

New Data on the Prevention of Mother-to-Child Transmission of HIV and their Policy Implications



Technical Consultation
UNFPA/UNICEF/WHO/UNAIDS Inter-Agency Team
on Mother-to-Child Transmission of HIV
Geneva, 11-13 October 2000

Conclusions and Recommendations



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Abbreviations

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
HIV	Human Immunodeficiency Virus
MTCT	Mother-To-Child Transmission of HIV
PCR	Polymerase Chain Reaction
STI	Sexually Transmitted Infection
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
VCT	Voluntary Counselling and Testing (for HIV)
WHO	World Health Organization
ZDV	Zidovudine

Introduction

Mother-to-child transmission (MTCT) of HIV is the most significant source of HIV infection in children below the age of 10 years. The strategy recommended by the United Nations agencies to prevent mother-to-child transmission of HIV includes: (1) the primary prevention of HIV infection among parents to be, (2) the prevention of unwanted pregnancies in HIV-infected women, and (3) the prevention of HIV transmission from HIV-infected women to their infants. While the best ways to prevent HIV infection in infants remain primary prevention of HIV infection and reduction of unwanted pregnancies among women who are infected with HIV, many HIV-infected women become pregnant. In 1994, a long and complex regimen of the antiretroviral drug zidovudine (ZDV) taken 5 times daily from the 14th week of pregnancy and intravenously during labour was shown to reduce the risk of transmission from mother to child by two-thirds, from 26% to 8%. This regimen had little practical value in developing countries and more appropriate short course ZDV regimens starting later in pregnancy were evaluated and also shown to be effective. Other interventions shown to prevent transmission of HIV include elective caesarean section and the avoidance of breastfeeding. While these interventions have become standard practice in developed countries, they are not always practical or safe in resource-limited settings.

Following release of results in 1998 that a short course ZDV regimen starting from 36 weeks of pregnancy reduced the rate of transmission of HIV by 50%, a comprehensive strategy for MTCT-prevention was developed.^a

^a WHO *Weekly Epidemiological Record* 1998: 73: 313-320

Considerable experience has been obtained with pilot intervention projects, many initiated by UNICEF under the umbrella of the UN Inter-Agency Task Team (IATT) on Mother-to-Child Transmission (MTCT). The entry point to the interventions is voluntary counselling and testing (VCT) for HIV, followed by ZDV from 36 weeks and during labour to mothers who are HIV-infected, and counselling on infant feeding options. More recent clinical trials have shown that other short-course ARV regimens using ZDV, the combination ZDV + lamivudine (3TC), and nevirapine are also effective in reducing the risk of transmission.

MTCT-prevention interventions should not stand in isolation, but be integrated where possible into existing health care infrastructures and reproductive health services.

Moreover, the interventions should be seen as part of a wider response to HIV/AIDS, which includes expanding access to care and support for HIV-infected mothers and their families, including treatment of opportunistic infections and accelerating access to HIV treatment.

While the efficacy of ARV regimens in reducing the risk of HIV transmission is important, other issues need to be considered about the use of ARVs in MTCT-prevention interventions:

Practicality and effectiveness

The selection process for enrolment and individual monitoring in clinical trials produce ideal conditions for women to access, and adhere to, the treatment under study. These ideal conditions are seldom achieved once the treatment is expanded to a wider population in implementation programmes and the actual reduction in the rate of mother-to-child transmission achieved (effectiveness) is likely to

be less than that observed in clinical trials (efficacy). The effectiveness of antiretroviral regimens that are more practical and simple to administer should be close to their efficacy observed from clinical trials, while the effectiveness of regimens complex and difficult to administer may be considerably less.

Safety

For women and infants who are offered antiretroviral prophylaxis, the risks of exposure to one or more drugs must be balanced by the benefit of preventing transmission of a fatal infection in the infant. In randomized controlled trials the incidence of adverse events can be compared between the treated and untreated groups, providing good comparative data on safety. However, observational studies and long-term monitoring of exposed mothers and infants are important additional sources of information that better reflect the actual conditions under which the ARV regimens are used.

Drug Resistance

Drug resistance has been reported in some women exposed to short course antiretroviral regimens used for MTCT-prevention. The implications of such resistance are uncertain and need to be considered in the context of increasing access to ARV treatment for patients in developing countries.

There is continued concern that up to 20% of infants born to HIV-infected mothers may acquire HIV through breastfeeding, depending on duration and other risk factors. Replacement feeding^b is the only way to completely

^b *Replacement Feeding* is defined as the process of feeding a child, who is not receiving any breast milk, with a diet that provides all the nutrients the child needs.

avoid post-natal HIV transmission; however, this may not be possible in many locations in the developing world. Despite the risk of HIV transmission, breastfeeding provides appropriate nutrition, passively conveys protection against some micro organisms including respiratory and gastrointestinal pathogens, and is more economical. Exclusive breastfeeding^c provides the infant's complete nutritional needs up to the age of four to six months, and delays the return of fertility playing an important role in birth spacing. To protect breastfeeding from commercial influences, the World Health Assembly adopted the International Code of Marketing of Breast-milk Substitutes, now implemented world-wide. UNICEF and WHO launched the Baby-friendly Hospital Initiative to improve maternity services so that they protect, promote, and support breastfeeding.

Breastfeeding remains the best source of nutrition for the great majority of infants and should continue to be promoted and supported among mothers who are not known to be HIV-infected. Implementation of the Code of Marketing in national legislation and regulations provides protection to

all women and their infants, whether or not they are breastfed.

New information on MTCT-prevention has emerged since WHO issued guidance on the choices of ARV regimens^d and the risks of HIV transmission through breast-milk.^e Important new research data related to the long-term efficacy and safety of different ARV regimens, to the dynamics and clinical implications of viral resistance, and to the role of infant feeding practices were published or presented at the 13th International AIDS Conference in Durban, South Africa in July 2000. In addition, considerable experience has accumulated over the past two years from pilot implementation of MTCT-prevention programmes in resource-limited settings. In particular, programme managers have identified problems implementing current recommendations on HIV and infant feeding and have asked for clarification.

On behalf of the Inter-Agency Task Team on MTCT, WHO's Department of Reproductive Health and Research, in collaboration with the HIV/STI Initiative, and the Department of Child and Adolescent Health, convened a

^c *Exclusive Breastfeeding* is defined as giving an infant no other food or drink, not even water, apart from breast milk (including expressed breast milk), with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines.

^d Available on UNAIDS web site <http://www.unaids.org/publications/documents/mtct>

- WHO/UNAIDS recommendations on the safe and effective use of short-course ZDV for prevention of mother-to-child transmission of HIV (WHO *Weekly Epidemiological Record*, 1998, 73: 313-320).
- *Technical Working Group Meeting to Review New Research Findings for the Prevention of Mother-to-Child Transmission of HIV*. Geneva, 10-11 August 1999.
- *Use of Nevirapine to Reduce Mother-to-Child Transmission of HIV (MTCT)*. WHO Review of Reported Drug Resistance. Geneva 24 March 2000.

^e Available on UNAIDS web site <http://www.unaids.org/publications/documents/mtct>

- *HIV and Infant Feeding: A Policy Statement Developed Collaboratively by UNAIDS, UNICEF and WHO*. May 1997.
- *HIV and Infant Feeding: a Guide for Health-Care Managers and Supervisors, Guidelines for Decision-Makers and Review of HIV Transmission through Breastfeeding*. Jointly issued by UNICEF, UNAIDS and WHO. June 1998.
- *HIV and Infant Feeding: WHO, UNICEF, UNAIDS Statement on Current Status of WHO/UNAIDS/UNICEF Policy Guidelines*. 4 September 1999.

Technical Consultation on new data on the prevention of MTCT and their policy implications. The objective was to review recent scientific data and update current recommendations on the provision of ARVs and infant feeding counselling. The Technical Consultation focused on these two components, although it was recognized that many other components are important for a comprehensive package for MTCT-prevention.

Objectives

The specific objectives of the meeting were:

1. to review the most recent scientific data on the use of ARV regimens to prevent MTCT, including issues of efficacy, safety, drug resistance and factors affecting optimal choices of ARV regimens in different settings;
2. to consider developments and likely time frame for access to and use of antiretroviral drugs for the treatment of HIV infection in resource-limited settings and the likely impact that MTCT-prevention programmes may have on the effectiveness of such treatments;
3. to review evidence on risks and benefits for mother and infant of breastfeeding, including exclusive breastfeeding, and of replacement feeding, and consider issues in conveying

complex information on risks and benefits of different feeding options to mothers and enabling informed choice;

4. to review, and revise if necessary, existing UN agency policies on choices of ARV regimens and infant feeding guidelines and counselling in MTCT-prevention programmes in resource-limited settings;
5. list outstanding research questions on the prevention of MTCT using ARV regimens or through infant feeding.

Participants

Participants included expert scientists and programme managers from the African region (11), Asia (2), Latin America (1), The Caribbean (1), Europe (4) and the USA (2), HIV-infected mothers (2), collaborating agency scientists (6), representatives from nongovernmental organizations implementing MTCT-prevention programmes (6) and UN agencies (UNAIDS, UNFPA, UNICEF, WHO). The full list of participants is given at the end of the report.

Background information

Background papers that were prepared for the consultation, presented in plenary sessions and discussed in the sub-groups, included:

- Munjanja S. *Antiretroviral regimens for the prevention of MTCT: the programmatic implications.*

- Farley TMM, Buyse D, Gaillard P, Perriens J. *Efficacy of antiretroviral regimens for prevention of MTCT and some programatic issues.*
- Mofenson L, Munderi P. *Safety of antiretroviral prophylaxis of perinatal transmission on HIV-infected pregnant women and their infants.*
- Nájera R. *MTCT and antiretroviral drug resistance.*
- Fowler MG, Newell ML. *Breastfeeding, HIV transmission and options in resource poor settings.*

These papers are available on the WHO and UNAIDS web sites^f together with a summary of information presented during the discussion.

The conclusions and recommendations from this meeting are given in the following section. They will be reconsidered as new information becomes available.

^f Available on WHO Department of Reproductive Health and Research web site: <http://www.who.int/reproductive-health> and on UNAIDS web site: <http://www.unaids.org/publications/documents/mtct>

Conclusions and recommendations on the use of antiretrovirals

Short-term efficacy of ARV prophylactic regimens

Several antiretroviral regimens evaluated in randomized controlled clinical trials showed short-term efficacy, as determined by infant infection status at 6-8 weeks.¹⁻⁸ This reflects the reduction of in utero, intrapartum and early postpartum transmission.

The drugs used in the effective antiretroviral prophylaxis regimens evaluated included zidovudine (ZDV) alone, ZDV + lamivudine (3TC), and nevirapine.

All regimens include an intrapartum component, with varying durations of antepartum and/or postpartum treatment (see table p.15).

The most complex effective regimen includes antepartum/intrapartum/postpartum ZDV, while the simplest effective regimen includes single dose intrapartum/postpartum nevirapine.

The mechanisms by which these regimens provide protection against mother-to-child HIV transmission include decrease of viral replication in the mother and/or prophylaxis of the infant during and after exposure to virus.

Long-term efficacy of ARV prophylactic regimens

Short-course ZDV, ZDV + 3TC, and nevirapine have been evaluated in breastfeeding populations. Long-term efficacy as measured by infant infection status through 24 months for the short-course ZDV regimen⁹ and 12 months for nevirapine regimen,¹⁰ showing that the early reduction in HIV transmission persists despite continued exposure to HIV during breastfeeding. Analysis of

long-term efficacy of the ZDV + 3TC regimens is in progress.⁵

Safety of ARV prophylactic regimens

Short-term safety and tolerance of the effective antiretroviral prophylactic regimens has been demonstrated in all the controlled clinical trials,^{1-4,6-8,10-12} while collection of long-term safety data is ongoing.

In the controlled clinical trials, the effective antiretroviral prophylaxis regimens have not been associated with an excess of severe adverse events (including mortality) compared with the control arms in HIV-infected women or their children.^{1-4,10,13,14}

Normal growth, neurologic development, and immunologic parameters have been demonstrated in industrialized countries in uninfected children with in utero/neonatal exposure to ZDV compared to those without such exposure.¹⁵

HIV-related disease progression in mothers does not appear to be altered by receipt of prophylactic antiretroviral regimens.¹⁶

There have not been significant differences in HIV disease progression or mortality in children who became infected despite receipt of prophylaxis compared with infants who became infected in the control arms in the clinical trials.^{17,18}

In the randomized, controlled clinical trials the only adverse effect attributable to drug exposure was mild transient anaemia in infants receiving ZDV-containing regimens.^{1-4,7,11,13,17}

Mitochondrial dysfunction has been reported to occur in a small number of infants in France exposed in utero or neonatally to nucleoside reverse transcriptase inhibitor (ZDV or ZDV/3TC),¹⁹ but no similar findings were reported following an extensive review of deaths in a cohort of 16000 infants in the USA,²⁰ nor in the PETRA study.²¹ However, neither of these studies did specific laboratory assessment for mitochondrial dysfunction. Non-nucleoside reverse transcriptase inhibitor drugs, like nevirapine, do not inhibit mitochondrial DNA polymerase and therefore should not be associated with such toxicity.²²

Conclusion: The WHO Technical Consultation concluded that benefit of these drugs in reducing mother-to-child HIV transmission greatly outweighs any potential adverse effects of drug exposure.

Selection of resistant viral populations

Selection for pre-existing resistant viral populations or development of new mutations may occur with all antiretroviral drugs or drug regimens that do not fully suppress viral replication. However, this is more likely to occur rapidly with drugs in which a single mutation is associated with development of drug resistance; such drugs include 3TC (with and without concomitant ZDV treatment) and nevirapine.²²⁻²⁴ Virus containing drug resistant mutations decreases in amount once antiretroviral drug prophylaxis is discontinued, and wild type virus dominates.²⁵ However, the mutant virus may remain present in an individual at very low levels.

This could decrease effectiveness of future treatment with antiretroviral regimens that contain the same drug, or drugs within the same class, as that used for prophylaxis.

It is unknown if such low-level drug resistance would affect the efficacy of the antiretroviral prophylaxis regimen if used in a subsequent pregnancy.

There is currently no evidence that drug-resistant viruses are more transmissible than non-resistant viruses.

There are currently no data to indicate that drug-resistant viruses are more virulent than non-resistant viruses.

Conclusion: The WHO Technical Consultation concluded that the benefit of decreasing mother-to-child HIV transmission with these antiretroviral drug prophylaxis regimens greatly outweighs concerns related to development of drug resistance.

Women who receive a sub-optimal antepartum regimen

For antiretroviral prophylaxis regimens that include an antepartum component, the minimum duration of antepartum treatment necessary for protection is not defined. However, it is likely that a major mechanism for effective antepartum prophylaxis is reduction in maternal viral load, which is likely to require at least one to two weeks of treatment.^{4,6}

Recommendation: For women receiving prophylactic regimens that include an antepartum component and who have received less than two weeks of ZDV antepartum treatment, prophylaxis with six weeks ZDV to the infant, intrapartum/postpartum ZDV +

3TC, or the two-dose nevirapine regimen may be considered.⁵⁻⁸

Scaling-up MTCT-prevention programmes and choice of ARV regimen

Since the last WHO Technical Consultations on prevention of mother-to-child HIV transmission with antiretroviral prophylaxis, important new data have become available related to the long-term efficacy and safety of these regimens. Additionally, longitudinal assessment has demonstrated that antiretroviral resistant virus detected at 6 weeks postpartum was no longer detectable when reassessed at 12 months postpartum. Furthermore, the presence of detectable resistant virus was not associated with either increased mother-to-child HIV transmission or increased mortality in infants who became infected despite prophylaxis.²⁵

Conclusion: Implementation of any of the antiretroviral prophylaxis regimens shown to be effective in randomized clinical trials (ZDV, ZDV + 3TC, or nevirapine regimens) can be recommended for general implementation. There is currently no justification to restrict use of any of these regimens to pilot project or research settings.

Recommendation: The local choice for the antiretroviral prophylactic regimen to include in the standard package of care should be determined by issues of feasibility, efficacy and cost. Considerations that contribute to decisions regarding the composition of the standard prophylactic package include: proportion of women attending antenatal care; time of initiation of antenatal care; frequency

of antenatal visits; type of HIV voluntary counselling and testing available; logistics and acceptability of antiretroviral prophylaxis administration; and cost of drugs.

Recommendation: The prevention of mother-to-child HIV transmission should be part of the minimum standard package of care for women who are known to be HIV infected and their infants.

Conclusions and recommendations regarding infant feeding

Risks of breastfeeding and replacement feeding

The benefits of breastfeeding are greatest in the first six months of life (optimal nutrition, reduced morbidity and mortality due to infections other than HIV, and delayed return of fertility).²⁶⁻³⁴

Exclusive breastfeeding during the first 4–6 months of life carries greater benefits than mixed feeding with respect to morbidity and mortality from infectious diseases other than HIV.^{27,29,35,36}

Although breastfeeding no longer provides all nutritional requirements after six months, breastfeeding continues to offer protection against serious infections and to provide significant nutrition to the infant (half or more of nutritional requirements in the second six months of life, and up to one-third in the second year).³⁷

Replacement feeding carries an increased risk of morbidity and mortality associated with malnutrition and associated with infectious disease other than HIV. This is especially high in the first six months of life and decreases thereafter. The risk and feasibility of replacement feeding are affected by the local environment and the individual woman's situation.³⁸⁻⁴¹

Breastfeeding is associated with a significant additional risk of HIV transmission from mother to child as compared to non-breastfeeding. This risk depends on clinical factors and may vary according to pattern and duration of breastfeeding. In untreated women who continue breastfeeding after the first year, the absolute risk of transmission through breastfeeding is 10-20%.⁴²⁻⁴⁵

The risk of MTCT of HIV through breastfeeding appears to be greatest

during the first months of infant life but persists as long as breastfeeding continues. Half of the breastfeeding-related infections may occur after six months with continued breastfeeding into the second year of life.^{9,44,45}

There is evidence from one study that exclusive breastfeeding in the first three months of life may carry a lower risk of HIV transmission than mixed feeding.⁴⁶

Recommendations: When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended.

Otherwise, exclusive breastfeeding is recommended during the first months of life.

To minimize HIV transmission risk, breastfeeding should be discontinued as soon as feasible, taking into account local circumstances, the individual woman's situation and the risks of replacement feeding (including infections other than HIV and malnutrition).

When HIV-infected mothers choose not to breastfeed from birth or stop breastfeeding later, they should be provided with specific guidance and support for at least the first 2 years of the child's life to ensure adequate replacement feeding. Programmes should strive to improve conditions that will make replacement feeding safer for HIV-infected mothers and families.

Cessation of breastfeeding

There are concerns about the possible increased risk of HIV transmission with mixed feeding during the transition

period between exclusive breastfeeding and complete cessation of breastfeeding. Indirect evidence on the risk of HIV transmission through mixed feeding, suggests that keeping the period of transition as short as possible may reduce the risk.

Shortening this transition period however may have negative nutritional consequences for the infant, psychological consequences for the infant and the mother, and expose the mother to the risk of breast pathology which may increase the risk of HIV transmission if cessation of breastfeeding is not abrupt.

The best duration for this transition is not known and may vary according to the age of the infant and/or the environment.

Recommendation: HIV-infected mothers who breastfeed should be provided with specific guidance and support when they cease breastfeeding to avoid harmful nutritional and psychological consequences and to maintain breast health.

Infant feeding counselling

Infant feeding counselling has been shown to be more effective than simple advice for promoting exclusive breastfeeding in a general setting.⁴⁷⁻⁵⁰ Good counselling may also assist HIV-infected women to select and adhere to safer infant feeding options, such as exclusive breastfeeding or complete avoidance of breastfeeding, which may be uncommon in their environment. Effective counselling may reduce some of the breast health problems which may increase the risk of transmission.

Many women find that receiving

information on a range of infant feeding options is not sufficient to enable them to choose and they seek specific guidance. Skilled counselling can provide this guidance to help HIV-infected women make a choice that is appropriate for their situation to which they are more likely to adhere. The options discussed during counselling need to be selected according to local feasibility and acceptability.

The level of understanding of infant feeding in the context of MTCT in the general population is very limited, thus complicating efforts to counsel women effectively.

The number of people trained in infant feeding counselling is few relative to the need and expected demand for this information and support.

Recommendations: All HIV-infected mothers should receive counselling, which includes provision of general information about the risks and benefits of various infant feeding options, and specific guidance in selecting the option most likely to be suitable for their situation. Whatever a mother decides, she should be supported in her choice.

Assessments should be conducted locally to identify the range of feeding options that are acceptable, feasible, affordable, sustainable and safe in a particular context.

Information and education on mother-to-child transmission of HIV should be urgently directed to the general public, affected communities and families.

Adequate numbers of people who can counsel HIV-infected women on infant

feeding should be trained, deployed, supervised, and supported. Such support should include updated training as new information and recommendations emerge.

Breast health

There is some evidence that breast conditions including mastitis, breast abscess, and nipple fissure may increase the risk of HIV transmission through breastfeeding, but the extent of this association is not well quantified.⁵¹⁻⁵³

Recommendation: HIV-infected women who breastfeed should be assisted to ensure that they use a good breastfeeding technique to prevent these conditions, which should be treated promptly if they occur.

Maternal health

In one trial, the risk of dying in the first 2 years after delivery was greater among HIV-infected women who were randomized to breastfeeding than among those who were randomized to formula feeding.⁵⁴ This result has yet to be confirmed by other research.

Women who do not breastfeed or stop breastfeeding early are at greater risk of becoming pregnant.

Recommendation: HIV-infected women should have access to information, follow-up clinical care and support, including family planning services and nutritional support. Family planning services are particularly important for HIV-infected women who are not breastfeeding.

Regimens of proven efficacy (randomized controlled clinical trials)

Study	Drug	Antepartum			Intrapartum	Postpartum/postnatal	
		14-27 wks	28-36 wks	>36 wks	Labour	1 wk PP	1-6 wks PP
ACTG 076	ZDV	[Bar]			[Bar]	[Bar: Infant]	
Harvard Thai	ZDV		[Bar]		[Bar]	[Bar: Infant]	
Harvard Thai	ZDV		[Bar]		[Bar]	[Bar: Infant]	
Harvard Thai	ZDV			[Bar]	[Bar]	[Bar: Infant]	
Harvard Thai	ZDV			[Bar]	[Bar]	[Bar: Infant]	
DITRAME	ZDV			[Bar]	[Bar]	[Bar: Mother]	
CDC	ZDV			[Bar]	[Bar]		
PETRA Arm A	ZDV + 3TC			[Bar]	[Bar]	[Bar: Mother and Infant]	
PETRA Arm B	ZDV + 3TC				[Bar]	[Bar: Mother and Infant]	
HIVNET/SAINT	NVP				[Bar]	[Bar: Infant]	

Identified needs for research

Highest priority issues are marked with an asterisk (*)

Type, duration and efficacy of antiretroviral prophylactic regimens	
	Continue evaluation of long-term efficacy and safety of antiretroviral regimens.
	Evaluate the short term and long term efficacy and safety of combination antiretrovirals during the peripartum period (e.g. ZDV + NVP).
	Evaluate the efficacy and safety of antiretroviral drugs not yet assessed for prevention of the MTCT, e.g. non-nucleoside reverse transcriptase inhibitors such as Efavirenz, and nucleoside reverse transcriptase inhibitors such as Stavudine (d4T), Didanosine (ddl).

Resistance to antiretroviral prophylactic regimens ^g	
*	Evaluate the development, timing, and evolution of genotypic and phenotypic drug resistance induced by antiretroviral prophylaxis regimens, including the relationship of resistance to viral subtype/subtype recombinants, and specific drugs and drug classes.
*	Assess the clinical significance of the occurrence of viral mutations in relationship to: <ul style="list-style-type: none"> ◆ The course of HIV disease in mothers and infants exposed to peripartum antiretroviral MTCT-prevention interventions; ◆ The treatment of HIV disease in mothers and infants exposed to peripartum antiretroviral MTCT-prevention interventions; ◆ Risk of transmission in current and subsequent pregnancies; ◆ Risk of sexual transmission following use of antiretrovirals for MTCT-prevention.
*	Encourage surveillance for emergence of viral resistance in populations where antiretrovirals have been introduced for prevention of the MTCT and/or treatment. This should be undertaken as part of an overall strategy for resistance surveillance, based for example, on the WHO global strategy for antimicrobial resistance containment.

^g Resistance should be evaluated in the context of clinical trials or sub-studies within implementation projects.

Risks and benefits of different patterns of infant feeding

*	Evaluate further the influence of infant feeding patterns (exclusive breastfeeding, exclusive formula feeding, mixed feeding and duration/timing of breastfeeding cessation) on MTCT, overall infant morbidity and mortality, and birth spacing.
	Evaluate the influence of breastfeeding on nutritional status, disease progression and mortality of HIV-infected women. Identify an appropriate package of nutritional support and care for HIV-infected women.
	Better quantify the rate of MTCT through breastfeeding among mothers who become infected with HIV after delivery.
	Conduct research on HIV in breastmilk to better understand the relationship between postnatal HIV transmission and HIV viral load, the presence of resistant virus in breastmilk, and other breastmilk components that influence transmission risk.
	Study the feasibility and practicality of improving the quality and safety of replacement feeding in different settings.

Reduction of MTCT during breastfeeding

*	Evaluate the efficacy of infant and/or mother ARV treatment (including full combination therapy for treatment of the mother) and immune-based interventions (i.e. infant HIV vaccines and passive immune therapy) on the prevention of MTCT through breastfeeding.
*	Evaluate how best to ensure that the transition period between exclusive breastfeeding and no breastfeeding carries a minimum HIV, nutritional and psychological risk for the infant and mother.
	Assess the feasibility and safety of heat treating expressed breastmilk in the home to inactivate the virus.
	Evaluate further the role of mastitis and other breast pathology in HIV transmission through breastmilk and develop strategies to minimize such problems.

Standardization of the methodology for HIV and infant feeding research

*	<p>Ensure the comparability between studies on MTCT in populations where breastfeeding occurs through:</p> <ul style="list-style-type: none"> ◆ Use of existing definition of breastfeeding patterns and when necessary, development of new definitions; ◆ Developing guidance on how to collect, analyse and interpret disaggregated data on infant feeding and timing of postnatal infection in a standardized way.
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Research Linked to Implementation, Monitoring and Evaluation	
	Study approaches to enhancing community preparedness and communication strategies.
*	Study barriers to different steps of VCT in pregnant women in different settings.
	Study barrier to antiretroviral adherence for MTCT prophylaxis.
	Study the acceptability and performance of rapid same day antenatal VCT.
	Study the acceptability and effectiveness of VCT and ARV prophylaxis starting in labour or soon after delivery in mothers who have not benefited from antenatal testing.
	Develop alternative methods to PCR (polymerase chain reaction) for early diagnosis of HIV infection in infants suitable for use in developing countries.
*	Study the effects of infant feeding recommendations for HIV-infected mothers on general population behaviours related to breastfeeding.
*	Determine ways to promote partner, family and community involvement to increase acceptance and support for infant feeding options and choices.
	Evaluate existing and develop improved techniques for infant feeding counselling.

Identified needs for research

Highest priority issues are marked with an asterisk (*)

Type, duration and efficacy of antiretroviral prophylactic regimens	
	Continue evaluation of long-term efficacy and safety of antiretroviral regimens.
	Evaluate the short term and long term efficacy and safety of combination antiretrovirals during the peripartum period (e.g. ZDV + NVP).
	Evaluate the efficacy and safety of antiretroviral drugs not yet assessed for prevention of the MTCT, e.g. non-nucleoside reverse transcriptase inhibitors such as Efavirenz, and nucleoside reverse transcriptase inhibitors such as Stavudine (d4T), Didanosine (ddl).

Resistance to antiretroviral prophylactic regimens ^g	
*	Evaluate the development, timing, and evolution of genotypic and phenotypic drug resistance induced by antiretroviral prophylaxis regimens, including the relationship of resistance to viral subtype/subtype recombinants, and specific drugs and drug classes.
*	Assess the clinical significance of the occurrence of viral mutations in relationship to: <ul style="list-style-type: none"> ◆ The course of HIV disease in mothers and infants exposed to peripartum antiretroviral MTCT-prevention interventions; ◆ The treatment of HIV disease in mothers and infants exposed to peripartum antiretroviral MTCT-prevention interventions; ◆ Risk of transmission in current and subsequent pregnancies; ◆ Risk of sexual transmission following use of antiretrovirals for MTCT-prevention.
*	Encourage surveillance for emergence of viral resistance in populations where antiretrovirals have been introduced for prevention of the MTCT and/or treatment. This should be undertaken as part of an overall strategy for resistance surveillance, based for example, on the WHO global strategy for antimicrobial resistance containment.

^g Resistance should be evaluated in the context of clinical trials or sub-studies within implementation projects.

Risks and benefits of different patterns of infant feeding

*	Evaluate further the influence of infant feeding patterns (exclusive breastfeeding, exclusive formula feeding, mixed feeding and duration/timing of breastfeeding cessation) on MTCT, overall infant morbidity and mortality, and birth spacing.
	Evaluate the influence of breastfeeding on nutritional status, disease progression and mortality of HIV-infected women. Identify an appropriate package of nutritional support and care for HIV-infected women.
	Better quantify the rate of MTCT through breastfeeding among mothers who become infected with HIV after delivery.
	Conduct research on HIV in breastmilk to better understand the relationship between postnatal HIV transmission and HIV viral load, the presence of resistant virus in breastmilk, and other breastmilk components that influence transmission risk.
	Study the feasibility and practicality of improving the quality and safety of replacement feeding in different settings.

Reduction of MTCT during breastfeeding

*	Evaluate the efficacy of infant and/or mother ARV treatment (including full combination therapy for treatment of the mother) and immune-based interventions (i.e. infant HIV vaccines and passive immune therapy) on the prevention of MTCT through breastfeeding.
*	Evaluate how best to ensure that the transition period between exclusive breastfeeding and no breastfeeding carries a minimum HIV, nutritional and psychological risk for the infant and mother.
	Assess the feasibility and safety of heat treating expressed breastmilk in the home to inactivate the virus.
	Evaluate further the role of mastitis and other breast pathology in HIV transmission through breastmilk and develop strategies to minimize such problems.

Standardization of the methodology for HIV and infant feeding research

*	<p>Ensure the comparability between studies on MTCT in populations where breastfeeding occurs through:</p> <ul style="list-style-type: none"> ◆ Use of existing definition of breastfeeding patterns and when necessary, development of new definitions; ◆ Developing guidance on how to collect, analyse and interpret disaggregated data on infant feeding and timing of postnatal infection in a standardized way.
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Research Linked to Implementation, Monitoring and Evaluation	
	Study approaches to enhancing community preparedness and communication strategies.
*	Study barriers to different steps of VCT in pregnant women in different settings.
	Study barrier to antiretroviral adherence for MTCT prophylaxis.
	Study the acceptability and performance of rapid same day antenatal VCT.
	Study the acceptability and effectiveness of VCT and ARV prophylaxis starting in labour or soon after delivery in mothers who have not benefited from antenatal testing.
	Develop alternative methods to PCR (polymerase chain reaction) for early diagnosis of HIV infection in infants suitable for use in developing countries.
*	Study the effects of infant feeding recommendations for HIV-infected mothers on general population behaviours related to breastfeeding.
*	Determine ways to promote partner, family and community involvement to increase acceptance and support for infant feeding options and choices.
	Evaluate existing and develop improved techniques for infant feeding counselling.

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