Improving Child survival through enhancing Prevention of Mother to Child Transmission of HIV

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ABSTRACT

Background: Although highly effective prevention interventions exist, the epidemic of paediatric HIV continues to challenge control efforts in resource-limited settings. Effective strategies are needed for the Prevention of Mother-To-Child Transmission of HIV (PMTCT). The complete PMTCT package includes comprehensive antenatal (ANC) care, modified obstetric practices, antiretroviral therapy and infant feeding counseling and support.

Aim: This article presents syntheses of evidence on the cost-effectiveness of HIV MTCT strategies for LMICs, investigates whether a maternal triple-antiretroviral regimen that was designed to maximally suppress viral load in late pregnancy and the first 6 months of lactation was safe and well-tolerated, investigates acceptability of the PMTCT programme components, and identifies structural and cultural challenges to male involvement in the reduction of MTCT.

Methods: I identified articles on the use of ARVs to prevent MTCT of HIV through a comprehensive database search including PubMed and Embase. I screened the titles and abstracts from the individual database search results from year 2002-2011, pooled the potentially eligible studies, retrieved full-text articles, and then assessed whether they met the inclusion criteria. I extracted the data based on publication date, demographic characteristics and HIV transmission rates to babies.

Results: The articles suggest that interventions to prevent paediatric infections are cost-effective in a variety of LMICs. HIV-transmission rates among subgroups defined by maternal risk factors, including baseline CD4 cell count and viral load was 15% after 24 months, while transmission rates for those who have received ARVs was 7% for the same period. This reveals that triple-antiretroviral regimen for pregnant-women was safe and feasible. Routine testing for HIV of women at the antenatal clinic was found to be highly acceptable and appreciated by men, while other programme components, notably partner testing, condom use and the infant feeding recommendations, were met with continued resistance. The vision, goal, objectives and targets noted by Global Partners Forum will serve as a framework for WHO to support countries to focus on and prioritize the accelerated scale-up of effective and comprehensive PMTCT services.

Conclusion and recommendations: Interventions to prevent HIV MTCT are compelling on economic grounds in many resource-limited settings and should remain at the forefront of global HIV prevention efforts. Deep-seated ideas about gender roles and hierarchy are major obstacles to male participation in the PMTCT programme. Empowering men to participate by creating a space within the PMTCT programme that is male friendly should be feasible and should be highly prioritized for the PMTCT programme to achieve its potential. Increased community sensitization, counseling and testing, treatment and support of women identified as HIV infected should improve acceptance of PMTCT services in Africa and subsequently reduce paediatric HIV.

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INTRODUCTION

In 2008, approximately 2.1 million children were living with HIV which is up from 1.6 million in 2001. An estimated 430,000 children were newly infected with HIV in 2008, which is approximately 16 percent of the total number of new infections. Therefore children make up approximately 6 percent of the total number of people living with HIV [1]. Nearly 1,200 children under 15 years of age are infected with HIV every day, mostly as a result of mother-to-child transmission of the virus. Without treatment, almost half of newborns infected with HIV will die before their second birthdays [1-2].
In 2008, approximately 390,000 children in sub-Saharan Africa were newly infected with HIV. This represents more than 90 percent of all new HIV infections among children worldwide [1].
In 2009, an estimated 107,000 infant HIV infections were averted through prevention of mother-to-child transmission services supported by the U.S. government and partner organizations [3].
PMTCT was identified as one of five priority areas for response at the United Nations Special Session on HIV/AIDS in 2001. Heads of state committed their governments to reducing the proportion of infected infants by 20% by 2005 and by 50% by 2010 [4]. Virtually all HIV-infected children acquire the infection through MTCT, which can occur during pregnancy, labour and delivery, or through breastfeeding. In the absence of any intervention, an estimated 15-30% of mothers with HIV infection will transmit the infection during pregnancy and delivery, and breastfeeding by an infected mother increases the risk by a further 5-20% to a total of 20-45% [6-8]. Without treatment, most HIV-infected children experience severe morbidity and early death.

WHO recommends the 4 pronged approach to PMTCT that includes primary prevention of HIV, prevention of unintended pregnancies in HIV infected women, PMTCT, and care and support for HIV infected women, infants and families. The complete PMTCT package includes comprehensive antenatal (ANC) care, modified obstetric practices, antiretroviral therapy and infant feeding counseling and support. Recently, the risk of MTCT has been reduced to below 2% in high-income countries by universal HIV screening of pregnant women and a suite of interventions for those identified as HIV+ that includes: (1) antiretroviral (ARV) prophylaxis in combinations of three or more drugs given to women during pregnancy and labour, and ARV prophylaxis given to the infant during the first weeks of life; (2) obstetrical interventions including elective caesarean delivery (prior to onset of labour and membrane rupture); and (3) complete avoidance of breastfeeding.

Although evidence suggests that the three-pronged approach described above is clinically most efficacious, a variety of less complex strategies to prevent HIV MTCT (PMTCT) have been proposed for developing countries each with different resource requirements and levels of associated clinical benefit [9-14]. As access to services for preventing MTCT has increased worldwide, the number of children newly infected with HIV has dropped sharply. Incident cases for 2009 are down by almost one quarter as compared to five years earlier [15]; an unprecedented achievement that brings renewed hope to the global community. To build upon these successes, policies and programmes must reflect bold and intelligent choices.

OBJECTIVES

- To assess the cost-effectiveness of interventions aimed at preventing mother-to-child transmission (MTCT) of HIV in low- and middle-income countries (LMICs)

- To assess whether the maternal triple-antiretroviral regimen that was designed to maximally suppress viral load in late pregnancy and the first 6 months of lactation was a safe, well-tolerated, and effective PMTCT intervention

- To explore acceptability of the PMTCT programme components

- To identify structural and cultural challenges to male involvement on PMTCT programme.

METHODS

Literature search: I searched Medline (using PubMed) and EMBASE for published articles on the use of ARVs to prevent MTCT of HIV, on the cost-effectiveness of interventions aimed at preventing mother-to-child transmission (MTCT) of HIV in low- and middle-income countries (LMICs), on the acceptability of the PMTCT programme components, and articles that identify structural and cultural challenges to male involvement in the PMTCT programme.
I divided the search to capture the themes of (1) prevention and intervention, (2) disease transmission or infection, vertical or mother-to-child or maternal–fetal or perinatal, (3) HIV infection or AIDS, (4) antiretroviral drugs, agents, or therapy, and (5) Sub Saharan Africa (SSA).
I developed search terms for these themes, combined the terms using OR for each theme, and then combined the different theme searches.

Inclusion and exclusion criteria: I screened the titles and abstracts from the individual database search results from 2002-2011, pooled the potentially eligible studies, retrieved full-text articles, and then assessed whether they met the inclusion criteria. I restricted inclusion to publications of clinical trials that reported primary data, measured HIV transmission from mothers to babies, and had antiretroviral drugs as the exposure to the mother. I excluded publications that did not report primary data (commentaries, perspectives, laboratory studies, secondary and meta-analyses)

Data extraction: I extracted the data based on citation, publication date, study name, location, and dates carried out. Subjects (demographic characteristics, inclusion/exclusion criteria, number enrolled, and loss to follow-up), the exposure (ARV regimen used for each arm, dosage, duration, adverse events), the endpoint (HIV transmission rates to babies, when the endpoint was measured, how the endpoint was measured), and other data relevant for transmission (mode of delivery, breastfeeding).

Methodological quality: I described how randomization was generated, the adequacy of blinding, and loss to follow-up; I however, did not assign a quantitative score for quality. I also assessed adherence to medications and the test used to determine HIV status in the baby.

6. RESULTS AND FINDINGS

I identified 16 articles in 12 of which the study design was descriptive cross sectional and 4 of which were randomized control trials. Four studies were performed on cost-effectiveness of PMTCT interventions, 4 control trials performed on effectiveness of anti-retroviral therapy to prevent MTCT in pregnant women, 5 assess the challenges facing male involvement in PMTCT programmes and 3 were performed on acceptance towards PMTCT programmes.

6.1 Cost-effectiveness

By systematic search, 4 published articles out of 16 in 2002-2011 collectively suggest that interventions to prevent paediatric infections are cost-effective in a variety of LMIC settings as measured against accepted international benchmarks. Cost effectiveness of PMTCT interventions was positively correlated with rates of HIV prevalence and highly sensitive to changes in this variable. Drug costs, VCT costs, natural history MTCT rate, adherence to therapy, drug efficacy, and feeding practices also had an important effect on implied optimal strategy.

In concentrated epidemics where HIV prevalence in the general population is very low, MTCT strategies based on universal testing of pregnant women may not compare well against cost-effectiveness benchmarks, or may satisfy formal criteria for cost-effectiveness but offer a low relative value as compared to competing interventions to improve population health.

TABLE 1

Perspective[1]	Cost Year & Currency	Discount Rate[2]	Cost Breakdown	
			Direct costs to the public payer	
			Intervention costs[3]	Costs generated or offs
SOC	1994 US$	5%	Standard[6]	LMC[7] (HIV+ children)
PPHC	1994 US$	5%	Standard	LMC (HIV+ children)
PPHC	US$	5%	Standard	LMC (HIV+ children)
PPHC	1997 US$	3%; 6%	Standard + Training	
PPHC	US$	3%	Standard	Net LMC (HIV+ children)
PPHC	1998 US$	5%	Standard + Formula feed	Net LMC (HIV+ children)
PPHC	1999 US	3%	Standard	LMC (HIV+ children)
PPHC	1997 Rand	Not stated	Standard + Training	
PPHC	2000 US$	Not stated	Drugs	

SOC- Societal (considers direct and indirect costs)

PPHC-Public payer of healthcare costs (considers direct costs only)

Source: Cost Eff Resour Alloc. 2011; 9: 3.

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6.2 Maternal triple-antiretroviral regimen

In a study done in Kenya by Timothy K. Thomas and his colleague [16], women were recruited through the PMTCT program in the antenatal clinics of the New Nyanza Provincial General Hospital and the Kisumu District Hospital. Pregnant women were invited to enroll if they were HIV positive and if, after receiving risk-benefit counseling on infant feeding options, they indicated intent to breastfeed.
HIV-infected pregnant women took zidovudine, lamivudine, and either nevirapine (NVP) or nelfinavir from 34–36 weeks gestation to 6 months postpartum. Infants received single-dose nevirapine at birth. Women were advised to breastfeed exclusively and wean rapidly just before 6 months. Using a Kaplan-Meier method, HIV-transmission was estimated and death rates from delivery to 24 months determined. HIV-transmission rates were compared among subgroups defined by maternal risk factors, including baseline CD4 cell count and viral load.

Among 487 live-born, singleton, or first-born infants, cumulative HIV-transmission rates at birth, 6 weeks, and 6, 12, and 24 months were 2.5%, 4.2%, 5.0%, 5.7%, and 7.0%, respectively. The 24-month HIV-transmission rates stratified by baseline maternal CD4 cell count <500 and

≥500 cells/mm^3 were 8.4% (95% confidence interval [CI] 5.8%–12.0%) and 4.1% (1.8%–8.8%), respectively ($p = 0.06$); the corresponding rates stratified by baseline maternal viral load <10,000 and ≥10,000 copies/ml were 3.0% (1.1%–7.8%) and 8.7% (6.1%–12.3%), respectively ($p = 0.01$). None of the 12 maternal and 51 infant deaths (including two second-born infants) were attributed to antiretrovirals. The cumulative HIV-transmission or death rate at 24 months was 15.7% (95% CI 12.7%–19.4%).

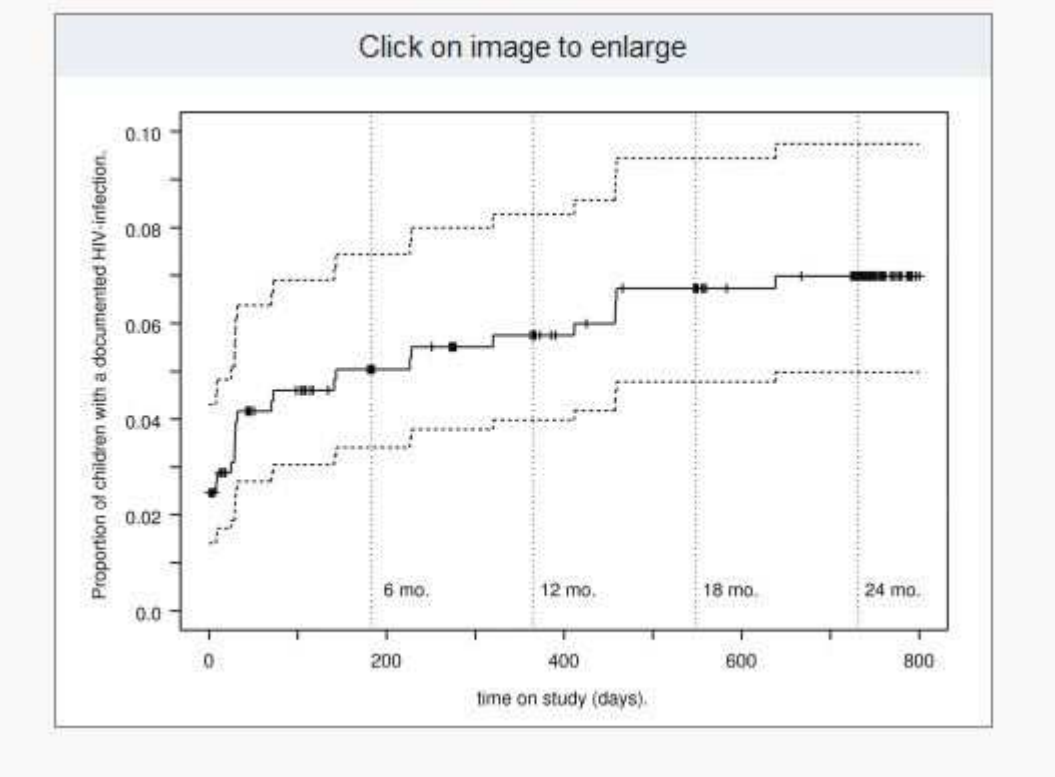
TABLE 2

Kaplan-Meier estimates of rates of HIV transmission and infant death.

	HIV Transmission ($n = 487$)			Infant Death ($n = 491$)			Combined Outcome ($n = 491$)		
Age	Events	Rate	95% CI	Events	Rate	95% CI	Events	Rate	95% CI
7 d	12	2.5	(1.4–4.3)	7	1.4	(0.7–3.0)	19	3.9	(2.5–6.0)
14 d	14	2.9	(1.7–4.8)	9	1.8	(1.0–3.5)	23	4.7	(3.1–7.0)
30 d	19	3.9	(2.5–6.1)	9	1.8	(1.0–3.5)	28	5.7	(4.0–8.2)
42 d	20	4.2	(2.7–6.4)	11	2.3	(1.3–4.0)	31	6.4	(4.5–8.9)
2 m	20	4.2	(2.7–6.4)	11	2.3	(1.3–4.0)	31	6.4	(4.5–8.9)
3 m	22	4.6	(3.0–6.9)	12	2.5	(1.4–4.3)	34	7.0	(5.0–9.6)
4 m	22	4.6	(3.0–6.9)	14	2.9	(1.7–4.8)	36	7.4	(5.4–10.1)
6 m	24	5.0	(3.4–7.4)	18	3.7	(2.4–5.9)	41	8.5	(6.3–11.4)
9 m	26	5.5	(3.8–8.0)	35	7.4	(5.4–10.1)	58	12.2	(9.6–15.5)
12 m	27	5.7	(4.0–8.3)	42	8.9	(6.7–11.9)	64	13.5	(10.7–16.9)
18 m	31	6.7	(4.8–9.4)	47	10.0	(7.6–13.1)	72	15.3	(12.3–18.9)
24 m	32	7.0	(5.0–9.7)	49	10.4	(8.0–13.6)	74	15.7	(12.7–19.4)

Source: PLoS Med. 2011 March; 8(3): e1001015.

FIGURE 1



Kaplan-Meier estimates of HIV-transmission rates.
Kaplan-Meier estimates of HIV-transmission rates among live-born singletons and first-born infants of mothers who received triple-ARV prophylaxis between 34 weeks gestation and 6 months postpartum with 95% CIs.

6.3 Acceptability of PMTCT Programmes and cultural challenges to male involvement

A study conducted by Sia E Msuya and her colleagues in 2007-2008 in rural and urban areas of Moshi in the Kilimanjaro region of Tanzania [15] showed that routine testing for HIV of women at the antenatal clinic was highly acceptable and appreciated by men, while other programme components, notably partner testing, condom use and the infant feeding recommendations, were met with continued resistance. Very few men joined their wives for testing and thus missed out on PMTCT counseling. The main barriers reported were that women did not have the authority to request their husbands to test for HIV and that the arena for testing, the antenatal clinic, was defined as a typical female domain where men were out of place.

6.3.1 For the sake of the baby

The qualitative findings indicated that the majority of the mothers had discussed HIV testing with their partners before arriving at the antenatal clinic. Routine clinical activities, including HIV testing for pregnant women, appeared to be highly valued and accepted among the fathers. Fathers stated that it was important to follow advice provided at the antenatal clinic for the sake of the baby. Most of them expressed that it was unnecessary for their wives to ask for permission to be tested at the antenatal clinic as it was part of the routine antenatal care.

6.3.2 Women should not tell us men what to do

Almost all women (95.5%) were encouraged by the nurse counsellors to bring their partners to the antenatal clinic for testing [Table3]. However, according to the PMTCT antenatal clinic registers at four of the clinics, only 3% of the partners were tested in 2007. The nurse counsellors working at the recruitment clinics stated that very few partners attended the antenatal clinic and even fewer were tested for HIV.

TABLE 3

HIV testing and disclosure of mothers attending reproductive and child health clinics for childhood immunizatior

Practice	N	n (%)
Mother offered HIV test	426	416 (97.7)
Asked partner for permission to test	416[a]	327 (78.6)
Partner agreed for her to test	327[b]	327 (100.0)
Mother tested	416[a]	416 (100.0)
Shared the test results with partner	416[a]	399 (95.9)
Counsellor suggested testing of partner	426	407 (95.5)
Partner as primary confidant	426	263 (61.7)

[a] 10 mothers were not offered a test

[b] 10 mothers were not offered a test and 89 mothers did not ask their partners for permission

Source: J Int AIDS Soc. 2011; 14: 21.

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6.3.3 The antenatal clinic as a female arena

Furthermore from this study, the organization of the PMTCT programme inhibited men from participating. Several fathers did not attend the antenatal clinic owing to fear of the reactions of other men and feeling uncomfortable about the idea of being the only man present. Furthermore, antenatal clinic activities were perceived by many fathers as outside their responsibility.

6.4 Strategic vision to promote PMTCT

Since 1998, the international community has recognized the magnitude of mother-to-child transmission of HIV and sought to reinforce countries' efforts to scale up PMTCT programmes. As one of the first clinical HIV interventions to be widely implemented in resource-constrained settings, PMTCT programmes helped to create the environment for the later roll-out of antiretroviral therapy and to galvanize political support for the broadening of the global response to the HIV epidemic [17].

The vision, goal, objectives and targets outlined in this strategic vision, as well as the strategic directions, elements and activities, will serve as a framework for WHO to support countries to focus on and prioritize the accelerated scale-up of effective and comprehensive PMTCT services, demonstrate the public health impact of PMTCT interventions, and integrate HIV and PMTCT with other key programmes.

DISCUSSION

This mixed-method study on partner involvement in the PMTCT programme carried out in the Kilimanjaro region of Tanzania revealed that women's participation in the programme was highly appreciated by their partners, but that men's involvement was very limited. This was not primarily related to lack of knowledge and interest on the part of men, but seemed to be connected rather to the local definition of gender roles and responsibilities. The major obstacle was the definition and organization of the programme as fundamentally female oriented.

In developed countries the use of Highly Active Anti-Retroviral Therapy (HAART) in pregnancy has reduced MTCT to less than 2 %. In a resource constrained setting WHO recommends HAART in pregnancy for women at highest risk of MTCT. These include women with WHO clinical category III and IV and/or CD4 count less than 200 cells/ mm^3. For those women who do not require HAART for their own health, different PMTCT regimens can be provided according to the national guidelines. Further areas of research include: the need to determine the effectiveness of HAART in pregnant and lactating women in Africa, measurement of antiretroviral drug levels in the breast milk of women on HAART, the impact of single dose NVP for PMTCT on future response to HAART regimens containing Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI's) and observing the impact of early cessation of breastfeeding and infant replacement feeding in resource limited settings.

PMTCT remains a critical area for scaling up in Africa, where despite multiple programmes; the number of HIV infected pregnant women who access them is less than 5%. There is still an urgent need to expand and scale up services in resource poor settings and prevent further infections in children. Efforts to increase the level of HIV testing in ANC, acceptance of PMTCT services, disclosure to partners and couple testing remain a priority. Increased community sensitization, counseling, treatment and support of women identified as HIV infected should improve acceptance of PMTCT services in Africa and subsequently reduce paediatric HIV.

CONCLUSION AND RECOMMENDATIONS

Interventions to prevent HIV MTCT are compelling on economic grounds in many resource-limited settings and should remain at the forefront of global HIV prevention efforts. Future cost-effectiveness analyses can help to ensure that PMTCT interventions for LMICs reach their full potential by focusing on unanswered questions in four areas: local assessment of rapidly evolving HIV MTCT options; strategies to improve coverage and reach underserved populations; evaluation of a more comprehensive set of MTCT approaches including primary HIV prevention and reproductive counselling; integration of HIV MTCT and other sexual and reproductive health services.

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