon ausgegangen werden, dass sich bei diesen Frauen der nachteilige Effekt von HIV sowie von ARV-Einnahme auf Geburtsergebnisse gegenseitig nivellierte. Insgesamt war die Anzahl der untersuchten negativen Geburtsoutcomes, d.h. Totgeburten, Frühgeburten und in der Reifeentwicklung verzögerte Kinder, in unserer Kohorte äußerst hoch, auch im Vergleich zu anderen Studien in tertiären Kliniksettings (Adane et al. 2014). Risikofaktoren wie Hypertonie, Anämie, Malaria in der Schwangerschaft oder Verzögerung in der Versorgung durch mangelnde Transportmöglichkeiten waren im Gegensatz zu ART signifikant mit negativen Geburtsergebnissen assoziiert und bestätigen darin vergleichbare Untersuchungen (Olusanya et al. 2009; Landis et al. 2009; Rijken et al. 2012).

Die Untersuchungen zu Adhärenz unter Option B+ im Rahmen desselben Studiensettings (2.4., 2.5.) zeigten höchst unterschiedliche Ergebnisse in der prä- bzw. der postnatalen Phase. Wie die unter 2.4. vorgestellte Arbeit darlegt, kehrte zunächst einmal ein Drittel der HIV-positiven Frauen nach dem ersten ANC-Besuch nicht wieder in die Gesundheitseinrichtungen zurück und schied damit unmittelbar aus dem PMTCT-Programm aus. Diese hohe initiale *loss to follow-up* (LTFU)-Rate wird von zahlreichen weiteren Untersuchungen zum Verbleib in PMTCT-Programmen, unabhängig vom angewandten Medikamentenregime, bestätigt (Clouse et al. 2013; Phillips et al. 2014; Schnippel et al. 2015; Rawizza et al. 2015), und deutet auf einen hohen Bedarf an individueller Beratung insbesondere während des ersten ANC-Besuches hin. Frauen, die ihren HIV-Status vor ANC-Erstbesuch nicht kannten, hatten in unserer Studie ein signifikant höheres Risiko für LTFU. Es ist davon auszugehen, dass die erstmalig mitgeteilte Diagnose einer HIV-Infektion bei betroffenen Frauen hohen emotionalen Stress auslöst, der bewirkt, dass Informationen zu PMTCT und ART nicht adäquat aufgenommen werden können oder zunächst verdrängt werden. Unter denjenigen Frauen, die ihren HIV-Status bereits kannten, stellte in Übereinstimmung mit früheren Studien (Kirsten et al. 2011; Ebuy et al. 2014) eine vorausgegangene Statusoffenbarung gegenüber dem Partner oder Familienmitgliedern einen positiven Einflussfaktor für die Aufnahme der PMTCT-Maßnahme dar.

Anders als die Programmaufnahme bei nur zwei Dritteln der Frauen vermuten ließ, fiel bei denjenigen Studienteilnehmerinnen, die nach dem ersten ANC-Besuch mit der Maßnahme begannen, die vorgeburtliche Adhärenz hingegen äußerst hoch aus. Die Frauen nahmen durchschnittlich 95% der vorgesehenen monatlichen ARV-Medikamente ein; im Verlauf der Schwangerschaft bis zur Geburt blieb dieses hohe Niveau konstant. Vergleichbare Studien zur Adhärenz lagen zum Durchführungszeitpunkt zumeist nur zu anderen PMTCT-Regimes vor, z.B. in einer Untersuchung zu Option A in Tansania, in der ein medianes pränatales Adhärenzniveau von lediglich 77% festgestellt wurde (Kirsten et al. 2011). Eine Studie zu Option B in Kenia zeigte hingegen eine Adhärenz von >95% Medikamenteneinnahme bei über 80% der Patientinnen in einem zeitlichen Verlauf bis 24 Wochen *post partum*, möglicherweise befördert durch den temporären Charakter dieser Option im Vergleich zu Option B+ (Okonyi et al. 2012). Eine weitere Studie aus Uganda zu Option B+ untersuchte zwar nicht die Adhärenz an sich, zeigte aber fünf Jahre nach Einnahmebeginn des Regimes eine vorhandene Virussuppression bei 80% der untersuchten Patientinnen, was auf eine dauerhaft hohe Adhärenz schließen lässt (Koss et al. 2017).

Für die postpartale Adhärenz in unserem Studiensetting kam die unter 2.5. vorgestellte Arbeit hingegen zu dem Ergebnis, dass nach 6 Monaten *post partum* etwa die Hälfte der Frauen, nach 12 bzw. 18 Monaten nur noch ein Fünftel der Frauen die Kategorie „adhärent“ erfüllte. Keine einzige Frau wurde während des gesamten Zeitraumes bis 18 Monate nach Geburt durchgehend als „adhärent“ eingestuft. Die Phase nach Entbindung und während der Stillzeit muss damit als hochgradig kritisch für die Einhaltung des Medikamentenregimes angesehen werden (Nachega et al. 2012). HIV-positive Mütter benötigen in dieser Zeit besondere Betreuung und Unterstützung, um die Anforderungen der regelmäßigen monatlichen Medikamentenabholung in den Gesundheitseinrichtungen sowie der konsequenten Einnahme erfüllen zu können. Handlungsbarrieren für Adhärenz scheinen sich in der postpartalen Phase stärker auszuwirken als in der pränatalen Phase. Extrinsische Barrieren wie lange Transportstrecken und hohe damit verbundene Kosten fallen bei Müttern mit Neugeborenen möglicherweise stärker ins Gewicht (Jones et al. 2005; Chinkonde et al. 2009); auch eine höhere Anzahl vorausgegangener Geburten und damit verbunden eine größere Betreuungslast der Frauen waren in unserer Studie ein Hinderungsfaktor, regelmäßig die Gesundheitseinrichtung zur Medikamentenabholung aufzusuchen.

Eine für die postpartale Phase spezifische intrinsische Barriere könnte auch darin liegen, dass eine möglicherweise symptomlose HIV-positive Mutter, sobald ihr Baby geboren ist und zur Geburt HIV-negativ getestet wurde, die Gefährdung durch Transmission während der Stillzeit als nicht mehr allzu bedrohlich einschätzt (Clouse et al. 2014; Etoori et al. 2018). Hier sollten mit noch mehr Nachdruck Aufklärungskampagnen betrieben werden, die auf die Bedeutung der Transmissionsprävention während der gesamten Stillzeit aufmerksam machen. In unserer Untersuchung stillten ca. drei Viertel aller Frauen trotz der suboptimalen postpartalen Adhärenz bis zum vollendeten ersten Lebensjahr des Kindes oder darüber hinaus, entsprechend der mit Option B+ einhergehenden Stillempfehlung (WHO 2010a). Um den Erfolg von Option B+ als hocheffektivem PMTCT-Regime nicht zu gefährden, ist es von äußerster Dringlichkeit, dass diese verlängerte Stillempfehlung als untrennbar verbunden mit der Notwendigkeit fortgesetzter und konsequent adhärenter Medikamenteneinnahme kommuniziert wird. Die verlängerte Stilldauer bei HIV-positiven Frauen kann andernfalls langfristig zu einem Rückschlag in Bezug auf postpartale Transmissionraten führen.

Mangelnde mütterliche Adhärenz steht in direktem Zusammenhang mit der Entstehung resistenter Virusmutationen, und kann dadurch die Wirksamkeit der eingesetzten ARV-Medikamente vermindern (Paredes et al. 2013, Machnowska et al. 2017). In unserem Studiensetting zeigten sich in einer nicht in dieser Arbeit enthaltenen Untersuchung zur Resistenzbildung bei Option B+ bis zum Zeitpunkt nach einem Jahr äußerst niedrige Selektionsraten für resistente Virusmutationen; jedoch sollte dieses Ergebnis in weiteren Studien anhand von größeren Kohorten verifiziert werden (Machnowska et al. 2017).

Stärken und Schwächen der Arbeiten

Die unter 2.3.-2.5. vorgestellten Arbeiten waren Teil eines der ersten operationalen Forschungsvorhaben zu Option B+ in Uganda und waren daher in den Fragestellungen zu Einflüssen auf Geburtsergebnisse, Programmaufnahme und Adhärenz bis zum Ende der Stillzeit von höchster Relevanz für implementierende Gesundheitsdienstleister.

Eine Schwäche der Studie zu Geburtsergebnissen (2.3.) bestand darin, dass der Risikofaktor „HIV-Infektion“ nicht isoliert von „ARV-Exposition“ analysiert werden konnte, da die Anzahl der HIV-positiven, nicht ARV-exponierten Frauen in der Kohorte

verschwindend gering war. Durch die sukzessive Ausweitung von HIV-Testung und ART entsprechend der *Sustainable Development Goals* der Vereinten Nationen (UNAIDS 2018) wird die Anzahl nicht-ARV-exponierter HIV-positiver Frauen jedoch generell in der Zukunft mehr und mehr abnehmen, so dass diese Unterscheidung aus Public Health-Perspektive ohnehin kaum noch Relevanz besitzt. Weiterhin wurde bei Frauen, die nach Selbstauskunft HIV-negativ waren, vom Krankenhauspersonal bei der Entbindung häufig auf eine Nachtestung verzichtet. Diese Frauen wurden nicht in die Studie rekrutiert, da eine Serokonversion zum Zeitpunkt der Geburt nicht ausgeschlossen werden konnte und dies die Ergebnisse möglicherweise verfälscht hätte. Da es sich um eine nicht-interventionelle Beobachtungsstudie handelte, entfiel die Möglichkeit eines gezielten Nachtestens der Frauen im Rahmen der Studie. Wir erachten unsere Stichprobe jedoch trotz dieser Verluste aus der Gesamtkohorte insgesamt als groß genug, um zu aussagekräftigen Ergebnissen zu gelangen.

Die Arbeiten zur Adhärenz unter Option B+ (2.4. und 2.5.) verfügten über verhältnismäßig kleine Stichprobengrößen, welche in der pränatalen Gruppe 124 Frauen umfasste, in der postpartalen Gruppe durch hohe LTFU-Raten jedoch weiter abnahm. Die statistische Auswertung anhand einer größeren Stichprobe wäre möglicherweise aussagekräftiger gewesen. Gleichzeitig gibt es auch hier durch die Ausweitung der ART-Programme in allen betroffenen Ländern zunehmend weniger ART-naive HIV-positive schwangere Frauen, die in solche Untersuchungen rekrutiert werden können. Kleine Kohorten sind daher in diesem Zusammenhang eine häufige methodische Herausforderung, welcher zukünftig vor allem durch multizentrische Studien begegnet werden muss. Durch den Mangel an vergleichbaren Forschungsarbeiten zum Zeitpunkt der Einführung von Option B+ in Uganda waren unsere Ergebnisse dennoch von hohem Erkenntnisgewinn. Eine weitere Schwäche unserer Untersuchungen ist, dass die Adhärenz nicht durch Medikamentenspiegel im Blutplasma gemessen werden konnte, sondern durch *Pill Counts* bzw. durch Eigenangaben zur Einnahme/Abholung erhoben wurde. Diese sind abhängig von der Kooperationsbereitschaft der Studienteilnehmerinnen und können einer Verzerrung durch falsche Berichterstattung (*Reporting Bias*) oder Erinnerungslücken (*Recall Bias*) unterliegen. Im Rahmen eines observationalen Studiendesigns war es jedoch nicht möglich, Blutplasma der Teilnehmerinnen zu gewinnen, da dies die Bereitschaft für die erforderlichen Besuche der Gesundheitseinrichtungen möglicherweise nachteilig beeinflusst hätte.

4. Zusammenfassung

Die vorgelegte Habilitationsschrift befasst sich mit der Durchführung unterschiedlicher Interventionsschemata zur Prävention der Mutter-Kind-Übertragung von HIV in strukturschwachen *real life*-Settings in Ostafrika unter Betrachtung spezifischer operationaler Herausforderungen. Untersucht wurden die Überweisungsmechanismen zwischen verschiedenen HIV-Versorgungsdiensten; Strategien zur Einbeziehung männlicher Partner in die Schwangerschaftsvorsorge; sowie die Einführung des Option B+-Regimes hinsichtlich eines Einflusses auf Geburtsergebnisse und der mütterlichen Adhärenz während Schwangerschaft und Stillzeit. Die genannten Problemstellungen decken thematisch ein breites und interdisziplinäres Spektrum bezüglich der Umsetzbarkeit von PMTCT-Maßnahmen ab. Durch zahlreiche langjährige Vorarbeiten zum Themenkomplex PMTCT in Ostafrika im Rahmen eines übergeordneten Forschungsprojektes des Instituts für Tropenmedizin und Internationale Gesundheit, welches in enger Kooperation mit den zuständigen örtlichen Gesundheitsbehörden durchgeführt wurde, waren die vorliegenden Fragestellungen von hoher Praxisnähe, Aktualität und Public-Health-Relevanz gekennzeichnet.

In der unter 2.1. vorgestellten retrospektiven Kohortenstudie in Tansania zeigten wir, dass die Überweisung von schwangeren Frauen mit ART-Indikation in eine generelle HIV-Abteilung dazu führte, dass zahlreiche dieser Frauen entweder vor Geburt des Kindes gar nicht mit einer lebenslangen ART begannen, oder diese zu kurz oder lückenhaft einnahmen. Diese Frauen stellen aufgrund ihrer niedrigeren CD4-Werte eine Hochrisikogruppe für die vertikale HIV-Übertragung dar. Die Versorgung dieser Zielgruppe mit ART innerhalb der Schwangerschaftsvorsorge ist einer Überweisung in andere Abteilungen vorzuziehen, um den frühzeitigen Behandlungsbeginn zu sichern und die Medikamentenadhärenz zu unterstützen.

PMTCT-Teilnahme und Adhärenz von schwangeren Frauen lassen sich durch die Einbeziehung ihrer männlichen Partner allgemein verbessern. In der unter 2.2. vorgestellten Implementierungsstudie in Tansania wiesen wir nach, dass offizielle Einladungsschreiben der Gesundheitseinrichtungen an die männlichen Partner zu hohen Teilnahmeraten der Partner führen und die gemeinsame HIV-Testung bei Paaren befördern können. Die Einladungsbriefe waren in ländlichem Umfeld deutlich effektiver als in urbanen, anonymeren Settings, grundsätzlich können sie aber als wirkungsvolles Instrument zur Erhöhung männlicher Beteiligung empfohlen werden.

In drei Beobachtungsstudien in Uganda begleiteten wir die Einführung des Option B+-Regimes entsprechend der neuesten PMTCT-Leitlinien. Dabei stellten wir in einer Querschnittsstudie (2.3.) bei Frauen unter Option B+ fest, dass das Regime trotz der langandauernden pränatalen Medikamentenexposition keine Auswirkungen auf die Anzahl von Totgeburten, Frühgeburten oder Reifeverzögerungen beim Neugeborenen hatte. In zwei longitudinalen Kohorten untersuchten wir des Weiteren die pränatale sowie die postpartale mütterliche Adhärenz bis zum Ende der Stillzeit nach 18 Monaten. Während der Schwangerschaft (2.4.) stellten wir bei den Frauen, die mit dem Regime begonnen hatten, ein sehr hohes mittleres Adhärenzniveau bis zur Geburt fest. Gleichzeitig fiel jedoch ein Drittel der Kohorte unmittelbar nach dem ersten ANC-Besuch aus der Beobachtung heraus; hiervon waren vor allem Frauen betroffen, denen ihr HIV-Status zuvor noch nicht bekannt gewesen war. In der postpartalen Kohorte (2.5.) zeigte sich, dass die hohe pränatale Adhärenz nicht aufrechterhalten werden konnte, sobald das Kind geboren war. Während drei Viertel der Frauen ihr Kind mindestens bis zum 12. Lebensmonat stillten und damit dem Risiko einer HIV-Transmission aussetzten, war nur eine von fünf Frauen bis zu diesem Zeitpunkt adhärent. Um einen Rückschlag hinsichtlich vertikaler Transmissionsraten in der Stillzeit zu verhindern, sollte HIV-positiven Müttern nur dann zum Stillen bis zum Ende des ersten Lebensjahres oder länger geraten werden, wenn sie in ihrer Adhärenz engmaschig betreut und unterstützt werden können.

Trotz der großen Fortschritte auf dem Weg zur Eliminierung der vertikalen HIV-Transmission zeigt die vorliegende Habilitationsschrift, dass die Umsetzung von PMTCT in HIV-endemischen Ländern Subsahara-Afrikas weiterhin zahlreiche Herausforderungen mit sich bringt. Unsere Untersuchungen legen nahe, dass das bloße Zur-Verfügung-Stellen von hochwirksamen Medikamentenregimes für PMTCT innerhalb der komplexen Lebensrealitäten, die insbesondere in strukturschwachen und armutsgeprägten Settings solcher Länder vorzufinden sind, zu kurz greift. HIV-positive schwangere Frauen repräsentieren eine in psychosozialer, ökonomischer und gesundheitlicher Hinsicht hochvulnerable Bevölkerungsgruppe, auf deren spezifische Bedürfnisse in HIV-bezogenen Versorgungsdiensten eingegangen werden muss, um langfristig das Ziel einer *„AIDS-free generation*“ erreichen zu können. Die vorgelegte Arbeit leistet einen Beitrag dazu, die Herausforderungen in der Umsetzung von PMTCT-Maßnahmen am Beispiel von Tansania und Uganda besser zu verstehen, kontextuell einzuordnen, und mögliche Lösungsansätze zu entwickeln.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,

- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,

- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

…… ……..

Datum Unterschrift