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Case 6: Care for HIV Positive Women

Case of Ntombi and postpartum HIV care

JIAS Journal of the International AIDS Society

Telling my husband I have HIV is too heavy to come out of my mouth": Pregnant women's disclosure experiences and support needs following antenatal HIV testing in eastern Uganda, *JIAS* (2012)

This article entails the experiences of fifteen HIV positive and fifteen HIV negative women. Through these narratives the challenges, sociocultural responses, and stigma of HIV positive women is depicted. Areas of support before and after status disclosure is discussed.

JAMA® The Journal of the American Medical Association

A randomized trial: The Mashi Study, *JAMA (2006)*

An RCT looking at breastfeeding and Zidovudine for six months vs. formula feeding and Zidovudine for one month to reduce mother-to-child HIV transmission. The efficacy of these two feeding strategies are compared.

World Health Organization

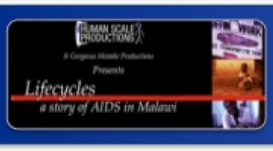
Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Programmatic update, *WHO* (2012)

Discusses the new WHO guidelines on ARV use in HIV-infected pregnant women. Special attention is paid to B+ policy advantages.

TM&IH Tropical Medicine & International Health

Linking women who test HIV-positive in pregnancy-related services to long-term HIV care and treatment services: A systematic review, *TM&IH* (2012)

A systematic review looking at barriers and points of attrition within patient cascades. Health worker-related and individual factors, along with suggested practices to account for these are discussed.



Lifecycles: A story of AIDS in Malawi, *Human Scale Productions* (2003).

A short documentary exploring various themes—e.g. povery, sex, witchcraft, religion, and death—with respect to AIDS. Official selection of the Atlantic Film Festival.

Trailer: https://www.youtube.com/watch?v=HEx2tj6vliA

Case 6: Care of HIV positive women

Ntombi is a 24 year old, G3P2, who is quite anxious with her current pregnancy as her two previous children died in infancy. She is admitted under your care at 31 weeks GA with TPTL. She indicates to you that she is HIV positive, but at the time was told she "wasn't sick enough to need medication". As such, she is not and has never been on antiretroviral therapies (ARTs). She is admitted and does well under observation.

After a few weeks and consultation with your medical team, Ntombi is induced at 38+ weeks. She undergoes an uneventful labor and receives intrapartum ART prophylaxis. Much to her relief, she safely delivers a healthy male at 3.8kg (8lb 6oz).

You discuss the topic of breastfeeding with Ntombi; she shares that she intends to breastfeed her son as she's heard about the benefits of breast milk, and also can't afford formula. She's understandably worried about her son's HIV status and health. You consult her on what her and her son's postpartum care might entail to prevent maternal-to-child HIV transmission (PMTCT).

Questions for Discussion:

1. Understand and discuss the WHO PMTCT recommendations.
    a. What do Options A, B, and B+ entail? What are the nuances between these recommendations (please refer to Table 1 in 2012 PMTCT update)?
    b. Who is covered under the newest B+ recommendations?
2. What is Ntombi's eligibility for treatment?
3. What are some of the barriers to receiving appropriate care and treatment in HIV positive women during and after pregnancy?

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JIAS Journal of the International AIDS Society

Research article

"Telling my husband I have HIV is too heavy to come out of my mouth": pregnant women's disclosure experiences and support needs following antenatal HIV testing in eastern Uganda

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Abstract

Introduction: Disclosure of HIV serostatus by women to their sexual partners is critical for the success of the prevention of mother-to-child transmission of HIV (PMTCT) programme as an integrated service in antenatal care. We explored pregnant HIV-positive and HIV-negative women's partner disclosure experiences and support needs in eastern Uganda.

Methods: This was a qualitative study conducted at Mbale Regional Referral Hospital in eastern Uganda between January and May 2010. Data collection was through in-depth interviews with 15 HIV-positive and 15 HIV-negative pregnant women attending a follow up antenatal clinic (ANC) at Mbale Hospital, and six key informant interviews with health workers at the clinic. Data management was done using NVivo version 9, and a content thematic approach was used for analysis.

Results: All HIV-negative women had disclosed their HIV status to their sexual partners but expressed need for support to convince their partners to also undergo HIV testing. Women reported that their partners often assumed that they were equally HIV-negative and generally perceived HIV testing in the ANC as a preserve for women. Most of the HIV-positive women had not disclosed their HIV status to sexual partners for fear of abandonment, violence and accusation of bringing HIV infection into the family. Most HIV-positive women deferred disclosure and requested health workers' support in disclosure. Those who disclosed their positive status generally experienced positive responses from their partners.

Conclusions: Within the context of routine HIV testing as part of the PMTCT programme, most women who test HIV-positive find disclosure of their status to partners extremely difficult. Their fear of disclosure was influenced by the intersection of gender norms, economic dependency, women's roles as mothers and young age. Pregnant HIV-negative women and their unborn babies remained at risk of HIV infection owing to the resistance of their partners to go for HIV testing. These findings depict a glaring need to strengthen support for both HIV-positive and HIV-negative women to maximize opportunities for HIV prevention.

Keywords: pregnant women; HIV disclosure to partner; HIV testing by proxy; support needs; intersectionality.

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Introduction

In Uganda, prevention of mother-to-child transmission of HIV (PMTCT) programme was initiated in 2000, originally using the voluntary counselling and testing (VCT) approach. Since 2006, HIV testing for PMTCT in Uganda has been provided routinely, integrated within the antenatal, child birth and post-partum healthcare clinics [1,2]. Routine HIV counselling and testing, though relatively new in most low-income settings, has been part of the standard of care in many high-income countries since the late 1980s and early 1990s [3–5]. In line with WHO recommendations, the main pillars of Uganda's PMTCT programme are (1) preventing HIV infection in women of child-bearing age, (2) preventing unwanted pregnancies among women living with HIV, (3) reducing HIV transmission from women living with HIV to their infants and (4) providing care and support for women living with HIV, their children and families [2,6]. Disclosure of HIV status by women to their sexual partners is critical for the success of each of the four pillars of the PMTCT programme. Therefore, disclosure is encouraged and promoted during pre- and post-test HIV counselling, but it could be a challenge for many women. Studies done in the African setting have documented fear of stigma [7], loss of economic security and accusations of infidelity [8], violence [9] as well as the desire to retain moral integrity and status [10] as some barriers to HIV status disclosure among pregnant women. In Uganda, HIV-related stigma remains a challenge for women in accessing HIV prevention and care services including PMTCT [11]. Stigma also hinders early initiation of antiretroviral therapy (ART) [12]. Rates of disclosure ranging from 17 to 86% have been documented among women in different African settings, with those tested at VCT clinics more likely to disclose their HIV status to their sexual partners than women tested in the context of antenatal care [8].

However, most studies on disclosure have focused on people who test HIV-positive [13,14] than those who test HIV-negative, more so HIV-negative women may have unique experiences and support needs. Besides, women's disclosure experiences could vary by HIV status or even within each of these sub-groups depending on the varied social groups women belong to.

In this paper, we draw upon intersectionality theory as an analytical framework to underscore the relationships between women's disclosure, or lack of disclosure, and the influence of various social categories assigned to women. Intersectionality was advanced by ''feminists'' to challenge the unitary concept of ''women''. For example, feminists have argued that race and gender interacted to shape the multiple dimensions of black women's employment experiences [15], and to speak of ''women'' as a homogeneous group who faced the same issues, marginalized other categories of oppression [15,16]. Intersectionality relates to the multi-dimensional nature of identity [15,16], focuses on differences among groups and seeks to illuminate various interacting social factors that affect human lives [17]. The basis for intersectionality is that various dimensions of social stratification including socio-economic status, gender and age, among others, can add up to great disadvantage for some people or advantage for others [17,18]. Intersectionality theory strives to elucidate and interpret multiple and intersecting systems of oppression and privilege [19]. The concept of intersectionality is particularly relevant in our study of women's disclosure experiences of their HIV status to sexual partners, as it aids an in-depth examination of how women's experiences are linked to their social identities like age, women's care giving roles as mothers, type of marital relationship, women's degree of dependency on men, among other social factors operating within the social context where women lead their lives. Indeed Gita and Ostlin [20] argued that an understanding of how gender intersects with economic inequality or a number of other social markers is important for awareness of how gender power relations work to produce health inequality, in our case how gender power relations influence women's disclosure experiences as a key determinant of access to HIV prevention, care and support services.

Within the context of the ongoing expansion of HIV counselling and testing services, integrated in the antenatal clinic (ANC) in Uganda [21], understanding women's experiences of HIV status disclosure to their partners and the support women require before and/or after disclosure could provide insights for how best to enhance programme success. This study explored pregnant HIV-positive and HIV-negative women's partner disclosure experiences and support needs at Mbale Regional Referral Hospital, eastern Uganda.

Methods

Study area

The study was conducted in the ANC at Mbale Regional Referral Hospital, eastern Uganda, between January and May 2010. Mbale Regional Referral Hospital is located in Mbale District, about 245 km east of Kampala, the capital city of Uganda. The district has a population of 428,800 people [22], the majority being rural dwellers [23]. Mbale Regional Referral Hospital serves an estimated catchment population of 1.9 million people [24] from 13 districts in eastern Uganda. In Uganda, 94% of the women attend antenatal care at least once, while 47% of the women make at least four ANC visits [22]. In 2005, overall HIV prevalence in eastern Uganda, where Mbale District is located, was estimated at 5.3% while prevalence was 6.3% among women aged 15 to 49 years [25] in the same period.

The ANC at the hospital operates daily on weekdays and serves about 60 pregnant women per clinic day. All antenatal attendees are given HIV education, which doubles as pre-test HIV counselling in line with the Uganda national HIV counselling and testing guidelines [1]. The pre-test health education covers the general maternal and child healthcare, as well as HIV-specific issues including HIV prevention, transmission, testing and care. Since 2006, all women who attend ANC at Mbale Hospital are tested for HIV, unless they opt not to be tested, and they are encouraged to disclose their HIV status to their sexual partners. A previous study conducted at the Mbale Hospital ANC in 2009 documented a high, almost universal, HIV testing rate among pregnant women [26]. Mbale Hospital was chosen for being one of the oldest PMTCT sites in Uganda and for serving largely rural residents like the vast majority of Uganda's population [22].

Study design

We conducted a qualitative study to explore pregnant women's experiences of routine HIV counselling and testing as part of antenatal care, including women's experiences as in disclosure of their HIV status to their sexual partners. In this paper, we focus on the disclosure aspects of the study. A qualitative research design was deemed appropriate to obtain an in-depth understanding of pregnant HIV-positive and HIV-negative women's partner disclosure experiences as well as the support that women feel they required before and after disclosure [27]. In addition, a qualitative design facilitated an in-depth examination of the influence of factors, such as gender, age, economic status and women's roles as mothers, on women's HIV status disclosure to their sexual partners.

Study participants and sampling

Thirty pregnant women (15 HIV-positive and 15 HIV-negative) participated in the study during their follow up ANC visit at Mbale Regional Referral Hospital. Study participants were selected purposively from women who had gone through routine HIV counselling and testing in their previous ANC visit during the current pregnancy. Study participants who provided written consent to participate in the study, were pregnant, had taken an HIV test on a previous ANC visit and were 18 years old or more were eligible. Variation in age, parity and education level were considered in selection of study participants. Only women who came back for subsequent ANC visits after HIV testing were included in the study. Tracing pregnant women who had tested for HIV as part of ANC at community level was not feasible in our case, given the challenges of HIV stigma, especially, for those who tested HIV-positive. Eligible women who agreed to participate in

the study were identified through health workers at the ANC who served as gatekeepers (people who can allow and facilitate access to study participants) [28] and referred to members of the study team stationed at the ANC. The researchers obtained consent and enrolled study participants consecutively after undergoing their routine consultation and assessment. After interviewing 15 women in each of the two groups, we felt that the information generated by later interviews did not vary from earlier interviews, and thus no further interviews were conducted.

Data collection

Individual interviews with pregnant women

A pre-tested interview guide [29,30] was used to explore study concerns. The interview guide was pre-tested by the research team at the ANC at Mbale Hospital. Data from this phase were not included in the final analysis. Semi-structured individual interviews [31] rather than focus group discussions were conducted to allow free and confidential interaction between researchers and women as HIV is still a sensitive condition in the study setting. The interview guide consisted of structured questions on women's background characteristics as well as open-ended qualitative questions with probes, to allow an in-depth understanding of women's disclosure experiences. The key issues explored were: whether women had disclosed their HIV status to their partners or not, how women found the process of disclosure, anticipated benefits and fear of disclosure, partners' reaction to disclosure as well as the support required by women before and after disclosure. The interviews lasted for about 40 to 45 minutes, and most interviews (27) were audio recorded, with exception of three women (one HIV-positive and two HIV-negative) who did not consent for audio recording. For all interviews, interviewers were paired up (one asked questions and the other took notes). We made this provision after the pre-test, where we realized that if one person were to interview and take notes the interview would become stilted and would take longer. Interviews were conducted in Lumasaba, Luganda (main languages in the study area) and a few in English. JR conducted interviews in Luganda, and English and was assisted by three female research assistants (university graduates, experienced in qualitative research and conversant with the three languages). Audio-recorded interviews were transcribed and translated into English. JR, together with one research assistant, cross-checked the transcripts. While it was possible that the male gender of one researcher (JR) could have influenced women's responses, this influence might have been minimal. Being a social scientist with extensive training and experience in conducting qualitative interviews involving women might have helped to neutralize this likely bias. In all interviews, JR paired up with a female research assistant and took time to build rapport with study participants before commencing interviews. Besides, the findings that were obtained from interviews conducted by female researchers did not vary from those conducted by JR. The study also benefited from peer briefing sessions involving multidisciplinary male and female investigators, which we believe improved the credibility of study results.

Key informant interviews

Six health workers (one doctor, two counsellors and three nurse midwives), involved in the antenatal care clinic, participated in key informant interviews. These were intended to contribute to a better understanding of women's disclosure experiences as well as providing an opportunity for data triangulation involving comparing results from women and healthcare providers [28]. A key informant interview guide was used to conduct the interviews. Interviews explored whether women tested for HIV as part of antenatal care services, disclosed their HIV status to partners, women's experiences, fears and support required before and after disclosure.

Data analysis

Interim data analysis occurred concurrently with data collection through daily research team meetings, where emerging issues and further data collection needs were identified. This process was important in keeping track of the number of interviews that were conducted and in identifying emerging issues as well as those that required further probing. For instance, the fears of HIV-positive women of disclosure and men assuming similar HIV status as that of their partners were probed further in interviews with health workers. In addition, JR, who supervised data collection, briefed all co-authors on preliminary insights and emerging issues of the study. Further analysis was conducted by JR in close collaboration with HKH using a content thematic approach [32]. The English version of transcripts were imported into NVivo version 9.0 [33] for coding and analysis. The analysis was guided by the themes already contained in the interview guide, which were further refined following multiple readings of interview scripts to better understand the data, identify sub-themes and to group the data according to themes for analysis and interpretation. Quotations reflecting pregnant women's HIV disclosure experiences and support needs were identified and have been used in the presentation of study findings. The identities of study participants were masked; for women we use ''marital status, age and HIV status'' as key identifiers. The term ''married'' in this regard is used for women who are formally married and those in informal unions (cohabiting). A similar categorization was used in the Uganda HIV/AIDS sero-behavioural survey [25] and is a common practice for collecting routine health information at health facilities in Uganda. For health workers we use ''health worker''.

Concurrent triangulation was conducted in analysis of data from pregnant women and those of key informants. This enabled us to have an in-depth understanding of HIV-positive and HIV-negative women's disclosure experiences, response from partners and the support women require before and after disclosure. In addition, we conducted sub-group analysis for similarities and differences in disclosure experiences of HIV-positive and HIV-negative women.

Ethical considerations

Ethical approval for the study was obtained from the Uganda National Council for Science and Technology, Makerere University, College of Health Sciences, Research and Ethics Committee and Mbale Regional Referral Hospital Institutional

Review Committee. Permission was also obtained from management of Mbale Hospital and the Mbale District administration. All study participants provided written consent to participate in the study. Ink pads for thumb print were provided for those who could not read or write. Research assistants were trained on the approach to data collection and the ethical issues involved in HIV research. Study participants were assured of confidentiality, and each interview was conducted in a separate room provided by the ANC management.

Results

Characteristics of study participants

The age of women ranged between 18 and 43 years, most of them (25/30) were married and (26/30) depended on agriculture for survival, and half of them had attained primary education (Table 1).

The women's experiences of disclosing their HIV status to sexual partners are organized on the basis of major themes that emerged from the interviews. These were (1) the divergent and complex path to disclosure, which denotes the difference in disclosure among pregnant HIV-negative and HIV-positive women; (2) anticipated benefits and losses of disclosure; (3) partner reaction to disclosure; and (4) the support needed before and after disclosure (Table 2).

Table 1. Characteristics of study participants

Characteristic	HIV-negative women ($n=15$)	HIV-positive women ($n=15$)	Frequency ($n=30$) (%)
Age (years)			
18 to 20	4	2	06 (20)
21 to 25	6	5	11 (37)
26 to 30	1	3	04 (13)
31 to 39	4	3	07 (23)
40 to 43	0	2	02 (07)
Education attained			
None	1	1	02 (07)
Primary	7	8	15 (50)
Secondary	4	5	09 (30)
Tertiary	3	1	04 (13)
Main source of income			
Agriculture	12	14	26 (87)
Formal employment	3	1	04 (13)
Marital status			
Single	2	3	05 (17)
Married/ cohabiting	13	12	25 (83)
Type of marriage ($N=25$)			
Monogamy	10	7	17 (68)
Polygamy	3	5	08 (32)
Number of children ever given birth to			
None	1	3	04 (13)
1 to 2	7	6	13 (43)
Three and more	7	6	13 (43)

The divergent and complex path to disclosure of HIV status to sexual partner

Different and complex paths to disclosure of HIV status to sexual partners emerged for HIV-positive and HIV-negative pregnant women. All pregnant women who had tested HIV-negative reported that they had disclosed their HIV status to their sexual partners and found the process easy, as one woman explained:

> Since I was HIV-negative, I was excited. When I reached home I told my husband that when I went for pregnancy check up, health workers tested my blood and found I do not have HIV ... I felt happy because I was safe from HIV and I could not hide this from my husband. I wanted him to know so that he can remain faithful to me ... if I was positive it would have been difficult for me to tell him. HIV-positive! ... the man can say you gave him HIV and he can chase you away or beat you ... (Married, 24 years old, HIV-negative)

The common terminologies that run through HIV-negative women's disclosure narratives included ''... I don't have HIV, I am negative, ... we are safe, ... I don't have the virus, ... I know you are faithful to me, we should remain faithful to each other'' among others. As indicated in the quotation above, HIV-negative women acknowledged that disclosure would have been difficult if they had tested HIV-positive, for fear of being accused of infecting their partners with HIV, being sent away from home or being beaten.

On the contrary, most of the HIV-positive women (11/15) had not disclosed their HIV status to their sexual partners. They described the process of disclosure to their sexual partners as ''very difficult and too heavy'' for them to undertake; some did not know how to go about it, while many preferred to defer it:

> No, I have not told anyone since I tested, not even my sister! The nurses advised me to tell my husband, but every time I think about it I find myself crying ... I don't know how to start or how he will take it. He may think I have been cheating on him. No, not now! I feel telling my husband I have HIV is too heavy to come out of my mouth. I do not even want to think about it. Not now. May be after giving birth we will go together and test so that health workers can tell us when we are together. (Married, aged 22 years, HIV-positive)

Many HIV-positive women found disclosure very difficult, especially when women thought that their partners would react negatively or interpret women's HIV status to mean women have been unfaithful. Only four of the fifteen HIV-positive women interviewed had disclosed to their sexual partners. Analysis of disclosure narratives indicated that fear

Table 2. Thematic presentation of pregnant women's experiences and fears of HIV disclosure to sexual partner

Sub-themes		
HIV-negative women	**HIV-positive women**	**Main themes**
● All disclosed ● Process was easy	● Most not disclosed ● Very difficult ● Too heavy to tell	The divergent and complex path to disclosure

● Expected partner to test for HIV
● Partner will be faithful
	● Expected partner to test for HIV
	● Fear of:
	  ● Abandonment
	  ● Violence
	  ● Accusation of bringing infection in family
		Anticipated benefits and losses of disclosure

● Partner said he was also HIV-negative ● No need to test ● Partner assumed HIV-negative status based on woman's/women's results	● Kept quiet ● Partner tested ● Partner disclosed own HIV status ● Partner supportive ● Partner denied HIV-positive results	Partners' reaction to disclosure
● Guidance on convincing partner to go for HIV testing ● Needed health workers to convince male partners to go for HIV testing	● Guidance on convincing partner to go for HIV testing ● Needed health workers to convince male partners to go for HIV testing ● Needed health workers to assist with disclosure	Support needed before and after disclosure

and stress underlie the complexities of HIV disclosure to sexual partners:

> I did not tell any one immediately when I went home, but later in the night, I had many thoughts, I could not sleep so I had to tell my husband on phone (husband had travelled). It was not easy but my heart pushed me to tell him. I was feeling bad and I said to myself if I don't tell him, I might die of stress. I told him with a lot of fear that when I went for antenatal they found me with the HIV virus (akawuka ka silimu). He first kept quiet and later told me we shall help each other. I felt some relief because I had told him, but I did not sleep that night, I prayed to God that my husband does not react badly because of what I had told him …. (Married, 36 years, HIV-positive)

Interviews with health workers confirmed that indeed most HIV-negative women find disclosure to their partners easy while those who test HIV-positive encountered disclosure as a difficult process: ''Most, if not all, women who test HIV negative tell their husbands but those who test HIV positive, many don't tell their partners, women fear that their husbands will abandon them or beat them for bringing HIV …'' (Health worker).

Anticipated benefits and losses of disclosure

Pregnant women were always involved in appraising the anticipated benefits and losses of their HIV status disclosure to their sexual partners. All HIV-negative women anticipated that their partners would be happy with the negative test results, accept to go for HIV testing and be faithful once they had disclosed to them. These anticipated benefits were major drivers of disclosure for such women: ''I told my husband because I felt he should know that I do not have HIV, I think it can help him to remain faithful to me and we avoid HIV in our marriage'' (Married, 25 years, HIV-negative). Another woman noted that: ''… I told my husband because I wanted him to go and also get the test'' (Married, 24 years, HIV-negative).

Narratives of most HIV-positive women who had not disclosed revealed profound fear of abandonment, violence and accusation of bringing HIV infection into the family as key anticipated losses, which made disclosure risky for them. HIV-positive women feared that their husbands would abandon them if they told them that they had HIV, which would mean loss of support for themselves and their children because they largely depend on their husbands as bread winners:

> … It is now 2 months, I have never told any one about my HIV status, not even to my husband … I fear that if I tell him, he can desert me and I don't want my children to suffer. Men are very difficult, he can decide to get another woman and then leave me to suffer alone. (Married, 30 years, HIV-positive)

The fear to lose material and financial support emerged as a key barrier to disclosure and was related to situations where men were sole providers and women being pregnant, which made it difficult for them to find jobs to support themselves in case their partners discontinued support:

> I have not told my boy friend, I fear if he knows he can stop supporting me. Where will I go with this

> pregnancy? I am not working and he is the only one who gives me money for food, rent, . . . Maybe after giving birth and the baby grows, I will tell him we go and test together, if he accepts the counsellor will tell him. If he stops giving me support, the child will have grown I will look for a job, but now with this pregnancy no one can give me a job. (Married, aged 19 years, HIV-positive)

The fear of abandonment by male partners was more pronounced among HIV-positive women in polygamous marital relationships and was compounded by the need to ensure that the care that husbands provided for the women and their children would remain uninterrupted:

> If I tell him, he may never come back to my place and shift forever to the second wife. How will I and my children survive? He can even send me away or say I brought HIV yet I have been faithful to him; I feel bad that I have HIV yet I have not been having other men. (Married, aged 28 years, HIV-positive)

Some HIV-positive women explained that their male partners would interpret women's HIV-positive results to mean that they (women) have killed their husbands:

> I cannot tell my husband, he will think I have been sleeping with other men . . . he will say I have killed him. Before I tested, I once talked to him about the issue of going to test for HIV and he told me that he will never test because that is one way of knowing and die quickly . . .. (Married, 28 years old, HIV-positive)

The above narrative reveals that some HIV-positive women fear that their partners might interpret the HIV-positive status to mean promiscuity by women as a source of HIV infection and HIV is still understood as a fatal infection.

In consonance with the above, health workers at the ANC revealed that some HIV-positive women opted not to disclose their HIV status for fear of being accused of having been promiscuous and thus infecting their husbands, which would result in the breakdown of the marriage: ''We got one woman here who tested HIV positive, when she told the man, he told her to go away and called her a prostitute . . . those are the things that make women fear to tell their husband . . .'' (Health worker).

Although all HIV-negative women believed disclosure was good for themselves and their sexual partners, some HIV-positive women thought not disclosing protected their partners from worry and was thus beneficial: ''I don't have plans of telling my boyfriend. I don't want him to know that I have HIV. It is better for him not to know. He will worry a lot. May be if he goes for testing himself . . .'' (Married, 21 years, HIV-positive).

Partner reaction to women's disclosure of HIV status

Most HIV-negative women expected their male partners to go for HIV testing, but most women reported that their partners instead assumed that they were equally HIV-negative (HIV testing by proxy):

> I told him that I did not have HIV; he said that it was good, we are both safe from HIV. I told him the nurse had said he should go and test, he just laughed and asked me why? Since they tested you . . . we both don't have HIV. (Married, 24 years, HIV-negative)

Narratives of women also revealed that men who had more than one wife tended to use HIV-negative results of their wives to confirm their assumed HIV-negative status: ''When I asked him to go and test for HIV, my husband told me that since me and my co-wife had tested HIV negative, our family is free from HIV, we should remain faithful to each other . . .'' (Married, 32 years, HIV-negative).

Interviews with health workers also indicated that while they did not have any statistics about men who assume they are HIV-negative based on their female partner results, this practice was common: ''Men think that since their women have tested HIV negative, they are also negative and so men see no need to go for HIV testing'' (Health worker).

Some women repeatedly mentioned that their partners perceived HIV testing as part of antenatal care to be meant only for pregnant women and not the men:

> Yes, I told him but he said he cannot test because he is not a woman and he is not pregnant. He said that since both of his two wives were HIV negative there is no need for him to test. (Married, 24 years, HIV-negative)

When probed, women revealed that they often gave up trying to persuade their male partners to go for HIV testing whenever men showed unwillingness to go for the test. Women also assumed and hoped that they and their male partners were really HIV-negative:

> I told him that the nurse had said he should also go and test, he said why should he? The good thing they tested me and I am negative. Even if he has not tested I think we do not have HIV . . .. (HIV-negative 32 years old, married)

The four HIV-positive women who had disclosed encountered varying outcomes from their partners. One woman, with tremendous fear, disclosed her serostatus to her partner and she discovered that he was already receiving HIV treatment from The AIDS Support Organisation (TASO), which is one of the major HIV and AIDS care organizations in Uganda:

> I told my husband, but with a lot of fear, he first kept quiet and later told me we shall help each other. He then told me that he is a member of TASO. He advised me to join TASO to get treatment, and that I should be strong. I had a lot of fear but God was on my side that he was also positive . . . When he told me at first I felt bad and I was annoyed with him for infecting me with HIV. These men, I asked myself why he had kept it to himself. I remembered how he used to go to Mbale town every end of month; I knew that is when he was picking his drugs. As a Christian I have forgiven him . . .. (Married, 36 years old, HIV-positive)

The discovery by this woman after disclosure that her partner already knew his HIV status before the woman tested elicited anger, but the profound fear and expectation of negative reaction from the man, together with faith in God, helped her to cope.

The second HIV-positive woman disclosed to the partner out of anger, but she was surprised by her husband's response; he became supportive and went for HIV testing:

> I had to tell him because anger was killing me**.** We spent some days without talking. I would find myself crying most of the time at home. Although, I was annoyed, my husband kept encouraging me. He also went and tested. They found him positive . . . he started ARVs. (Married, 43 years, HIV-positive)

For the third HIV-positive woman, aged 18 years, who disclosed, the partner denied her HIV-positive test results and insisted that they both did not have HIV. The fourth HIV-positive woman explained that her religious conviction helped her in disclosure. The partner was angry but later tested HIV-positive and encouraged his wife to go for treatment so that they can care for their children:

> I told my husband because I wanted him also to go and test. When I told him, he was annoyed, but I reminded him about the many women he has so he kept quiet . . . he went to the field and stayed longer than usual. Later, he came and told me that he had also tested HIV positive, he said we should start treatment and bring up our children. After testing positive, he realized his mistake. What helped me to disclose was my faith in God. I didn't want to stay with a lie in my heart . . .. (Married, aged 40 years, HIV-positive)

What is emerging from the four narratives is that most of the HIV-positive women who disclosed were between 36 and 43 years, while only one was 18 years old. This in part depicts young age as a likely barrier to disclosure among women. In addition, two of the women who disclosed had attained secondary education. In view of age, healthcare providers indicated that disclosure was more difficult for young women:

> What I have seen, it is more hard for young women to disclose to their partners especially those in their early 20s or younger. They have many fears and they are not sure if the relationship will continue; for the older women it is easier, for them they have children and they are known in the family so they cannot easily be chased away . . .. (Health worker)

Support needed before and after disclosure

Generally, most HIV-positive and HIV-negative women expressed need for support from health workers to convince their male partners to undergo HIV testing:

> Health workers need to find a way of telling men to test. When we tell them they say they are also negative others say they do not have time to come to hospital. (Married, aged 24 years, HIV-negative)

Some women explained that their partners fear to test thinking that if they are found HIV-positive they will die quickly:

> But I once talked to him about the issue of HIV testing and he told me that he will never test because that is one way of knowing and die quickly. (Married, aged 28 years, HIV-positive)

HIV-positive women also felt that they should be provided with more counselling after HIV testing to address fears related to living with HIV and coping with the HIV-positive diagnosis:

> Even counsellors visiting people who have recently tested may help, but they should not go with TASO uniform. After being told you have HIV you get many thoughts, you fail to sleep, you don't know where to begin from. More help is needed. (Married, aged 36 years, HIV-positive)

Discussion

The narratives of women in this study showed that disclosure of HIV status to sexual partners was common and easy for pregnant women who had tested HIV-negative. However, disclosure of HIV status to partners was frightening for most HIV-positive women. Thus, most HIV-positive women had not disclosed their HIV status to sexual partners mainly due to fear of abandonment, being sent away from home, domestic violence and accusation of bringing HIV infection into the family. Our findings on HIV-positive women's fear of serostatus disclosure to their partners support what have been documented in other sub-Sahara African settings [7–10,13].

Non-disclosure by HIV-positive women in our study for fear of being accused by their partners for bringing HIV infection into the family underpins HIV prevalence as a sexually transmitted disease, which in this case would be interpreted to mean HIV-positive women have been promiscuous or had other sexual partners. Having other sexual partners among women goes against the expected gender norms in the study setting, where, for instance, it is acceptable for a man to have more than one partner but a taboo for women to do so.

Using the intersectionality framework [16,17,19,20], our study adds to the understanding of how these barriers to disclosure are compounded by the intersection of gender and other social positions that women occupy. For instance, the fear of abandonment among HIV-positive women was associated with the profound fear to lose support for the women and their children. This finding shows how women's economic dependency on men and women's roles as mothers caring for children intersect to act as a barrier for HIV serostatus disclosure to partner. This finding is not surprising given that within the study setting, like other parts of Uganda, most women depend on their male partners for their care and that of children. In eastern Uganda, 72% of the households are headed by men, implying that men have power and control over allocation of resources [34] and can choose to withdraw such resources as a form of punishment.

Our findings also showed that young women and those in polygamous relationships who tested HIV-positive found

disclosure extremely difficult. Young women feared that disclosure would mean an end to their relationships while women in polygamous relationships feared that their partners would abandon them and shift to co-wives, which would lead to loss of support for the women and their children. These findings reflect a real case in which gender intersects and works in tandem with other social identities to shape the lived experiences of women, in our case, non-disclosure of HIV status to partners was influenced by women's economic dependency on men, women's roles as mothers caring for children and polygamy as a form of marital relationship. Polygamy as a barrier to disclosure has also been documented in Ivory Cost [14]. In this regard, our findings are in agreement with proponents of intersectionality theory who argue that individual's social identities profoundly influence one's experience of gender [16] and that the various social stratifications like age, gender and socio-economic status can lead to greater disadvantage or advantage [18,19]. In our case, while all our study participants were women, their varied identities in addition to being women worked together to hinder disclosure. The implication here is that health workers should consider the varying social positions in preparing and supporting women for disclosure, for instance, young women, those in polygamous relationships and those largely dependent on their male partners, may require more counselling and support for disclosure and convincing men to test for HIV.

Our finding that some HIV-positive women felt non-disclosure helped to protect their sexual partners from stress and worry was a surprise, but could in part be a reflection that these women are aware of the risks of HIV disclosure to their partners and re-echoes the need to facilitate disclosure as a process. Some HIV-positive women reported that they do not disclose to their partners because they (partners) would associate HIV-positivity to quickening their death. In this regard, the perception of HIV–related disease as fatal seems to persist despite ARVs increasingly becoming available in Uganda [21].

Most of the HIV-positive women in our study deferred disclosure of their HIV status to partners until after giving birth or until their male partners would agree to go with them for HIV counselling and testing. These findings depict the challenges that HIV-positive women are confronted with but also represent a threat to primary HIV prevention in case of discordant relationships, which is a common reality in Uganda [35,36]. Moreover, non-disclosure can prevent HIV-positive women from adhering to PMTCT interventions, thus increasing the risk of HIV transmission to the infants.

While all HIV-negative women in our study reported that they had disclosed to their partners, most men did not go for HIV testing, but instead many of them assumed that they were HIV-negative like their female partners ''testing by proxy'' [37]. The practice of ''testing by proxy'' among men is a big problem indicating that disclosure support interventions need to focus on women who test HIV-negative as well as those who test HIV-positive to enable them convince their male partners to test for HIV. Some HIV-negative women in polygamous relationships reported that their husbands often used HIV-negative test results of their wives as ''confirmatory tests'' for men's HIV-negativity. For such women, attempts to convince their partners to go for HIV testing were more problematic, again indicating how polygamous relationships as a social classification kept women and their babies at risk of HIV infection.

The practice of ''testing by proxy'' [37] by male partners of women who tested HIV-negative is worrying, given that in Uganda, an incidence modelling study indicated that 43% of the new HIV infections among adults in the reproductive age group in 2008 occurred in discordant, supposedly monogamous, relationships [35]. While a recent community cohort in Rakai District revealed that new HIV infections within identifiable HIV-discordant couples were lower (18% in the pre-ART and 14% in post-ART period) [38], studies in Uganda have documented HIV sero-discodance among married or cohabiting relationships of 5 to 65% [25,36,39]. The assumption of HIV-negative status by men is a threat to the effectiveness of the PMTCT programme and to the attainment of the goal of eliminating new HIV infections in children [6]. These findings question the effectiveness of the dominant model of reaching men for HIV testing through their female partners and provide further support for the need to expand couple counselling and testing. Couple counselling and testing provides opportunities to address the gender imbalanced power relations including relieving women of the burden of disclosure [40], and it is associated with increased uptake of PMTCT interventions [41].

Women who tested HIV-negative generally gave up on attempts to convince their male partners to go for HIV testing, whenever the men refused, indicating how gender and power relations come into play to shape the lived experiences of women. Indeed, HIV-negative and HIV-positive women alike expressed the need for support from health workers to convince their male partners to go for HIV testing. Male partner testing for HIV infection is key to preventing new HIV infections among women [42] but remains a challenge in many high HIV prevalent settings. Some interventions with promising results on male partner HIV testing include use of an invitation letter [43,44], home-based VCT [45,46] and routine HIV counselling and testing within the hospital setting [47].

Generally, the few HIV-positive women, who had shouldered the fear of disclosure, reported positive responses from their partners. These included male partner going for HIV testing, men already receiving HIV treatment disclosed their own status, as well as encouragement and support for the woman. The positive outcomes experienced by HIV-positive women in our study concur with what has been revealed by other scholars [13,14]. However, the fact that most HIV-positive women in our study encountered enormous fear of negative outcome for themselves and their children as a barrier to disclosure raises concern about the need for health workers to identify such women and develop appropriate support mechanisms to deal with their fears and negative outcomes when they really occur. Health worker mediated disclosure and collaboration with support groups of men and women living with HIV like those under the

AIDS Support Organization (TASO) could be of help to such women.

Strengths and limitations

The use of in-depth qualitative methods facilitated understanding of women's disclosure experiences and the implications these have on HIV prevention including PMTCT. The inclusion of HIV-positive and HIV-negative women in our study provided an opportunity to uncover the unique experiences and support needs for each of the two groups of women. Indeed most studies on disclosure tend to focus only on HIV-positive women. Our findings should be interpreted in view of the following limitations: (1) our study involved only women, thus we did not get firsthand information from men on their reactions and feelings about serostatus disclosure by their female partners. Women's reports of disclosure may have been affected by social desirability bias. Thus, future studies should seek to capture perspectives of both men and women. (2) Only women who came for their subsequent ANC visit after HIV testing were included in the study, implying a possible selection bias. Given the stigma that still surrounds HIV and AIDS in Uganda, identifying women who have recently tested for HIV infection at community level, especially those who tested HIV-positive, would have been difficult. However, the findings of our study on women's fear of disclosure are in consonance with what has been documented in other African settings [7,8,10]. In addition, findings from women were highly consistent with those of health workers, suggesting that the influence of selection bias on our findings might have been minimal. Although conducting all interviews at the health facility might have biased respondent's responses, there was an attempt to minimize this by the use of qualitative interviews with room for probing, as well as triangulation of data from interviews with women and those of health workers. This improved the trustworthiness of our findings.

Conclusions

Within the context of routine HIV testing as part of the PMTCT programme, women who tested HIV-positive found disclosure of their HIV status to their sexual partners extremely difficult. The general fear of disclosure among HIV-positive women was influenced by the intersection of gender norms, women's economic dependency on men, women's roles as mothers caring for children, being in polygamous relationships and young age. Pregnant HIV-negative women and their unborn babies remained at risk of HIV infection owing to the reluctance of their partners to go for HIV testing. These findings depict a glaring need to strengthen the support for both HIV-positive and HIV-negative women to maximize opportunities for HIV prevention. Pregnant women who test HIV-positive should be supported to disclose and those who test HIV-negative need support to get their partners tested. Further research is needed to shed more light on the prevalence of ''testing by proxy'' as well as how HIV-positive and HIV-negative women accessing antenatal care can be better supported.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JR conceived the study. JR, SN, JKT, TT, & HKH participated in the design of the study. JR participated in data collection. JR, RB and HKH participated in data analysis. JR wrote the initial draft of the manuscript. All authors (JR, SN, RB, JKT, TT, & HKH) participated in the interpretation, revision of manuscript and approved the final manuscript.

Abbreviations

AIDS, acquired immune deficiency syndrome; ANC, antenatal clinic; ART, antiretroviral therapy; ARVs, antiretroviral drugs; CDC, Centers for Disease Control and Prevention, USA; HIV, human immune-deficiency virus; IDC, infectious diseases clinic; JCRC, Joint Clinic Research Centre; MTCT, mother-to-child transmission; NVP, nevirapine; PMTCT, prevention of mother-to-child transmission of HIV; RCT, routine HIV counselling and testing; TASO, The AIDS Support Organisation; UAC, Uganda AIDS Commission; VCT, voluntary HIV counselling and testing.

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Breastfeeding Plus Infant Zidovudine Prophylaxis for 6 Months vs Formula Feeding Plus Infant Zidovudine for 1 Month to Reduce Mother-to-Child HIV Transmission in Botswana

A Randomized Trial: The Mashi Study

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Context Postnatal transmission of human immunodeficiency virus-1 (HIV) via breastfeeding reverses gains achieved by perinatal antiretroviral interventions.

Objective To compare the efficacy and safety of 2 infant feeding strategies for the prevention of postnatal mother-to-child HIV transmission.

Design, Setting, and Patients A 2 × 2 factorial randomized clinical trial with peripartum (single-dose nevirapine vs placebo) and postpartum infant feeding (formula vs breastfeeding with infant zidovudine prophylaxis) interventions. In Botswana between March 27, 2001, and October 29, 2003, 1200 HIV-positive pregnant women were randomized from 4 district hospitals. Infants were evaluated at birth, monthly until age 7 months, at age 9 months, then every third month through age 18 months.

Intervention All of the mothers received zidovudine 300 mg orally twice daily from 34 weeks' gestation and during labor. Mothers and infants were randomized to receive single-dose nevirapine or placebo. Infants were randomized to 6 months of breastfeeding plus prophylactic infant zidovudine (breastfed plus zidovudine), or formula feeding plus 1 month of infant zidovudine (formula fed).

Main Outcome Measures Primary efficacy (HIV infection by age 7 months and HIV-free survival by age 18 months) and safety (occurrence of infant adverse events by 7 months of age) end points were evaluated in 1179 infants.

Results The 7-month HIV infection rates were 5.6% (32 infants in the formula-fed group) vs 9.0% (51 infants in the breastfed plus zidovudine group) ($P = .04$; 95% confidence interval for difference, –6.4% to –0.4%). Cumulative mortality or HIV infection rates at 18 months were 80 infants (13.9%, formula fed) vs 86 infants (15.1% breastfed plus zidovudine) ($P = .60$; 95% confidence interval for difference, –5.3% to 2.9%). Cumulative infant mortality at 7 months was significantly higher for the formula-fed group than for the breastfed plus zidovudine group (9.3% vs 4.9%; $P = .003$), but this difference diminished beyond month 7 such that the time-to-mortality distributions through age 18 months were not significantly different ($P = .21$).

Conclusions Breastfeeding with zidovudine prophylaxis was not as effective as formula feeding in preventing postnatal HIV transmission, but was associated with a lower mortality rate at 7 months. Both strategies had comparable HIV-free survival at 18 months. These results demonstrate the risk of formula feeding to infants in sub-Saharan Africa, and the need for studies of alternative strategies.

Trial Registration clinicaltrials.gov Identifier: NCT00197587

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According to some estimates, approximately 25% to 48% of infants born to human immunodeficiency virus (HIV)-infected breastfeeding women in certain populations may become infected with HIV-1.[1,2] A relatively high proportion of mother-to-child transmission in breastfeeding populations may occur through breastfeeding, perhaps more than 40%.[3,4] Perinatal antiretroviral prophylaxis can greatly reduce the risk of mother-

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to-child transmission of HIV,[5-10] but this efficacy is eroded by transmission via breastfeeding.[3-6,10-12] Exclusive breastfeeding with abrupt early weaning after 3 to 6 months,[4,13] pasteurization,[14,15] hot water bath,[16] and microbicidal treatment of breast milk with alkyl sulfates[17] have been proposed as methods to make breastfeeding safe. However, so far they have been either unsuccessful or cumbersome and expensive to implement.

Although avoidance of breastfeeding can eliminate HIV transmission through breast milk,[8,9,12,18] excess infant morbidity and mortality have been associated with the use of infant formula,[19-23] particularly where access to clean water is limited. In much of the world, cost and stigma also limit the use of formula feeding. However, a trial conducted among HIV-infected women and their infants in Nairobi, Kenya, found that formula feeding prevented an estimated 44% of infant HIV infections without leading to excess infant mortality, and that infants randomized to formula feed were therefore more likely to survive and to be HIV-uninfected at age 2 years than infants randomized to breastfeed (70% vs 58%, respectively, $P=.02$).[12] It should be noted that this study population was urban, had to have access to clean municipal water in order to participate in the Kenyan study, and did not receive antiretroviral treatment or mother-to-child transmission prophylaxis.

Only 2 unpublished studies[24,25] have assessed the use of extended antiretroviral prophylaxis (lamivudine and nevirapine) in breastfed infants for the prevention of postnatal transmission of HIV. Both studies reported low HIV transmission rates, but they did not include a control group. Zidovudine has been shown to effectively prevent mother-to-child transmission of HIV when taken during pregnancy,[9,26,27] when given as postexposure prophylaxis to newborns,[28-30] or in the setting of occupational exposure to HIV-1.[31] There have been no previous trials of infant zidovudine prophylaxis throughout the breastfeeding period, however. To date, there have also been no comparisons of a formula-feeding strategy with a strategy in which breastfed infants were given an intervention aimed at preventing infection from exposure to HIV in breast milk.

In 2001, we initiated the Mashi (milk) study to evaluate both perinatal and postnatal intervention strategies for reducing mother-to-child transmission of HIV in Botswana, where a national program for the prevention of mother-to-child transmission had been implemented in 1999. This program offered antenatal zidovudine to mothers, followed by 1 month of prophylactic infant zidovudine and the provision of infant formula, and was the first perinatal HIV prevention program in Africa to provide infant replacement feeding nationwide.

METHODS

Trial Design

The Mashi study was a randomized 2×2 factorial clinical trial for HIV-infected pregnant women and their infants, designed to compare interventions for both preventing perinatal HIV transmission (part 1) and reducing postnatal HIV infection and mortality (part 2).

The results of part 1, which was designed to assess the efficacy of adding single-dose nevirapine to maternal and infant zidovudine to reduce perinatal mother-to-child transmission, are presented elsewhere.[32] In the original design of part 1 of the study, 1 dose of nevirapine (200 mg for women at labor onset; 6 mg for infants within 72 hours of birth) or placebo was taken. In August 2002, as a result of efficacy data from Thailand,[8] the peripartum intervention was revised to eliminate infant placebo and provide all infants with open-label nevirapine immediately after being born. The maternal intervention remained unchanged.

Part 2, which is the focus of this paper, was randomized, nonblinded, and the first study to compare the efficacy and safety of breastfeeding plus infant zidovudine prophylaxis for 6 months (breastfed plus zidovudine) to formula feeding from birth plus 1 month of infant zidovudine (formula fed) for reducing postnatal transmission of HIV. Prior studies had informed the existing strategies for reducing postnatal HIV transmission, specifically the recommendation of exclusive formula feeding or exclusive breastfeeding with early weaning of infants.[12,13,33]

The Health Research Development Committee from Botswana and the Harvard School of Public Health Human Subjects Committee approved the study protocol and amendments.

Study Population

HIV-infected pregnant women attending antenatal clinics were referred to study locations at the district hospitals in the southern region of Botswana in 1 city, 1 town, and 2 large villages. Of the 11 881 pregnant women screened for HIV infection, 3935 (33%) had positive results and 1200 (30%) of these women were enrolled in the study between March 27, 2001 and October 29, 2003.

Eligibility criteria included being between 33 and 35 weeks' gestation; having a positive HIV-1 enzyme-linked immunosorbent assay (ELISA) on 2 separate samples; being aged 18 years or older; having levels of hemoglobin at 80g/L or above, absolute neutrophil count of 1000 or more cells/mm, alanine aminotransferase and aspartate aminotransferase at 10 or less times upper limit of normal, and creatinine 1.5 mg/dL (132.6 µmol/L) or less; and not having known intolerance to zidovudine or nevirapine.

All HIV-positive women who agreed to join the study signed a written consent form explaining the purposes of the study, the schedule of clinical and laboratory evaluations, the risks and benefits of both feeding strategies, the option to withdraw from the study at any given time without prejudice, the option to join the national prevention of mother-to-child transmission program at any time, that no identifying information would be included in any publications or presentation of the results, and the names of key people to contact about their rights or for any questions about the study. These women were encouraged to discuss the study or elements of the consent form with their partners or family members before joining the study. Study participants signed updated informed consent

Table 1. Comparison of Interventions for Preventing Perinatal HIV Transmission (Part 1) and Reducing Postnatal HIV Infection and Mortality (Part 2): The Mashi Study*

	N = 1200†	
Study Factor	Group	Group
Original design March 27, 2001 (study opening) to August 11, 2002 perinatal factor (part 1)‡	Single-dose placebo to mother plus single-dose placebo to infant (placebo/placebo)	Single-dose nevirapine to mother plus single-dose nevirapine to infant (nevirapine/nevirapine)
Postnatal factor (part 2) No.		
Breastfed plus zidovudine‖	122	120
Formula-fed‖	123	126
Revised design August 12, 2002, to October 29, 2003 (completion of study accrual) perinatal factor (part 1)§	Single-dose placebo to mother plus single-dose nevirapine to infant (placebo/nevirapine)	Single-dose nevirapine to mother plus single-dose nevirapine to infant (nevirapine/nevirapine)
Postnatal factor (part 2) No.§		
Breastfed plus zidovudine‖	179	177
Formula-fed‖	176	177

*All mothers received antenatal zidovudine and all babies received zidovudine during the first month of life.
†All mother/infant pairs randomized.
‡In the original design of part 1 of the study, mothers and infants were randomized to single-dose nevirapine or placebo (200 mg for mothers at labor onset and 6 mg for infants within 72 h of birth).
§In August 2002, in response to efficacy data from Thailand,[8] the perinatal intervention (part 1) was revised to eliminate infant placebo and provide all infants with open-label nevirapine immediately following birth. The maternal intervention remained unchanged. The postnatal intervention (part 2) also remained unchanged.
‖Infants were randomized to 6 mo of breastfeeding plus prophylactic infant zidovudine (breastfed plus zidovudine), or formula feeding plus 1 mo of infant zidovudine (formula-fed).

forms for amendments that affected the information in the consent form they originally signed for their participation in the study.

Randomization and Study Interventions

Centralized randomization to both part 1 and part 2 groups occurred at study enrollment (34 weeks' gestation), using permuted blocks of size 8 within each site. All women received zidovudine 300 mg orally twice daily from 34 weeks' gestation until labor onset, and every 3 hours during labor until delivery. Mothers and infants were assigned to single-dose nevirapine or placebo, depending on the randomized perinatal intervention group (part 1). See TABLE 1 for a schematic representation of the factorial design, including the revision of the part 1 design.

Infant zidovudine syrup was administered 4 mg/kg/12 hours from birth until 1 month of age in all infants, and discontinued at 1 month in the formula-fed group. For the breastfed plus zidovudine group, infant zidovudine prophylaxis continued from 1 to 2 months of age at 4 mg/kg/8 hours, and from 2 to 6 months of age (while still breastfeeding) at 6 mg/kg/8 hours. Exclusive breastfeeding was recommended (as per Botswana guidelines), although the introduction of foods/liquids other than formula was not considered nonadherence to breastfeeding. Mothers were instructed to begin and complete weaning between 5 and 6 months of age. Free infant formula was provided from 5 through 12 months of age to facilitate safe weaning. For infants in whom zidovudine was discontinued due to toxicity, mothers were instructed to simultaneously discontinue breastfeeding and begin formula. Mothers randomized to the formula-fed group were supplied with formula for 12 months. All mothers were educated about safe formula preparation and administration, and provided with high-protein food for infants from 6 through 12 months of age.

Antiretroviral Treatment

In October 2002, combination antiretroviral treatment consisting of zidovudine, lamivudine, and nevirapine (highly active antiretroviral treatment [HAART]) became accessible through a national program. Women with a CD4 cell count of less than 200 cells/mm^3 or an AIDS-defining illness at enrollment or during follow-up were offered HAART, as were all HIV-infected infants.

Follow-up and Evaluation

Infant evaluations were scheduled at birth, monthly until age 7 months, at age 9 months, and then every third month through age 18 months. Peripheral blood was obtained at birth, at age 4 weeks, and at ages 4, 7, 9, and 12 months for HIV testing by polymerase chain reaction (PCR) DNA assay, and at age 18 months by 2 independent ELISAs. Full blood counts with differential were performed for all infants at birth and at ages 1, 4, 7, 9, and 18 months, and additionally at ages 2, 3, 5, and 6 months for those in the breastfeeding plus zidovudine group. Quantifications of alanine and aspartate aminotransferases (by enzymatic method according to the International Federation of Clinical Chemists without pyrodoxal-5′-phosphate) and serum creatinine (by buffered kinetic Jaffe reaction without deproteinization) were performed at age 1 month for all babies, and at age 6 months for those in the breastfeeding plus zidovudine group. Signs, symptoms, and diagnoses were collected based upon targeted clinical assessment.

Adherence to infant feeding strategy and zidovudine was assessed by maternal report at each scheduled visit using standardized questionnaires. For zidovudine, adherence was assessed by collecting information on study drug intake and the primary reason for any missed doses. For infant feeding strategy, adherence was assessed by recording the date of weaning; frequency of breast milk and formula intake; purpose and time of the introduction of fluids, solid foods, and other nonhuman milk; and water source since the previous visit.

The following definitions were used when describing infant feeding: (1) exclusive formula feeding (formula feeding only, never breastfed); (2) exclusive breastfeeding (breastfeeding only, no other fluids, milks, or foods); (3) mixed breastfeeding (breastfeeding with the ad-

dition of fluids, solid foods, and nonhuman milks); and (4) predominant breastfeeding (breastfeeding with the addition of only fluids other than milks).

Definition of HIV Infection and Primary Study End Points

Infants with a positive PCR were retested on a separate sample (or by ELISA at age 18 months); time of HIV infection was based on the date of the earliest positive test result. Infants who died or were lost to follow-up after a single positive PCR test were considered HIV positive. The primary efficacy end points were infant HIV infection through the 7-month visit window (up to 243 days of age), and the composite end point of HIV infection or death (or HIV-free survival) through the 18-month visit window (up to 593 days of age). The primary safety end point was infant toxicity by the 7-month visit.

Statistical Methods and Interim Monitoring

The trial was designed to enroll 1200 mother/infant pairs to provide adequate power for the main objectives of both the peripartum and the feeding strategy components. The latter was designed as a superiority study to detect differences between the formula-fed and breastfed plus zidovudine groups. Based on a 2-sided type I error of .05, and an annual loss to follow-up rate of 10%, 1200 mother/infant pairs provided 80% power to detect a 7% difference in rates of HIV infection by age 7 months, and more than 90% power for a 10% difference in HIV-free survival at 18 months of age, based on reference rates of 17% and 79%. While the formula-fed group was regarded as the best strategy to prevent breastfeeding-associated mother-to-child transmission at the time the trial was initiated, neither regimen had been evaluated in Botswana at the time; thus, 2-sided tests were used to assess differences between the formula-fed and breastfed plus zidovudine groups in either direction. Additionally, the power of the study for differences of 7% and 10% is relatively stable across a range of reference rates. The power for the peripartum comparisons is presented elsewhere.[32]

The study was monitored by an independent data and safety monitoring board. Two preplanned interim efficacy reviews occurred in June 2002 and April 2003 using the O'Brien-Fleming spending function to control type I error rates (false positives) due to multiple statistical tests carried out in the interim and final analyses.[34]

This report is based on all study visits occurring and specimens collected through October 24, 2005, which corresponded to the latest specimen date collected for an HIV test (ELISA). All infants were born at least 18 months prior to this date and therefore, all study end points were potentially observable. All analyses were based on live, first-born infants, and included all observed HIV transmissions (and other follow-up data), regardless of timing. All part 1 perinatal randomized participants were grouped together in order to test between feeding strategies (part 2). Because of the factorial design, tests of interactions between part 1 and part 2 groups were performed. Since the part 1 groups were modified during the trial, assessments of interactions were conducted separately for the original and revised part 1 groups. All statistical comparisons used a nominal, 2-sided .05 significance level, and have not been corrected for multiple testing.

Comparisons of treatment groups for baseline characteristics used the Fisher exact test (Wilcoxon rank-sum test) for discrete (continuous) measurements. Time-to-event data were analyzed using the Kaplan-Meier estimator, the log rank test, and Cox proportional hazards modeling. Estimated rates of HIV infection at age 7 months and HIV-free survival at age 18 months were obtained from Kaplan-Meier estimators. For HIV infection, death was a censoring event, and for HIV-free survival, the time of the event was the earlier of HIV infection or death. Infants who were lost to follow-up before reaching study end points were censored at their last negative HIV test (for the transmission end point and the HIV-free survival end point), and were censored at their last study visit for the infant mortality end point. Treatment group comparisons for these end points are based on standardized differences between the Kaplan-Meier estimates, stratified by part 1 group. The standard error of the difference, obtained as the square root of the estimated variance of the difference, was also used to compute 95% confidence intervals (CIs) for the differences.

Secondary efficacy end points included time to HIV infection and time to the earlier of HIV infection or death, stratified by part 1 group. Treatment group comparisons of these end points used log rank tests and the Cox proportional hazards model (with the proportional hazards assumption assessed for each model). *P* values were obtained from the corresponding Wald tests, and estimated relative risk (RR) and corresponding CIs were obtained from the estimated coefficients of the model and their estimated standard errors. Time to infant death is compared by an unstratified log rank test, and tests of interactions are based on the Cox model. Covariate-adjusted Cox models included maternal baseline HIV RNA and CD4 cell count, mode of delivery, and infant gestational age and weight. Covariate-adjusted treatment group comparisons gave similar results to unadjusted comparisons and are omitted.

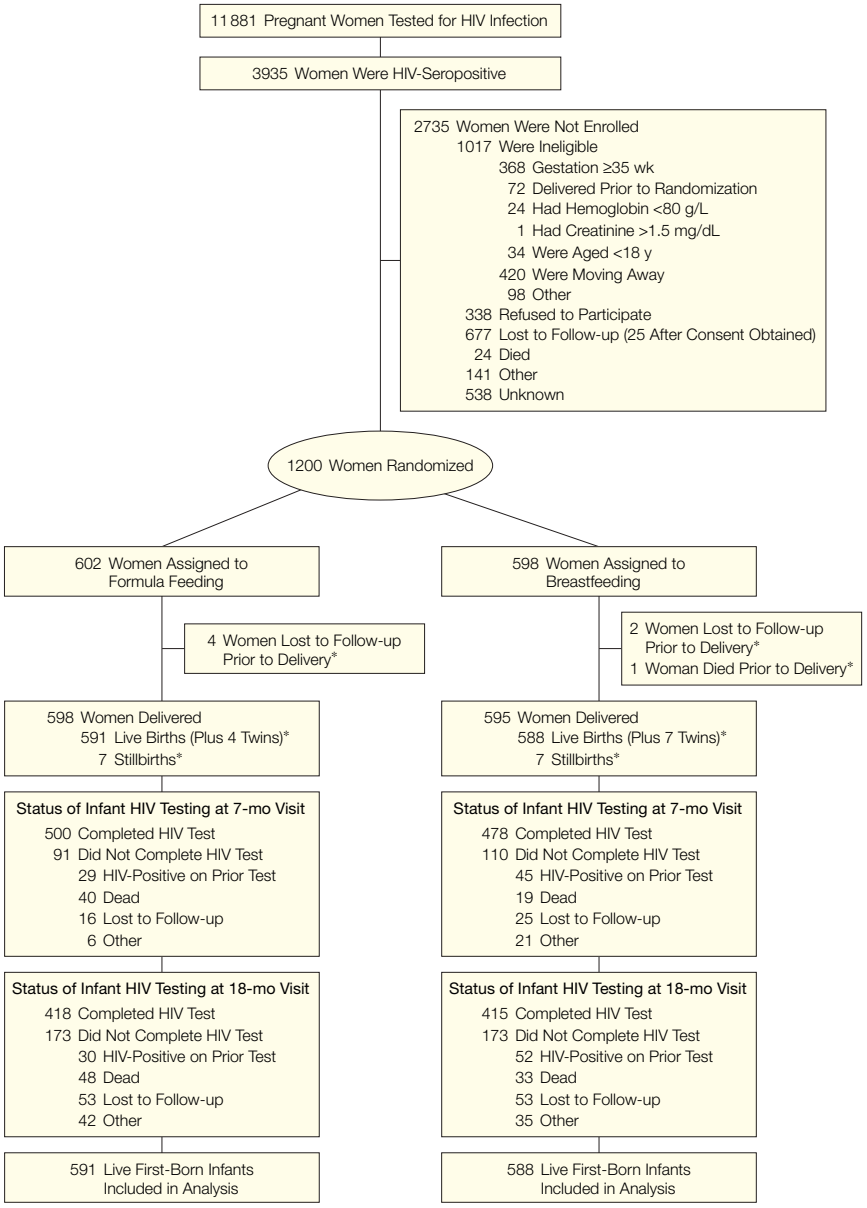
Statistical software used to carry out the final analysis included SAS version 9.1 (SAS Institute Inc, Cary, NC) and StatXact version 5 (Cytel, Inc, Cambridge, Mass). The primary analysis was originally carried out (as specified by the study protocol) between December 2004 and January 2005, following evaluation of all infant participants for a minimum of 7 months. The analyses presented in this report have been updated to March 2006, allowing 18 months of follow-up for all randomized infants.

RESULTS

There were 1200 HIV-positive pregnant women randomized between

March 27, 2001 and October 29, 2003, of whom 1193 reached delivery, resulting in 591 and 588 live first-born infants in the formula-fed and breastfed plus zidovudine groups, respectively (FIGURE 1). Maternal characteristics at enrollment and delivery and infant characteristics at birth were well balanced between the formula-fed and breastfed plus zidovudine groups (TABLE 2; $P>.05$ for all comparisons other than sanitation facilities, for which $P=.04$). These infants were born between April 22, 2001 and December 23, 2003. By the 7- and 18-month evaluations, 16 (2.7%) and 53 (9.0%) of the 591 formula-fed and 25 (4.3%) and 53 (9.0%) of the 588 breastfed plus zidovudine infants were lost to follow-up, respectively (Figure 1). There were also very few (<1%) missed DNA PCR tests for reasons other than loss to follow-up (Figure 1).

Figure 1. Enrollment and Randomization of HIV-1–Infected Pregnant Women and Delivery of Their Infants According to Study Group and Completeness of HIV Testing at Scheduled Infant Evaluation Time Points



HIV denotes human immunodeficiency virus. *Infants from mothers lost to follow-up or dying before delivery, second-born twins, and stillbirths were excluded from all analyses.

HIV Infection

A total of 32 and 51 infants in the formula-fed and breastfed plus zidovudine groups, respectively, became HIV positive by 7 months of age (TABLE 3), corresponding to cumulative positivity rates of 5.6% (formula fed) and 9.0% (breastfed plus zidovudine) ($P=.04$). The estimated treatment hazard ratio for time until HIV infection (FIGURE 2A) is 1.65 ($P=.02$; 95% CI, 1.07-2.55).

There was a statistically significant interaction between feeding strategy and the original part 1 group ($P=.04$; FIGURE 3A), with a greater difference in 7-month HIV infection rates among infants in the nevirapine/nevirapine part 1 group (3.4% vs 14.0%) than in the placebo/placebo part 1 group (8.6% vs 11.0%). There was no suggestion of an interaction ($P=.75$) between feeding strategy and the revised part 1 groups when all infants received nevirapine and maternal HAART was available for qualifying women, and the HIV infection rates for the formula-fed and breastfed plus zidovudine groups were lower and more similar (Figure 2D).

When only infants who were alive and HIV-free at age 1 month were analyzed, the estimated cumulative proportions of infants with a diagnosis of HIV infection occurring between ages 1 and 7 months in the breastfed plus zidovudine and formula-fed groups were 4.5% and 0.6%, respectively. These results should be interpreted with caution because the infants included in the analysis were selected on the basis of an event (being HIV-1-free at age 1 month) that may have been affected by feeding assignment, making the comparison susceptible to postrandomization selection bias.[35]

Mortality

One hundred fourteen infants died after birth, 63/591 (10.7%) from the formula-fed group and 51/588 (8.7%) from the breastfed plus zidovudine group. Of the 77 infants who died with an HIV-negative status, 45 (58%) had a negative HIV test result within the 2 weeks preceding death, and 73 (95%) had a negative HIV test result within the 3 months preceding death. A total of 5 infants died before an initial PCR result was obtained. The remaining 32 infant deaths (15 from the formula-fed group and 17 from the breastfed plus zidovudine group) were among babies who tested HIV positive before death. The most common causes of infant death were diarrhea and pneumonia. The deaths in the breastfed plus zidovudine group were more likely to be in HIV-infected infants and at older ages as compared with the deaths in the formula-fed group. There were 3 deaths due to anemia, of which 2 (1 in each group) were judged as possibly related to zidovudine.

The cumulative incidence of infant death by month 7 was significantly higher in the formula-fed group than in the breastfed plus zidovudine group (9.3% vs 4.9%; $P=.003$), but this difference diminished beyond month 7, such that the time-to-mortality distributions through 18 months of age were not significantly different ($P=.21$) (Figure 2B). There was a significant interaction ($P=.03$) between feeding strategy groups and the original part 1 group with respect to time to infant death, with a larger formula-fed vs breastfed plus zidovudine difference among infants in the placebo/placebo group (RR=2.75; 95% CI, 1.15-6.57) than among infants in the nevirapine/nevirapine group (RR=0.75; 95% CI, 0.34-1.66) (Figure 3B). This interaction was no longer statistically significant ($P=.12$) after adjustment for covariates. There was no interaction between feeding strategy and the revised part 1 groups ($P=.14$), and the rates of death in the formula-fed and breastfed plus zidovudine groups were somewhat lower than in the original study period and similar to each other

Table 2. Baseline and Delivery Characteristics of All Randomized Mothers (N = 1200) and All Live, First-Born Infants (N = 1179)*

Variables	Total*	Randomized Feeding Strategy	
		Formula-Fed	Breastfed Plus Zidovudine
Enrollment site, No./total (%)	1200 (100)	602 (50)	598 (50)
Molepolole	349/1200 (29)	176/602 (29)	173/598 (29)
Mochudi	315/1200 (26)	157/602 (26)	158/598 (26)
Lobatse	268/1200 (22)	136/602 (23)	132/598 (22)
Gaborone	268/1200 (22)	133/602 (22)	135/598 (23)
Part 1 randomized treatment group, No./total (%) †	1200 (100)	602 (50)	598 (50)
Placebo/placebo	245/1200 (20)	123/602 (20)	122/598 (20)
Nevirapine/nevirapine	246/1200 (20)	126/602 (21)	120/598 (20)
Placebo/nevirapine revised	355/1200 (30)	176/602 (29)	179/598 (30)
Nevirapine/nevirapine revised	354/1200 (30)	177/602 (29)	177/598 (30)
Maternal age median, y	26.78	26.76	26.87
No./total (%)	1200 (100)	602 (50)	598 (50)
Highest education level completed, No./total (%)	1181 (100)	591 (50)	590 (50)
None	40/1181 (3)	20/591 (3)	20/590 (3)
Primary	308/1181 (26)	163/591 (27)	145/590 (24)
Secondary	804/1181 (68)	397/591 (67)	407/590 (69)
University	29/1181 (2)	11/591 (2)	18/590 (3)
Monthly person income (USD), No./total (%)	1175 (100)	587 (50)	588 (50)
None	717/1175 (61)	360/587 (61)	357/588 (61)
≤100	243/1175 (21)	121/587 (21)	122/588 (21)
101-1000	215/1175 (18)	106/587 (18)	109/588 (18)
Source of drinking water, No./total (%)	1063 (100)	532 (50)	531 (50)
Piped into home	75/1063 (7)	42/532 (8)	33/531 (6)
Tap in the yard	587/1063 (55)	278/532 (52)	309/531 (58)
Communal standpipe	388/1063 (37)	205/532 (39)	183/531 (34)
Others	13/1063 (1)	7/532 (1)	6/531 (1)
Sanitation facilities most used, No./total (%)‡	1181 (100)	591 (50)	590 (50)
Indoor toilet	157/1181 (13)	89/591 (15)	68/590 (11)
Private latrine/house	872/1181 (74)	428/591 (72)	444/590 (74)
Shared latrine/compounds	118/1181 (10)	55/591 (9)	63/590 (11)
No latrine facilities	28/1181 (2)	13/591 (2)	15/590 (3)
Other	6/1181 (1)	6/591 (1)	0/590 (0)
Electricity in home, No./total (%)	280/1181 (24)	150/591 (25)	130/590 (22)
Refrigerator in home, No./total (%)§	350/1181 (30)	173/591 (29)	177/590 (30)
Maternal baseline $CD4^+$ count, cells/mm^3 No./total (%)	1151 (100)	576 (50)	575 (50)
Median	366.0	358.5	372.0
Maternal baseline plasma HIV-1 RNA, log_{10} copies/ml No./total (%)	1182 (100)	591 (50)	575 (50)
Median	4.35	4.33	4.39
Male infants	625/1179 (53)	312/590 (53)	313/589 (53)
Premature (<37 wks) gestational age (Dubowitz), No./total (%)	61/1160 (5)	24/581 (4)	37/579 (6)
Birth weight median, kg	3.1	3.1	3.1
<2.5 kg, No./total (%)	92/1173 (8)	45/590 (8)	47/583 (8)
Congenital abnormalities	20/1175 (2)	9/589 (2)	11/586 (2)

*Baseline characteristics of mothers and infants were well balanced across feeding groups ($P>.05$) except for sanitation facility (groups compared using χ^2 [Wilcoxon Rank-Sum] tests for categorical [continuous] measurements).
†In part 1, mother/infant pairs were randomized to receive blinded maternal and infant single-dose nevirapine (nevirapine/nevirapine) or maternal and infant placebo (placebo/placebo). The study was revised 17 mo after initiation to compare maternal and infant single-dose nevirapine (nevirapine/nevirapine revised) with maternal placebo and infant single-dose nevirapine (placebo/nevirapine revised).
‡$P = .04$ for sanitation facilities most used.
§Refrigerator powered by electricity or gas.

(Figure 2E). Birth weight (RR=2.77 for <2.5 kg vs normal; 95% CI, 1.69-4.54) and maternal delivery viral load (RR=1.46/1 $\log_{10}$ higher viral load; 95% CI, 1.19-1.78) were significantly associated with time to infant death.

HIV-Free Survival

A total of 166 infants died or became HIV positive through the 18-month visit. Of these, 80 and 86 were in the formula-fed and breastfed plus zidovudine groups, respectively, corresponding to a cumulative 18-month rate of HIV infection or mortality of 13.9% and 15.1% (Table 3; *P*=.60; 95% CI for difference, –5.3% to 2.9%) (see also Figure 2C). There was a statistically significant interaction (*P*=.02) between feeding strategy and original part 1 group with evidence of a greater difference in HIV-free survival between the formula-fed and breastfed plus zidovudine groups among patients receiving nevirapine/nevirapine than among patients receiving placebo/placebo (Figure 3C).

There was no suggestion of an interaction between feeding strategy and the revised part 1 group (*P*=.42) when HAART was available. Rates of HIV-free survival for the formula-fed and breastfed plus zidovudine groups were similar and higher during the revised study period when HAART was available (Figure 2F). When only infants who were alive and HIV-free at 1 month were analyzed, the breastfed plus zidovudine/formula-fed hazard ratio of infant death or HIV infection between 1 and 7 months of age was 1.30 (*P*=.28; 95% CI, 0.81-2.10). These results should be interpreted with caution for the same reason noted previously.

Safety

TABLE 4 summarizes the occurrence of any grade 3 (severe) or worse laboratory toxicities and clinical adverse events within infants' first 7 months of life. The rates of grade 3 or higher signs or symptoms (17.6% vs 13.1%; *P*=.03) and of hospitalization (20.3% vs 15.6%; *P*=.04) by 7 months were significantly higher among infants in the formula-fed group than in the breastfed plus zidovudine group. The rate of grade 3 or higher laboratory abnormality associated with zidovudine toxicity was significantly higher in the breastfed plus zidovudine group than in the formula-fed group (24.7% vs 14.8%; *P*<.001).

Adherence to Infant Zidovudine and Feeding Strategy

Of the 1179 live-born babies, 1172 (99.4%) initiated study zidovudine following birth. The median duration of infant zidovudine was 5.9 months in the breastfed plus zidovudine group, and 84% (479 of 567) of responding mothers in the breastfed plus zidovudine group reported never missing 1 or more full days of infant zidovudine; 95% (562 of 591) of live-born infants in the formula-fed group received at least 2 weeks dosage of zidovudine. Full adherence to exclusive formula feeding was self-reported by 93% of mothers in the formula-fed group. Three infants in the formula-fed group were infected between months 1 and 7, presumably because they were exposed to breast milk.

Among mothers in the breastfed plus zidovudine group, self-reported adherence to exclusive breastfeeding was 57.1% at month 1, 31.3% at month 3, and 17.5% at month 5. Predominant breastfeeding was practiced by 21.2%, 20.1%, and 7.5% of mothers in the breastfed plus zidovudine group by 1 month, 3 months, and 5 months, respectively. Mixed breastfeeding was practiced by 21.7%, 48.6%, and 75.0%

Table 3. Primary Efficacy End Points for Infants According to Intervention Group

	HIV Infection				Death				HIV Infection or Death			
	Cumulative HIV Infection Rate, No. (%)*				Cumulative Death Rate, No. (%)*				Cumulative HIV Infection or Death Rate, No. (%)*			
Infant Age	Formula-Fed	Breastfed + Zidovudine	Rate Difference, % (95% CI)†	*P* Value‡	Formula-Fed	Breastfed + Zidovudine	Rate Difference, % (95% CI)†	*P* Value‡	Formula-Fed	Breastfed + Zidovudine	Rate Difference, % (95% CI)†	*P* Value‡
Birth§	22 (3.8)	19 (3.3)	0.5 (–1.6 to 2.6)	.62	15 (2.5)	8 (1.4)	1.2 (–0.4 to 2.8)	.14	36 (6.1)	27 (4.6)	1.5 (–1.1 to 4.1)	.25
No. at risk‖	591	588			591	588			591	588		
1 mo§	29 (5.0)	27 (4.6)	0.4 (–2.1 to 2.9)	.76	25 (4.3)	9 (1.5)	2.7 (0.8 to 4.6)	.005	52 (8.9)	36 (6.1)	2.7 (–0.3 to 5.7)	.08
No. at risk‖	546	557			573	579			549	558		
7 mo§	32 (5.6)	51 (9.0)	–3.4 (–6.4 to –0.4)	.04¶	54 (9.3)	28 (4.9)	4.4 (1.5 to 7.4)	.003	73 (12.5)	74 (12.9)	–0.4 (–4.2 to 3.5)	.86
No. at risk‖	526	541			559	575			530	543		
18 mo§	33 (6.0)	53 (9.5)	–3.6 (–6.7 to –0.5)	.02	62 (10.7)	48 (8.5)	2.2 (–1.2 to 5.6)	.21	80 (13.9)	86 (15.1)	–1.2 (–5.3 to 2.9)	.60¶
No. at risk‖	493	481			512	529			493	483		

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.
*Cumulative rates of each end point were estimated by Kaplan-Meier method for the time points listed.
†The rate difference is calculated as the difference in the Kaplan-Meier estimates, and SEs of the differences (to form 95% confidence intervals) were calculated using the Greenwood formula.
‡*P* values are from unstratified Z tests.
§Birth, months 1, 7, and 18 are defined as up to days 15, 45, 243, and 593, respectively.
‖Number at risk (by Kaplan-Meier method) at the end of the previous listed visit.
¶*P* values at primary end point times (age 7 mo for HIV infection, age 18 mo for HIV infection or death) are based on Z tests stratified by all (4) unique part 1 groups.

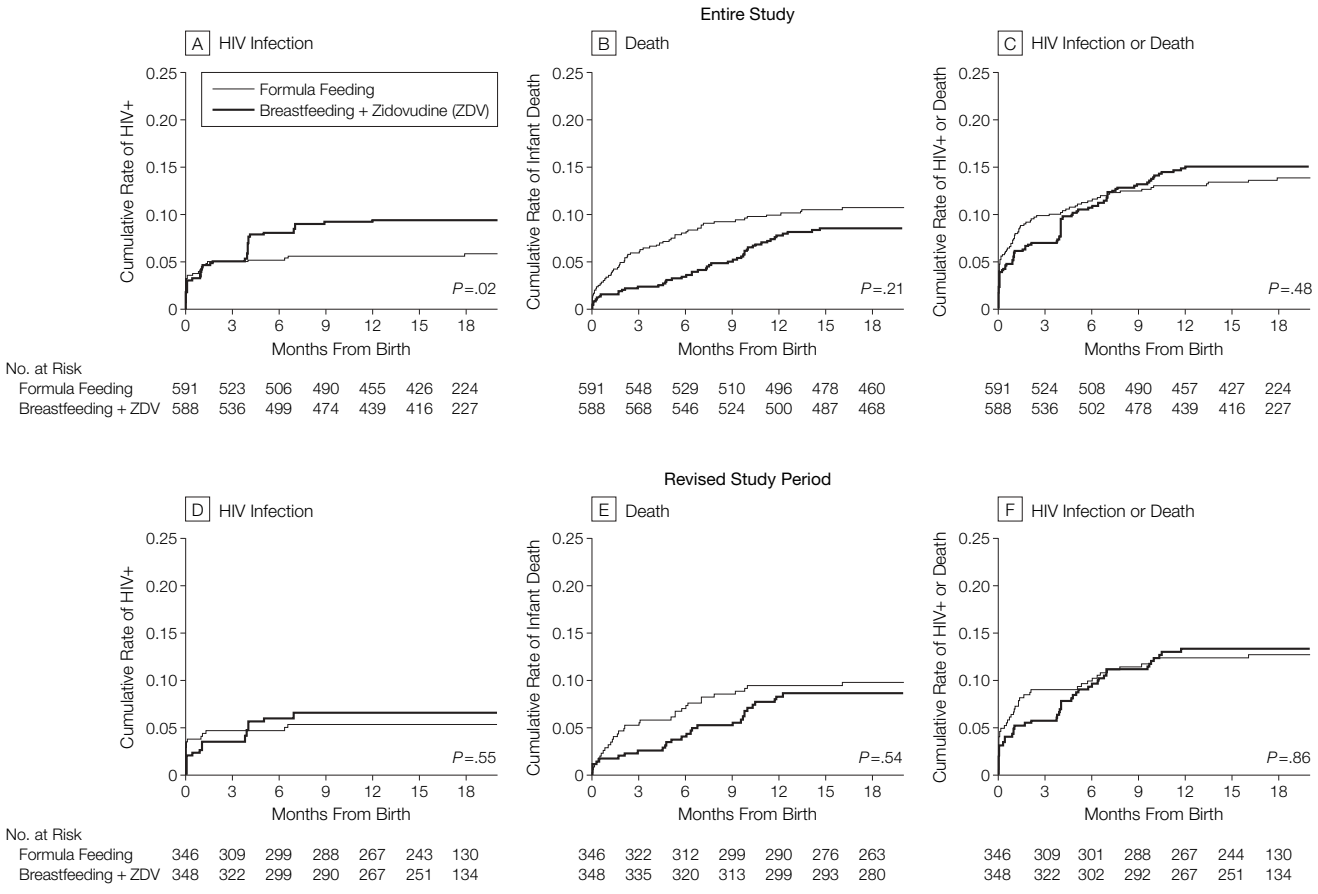
of mothers in the breastfed plus zidovudine group by 1, 3, and 5 months, respectively. Sixty-one events (54 due to infant zidovudine toxicity) requiring cessation of breastfeeding occurred through 5 months postpartum.

Use of HAART

Seventy-one women (37 in the formula-fed group and 34 in the breastfed plus zidovudine group) initiated HAART before delivery, 82 between delivery and 7 months postpartum, and 216 at more than 7 months postpartum (similar numbers started HAART during each of these periods in the formula-fed and breastfed plus zidovudine groups). Four infants (2 each assigned to the formula-fed and breastfed plus zidovudine groups) had an initial positive HIV test result following their mother's initiation of HAART. For the 2 infants assigned to the formula-fed group, mothers started HAART close to time of delivery and HIV positivity was identified on days 1 and 33 of life, respectively. For the 2 infants assigned to the breastfed plus zidovudine group, positivity was established in the fourth month of life, and both of their mothers had recently begun HAART (21 and 50 days prior to the initial positive DNA PCR). A total of 56 infants (38 breastfed plus zidovudine and 18 formula-fed) started HAART following confirmed HIV infection.

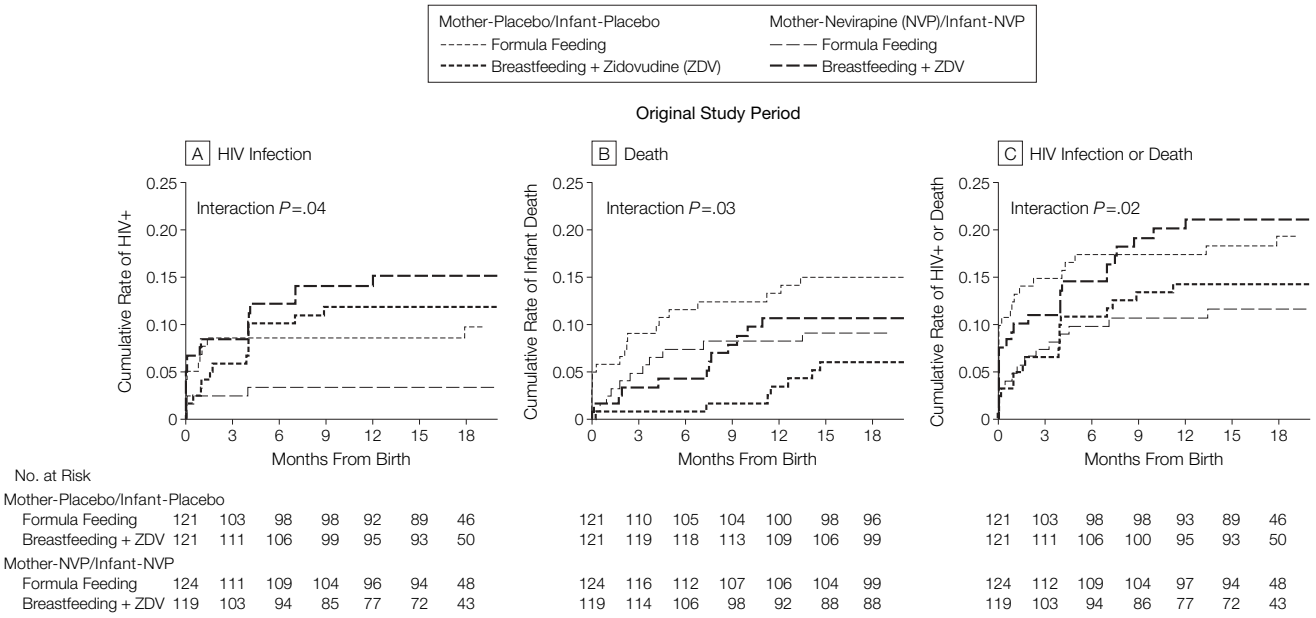
Exclusion of live-born infants whose mothers initiated HAART before delivery did not appreciably change feeding strategy comparisons for any study end point: at age 7 months, the cumulative rate of HIV positivity was 5.6% and 9.6% ($P=.02$) in the formula-fed and breastfed plus zidovudine groups, respectively; at 18 months, the rate of HIV-positivity or mortality was 13.9% and 15.5% ($P=.48$) in the formula-fed and breastfed plus zidovudine groups, respectively; and the cumulative incidence of infant death by month 7 was 9.3% and 4.6% ($P=.002$) in the formula-

Figure 2. Cumulative Rate (Proportion) of Infant End Points (Entire Study and Revised Study Period)



HIV denotes human immunodeficiency virus. Top row (panels A,B,C) shows cumulative event rate by randomized feeding strategy (and collapsing over peripartum groups) over the entire study period (including 591 infants assigned to the formula-fed group and 588 infants assigned to the breastfed plus zidovudine group). Bottom row (panels D, E, F) shows cumulative event rate for the revised study period (births after August 12, 2002) reflecting change in perinatal intervention study group (active, open-label nevirapine to all infants and availability of HAART to qualifying mothers and infants). The analyses in the bottom row consist of 348 infants assigned to the breastfed plus zidovudine group including 177 whose mothers were assigned to single-dose placebo, and 346 infants assigned to the formula-fed group including 172 whose mothers were assigned to single-dose placebo. Rates over time are calculated from the Kaplan-Meier method. *P* values are based on stratified log rank test (efficacy end points) and log rank test (mortality).

Figure 3. Cumulative Rate (Proportion) of Infant End Points (Original Study Period)



Cumulative event rate during the original study period (births prior to August 12, 2002), where for each end point a significant interaction between the 2 randomized factors (perinatal intervention of active nevirapine to mothers/infants [mother-nevirapine/infant-nevirapine] vs placebo [mother-placebo/infant-placebo] and feeding strategy) was detected; analyses include 121 infants assigned to formula feeding and placebo/placebo, 121 infants assigned to breastfeeding plus zidovudine and placebo/placebo, 124 infants assigned to formula feeding and nevirapine/nevirapine, and 119 infants assigned to breastfeeding plus zidovudine and nevirapine/nevirapine. Rates over time are calculated from the Kaplan-Meier method. *P* values are based on stratified log rank test (efficacy end points), log rank test (mortality), and the Cox model (interaction).

Table 4. Grade 3 or 4 Infant Adverse Events in Formula-Fed and Breastfed plus Zidovudine Groups by Age 7 Months*

Adverse Event	Formula-Fed, No. (Rate)†	Breastfed plus Zidovudine, No. (Rate)†	*P* Value
Grade 3 or 4 signs and symptoms	100 (17.6)	74 (13.1)	.03
Hospitalization	116 (20.3)	89 (15.6)	.04
Grade 3 or 4 laboratory abnormalities	84 (14.8)	142 (24.7)	<.001
Toxicity leading to cessation of zidovudine‡	10 (1.7)	55 (9.2)	.001
Anemia	5	6	
Neutropenia	2	46	
Thrombocytopenia	1	0	
Others	2	3	

*Information on toxicity criteria is provided in the manual of operations for the study.
†Cumulative rates by age 7 months estimated by Kaplan-Meier method and groups compared by log-rank test.
‡Zidovudine was administered for 1 month to infants in the formula-fed group as compared with 6 months to infants in the breastfed plus zidovudine group.

fed and breastfed plus zidovudine groups, respectively. Exclusion of the 56 infants who started HAART also does not appreciably change infant mortality comparisons: at ages 7 and 18 months, the cumulative infant mortality rates were 9.3% and 10.7%, respectively in the formula-fed group vs 4.9% and 8.5%, respectively, in the breastfed plus zidovudine group. The rate is still significantly higher (*P*=.003) in the formula-fed group at 7 months of age, but is not significantly different (*P*=.21) by 18 months of age.

COMMENT

This trial compared 2 approaches for reducing postnatal HIV infection and infant mortality and found similar HIV-free survival rates. Overall, infants in the formula-fed group experienced lower rates of HIV infection and increased rates of early mortality and adverse events from infectious etiologies than those in the breastfed plus zidovudine group, such that HIV-free survival at 18 months was similar in the 2 groups. Our expectation was that formula-fed infants would have better HIV-free survival at age 18 months since we anticipated that deaths after 6 months of age would be predominantly due to HIV-1 infection.

External results led to the modification of the perinatal intervention component (part 1) of our trial almost midway through enrollment, and the modification coincided with HAART availability for qualifying women and infected infants. As a result, the trial can be viewed as two 2×2 factorial trials, one using the original study period perinatal groups (nevirapine/nevirapine and placebo/placebo) in a non-HAART setting, and the other using the revised study period perinatal groups (nevirapine/nevirapine and placebo/nevirapine) in a setting where HAART was available. Because HAART reduces vi-

ral load and mother-to-child transmission is directly associated with viral load, use of HAART likely reduced overall transmission rates in the revised study period.

In any factorial trial, it is important to consider the possibility of interaction between the factors, specifically whether the relative efficacy of the formula-fed and breastfed plus zidovudine groups depended on the perinatal intervention. We found a statistically significant interaction between the feeding strategies and the original perinatal interventions (nevirapine/nevirapine and placebo/placebo) with respect to HIV infection, with a greater difference favoring formula feeding over breastfeeding plus zidovudine among mother/infant pairs receiving nevirapine/nevirapine. Conversely, the interaction between factors for the infant mortality end point was for a greater difference favoring breastfeeding plus zidovudine over formula feeding among mother/infant pairs receiving placebo/placebo. Moreover, because the effects of formula feeding and breastfeeding plus zidovudine on HIV infection and mortality were in opposite directions for these 2 end points, HIV-free survival was comparable between the 2 groups. One possibility for the interaction with the part 1 intervention with respect to HIV infection is that maternal and infant nevirapine prevented perinatal HIV transmission in a subset of high-risk infants, and that those high-risk infants in the breastfed plus zidovudine group subsequently became infected from exposure to HIV in breast milk. If this were true, this interaction would likely have been reduced after the introduction of HAART, because HAART could decrease the risk of transmission among the high-risk subset of mother/infant pairs. In fact, none of the 34 women in the breastfeeding plus zidovudine group who received HAART from delivery have yet transmitted HIV to their infants.

For all end points, there was no suggestion of an interaction between feeding strategy and the revised perinatal intervention groups, which were implemented at the time HAART became available. Rates of HIV infection and infant mortality in the formula-fed and breastfed plus zidovudine groups were lower and more similar in the revised study than in the original study period (Figure 2D, E, and F and Figure 3). The availability of infant HAART may have lowered infant mortality in the revised study period. However, because infant HAART was initiated only after HIV infection, it did not affect our HIV-free survival end point, and thus our results for this end point are generalizable to regions where infant HAART may not be available.

Self-reported adherence to formula feeding was high (93%). While we cannot confirm this adherence, it is consistent with only 3 HIV infections diagnosed in the formula-fed group from 15 days to age 7 months. Although virtually all women in the breastfed plus zidovudine group breastfed, many did not do so exclusively, despite educational efforts. The early introduction of water was common, with 31% of infants receiving some water by age 1 month. Low adherence to exclusive breastfeeding in Botswana has been noted not only during the pilot period of our study,[36] but also during the 2001 evaluation of the national prevention of mother-to-child transmission program.[37] If mixed or nonexclusive breastfeeding were associated with increased risk of HIV transmission as reported by Coutsoudis et al,[33,38] the efficacy of 6 months of infant zidovudine in reducing breastfeeding infection in an exclusively breastfeeding population would be underestimated in our study. Although the degree of exclusivity for breastfeeding could have influenced the results, our goal in this study was to compare formula feeding to breastfeeding plus zidovudine under local conditions that would best reflect the potential value for future implementation if warranted by the results.

Ethical considerations and Botswana national policy excluded the option of an untreated control group as a comparator to the 2 feeding strategy groups. Thus, this study was unable to compare the additional benefit of either strategy to one in which infants were breastfed with no postnatal intervention prophylaxis. Comparison of our 12- and 18-month rates of HIV infection and HIV-free survival to those achieved in other studies[4,5,39,40] suggest that our combined perinatal/feeding strategy approach was relatively effective in preventing HIV infection and reducing mortality. However, HIV transmission rates due to breast milk in the breastfed plus zidovudine group of our study were similar to rates reported by some prevention of mother-to-child transmission studies with breastfeeding alone.[5,6,11] For example, mother-to-child transmission rates among breastfeeding infants in Cote d'Ivoire whose mothers received short-course zidovudine were 14.8% at age 6 weeks and 18% at age 6 months,[11] while an individual patient data meta-analysis of mother-to-child transmission occurring after 4 weeks of age in breastfeeding infants revealed an estimated rate of breastfeeding transmission of 0.6% to 0.9% per month.[4]

Comparison across studies that test divergent interventions among differing populations should be undertaken with caution, as the relative effects of antepartum/intrapartum and postnatal interventions may complicate comparisons of incremental transmission rates between trials with different interventions in 2 ways. First, antepartum/intrapartum interventions, by preventing early infections, increase the pool of HIV-negative infants at risk for infection through breastfeeding, which must be taken into account when interpreting incremental infection rates. Second, antepartum/intrapartum interventions may delay (to the breastfeeding period) transmissions to those infants at highest risk of becoming infected. Earlier studies have shown that mothers with the highest levels of viremia have an increased risk for infecting their infants during both the peripartum and breastfeeding periods.[41-44] Other regional differences, potentially including differences in viral subtype and feeding practices, may also complicate cross-study comparisons.[38,45-47] Thus, we cannot recommend the use of extended infant zidovudine prophy-

laxis for the prevention of breastfeeding-related mother-to-child transmission based upon the results of this study, given the significant number of infant HIV infections that occurred after 1 month of age in the breastfed plus zidovudine group compared with the formula-fed group.

Higher morbidity and mortality rates among formula-fed infants compared with breastfed infants in the developing world have previously been described.[21,22,48] One notable exception is the only other randomized study (in addition to Mashi) comparing these strategies among HIV-infected women, which was conducted in Nairobi, Kenya.[12] This latter study showed a similar 2-year mortality rate but a significantly lower HIV-free survival rate in the breastfeeding group.[12] In contrast, we found significantly higher rates of infant morbidity and mortality (mostly related to diarrheal diseases and pneumonia) in formula-fed infants than in breastfed infants. The differences in our findings compared with those of the Kenyan study may be explained by the fact that the Kenyan participants were urban and had to have access to clean municipal water in order to participate (and may therefore be less representative of women in much of the developing world).

CONCLUSIONS

In summary, our study showed that both formula feeding and breastfeeding with prophylactic infant zidovudine gave similar rates of HIV-free survival at 18 months. Formula feeding had a higher risk of early mortality, but breastfeeding with zidovudine prophylaxis had a higher risk of HIV transmission. Our study, which was the first to compare formula feeding to breastfeeding with extended antiretroviral prophylaxis, revealed relatively high morbidity and mortality rates associated with formula feeding among infants of HIV-infected mothers, but did not lend definitive support to the use of infant zidovudine prophylaxis to prevent breastfeeding-related mother-to-child transmission. Our study results highlight the need for a careful assessment of the local management of childhood illnesses (mostly diarrheal and respiratory diseases) before the implementation of a formula feeding strategy for the prevention of mother-to-child transmission of HIV in developing countries.

Breastfeeding with zidovudine prophylaxis was a feasible prevention of mother-to-child transmission strategy in Botswana, but further study is warranted to determine the efficacy and safety of other interventions to prevent mother-to-child transmission related to breastfeeding, such as the use of maternal HAART during the breastfeeding period.

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HIV/AIDS Programme

PROGRAMMATIC UPDATE

USE OF ANTIRETROVIRAL DRUGS FOR TREATING PREGNANT WOMEN AND PREVENTING HIV INFECTION IN INFANTS

EXECUTIVE SUMMARY

APRIL 2012

World Health Organization

EXECUTIVE SUMMARY

Recent developments suggest that substantial clinical and programmatic advantages can come from adopting a single, universal regimen both to treat HIV-infected pregnant women and to prevent mother-to-child transmission of HIV. This streamlining should maximize PMTCT programme performance through better alignment and linkages with antiretroviral therapy (ART) programmes at every level of service delivery. One of WHO's two currently recommended PMTCT antiretroviral (ARV) programme options, Option B, takes this unified approach.

Now a new, third option (Option B+) proposes further evolution—not only providing the same triple ARV drugs to all HIV-infected pregnant women beginning in the antenatal clinic setting but also continuing this therapy for all of these women for life. Important advantages of Option B+ include: further simplification of regimen and service delivery and harmonization with ART programmes, protection against mother-to-child transmission in future pregnancies, a continuing prevention benefit against sexual transmission to serodiscordant partners, and avoiding stopping and starting of ARV drugs. While these benefits need to be evaluated in programme settings, and systems and support requirements need careful consideration, this is an appropriate time for countries to start assessing their situation and experience to make optimal programmatic choices.

This programmatic update is meant to provide a current perspective for countries on the important changes and new considerations arising since publication of WHO's PMTCT ARV guidelines, 2010 version, especially as a number of countries are now preparing to adopt Option B+. WHO has begun a comprehensive revision of all ARV guidelines, including guidance on ARVs for pregnant women, planned for release in early 2013.

Prevention of mother-to-child transmission of HIV (PMTCT) is a dynamic and rapidly changing field. Current World Health Organization (WHO) PMTCT antiretroviral (ARV) guidelines on treating pregnant women and preventing infection in infants (*1*), issued in 2010, were a major step towards more efficacious regimens. The WHO guidelines emphasize the importance of providing lifelong antiretroviral therapy (ART) to all HIV-infected pregnant women eligible for such treatment and recommend two short-term antiretroviral prophylaxis options (Option A and Option B) for women not eligible under current criteria, as determined by CD4 count, for treatment for their own health (Table 1). Recently, a third option, to provide lifelong ART to all HIV-infected pregnant women, regardless of CD4 cell count, has emerged (Option B+), and a number of countries are already adopting or considering this approach.

Although many low- and middle-income countries are still in early stages of implementing the 2010 guidance, new evidence and recent experience warrant a programmatic update to reassess preferences between Options A and B for prophylaxis in HIV-infected pregnant women who do not need treatment for their own health and to weigh the potential advantages and considerations of the new Option B+ approach in a public health perspective.

Current WHO guidance on ARV use in HIV-infected pregnant women

The 2010 WHO PMTCT ARV guidelines are based on the need to distinguish between treatment and prophylaxis. Consistent with the 2010 WHO adult ART guidelines (*2*), they recommend and prioritize starting all women with CD4 counts ≤350 cells/mm^3 or WHO Stage 3 or 4 disease (approximately 40–50% of all HIV-infected pregnant women) on ART for life for their own health as well as for the prevention of infant HIV infection. For women with CD4 counts >350 cells/mm^3, who are not eligible for treatment according to current criteria, the PMTCT ARV guidelines recommend starting ARV prophylaxis early in pregnancy and, in breastfeeding settings, providing extended ARVs to either the mother or child during the postpartum risk period.

The two recommended prophylaxis options, A and B, are quite different programmatically but were judged to be equally efficacious, *if implemented appropriately*, in reducing the risk of infant infections for women with CD4 counts >350 cells/mm^3. Because of the difference in the prophylaxis options, it is sometimes not well understood that Options A and B include both treatment and prophylaxis components, as shown in Table 1. The overall effectiveness, both for the mother's health

Table 1. Three options for PMTCT programmes

	Woman receives:		Infant receives:
	Treatment (for CD4 count ≤350 cells/mm³)	**Prophylaxis (for CD4 count >350 cells/mm³)**	
Option A[a]	Triple ARVs starting as soon as diagnosed, *continued for life*	*Antepartum*: AZT starting as early as 14 weeks gestation *Intrapartum*: at onset of labour, sdNVP and first dose of AZT/3TC *Postpartum*: daily AZT/3TC through 7 days postpartum	Daily NVP from birth through 1 week beyond complete cessation of breastfeeding; or, if not breastfeeding or if mother is on treatment, through age 4–6 weeks
Option B[a]	*Same initial ARVs for both*[b]*:*		Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method
	Triple ARVs starting as soon as diagnosed, *continued for life*	Triple ARVs starting as early as 14 weeks gestation and *continued intrapartum and through childbirth if not breastfeeding or until 1 week after cessation of all breastfeeding*	
Option B+	*Same for treatment and prophylaxis*[b]*:*		Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method
	Regardless of CD4 count, triple ARVs starting as soon as diagnosed,[c] *continued for life*		

Note: "Triple ARVs" refers to the use of one of the recommended 3-drug fully suppressive treatment options.

[a] Recommended in WHO 2010 PMTCT guidelines

[b] True only for EFV-based first-line ART; NVP-based ART not recommended for prophylaxis (CD4 >350)

[c] Formal recommendations for Option B+ have not been made, but presumably ART would start at diagnosis.

and for preventing new infant infections, of implementing either of the options depends on providing both ARV treatment to those with low CD4 counts and prophylaxis to those with higher CD4 counts. Countries were asked to weigh the benefits and uncertainties of the two approaches, particularly the operational issues, in order to determine the best approach for their national programme.

Rationale for this update

In the short time since the 2010 PMTCT ARV guidelines were developed, the context and expectations for PMTCT programmes have changed considerably. Major changes include:

- the ambitious goals for eliminating paediatric HIV infection of the new *Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive* (*3*), together with substantial progress in the global scale-up of PMTCT and ART coverage (*4*);
- new evidence to support ARV treatment as HIV prevention—notably that provision of ART to HIV-infected individuals with higher CD4 cell counts, who are not eligible for treatment, significantly reduces sexual transmission to a serodiscordant (uninfected) partner (*5*); this evidence has led to new WHO recommendations on couples counselling and treatment for serodiscordant couples regardless of CD4 count (*6*);
- increasing country experience with operational and programme implementation challenges with both Option A and Option B;
- the proposal by some countries to move to the new Option B+ approach of lifelong ART for PMTCT for all HIV-infected pregnant women, rather than stopping ARVs for women not eligible for treatment, as in both Option A and Option B (*7*);
- the launch of the Treatment 2.0 Initiative to simplify and optimize the use of ARVs and standardize the first-line treatment regimen (*8*,*9*);
- reassuring data on the safety of efavirenz in pregnancy (*10*); and
- the decreasing cost of ARV drugs (*11*,*12*).

In addition, concerns have been raised that WHO's recommendation of two different options for PMTCT prophylaxis for HIV-infected women who do not require treatment for their own health might be confusing and should be reconsidered in light of newly recognized potential benefits, operational experiences and the programme requirements of the various options.

This programmatic update, while not presenting new guidelines, reviews the currently recommended Options A and B, discusses the rationale for Option B+, and provides an update from WHO indicating and weighing preferences as much as possible among the range of options. This update summarizes key issues that need to be addressed in field settings and in national programmes. It also highlights evidence gaps that need to be addressed to build a base for future revision of guidelines.

Key findings

This programmatic update indicates that Options B and specifically B+ are likely to prove preferable to Option A for operational, programmatic and strategic reasons. While Option A has been successfully implemented in a number of high-burden countries, generally it has been difficult to implement in many low-resource settings due to the changes in drugs delivered across the care continuum (antenatal, delivery and postpartum) and the requirement for timely CD4 testing to determine which women should initiate ART for their own health. In contrast, Option B and Option B+ start all HIV-infected pregnant women on triple ARV regimens without need for an initial CD4 cell count (although CD4 testing is still needed in Option B and desirable in Option B+). Thus, Options B and B+ provide greater assurance that women in need of treatment receive a fully suppressive triple ARV regimen, to minimize the risks of infant infection and maximize the benefit to their own health, and avoid inadvertently receiving a suboptimal ARV prophylaxis intervention, particularly in settings with limited access to CD4 testing. Limited access to timely, reliable CD4 testing, and thus the inability to identify women in need of treatment and to initiate treatment, is a major concern in many resource-constrained settings, especially at the primary care level, where most women obtain maternal and child health (MCH) care.

Regimen efficiency and simplification. Another key advantage of Options B and B+ is greater efficiency, very much in accord with Treatment 2.0 principles. First, the same simplified, fixed-dose combination ARV regimen can be used throughout the PMTCT intervention. Further, it is possible, and highly desirable, to provide the same regimen both for PMTCT and as the first-line national ART regimen for non-pregnant individuals. The ability to use the same regimen for PMTCT and for first-line ART considerably simplifies drug forecasting, procurement, supply to facilities, and drug stock monitoring. The first-line regimen of tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) is available as a single-pill fixed-dose combination and has been recommended recently as the optimized regimen for first-line adult treatment, including for pregnant women (*9*). An important advantage of efavirenz in the first-line regimen is that it can be used in all women, regardless of CD4 count (unlike nevirapine, which cannot be used in women with high CD4 counts). Although concerns remain about the safety of efavirenz in early pregnancy, and enhanced pharmacovigilance monitoring is needed, review of recent data is reassuring, and benefits are likely to outweigh risks (*10*).

Many HIV high-burden countries initially chose Option A because of limited PMTCT programme support, challenges of scale-up, lower drug costs, ease of adding on to prior PMTCT approaches and training, and limited capacity to provide triple ARVs in MCH settings. However, these factors are changing, and a number of high-burden countries are considering moving from Option A to Option B or B+.

Costs. The cost of ARV drugs was a major determinant in countries' choice of a PMTCT option. In 2009 the average ARV drug cost of Option B was three to five times higher than the cost of Option A (depending on regimen and assuming the provision of both ART and prophylaxis). However, by the end of 2011, this differential had diminished to two times higher. The annual cost of two-pill formulations of TDF/3TC/EFV has decreased by 30% over the past three years and is now US$150; the newer TDF/3TC/EFV single-pill fixed-dose regimen costs approximately US$180 per year (*11*,*12*). Further declines are anticipated. With the differing initial cost of drugs now less of a factor, analyses of long-term costs, cost-benefit and cost-effectiveness will be more appropriate for guiding policy decisions than per person initial cost.

Option B+ advantages. The Option B+ approach of lifelong ART for all HIV-infected pregnant women, regardless of CD4 count, has important advantages over both Options A and B (*if viral suppression is maintained*) but needs to be evaluated in programme and field settings. These advantages include:

1. further simplification of PMTCT programme requirements—no need for CD4 testing to determine ART eligibility (as required in Option A) or whether ART should be stopped or continued after the risk of mother-to-child transmission has ceased (as in Option B) (although CD4 counts or viral load assays are still desirable for determining baseline immunological status and monitoring response to treatment);
2. extended protection from mother-to-child transmission in future pregnancies from conception;
3. a strong and continuing prevention benefit against sexual transmission in serodiscordant couples and partners;
4. likely benefit to the woman's health of earlier treatment and avoiding the risks of stopping and starting triple ARVs, especially in settings with high fertility; and
5. a simple message to communities that, once ART is started, it is taken for life.

Challenges and questions. Still, there are important programmatic, operational and clinical challenges and questions about Option B+ that need to be addressed, including service organization and service delivery of ART in MCH and primary care settings, cost and sustainability, ARV adherence and retention in care, referral mechanisms and transitions from the PMTCT programme to HIV care and treatment programmes, concerns about HIV drug resistance with long-term use of ART when initiated in early HIV disease, safety of increased ARV exposure for the fetus/infant, acceptability and equity. Thus, countries implementing Option B+ or planning demonstration projects should be supported to monitor this approach closely to address these issues and assess the feasibility, cost-benefit and public health impact of Option B+.

WHO advice to countries

In light of global and country commitments to elimination of new paediatric infections and the changes outlined in this programmatic update, all countries should examine their own policy, goals and implementation experiences and assess how they can better simplify, optimize and integrate their PMTCT and ART programmes. Countries that are successfully implementing Option A and achieving their targets of decreasing mother-to-child transmission of HIV and treating mothers eligible for ART do not need to plan an immediate change to Option B or B+. Countries that are considering changing their PMTCT guidelines should anticipate and prepare adequately for the changes, to assure that clear policy, implementation strategy, proper messaging, training and an ARV demand forecasting and supply system are in place.

Options B and specifically B+ seem to offer important programmatic and operational advantages and thus could accelerate progress towards eliminating new paediatric infections. If Option B+ can be supported, funded, scaled up at the primary care level and sustained, it will also likely provide the best protection for the mother's health, and it offers a promising new approach to preventing sexual transmission and new HIV infections in the general population.

There is an urgent need to assess country experiences and evidence that address the preferences among Options A, B and B+ outlined here. Evidence on the operational advantages of providing triple ARVs to all HIV-infected pregnant women (Options B and B+), on how to best meet the programme requirements of these approaches, and on the acceptability, effectiveness and prevention impact of providing lifelong ART to all HIV-infected pregnant women (Option B+) will help inform upcoming guidelines revision.

This programmatic update is meant to provide a current perspective for countries on the important changes and new considerations arising since the 2010 PMTCT ARV guidelines, especially as a number of countries are now preparing to adopt Option B+. WHO has begun a comprehensive revision of all ARV guidelines, including guidance on ARVs for pregnant women, planned for release in early 2013.

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Programmatic update on ARVs for pregnant women and PMTCT: Key points

- **Time to reassess.** New developments warrant reassessment of current PMTCT and treatment options. WHO is not changing its guidance now but will review its PMTCT ARV guidelines as part of a comprehensive review and consolidation of all ARV-related guidance in 2013.
- **Options B and B+ have advantages.** WHO recognizes that in many settings there are likely to be important clinical and programmatic advantages to the currently recommended Option B (maternal triple ARVs for all HIV-infected pregnant women and continued lifelong for those eligible for treatment) and the emerging Option B+ (lifelong treatment for all HIV-infected pregnant women, regardless of CD4 count) over Option A (ART for pregnant women eligible for treatment; AZT antenatal single-drug prophylaxis and infant prophylaxis during breastfeeding).
- **Options B and B+ better assure treatment.** While current data do not indicate differences in the efficacy of Options A and B when used as prophylaxis for women not eligible for treatment, Options B and B+ provide greater assurance that women in need of treatment, especially in settings with limited access to CD4 testing, receive a fully suppressive triple ARV regimen to minimize the risk of infant infection and to benefit their own health.
- **Benefits beyond PMTCT.** Option B and particularly Option B+ offer women benefits beyond PMTCT, including likely additional benefit for women's own health by starting treatment earlier and prevention of sexual HIV transmission to uninfected partners, including the common situation of HIV serodiscordant couples.
- **Higher cost but more cost-effective?** Initial drug costs are higher for Options B and B+ than for Option A, but the cost of the drugs is decreasing. The benefits gained for the costs expended are likely to be much greater.
- **Options B and B+ simpler for programmes.** These regimens are, in many aspects, simpler for programmes—the same regimen could be given to all HIV-infected pregnant women (available as a once-daily fixed-dose combination); there is no initial distinction between treatment and prophylaxis; CD4 counts are not needed for starting ARVs; there is no change in regimen during the pregnancy/postpartum period (as in Option A); and the regimen could be harmonized with adult ART regimens for easier logistics if an efavirenz-based regimen is used.
- **Option B+ has further advantages.** Compared with Option B, Option B+ would provide protection against sexual transmission of HIV that extends past the period of risk for mother-to-child transmission, protect the next pregnancy starting from conception, and avoid stopping and restarting ARVs with the next pregnancy or when CD4 count later drops below 350 cells/mm^3.
- **More countries moving toward Option B or B+.** Many high-burden countries in sub-Saharan Africa initially favoured Option A, due to lower drug cost and continuity with prior PMTCT recommendations, but some are now reassessing this choice. Countries with lower prevalence or more developed infrastructure tended to choose Option B. Malawi was the first to adopt Option B+, for its ease of implementation and potential prevention benefit; additional countries are now considering Option B+.
- **Easier implementation could expand services.** Reported difficulties with implementing PMTCT programmes, including the challenge of providing ARV treatment in MCH settings and at the primary care level, highlight the importance of simplifying drug regimens and operational delivery, as exemplified by Options B and B+. Easier implementation should facilitate expansion of services and more effective programmes. This will, however, require strengthened antenatal services, task-shifting, more effective ARV service delivery in MCH settings and direct linkages with ART programmes.
- **Unknowns need research.** Concerns and unknowns with Options B and B+ include possible increased ARV multi-drug resistance in women due to poor adherence and in infants infected despite maternal ART, and the acceptability and feasibility for women of remaining in care and on lifelong ART, especially for women starting treatment earlier than is currently recommended for adults generally. In particular, rapid scale-up of ARVs, including efavirenz, for pregnant women will greatly increase early fetal exposure, including exposure from conception in future pregnancies, and prolonged exposures during breastfeeding. Pharmacovigilance, drug resistance monitoring, implementation research and programme monitoring are necessary.
- **No easy fix.** Moving from current Option A or Option B to Option B+ will not, on its own, resolve the key challenges and problems of expanding coverage and successfully transitioning pregnant women from PMTCT programmes to HIV care and treatment programmes. Well-supported referral systems and strong MCH and ART programme linkages are essential.
- **Adherence and retention crucial.** Postpartum drop-out rates in PMTCT programmes are especially high, in part due to weak postpartum services. PMTCT interventions during breastfeeding have yet to be fully implemented successfully with any option. Maintenance of viral suppression with ARV treatment—achieved by supporting continued adherence to the ART regimen—is crucial to the additional benefits of the Option B and B+ interventions and to minimizing adverse consequences.
- **And especially with Option B+.** While programmes need to provide effective support for adherence and retention in care with all three PMTCT options, additional support will be required for Option B+. It is particularly important for programmes implementing Option B+ to develop strong systems to support adherence and retention and to build evidence of successful practices through implementation science.
- **Family planning still essential.** Even in the context of expanded access to ART for HIV-infected pregnant women, family planning services still need to be strengthened to avoid unintended pregnancies.
- **Quality assurance needed for HIV testing.** Reliable HIV rapid testing in antenatal settings is important for all options, as the entry point to PMTCT interventions. Robust quality assurance systems and confirmatory testing will be especially important in the context of Option B+, where every pregnant woman who tests HIV-positive is started on treatment for the rest of her life.

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Linking women who test HIV-positive in pregnancy-related services to long-term HIV care and treatment services: a systematic review

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Abstract

OBJECTIVES To quantify attrition between women testing HIV-positive in pregnancy-related services and accessing long-term HIV care and treatment services in low- or middle-income countries and to explore the reasons underlying client drop-out by synthesising current literature on this topic.

METHODS A systematic search in Medline, EMBASE, Global Health and the International Bibliography of the Social Sciences of literature published 2000–2010. Only studies meeting pre-defined quality criteria were included.

RESULTS Of 2543 articles retrieved, 20 met the inclusion criteria. Sixteen (80%) drew on data from sub-Saharan Africa. The pathway between testing HIV-positive in pregnancy-related services and accessing long-term HIV-related services is complex, and attrition was usually high. There was a failure to initiate highly active antiretroviral therapy (HAART) among 38–88% of known-eligible women. Providing 'family-focused care', and integrating CD4 testing and HAART provision into prevention of mother-to-child HIV transmission services appear promising for increasing women's uptake of HIV-related services. Individual-level factors that need to be addressed include financial constraints and fear of stigma.

CONCLUSIONS Too few women negotiate the many steps between testing HIV-positive in pregnancy-related services and accessing HIV-related services for themselves. Recent efforts to stem patient drop-out, such as the MTCT-Plus Initiative, hold promise. Addressing barriers and enabling factors both within health facilities and at the levels of the individual woman, her family and society will be essential to improve the uptake of services.

keywords antiretroviral therapy, female, patient dropouts, developing countries, HIV infections

Introduction

For more than a decade, effective antiretroviral (ARV) treatment has been available for the prevention of mother-to-child transmission of HIV (PMTCT), and highly active ARV therapy (HAART) for lifelong treatment is becoming increasingly accessible worldwide (UNAIDS 2010). Many studies have demonstrated the effectiveness of HAART during pregnancy and breastfeeding to reduce vertical transmission when compared with no intervention and with short-course PMTCT regimens (Thomas *et al.* 2008; Kilewo *et al.* 2009; Shapiro *et al.* 2009; de Vincenzi and Study Kesho Bora Group 2009; Kouanda *et al.* 2010, The Kesho Bora Study Group 2011). Even where it is impossible to initiate HAART during pregnancy, mother-to-child HIV transmission can be reduced by promoting rapid uptake of HAART following delivery (Taha *et al.* 2009).

Improved access to PMTCT services has decreased vertical HIV transmission, but parallel attention to women's access to HIV care and treatment for themselves has often been lacking. Initiating HAART during pregnancy can result in significant health benefits for women including a stronger immune system, decreased risk of HIV-related morbidity and reduced maternal mortality (Rabkin *et al.* 2004; Black *et al.* 2009). Survival of HIV-exposed infants is also higher among those whose mothers

are on HAART and/or co-trimoxazole preventive therapy (Newell *et al.* 2004; Mermin *et al.* 2008).

The PMTCT 'cascade' is the sequence of steps required for delivery of effective PMTCT interventions; it typically includes: attendance at antenatal care (ANC), HIV counselling, HIV testing, the provision of prophylactic ARVs, safe delivery, safe infant feeding, infant follow-up and HIV testing, and family planning. Attention to women's linkage into long-term HIV care and treatment services, assessment for eligibility for HAART and initiation of HAART if required is also essential but more rarely a priority within such 'cascades'.

This study aimed to quantify attrition along the pathway between women testing HIV-positive in pregnancy-related services and accessing long-term HIV care and treatment services in low- or middle-income countries[1] (LMIC) and to explore the reasons underlying client drop-out by synthesising current literature on this topic.

Methodology

We conducted a systematic search of literature published in English, French, Portuguese or Spanish between 1st January 2000 and 31st December 2010. Medline, EMBASE, Global Health and the International Bibliography of the Social Sciences were searched using the strategy outlined in Box 1. Experts in the field were consulted, and one PhD thesis was also included.

Articles were included in the review if the studies were carried out in a LMIC and contained information specific to access to long-term HIV care and treatment services among women who test HIV-positive in the context of pregnancy. Studies could be observational or descriptive. No publications were excluded on the basis of study design; rather they were assessed for 'fatal flaws' as defined in Appendix 1.

Two researchers (LF, TK) independently assessed a randomly selected 10% of all abstracts that were retrieved by the search and a randomly selected 10% of the articles selected for full-text review to determine the articles for the inclusion in the final review. There was adequate concordance between those included at each stage; 98% agreement, kappa 0.97 on titles/abstracts and 90% agreement, kappa 0.62 on full-text articles. Results were compared and disagreements resolved by consensus before the eligible articles were reviewed by a single researcher (LF). Reference lists for the articles included in the review were hand-searched for additional relevant publications.

[1]This is based on the World Bank's list of low- and middle-income economies.

Box 1 Search strategy for the literature search

Search terms
(HIV or AIDS).ti.
(pregnan* or antenatal or ANC or MCH or maternity).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, bt, ps, rs, nm, ui]
(diagnos* or test*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, bt, ps, rs, nm, ui]
1 and 2 and 3
Limit 4 to (English or French or Portuguese or Spanish)
Limit 5 to yr = '2000–2010'

Where sufficient data existed, client attrition along the pathway between HIV testing in ANC and initiating HAART if required was quantified, and extrapolations were made to estimate the overall number of missed opportunities for starting HAART. Piot-Fransen models were created for the three studies with the largest sample sizes that included data on the steps needed to access treatment, the proportion of women who accessed HAART and the potential effect of fully functional systems of linkages from HIV testing in pregnancy-related services to HAART services.

Results

Results of the systematic search

The search yielded 2543 unique articles. All abstracts were reviewed, and 93 were selected for full-text review, 18 of which met the inclusion criteria. One was excluded as it duplicated reporting in another article, (Tonwe-Gold *et al.* 2007) so 17 were retained. Three additional publications were found from the hand-searches and expert consultations. Twenty publications were included in the final review (Figure 1; Tables 1–3).

Of the 20 publications, 12 (60%) presented quantitative results, while three (15%) presented qualitative findings, one was a mixed methods study (5%) and four (20%) were programme reviews or evaluations, policy analyses or commentaries. Sixteen (80%) of these publications drew on data from sub-Saharan Africa, including four from South Africa.

Patient cascades between testing HIV-positive in ANC and accessing HAART

Thirteen publications showed attrition rates along the pathway to HAART services among women testing HIV-positive in pregnancy-related services. The findings are summarised in Tables 1 and 2 and divided into observational studies (n = 7), and studies that report data following some form of intervention (n = 6). The steps

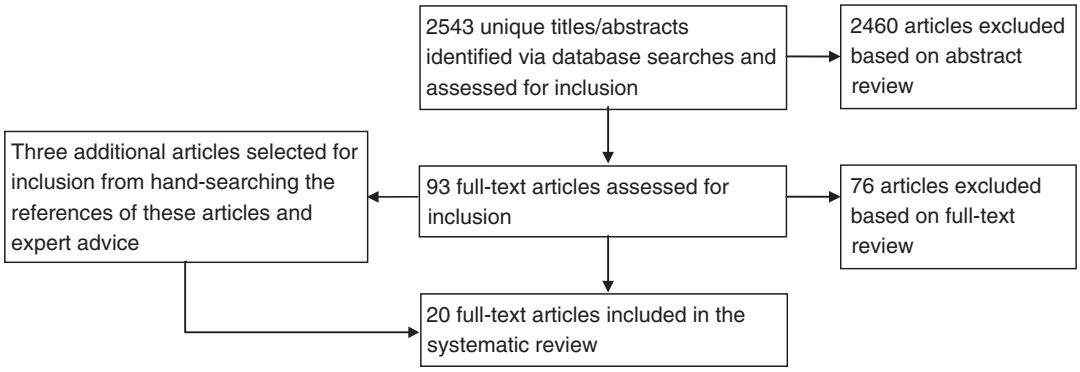

Figure 1 Results of search strategy.

reported along the cascade, PMTCT regimens used and timeframes varied by study.

Overall attrition

Pooling the data presented in Tables 1 and 2 for studies with sufficient data (Chen, Kranzer, Stinson, Balira, Chi, Killam, Mandala, Muchedzi) revealed many missed opportunities for initiating HAART. If all 27 001 HIV-positive women in these studies had been assessed for HAART eligibility and the same study-specific proportion found to be eligible as was found among the women who underwent CD4 count testing, an estimated 7376 women would have been identified as immediately HAART-eligible. Yet, only 1338 women initiated HAART, constituting 43% of those known to be eligible and, based on these extrapolations, only 18% of those who might have required it.

Points of attrition along the cascade

The individual studies document failure to initiate HAART among 38%–88% of known-eligible women. However, the points of attrition along the pathway to assessment and initiation of HAART varied. In the Tanzanian study, 38% of women failed to register at the HIV clinic after an HIV diagnosis in ANC (Balira 2010).

Across most studies, at least 70% of women who registered at the HIV clinic reportedly had blood taken for a CD4 count; studies in Botswana and Zambia are notable exceptions with CD4 count uptake of 59% and 17%, respectively (Mandala *et al.* 2009; Chen *et al.* 2010). The studies that documented the proportion of women returning for their CD4 count results found attrition of 30–33% at this point of the cascade (Chi *et al.* 2007; Mandala *et al.* 2009; Horwood *et al.* 2010).

In one South African study, the proportion of individuals who attended a blood-draw for a CD4 count within 6 months of diagnosis was 84.1% for those tested through STI services, 81.3% for women tested in ANC, 68.9% for those tested in tuberculosis services and 53.5% for people tested through voluntary counselling and testing (Kranzer *et al.* 2010).

In Zambia, uptake of HIV-related services was compared where women were referred from ANC to a separate HAART clinic (control arm) with uptake where HAART was initiated within ANC (intervention arm). Eighty-five per cent of women underwent initial evaluation for HAART eligibility in both study arms, but the proportion of eligible women who initiated HAART was low in both arms at 14% and 33% in control and intervention arms, respectively (Killam *et al.* 2010). Data from sites in 14 countries showed that only 1.4% of HIV-positive pregnant women had received HAART; the proportion of HAART-eligible women was not reported (Ginsburg *et al.* 2007). In contrast, the study in Ivory Coast showed exceptionally high uptake of CD4 count testing (100%) and HAART (95%) (Tonwe-Gold *et al.* 2009).

Figure 2 shows Piot-Fransen models for the three selected studies: two observational studies in South Africa and Zambia, and the intervention arm of Killam *et al.*'s study in Zambia. These studies all revealed high levels of patient attrition, including the intervention arm of Killam *et al.*'s evaluation (Figure 2c) where specific efforts were made to promote uptake of HAART following HIV testing in ANC.

Factors underlying client attrition along the pathway to HAART

Some articles in this review provided insufficient quantitative data to be included in Tables 1 or 2 but gave useful insights into factors affecting attrition along the pathway to HAART. These are outlined in Table 3. Then, factors underlying client attrition along the pathway that have

Table 1 Patient cascades for pregnant women from testing HIV-positive to initiating HAART – Observational studies

Country, author, year of publication	Study design	CD4 for HAART eligibility	HIV-positive	Referred to HIV clinic for HAART assessment	Registered at HIV clinic	Initial screening or CD4 test performed	Returned for results of CD4 test	Eligible for HAART	Started HAART	Should have started HAART (Estimate†)	% of those estimated HAART-eligible who started HAART	Comments
			a	b (% = b/a)	c (% = c/b)	d (% = d/a)‡	e (% = e/d)	f (% = f/d)	g (% = g/f)§	h (a × %f)	i (g/h)	
Kenya (Otieno *et al.* 2010)	Cross-sectional survey	<350	116	116 (100%)	86 (74%)				33			Based on self-reported data. Almost half the initial study population was LTFU. Study population had been part of a PMTCT study that included intensive and prolonged involvement with providers
South Africa (Kranzer *et al.* 2010)	Retrospective cohort	<200	150			125 (83%)		18 (14%)	13 (72%)	21	62%	Based on routinely collected health facility records. Would have missed women who chose to attend a different HIV clinic but the nearest alternative was 10 km away

Table 1 (*Continued*)

Country, author, year of publication	Study design	CD4 for HAART eligibility	HIV-positive	Referred to HIV clinic for HAART assessment	Registered at HIV clinic	Initial screening or CD4 test performed	Returned for results of CD4 test	Eligible for HAART	Started HAART	Should have started HAART (Estimate†)	% of those estimated HAART-eligible who started HAART	Comments
			a	b (% = b/a)	c (% = c/b)	d (% = d/a)‡	e (% = e/d)	f (% = f/d)	g (% = g/f)§	h (a × %f)	i (g/h)	
South Africa (Stinson *et al.* 2010)	Retrospective cohort	<200	3498			3405 (97%)		516 (15%)	262¶ (51%)	525	50%	As only four sites were used to represent three service delivery models, differences between the facilities rather than between the models might explain some of the findings
South Africa (Geddes *et al.*, 2008)	Retrospective cohort	<200	338			262 (78%)			130			Relied on routinely collected health facility data. 11% LTFU
South Africa (Horwood *et al.* 2010)	Cross-sectional study	<200	312			244 (78%)	171 (70%)		27			Based on self-report by women
Tanzania (Balira 2010)	Prospective cohort	<200††	244	199 (82%)	123 (62%)	78 (63%)		18 (23%)	10 (56%)	56	18%	Based on self-reported data. 20% LTFU by final follow-up

Table 1 (*Continued*)

Country, author, year of publication	Study design	CD4 for HAART eligibility	HIV-positive a	Referred to HIV clinic for HAART assessment b (% = b/a)	Registered at HIV clinic c (% = c/b)	Initial screening or CD4 test performed d (% = d/a)‡	Returned for results of CD4 test e (% = e/d)	Eligible for HAART f (% = f/d)	Started HAART g (% = g/f)§	Should have started HAART (Estimate†) h (a × %f)	% of those estimated HAART-eligible who started HAART i (g/h)	Comments
Zambia (Mandala *et al.* 2009)	Retrospective cohort	<350	14 815			2528 (17%)	1680 (67%)	796 (31%)	581 (73%)	4593	13%	Based on routinely collected health facility data. No data on age or WHO clinical staging

HAART, Highly active antiretroviral therapy; LTFU, lost to follow-up; PMTCT, prevention of mother-to-child HIV transmission.
†Estimated number of women who should have started HAART = % women eligible for HAART among those had a CD4 result × total HIV-positive women in the study.
‡Where c is available, % = d/c (Balira)
§Where f is unavailable, no % is given (Otieno, Geddes, Horwood)
¶In Stinson's study, the number of women who started HAART refers to the women who started HAART during pregnancy. Another 61 started HAART within 2 years post-partum, half of them within 7.5 months of delivery.
††Clients were also deemed eligible for HAART if CD4 < 350 and WHO Stage III, or if WHO Stage IV irrespective of CD4 count.

Table 2 Patient cascades for pregnant women from testing HIV-positive to initiating HAART – Intervention studies

Country, First author, Year of Publication	Study design	Intervention	CD4 for HAART eligibility	HIV-positive a	Referred to HIV clinic for HAART assessment b (% = b/a)	Registered at HIV clinic c (% = c/b)	Initial screening or CD4 test done d (% = d/a)	Returned for results of CD4 test e (% = e/d)	Eligible for HAART f (% = f/d)	Started HAART g (% = g/f)	Should have started HAART (Estimate) h (a × %f)	% of those estimated HAART-eligible who started HAART i (g/h)	Study limitations
Botswana (Chen *et al.* 2010)	Observational retrospective cohort	Concurrent clinical trial providing CD4 testing and rapid HAART initiation for women with a CD4 higher than the national eligibility threshold	<200	688			397 (59%)		62 (16%)	23 (37%)	107	21%	Based on routine hospital data.
Zambia (Killam *et al.* 2010)	Stepped-wedge evaluation	Integration of HAART into ANC services. Control arm shown in top row; intervention shown in bottom row	<250	3046		2589 (85%)			716 (28%)	103 (14%)	853	12%	Cost and human resources implications of such integration not reported
			<250	3753		3193 (85%)			846 (26%)	278 (33%)	976	28%	

Table 2 (*Continued*)

Country, First author, Year of Publication	Study design	Intervention	CD4 for HAART eligibility	HIV-positive a	Referred to HIV clinic for HAART assessment b (% = b/a)	Registered at HIV clinic c (% = c/b)	Initial screening or CD4 test done d (% = d/a)	Returned for results of CD4 test e (% = e/d)	Eligible for HAART f (% = f/d)	Started HAART g (% = g/f)	Should have started HAART (Estimate) h (a × %f)	% of those estimated HAART-eligible who started HAART i (g/h)	Study limitations
Zambia (Chi *et al.* 2007)	Evaluation	Scripted talk on the benefits of CD4 testing and long-term HIV care; encouragement to enrol into long-term care and treatment; and escort by CHWs to the on-site HIV facility for immediate attention	<200†	680	433 (64%)		302 (70%)	206 (68%)	72 (24%)	33 (46%)	163	20%	Based on routine clinic data
Ivory Coast (Tonwe-Gold *et al.* 2009)	Description of programme outcomes	MTCT + initiative: family-focused care and treatment with regular clinical and lab assessments	<200‡			605	605 (100%)		259 (43%)	246 (95%)			No information on the no. of women who declined programme enrolment.

Table 2 (*Continued*)

Country, First author, Year of Publication	Study design	Intervention	CD4 for HAART eligibility	HIV-positive	Referred to HIV clinic for HAART assessment	Registered at HIV clinic	Initial screening or CD4 test done	Returned for results of CD4 test	Eligible for HAART	Started HAART	Should have started HAART (Estimate)	% of those estimated HAART-eligible who started HAART	Study limitations
				a	b (% = b/a)	c (% = c/b)	d (% = d/a)	e (% = e/d)	f (% = f/d)	g (% = g/f)	h (a × %f)	i (g/h)	
Zimbabwe (Muchedzi *et al.* 2010)	Cross-sectional survey	Peer counsellors to provide additional support including home tracing in the case of missed appointments	<350	147¶		95 (65%)	77 (81%)		43 (56%)	35 (81%)	82	43%	Based on self-report. 23% LTFU
Multi-country (Ginsburg *et al.* 2007)	Review of programmatic indicators	NGO-supported PMTCT programme	Varied by country	98 304						1388			Based on routine programme monitoring data; incomplete reporting

HAART, Highly active antiretroviral therapy; LTFU, lost to follow-up; ANC, antenatal care; CHWs, community health workers; PMTCT, prevention of mother-to-child HIV transmission.
†Clients were also deemed eligible for HAART if CD4 < 350 and WHO Stage III, or if WHO.
‡These data were collected between August 2003 and August 2005. Until Dec 2004, the criteria for initiating HAART were CD4 < 350/mm^3 and WHO Stage 4, 3 or 2, or CD4 < 200 mm^3. From January 2005 patients with Stage 2 and CD4 < 350 mm^3 were not eligible for HAART.
§Where a is unavailable, %=d/c (Tonwe-Gold).
¶201 women were diagnosed with HIV and eligible for this study but, before the follow-up time, 46 were lost-to-follow-up (41 had moved out of the study area and five had relocated to other countries) and eight had died. Only the remaining 147 have been included here as the surviving others may have registered at a different HIV clinic.

Table 3 Studies in the review with insufficient data for creating a patient cascade

Author, year of Publication	Study setting	Study design	Comments
Abrams *et al.* (2007)	Review using data from 13 countries in sub-Saharan African and Southeast Asia	Review of rationales for linking PMTCT and HIV treatment services, focusing on PMTCT as a gateway to family-based HIV care and treatment.	Looked at why it is important to strengthen links between PMTCT and long-term care and treatment Promotion of family-centred care as an approach for achieving this
Chinkonde *et al.* (2009)	2 UNC-supported PMTCT programmes, Lilongwe, Malawi	Qualitative interviews and focus group discussions with women who had attended the PMTCT programme and their husbands	Sought to understand high levels of attrition from the PMTCT programme Major barriers to retention in the programme included: fear of involuntary HIV disclosure and negative community reactions; unequal gender relations; long walking distances; and lack of support from husbands Facilitator: social support
Duff *et al.* (2010)	PMTCT + programme in a regional hospital, Uganda	Qualitative descriptive exploratory study: qualitative interviews and a focus group discussion with HIV-positive mothers	Greatest barrier to accessing HAART: economic concerns, especially transport costs to clinics Other barriers: stigma, non-disclosure to sexual partners, long waiting times at clinics, and suboptimal provider–patient interactions
Gruskin *et al.* (2008)		Policy analysis	Analysis of the implications of WHO's guidance on provider-initiated HIV testing and counselling (PITC) for the health and human rights of pregnant women Potential of PITC as a gateway to long-term care and treatment services is highlighted Attention to the implementation processes needed to ensure the success of the guidance
Levy (2009)	Lilongwe, Malawi	Qualitative interviews and focus group discussions with women living with HIV participating in the PMTCT programme and key informant interviews with staff working in the PMTCT programme and health system	Identified a disjuncture between women's expectations of PMTCT and the services received Main problems: Marginalisation of the woman's health in favour of the infant's health Lack of attention to the social determinants of health Health system weaknesses
Nakanjako *et al.* (2009)	Resource-limited settings	Review of strategies to optimize treatment outcomes in resource-limited settings	Highlighted eight strategies for optimising HIV treatment outcomes, including strengthening the links between HIV diagnosis and long-term care and treatment services

Table 3 (*Continued*)

Author, year of Publication	Study setting	Study design	Comments
Pfeiffer *et al.* (2010)	Public sector health facilities, Mozambique	Case study	Comparison of sites pre- and post-integration of HIV clinics into primary health care Difficult to tease out the effect of integration as the intervention also included retraining health workers; strengthening laboratory, testing and referral linkages; and improving district-level health management

HAART, Highly active antiretroviral therapy; PITC, Provider-initiated HIV testing and counselling; PMTCT, Prevention of mother-to-child HIV transmission; UNC, University of North Carolina.

emerged from all the studies reviewed are presented, separated into health systems factors, health worker-related factors and individual-level factors.

Health systems-related factors

Lack of continuity of care, gaps in the referral process and the need to strengthen linkages between PMTCT and HAART services were noted across a wide range of settings (Levy 2009; Nakanjako *et al.* 2009; Otieno *et al.* 2010). A case study in Mozambique found that enrolment in HIV services increased from 30% to 75% after their integration into the facilities that provided ANC/PMTCT (Pfeiffer *et al.* 2010).

In South Africa, Stinson compared the PMTCT cascade across three models of health services delivery: 'integrated services' whereby a weekly HAART service was provided within ANC; 'proximal services' where women were referred from ANC to HAART services in a separate building on the same premises; and 'distal services' whereby women were referred from ANC to HAART services at a separate facility within 5 km (Stinson *et al.* 2010). The cascade is presented in aggregate in Table 1 because no significant association was found between the model of care and the proportion of women starting HAART during pregnancy. The authors noted that providing HAART services on-site only once a week in the 'integrated' model may have been insufficient to affect HAART initiation during pregnancy (Stinson *et al.* 2010).

In Killam's study in Zambia, the proportion of women who enrolled for HIV care both before delivery and within 60 days of HIV diagnosis was 25% and 44% in the control (non-integrated) and intervention (integrated) arms, respectively (AdjOR 2.06, 95% CI: 1.27–3.34). The proportion of women who initiated HAART before delivery and within 60 days of diagnosis was 14% and 33%, respectively (AdjOR 2.01, 95% CI: 1.37–2.95). The authors postulated that this might have been due to clients' relative comfort in the PMTCT setting as well as providers' increased ownership of, and commitment to, this task. They acknowledged that further work is required to elucidate the reasons underlying the persistently high client drop-out (Killam *et al.* 2010).

The co-location of HAART services within ANC in the Killam study did not lead to HAART initiation earlier in pregnancy. Elsewhere, the length of treatment adherence preparation that was required before a woman could be started on HAART was noted as a potential factor influencing women's ability to start HAART during pregnancy (Chen *et al.* 2010; Stinson *et al.* 2010).

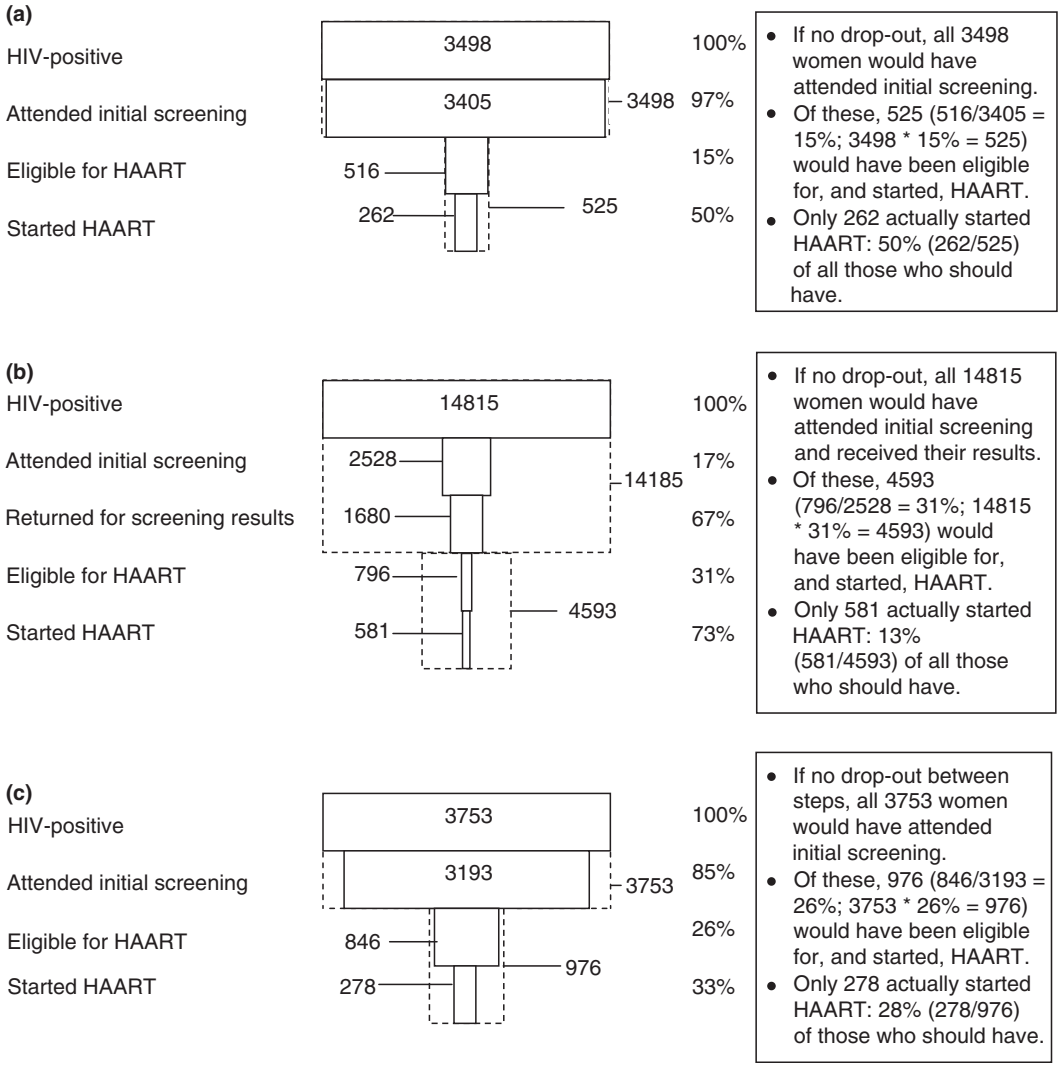

Figure 2 Piot-Fransen models illustrating patient cascades from HIV testing in pregnancy-related services to highly active antiretroviral therapy (HAART) services. (a) Piot-Fransen model for data from the Stinson *et al.* 2010 observational study in South Africa. (b) Piot-Fransen model for data from the Mandala *et al.* 2009 observational study in Zambia. (c) Piot-Fransen model for data from the intervention arm of the Killam *et al.* 2010 study in Zambia. The boxes with solid lines show the actual number of women who completed each step along this pathway. On the right-hand side are the proportions of women completing each step in the cascade. The dotted lines show an ideal patient cascade, i.e. with no patient drop-out, which is explained in the boxes on the right-hand side.

None of the studies in which HIV care and treatment services were initiated within ANC included data on client loss during transition from ANC to the site of long-term HIV care and treatment services.

Whether blood was drawn in ANC or the HIV clinic affected the proportion of women who had a CD4 count performed. Aggregating the studies in Tables 1 and 2 where the CD4 blood-draw was performed within ANC, 10 433 of 11 902 (88%) women had blood taken for a CD4 count compared with 379 of 827 (46%) in the studies where blood was drawn at the HIV clinic ($P < 0.001$). There was no difference between these two groups in the proportion of HAART-eligible women who started HAART ($P = 0.691$). None of the studies in this review used point-of-care CD4 tests.

Mandala *et al.* (2009) suggested that low uptake of CD4 count testing in their study might have been due to health workers not always drawing blood for CD4 counts

every day, limited sensitisation of providers and clients on the importance of CD4 count testing, repeated adjustment of the patient pathway and high levels of stigma. In Zambia, only two of the factors studied were independently associated with women having a CD4 count performed: ability to have blood drawn for the CD4 count on the day of diagnosis and urban location (Mandala *et al.* 2009).

On the basis of the observations in their study hospital in Botswana, Chen *et al.* (2010) proposed potential reasons for failure to undergo CD4 testing including a shortage of reagents; lack of access to transportation for specimens and test results; inability to perform the test before delivery and insufficient/lost specimens; and failure to initiate HAART such as delay in receipt of CD4 count results and lack of referral to the ART clinic. In other settings, women highlighted shortages of staff and supplies as well as cost of services as barriers to accessing services (Levy 2009; Otieno *et al.* 2010).

Health worker-related factors

As the interface between the health system and the client, health workers played a critical role in influencing women's care-seeking decisions. Negative provider–client interactions impeded uptake of services in Uganda (Duff *et al.* 2010). In Malawi, health workers' exclusive focus on the biomedical aspects of HIV and their failure to address social factors that might affect care-seeking, such as poverty and food insecurity, were highlighted as shortcomings (Levy 2009). In the same study, although women described accessing HIV-related services for their own health, providers sometimes failed to refer asymptomatic women to the HIV clinic and focused their attention on their infants' health (Levy 2009). The lack of sensitisation for providers and clients on the value of timely HAART initiation has also been noted as contributing to patient attrition (Mandala *et al.* 2009). Reflecting the power inequality between health provider and client, women's often unquestioning acceptance of providers' attitudes towards their health can affect their experiences of health services (Gruskin *et al.* 2008).

Individual-level factors

Women's fears regarding confidentiality, transport costs to access services, general dislike of health facilities, not feeling ready and low knowledge of HIV and HAART have also been cited as barriers to access (Duff *et al.* 2010; Otieno *et al.* 2010). The perceived stigma of being seen attending the clinic, being given food support that was only given to people with HIV and being visited at home contributed to the visibility of infection and potential involuntary disclosure, and therefore constituted reasons for non-attendance at services in a study in Malawi (Chinkonde *et al.* 2009).

Non-disclosure of HIV status to a woman's sexual partner contributed towards non-enrolment in HIV-related services in one study (Duff *et al.* 2010) but not in another (Otieno *et al.* 2010). The only study to examine the HIV status of women's sexual partners found no association with women's uptake of HIV-related services (Otieno *et al.* 2010).

Promising practices for addressing client attrition along the pathway to HAART

Perhaps the most promising model of service provision reported to date is the MTCT-Plus Initiative, which involves 'family-focused care', which aims to enrol not only the pregnant woman diagnosed with HIV into HIV care and treatment services but also her HIV-infected family members (Abrams *et al.* 2007; Tonwe-Gold *et al.* 2009). In a study in Ivory Coast, this approach resulted in all the 605 pregnant women who registered at the HIV clinic receiving their CD4 count result, and 95% of the 259 HAART-eligible women starting HAART (Tonwe-Gold *et al.* 2009). Although the study did not report attrition levels between HIV diagnosis and registering at the HIV clinic, these subsequent results were very impressive. The authors concluded that screening for HAART eligibility and initiation of HAART within pregnancy-related services were crucial for linking HIV-positive women into these services (Tonwe-Gold *et al.* 2009).

Other efforts to reduce attrition along the pathway to HIV care and treatment included the use of escorts for women between ANC and HAART services; pregnant women bypassing queues in HAART services; and regular meetings between staff from PMTCT and HAART services to track patients and discuss their needs (Abrams *et al.* 2007; Chi *et al.* 2007).

Discussion

The fragmentation of health services, with pregnancy-related services being managed separately from HIV care, for example, emerged as a major barrier to successful linkage into long-term HIV care and treatment services. Several initiatives designed to stem patient drop-out between HIV testing in pregnancy-related services and long-term HIV care and treatment services appear promising, but the plethora of barriers to accessing services means that single service change is likely to only partially solve the problem.

The rubric of 'integration' continues to be used to encompass a wide range of service delivery models. Specificity regarding which services are made available, when and by whom will be critical to understanding the effectiveness of different models of 'integrated' service delivery. Where staffing and infrastructure allow, it would seem most beneficial to ensure the daily availability within PMTCT services of assessment for HAART-eligibility and initiation of HAART. It will be important to ensure a smooth transition to the HIV clinic for women who initiate HIV-related services within pregnancy-related services, whenever this is performed. In addition, it would be useful for health workers to highlight within counselling sessions the benefits of HAART among women with a low CD4 count both for the woman's own health and for PMTCT. Point-of-care CD4 testing is increasingly being introduced and has considerable potential for improving retention in care at this stage of the cascade (Mtapuri-Zinyowera *et al.* 2010; Jani *et al.* 2011).

The provision of HAART within ANC has previously been shown to improve uptake and reduce time to treatment initiation (van der Merwe *et al.* 2006). It was therefore surprising that integration of HAART did not lead to earlier uptake of HAART during pregnancy in the studies led by Killam in Zambia and Stinson in South Africa. Further details of the study contexts, such as treatment preparation processes, might have helped to explain these differences.

A review of family-focused approaches to PMTCT underscored their importance for linkage into long-term care and treatment services, highlighting the MTCT-Plus Initiative and the CDC-Uganda Global AIDS Program as salient examples, although no quantitative data were provided on linkage into HIV-related services for the latter programme (Betancourt *et al.* 2010). However, both programmes have relied on high levels of external funding, and their sustainability needs confirmation (Myer *et al.* 2005).

A Cochrane review on integrating PMTCT services with other services found only one study that met its inclusion criteria, highlighting the weakness of the evidence base regarding the potential impact of integration on coverage and uptake of services, quality of care and health outcomes (Tudor Car *et al.* 2011). A systematic review of adult retention in HIV care between testing and treatment in sub-Saharan Africa revealed high patient drop-out across different populations and HIV testing locations and highlighted the need for improved health information systems to allow patient tracking across different service delivery points (Rosen & Fox 2011). The authors noted the difficulty inherent in cross-study comparison because of the lack of standardised terminology, definitions and time intervals, which applies equally to comparisons of the studies in this review (Rosen & Fox 2011).

Moving beyond the calls for increased attention to the health system factors affecting this attrition, addressing the personal and social factors that might constrain women's uptake of these services remains essential. Although disclosure of HIV status to a sexual partner has been shown to promote adherence to PMTCT interventions (Medley *et al.* 2004; Delva *et al.* 2006), this review found no clear-cut evidence of an association between such disclosure and initial uptake of HIV-related services. Despite limited autonomy in household decision-making (Berman *et al.* 1994; Nanda 2002; Vlassoff & Moreno 2002), women's decision-making around accessing long-term care and treatment services for their own HIV infection is an area that remains under-explored in current literature.

Limitations of this review

With the exception of one PhD thesis identified through discussions with experts, this systematic review only captures information on studies published in peer-reviewed academic literature; it may thus fail to capture lessons learned from interventions whose findings have not (yet) been published. Non-abstracted work and publications not listed within the databases searched will also have been excluded. Conference abstracts were not included in the review because of the paucity of detail they often include.

Certain caveats are important because of the assumptions in the extrapolations of data carried out. For example, the number of women requiring HAART would be over-estimated if the women who had blood drawn for a CD4 count were more likely to be symptomatic (and therefore more likely to need HAART) than the women who did not have blood taken for a CD4 count. Despite these limitations, such calculations can give a useful estimate of these missed opportunities.

Conclusion

This review provides strong evidence that, in most settings that have been studied to date in LMICs, relatively few women successfully negotiate the many steps between testing HIV-positive in pregnancy-related services and accessing HIV services for themselves. Improving this will require attention to barriers and enabling factors both within health facilities and at the level of the individual woman and her wider family and society. Box 2 lists health facility-level interventions recommended for improving linkage into HIV care and treatment services from HIV testing in pregnancy-related services.

Additional work is needed to better understand the effectiveness and sustainability of these interventions in varied settings. It is critical that the strengths and weaknesses of existing and new interventions be documented so that lessons learnt can be translated into concrete benefits in terms of access to HIV-related services for the pregnant women who require them.

Box 2 Health facility-level interventions to improve linkage between HIV testing in pregnancy-related services and long-term HIV care and treatment services

- Introduction into post-test counselling of messages on the importance of assessment for and, if eligible, initiation of HAART both for PMTCT and for women's health.
- Point of care CD4 count testing with in-session results available within pregnancy-related services.
- Full integration of HIV care and treatment services into ANC services (where infrastructure and staffing allow) with CD4 count testing and HAART initiation available daily, and women's transition to the HIV clinic weeks/months post-partum.
- Improved linkages between HIV testing in delivery and PNC services to HIV care and treatment services (whether in ANC or a separate HIV clinic).
- Provision of family-focused care, including, at a minimum, the offer of counselling, testing, treatment and psychosocial support for women's partner and children and other household members. Ideally, this would also include: male involvement in PMTCT and pregnancy-related counselling e.g. infant feeding counselling; accessing to reproductive health and family planning services; screening for intimate partner violence; nutrition counselling; attention to mental health issues; and attention to early childhood development.
- Peer support for women newly diagnosed with HIV, including escorts to the HIV clinic if these services are not available within the ANC setting.
- Improved health information systems that enable tracking of patients between hospital departments (and, ideally, across health facilities).
- Institution of communication systems that allow tracing of patients lost to follow-up.
- Incentives to attend the hospital e.g. transport subsidies, food supplements etc.

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Appendix 1

Criteria for considering a study 'fatally flawed'

A study was considered to be fatally flawed if, having read it, we answered 'no' to any one of the following questions

Are the aims and objectives of the research clearly stated?
Is the research design clearly specified and appropriate for the aims and objectives of the research?
Do the researchers provide a clear account of the process by which their findings were produced?
Do the researchers display enough data to support their interpretations and conclusions?
Is the method of analysis appropriate and adequately explicated?

Source: Dixon-Woods ***et al.*** (2006), Medical Research Methodology. ***BMC* 6**, 35.

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