

HIV AND INFANT FEEDING DATA ANALYSIS

Geneva, 12-14 November 2003

WORKSHOP REPORT

For further information please contact:

**Department of Child and Adolescent Health and Development (CAH)
World Health Organization**

20 Avenue Appia
1211 Geneva 27
Switzerland

tel ☐ ☐ + 41 22 791 32 81
fax ☐ ☐ + 41 22 791 48 53
website☐ <http://www.who.int/child-adolescent-health>



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Acronyms

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
CTL	Cytotoxic T-Lymphocytes
DNA	Deoxyribonucleic acid
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
MTCT	Mother-To-Child Transmission of HIV
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
UNICEF	United Nations Children's Fund
RNA	Ribonucleic acid
UN	United Nations
WHO	World Health Organization



Introduction

Mother-to-child transmission (MTCT) of HIV is the most significant source of HIV infection in young children. The virus may be transmitted during pregnancy, labour or delivery, or through breastfeeding. About two thirds of infants born to HIV-infected mothers will not be infected, even in the absence of interventions. About 15-25% of infants of HIV-infected women will be infected during pregnancy or delivery, and an additional 5-20% may become infected during breastfeeding (1, 2). While breastfeeding carries the risk of HIV-transmission, not breastfeeding carries other significant health risks to infants and young children, such as an increased risk of diarrhoea and pneumonia morbidity and mortality (3).

The mode of breastfeeding is one of many factors that may affect the risk of HIV transmission. There is some evidence that exclusive breastfeeding may be less likely to transmit HIV than mixed feeding. Several studies are currently underway or are planned in diverse settings to determine the association between infant feeding patterns and HIV-transmission and HIV-free survival.

A workshop was organized from 12-14 November 2003 in Geneva gathering investigators from six of these studies and other scientists involved in research in the area of HIV and infant feeding to discuss key issues related to collection and analysis of infant feeding data in the context of HIV transmission. The agenda of the workshop is shown in Annex 1; the list of studies represented at the meeting is shown in Annex 2.



Objectives

The workshop had the following specific objectives:

Primary

- To share the experience of analysing data on infant feeding and HIV transmission and HIV-free survival from groups that have already analysed data from their studies.
- To discuss analytical issues related to infant feeding patterns and HIV transmission and HIV-free survival.
- To come to an agreement on recommended approaches for analysis and presentation of data from studies on HIV and infant feeding.

Secondary

- To share tools/instruments used for data collection.
- To discuss experience with infant feeding data collection.

In order to achieve these objectives, an investigator from each participating study was asked to provide the following information.

- One page study summary including: study site, investigators, objectives, outcomes, design, tools used for infant feeding assessment, the current status of implementation, and any publications or reports.
- Brief description of the plan of analysis, and of issues and challenges faced in the analysis (or while developing the plan of analysis).
- A presentation including a brief description of the study design, measurement of infant feeding practices and outcomes, and issues in data analysis.

The information provided from each of these studies is summarised in Annex 3.

Issues in HIV and infant feeding studies, and recommendations arising

The studies discussed at the meeting were of three types:

- Cohort studies examining the association of infant feeding practices, chosen by the mother after counselling, with risk of HIV transmission and HIV-free survival;
- Randomized trials to compare the effect of exclusive breastfeeding on the risk of HIV transmission and HIV free survival with replacement feeding, with all participants receiving antiretroviral drugs for prevention of MTCT;
- Randomized trials to compare the effect of different antiretroviral drugs or regimens for prevention of MTCT, with mothers choosing one of the infant feeding options after counselling.

In light of the information given in the background and study-specific presentations, the group discussed issues relevant to current and future studies of this type, and made recommendations.

Measurement and classification of infant feeding practices

Feeding data to be collected

To a large extent, the specific feeding data that need to be collected depend on the objectives of the particular study and its context (e.g. programme-linked research or clinical trials). However, data that might be useful to collect in most HIV and infant feeding studies include:

- Breastfeeding initiation, current status and duration, reason for cessation.
- Consumption of non-milk liquids, non-human milks, solid foods, traditional and western medicines.
- Whenever a change in practice is reported during longitudinal follow up, the reason for the change in practice, and other measures for documenting possible reverse causality (i.e. morbidity in the period immediately prior to change of practice lead to the change in practice). The information that would be useful is clinical indicators in the period just before the change of feeding practice supplemented with reported information on reason for change of practice from mothers.
- Age at which certain liquids or foods were introduced in addition to breast milk (e.g. animal milk, solids).
- Process of breastfeeding cessation.
- Quality of diet beyond cessation of breastfeeding.

As research studies become more complex, with multiple postnatal interventions, data collection burdens will be high. The amount of data to collect and the degree of detail will continue to depend on the study objectives. For example, for examining whether exclusive breastfeeding is associated with a lower risk of HIV transmission than predominant or partial breastfeeding, detailed feeding data is needed. In studies comparing different antiretroviral drug regimens, where the objective may only be to generate adjusted transmission estimates that take into account breastfeeding patterns, less detailed feeding information using only general categories may be required. Intermediate amounts of detail in feeding information may be required to produce programme or policy recommendations.



Recommendation for research studies:

- Enough feeding information necessary to classify infants into exclusive, predominant and partial breastfeeding, or non-breastfeeding groups should be collected. These definitions are given below:
 - *Exclusive breastfeeding* means giving a child no other food or drink, including no water, in addition to breastfeeding with the exception of medicines, vitamin drops or syrups, and mineral supplements (4) ;
 - *Predominant breastfeeding* means breastfeeding a child but also giving small amounts of water or water-based drinks. Neither food-based fluid nor solid food are allowed under this definition (4) ;
 - *Partial breastfeeding* means breastfeeding while giving non-human milk such as infant formula or food-based fluid or solid food (4).

Mixed feeding means feeding both breast milk and other foods or liquids. This term has been widely used in the MTCT literature. An infant who is either *predominantly* or *partially* breastfed is considered to be receiving mixed feeding.

- In studies with prospective follow up, the reasons for change in feeding practice should be carefully documented to address the possibility of reverse causality.
- It is particularly important to collect detailed information on infant feeding, including the reasons for breastfeeding cessation, the completeness of cessation and the quality and quantity of diet, around the period of breastfeeding cessation.
- Further guidance to researchers on collection of infant feeding data based on analyses of existing data sets will be valuable.

Methods for measuring feeding practices - including tools to be used, frequency of visits and recall period

Many past studies on MTCT prevention did not focus on collection of detailed infant feeding data. Most of the current studies on HIV and infant feeding are collecting detailed and frequent information on infant feeding practices. The WHO tool for measuring feeding (5) has worked well in these settings. Studies in which antiretrovirals are a part of the MTCT prevention interventions will result in very low transmission rates, i.e. few events. In this context, frequent and detailed infant feeding data might be difficult to collect due to the large number of participants needed to demonstrate any effect of one factor on MTCT through breastfeeding.

The optimum frequency of visits to collect feeding information was discussed. It has been recently reported that a single recall at 6-9 months for ascertaining the duration of exclusive breastfeeding had reasonable sensitivity (79%) but poor specificity (40%) in identifying exclusive breastfeeding status as compared to weekly follow up data (6). However, it may not be feasible to collect feeding information every week in either clinical trials or programme settings. At the same time, a single 24 hour recall or recall duration greater than 2 weeks may not be adequate to accurately capture whether exclusive breastfeeding is being practised. The frequency of visits thus determines what it is worthwhile asking – if visits are infrequent, asking about the previous 7 days may not add more than valid information on the previous 24 hours. It is more important to ask about feeding in the period since the last visit, and about any changes in feeding practices that have been introduced. A question on foods given in the previous 24 hours allows a comparison with large-scale surveys carried out for other purposes.

There may be a need to collect more detailed information on feeding around and after the time of breastfeeding cessation. Detailed data on dietary intake may be available in sub-samples. The practices associated with the process of cessation and feeding during and immediately after this period should also be collected. In-depth qualitative work is needed to aid counsellors to help mothers during this time. Documentation of observations related to infant feeding during an interview with the mother and in the home setting may be useful to supplement information provided by the mothers. Methods such as serial prolactin levels and the ability to express breast milk

are under investigation but as yet no reliable method has been found for identifying whether complete cessation of breastfeeding has actually occurred.

Recommendations for research studies:

- The WHO tool for measuring infant feeding (5) should be adapted for use in the evaluation of programmes to prevent MTCT.
- Home or clinic visits to collect data on feeding practices should preferably not be more than 2 weeks apart.
- Self-reporting of breastfeeding cessation should be used until further information is available on newer indicators.

Quality of interaction between data collectors and mothers

The quality of interaction between data collectors and mothers may influence the quality and accuracy of reported data. Sequencing of counselling and data collection may also be important; it may be preferable to collect data before counselling if both are planned at the same visit. The quality of staff, training and supervision are as important as the data collection tool itself.

Recommendation for research studies:

- Wherever possible, counselling activities should be separated from data collection through using different staff or making the collection a separate interaction.

Defining and classifying feeding practices

Consistent definitions of feeding patterns should be used to ensure comparison of findings across studies. It is also desirable to specify allowable lapses and provide complete information about how feeding patterns are defined for analysis.

An important issue to consider is whether to use a single classification for an infant or to use time varying classifications for different periods. This choice would depend on the research question being addressed. In addressing the issue of HIV transmission through breastfeeding, it might be appropriate to use a hierarchical definition of feeding status with some allowable lapses. For example, an infant classified as partially breastfed at 6 weeks of age, who has been given formula on more than 3 occasions, would not be classified as predominantly breastfed at 10 weeks even if the mother stops giving formula.

Recommendation for research studies:

Existing WHO definitions of exclusive, predominant and or partial breastfeeding (4) given above should be used in HIV and infant feeding studies. Studies should clearly specify allowable lapses, if any.

The need for individual record meta-analyses

Meta-analyses of ongoing studies would be very useful to conclusively answer the question about whether the transition from exclusive to predominant or partial breastfeeding results in an increased risk of HIV transmission at different ages. This issue is particularly important as many studies are including perinatal interventions that would make events (i.e. HIV transmissions) rare. Further, it may be desirable to look at the effect of breastfeeding patterns on HIV transmission in subgroups of women with CD4 <200 or those with counts <350.

Recommendations for research studies:

- The possibility of conducting meta-analyses on the issue of HIV transmission during transition from exclusive breastfeeding to other modes of feeding should be considered in the future, when more data sets are available.
- These meta-analyses should be anticipated at the design stage itself so that there is consistency regarding questions and definitions in the various studies.

A meeting in Bordeaux in 2000 (8) recommended using Turnbull's extension of the Kaplan-Meier procedure for interval-censored data (10) in studies examining both short-term (usually at 6 weeks of age) and long-term (usually at 18-24 months of age) efficacy of perinatal interventions to prevent MTCT of HIV. A recently published re-analysis of data from four randomized clinical trials compared the results obtained using Kaplan-Meier procedure, Turnbull's method and its adaptation by Hughes and Richardson (12). This re-analysis found that the three statistical methods yielded similar estimates of short-term efficacy when tests were conducted at birth and 6 weeks of age but the assessment of long-term efficacy, which is of relevance here, was more difficult to standardize (9).

2. **Cessation of breastfeeding as a competing risk for HIV infection.** Because non-breastfed children are no longer at risk for HIV transmission through breastfeeding, cessation of breastfeeding is a competing risk for infection.

Hudgens et.al. adapted the Turnbull extension of the standard Kaplan-Meier analysis to include one or more competing risks (11). This takes into account the fact that infection risk ends after cessation of breastfeeding. This approach is suggested whenever HIV testing continues beyond the age when breastfeeding is stopped, which is relevant to studies assessing the long-term efficacy of interventions on HIV-infection.

3. **Death as informative censoring.** When HIV transmission is the outcome and a proportion of children die before assessment of their HIV status or had their last negative test several months prior to dying, death is a source of informative censoring because HIV infection increases the risk for early death.

Hughes and Richardson extended Turnbull's procedure to allow informative censoring (12). However, this approach does not account for competing risks. There are no methods yet available that account for both competing risks and informative censoring, and therefore one has to choose one of these based on study data.

For assessment of long-term efficacy in terms of HIV infection risk and HIV-free survival, the re-analysis found good agreement between the point estimates and confidence intervals from the competing risks and Hughes-Richardson analyses.

4. **Time dependent sensitivity of HIV tests.** The sensitivity of an HIV test (e.g. DNA PCR) is dependent on the time of testing after the infection occurs.

Balasubramanian and Lagakos (13) have developed a method to account for different test schedules, time dependent sensitivity of DNA PCR, and differing exposure (breastfeeding) among infants.

Confounding and effect modification. When HIV transmission is the outcome, confounding will not be a problem if breast milk is the only exposure route for postnatal transmission. Risk modification will be of interest (see below). However, the choice to breastfeed may still be influenced by the stage of maternal illness (e.g. the sickest mothers may choose not to breastfeed).

There will be potential for confounding when the outcome is HIV-free survival. Potential confounders include risk factors for deaths not related to HIV that may also be associated with infant feeding practices, e.g. maternal education, socio-economic status, birth weight, etc.

Consideration of possible modification of the relationship between infant feeding pattern and both HIV transmission and HIV-free survival by factors such as maternal CD4 counts, breast health and antiretroviral treatment is very important. While estimating risk modification, additive models (i.e. modelling absolute changes in risk) may be more appropriate than multiplicative models.

Recommendations for research studies:



- The standard Kaplan-Meier approach should be used in studies measuring HIV transmission at 6 weeks of age as it is likely to yield valid results because the intervals between the tests are short.
- When the outcomes are assessed after 6 weeks of age, with tests usually at an interval of 3 months or greater, the Turnbull procedure for interval-censored data should be used.
- The extension of Turnbull procedure that includes competing risks should be used if outcomes continue to be measured after cessation of breastfeeding. However, this procedure may not be appropriate if there are many deaths among children without an HIV test because it does not take into account the fact that death may represent informative censoring.
- Hughes and Richardson extension of Turnbull's procedure to allow informative censoring can be used if there are many deaths among children without an HIV test. However, it should be remembered that this approach does not account for competing risks, is computationally very cumbersome and will in practice make little difference.
- Estimates of HIV-free survival should be adjusted for relevant confounders. Confounding is not likely to be important when the outcome is HIV transmission.
- Modification of the relationship between infant feeding practices and both HIV transmission and HIV-free survival by factors such as maternal CD4 counts or breast health should be investigated in studies, if sample size permits. It will be more feasible to address risk/effect modification in individual record meta-analyses.



Next steps

The workshop met its objectives of sharing experiences and coming up with recommended approaches for analysis and presentation of data from studies on HIV and infant feeding. The participants appreciated the opportunity to exchange information and generate ideas based on the work done in related research settings. There was generous sharing of results which enabled realistic discussions.

Suggestions to facilitate continued exchange of information in the future included using available web sites or setting up a new web site; publishing a letter to the editor in a journal; and convening further meetings.

Other possible steps included the development of guidance for collection and analysis of data in the programme context, as future infant feeding studies may revolve around programme evaluation. It was recommended that UNICEF/WHO should generate a list of programme evaluations and observational studies related to HIV and infant feeding.

List of participants

Simon Cousens

Professor of Epidemiology and Medical Statistics
London School of Hygiene and Tropical Medicine
Keppel Street, London
WC1E 7HT, UK
Tel: +44 20 7636 8636
Fax: +44 20 7636 8739
E-mail: simon.cousens@lshtm.ac.uk

Francois Dabis

Unité INSERM 593 (ex-330)
Institut de Santé Publique, Epidémiologie et
Développement (ISPED)
Université Victor Segalen Bordeaux 2
BP INSERM U.593 - ISPED (Case 11)
33076 Bordeaux - Cedex - FRANCE
Tel: +33 5 57 57 14 36 (direct) 17 67 (Sec)
Fax: + 33 5 57 57 45 28
E-mail: Francois.dabis@isped.u-bordeaux2.fr

Elly Hassink

Epidemiologist
AMC, T0-122
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands
Tel: +31 20 5667693 (direct)
Tel: +31 20 5664479
Fax: +31 20 6918821
E-mail: e.hassink@iatec.com

Marie-Louise Newell

Professor of Paediatric Epidemiology
Centre for Paediatric Epidemiology and Biostatistics
Institute of Child Health
30 Guilford Street
London WC1N 1EH - UK
Tel: +44 20 7829 8699
Fax: +44 20 7813 8145
E-mail: M.Newell@ich.ucl.ac.uk

Ellen Piwoz

Co-Director
Centre for Nutrition
Academy for Educational Development
AED Headquarters
1825 Connecticut Ave., NW
Washington, D.C. 20009-5721 - USA
Tel: +1 202-884-8816 (office)
+1 410-295-9192 (home)
Fax: +1 202-884-8447
E-mail: epiwoz@smtp.aed.org

Barbra A. Richardson

Research Associate Professor
Department of Biostatistics
University of Washington
Joint Assistant Member
Division of Public Health Sciences
Fred Hutchinson Cancer
Research Center
Harborview Medical Center
325 Ninth Avenue -Box 359909
Seattle WA 98104-2499 -USA
Tel: +1 206-731-2425
Fax: +1 206-731-2427
E-mail: barbrar@u.washington.edu

Nigel Rollins

Senior Lecturer
Maternal and Child Health Unit
Department of Paediatrics and Child Health
Nelson R Mandela School of Medicine
University of Natal
Private bag 7
4th floor, 719 Umbilo Road
Congella 4013 - Durban
South Africa
Tel: +27 31 260 4352
Fax: +27 31 260 4388
E-mail: 'rollinsn@africacentre.ac.za'

**Charlotte Sakarovitch**

Unité INSERM 593 (ex-330)
Institut de Santé Publique, Épidémiologie et
Développement (ISPED)
Université Victor Segalen Bordeaux 2
BP INSERM U.593 – ISPED (Case 11)
33076 Bordeaux - Cedex
France
Tel: +33 5 57574517 (Direct) or 1767 (Sec)
Fax: +33 5 57574528
E-mail: Charlotte.Sakarovitch@isped.u-bordeaux2.fr

Laura Smeaton

Harvard School of Public Health
Statistical and Data Analysis Center
651 Huntington Avenue, 5th Floor
Boston, MA 02115-6017
USA
Tel: +1 617-432-2525
Fax: +1 617-432-3163
E-mail: smeaton@sdac.harvard.edu

Arjan de Wagt

Project Officer Nutrition and HIV
Nutrition Section
UNICEF New York/HQ
3, United Nations Plaza
New-York 10017
USA
Tel: +1 212 326 7159
fax: +1 212 735 4405
E-mail: adewagt@unicef.org

Secretariat**Tim Farley** (WHO/FCH/RHR)

Email: farleyt@who.int

Mohammed Ali (WHO//FCH/RHR)

Email: alim@who.int

Rene Ekpini (WHO/HTM/HIV)

Email: ekpinir@who.int

Jose Martines (WHO//FCH/CAH)

Email: martinesj@who.int

Peggy Henderson (WHO//FCH/CAH)

Email: hendersonp@who.int

Rajiv Bahl (WHO//FCH/CAH)

Email: bahlr@who.int



Agenda

Day 1

	Session 1: Introduction	
9:00 – 9:15	Welcome and objectives of the meeting	Jose Martines
	Session 2: Sharing experiences – brief description of the study (Site, investigators, objectives, key outcomes, status of implementation of the study)	Chair: Jose Martines
9:15 – 10:45	(Each site: presentation – 10 minutes, discussion – 5 minutes)	
	Botswana	Laura Smeaton
	Kenya	Barbra Richardson
	South Africa	Nigel Rollins
	Zimbabwe	Ellen Piwoz
	SIMBA study	Elly Hassink
	Kesho Bora study	Tim Farley
10:45 – 11:15	Coffee	
11:15 – 11:40	(presentation – 15 minutes, discussion – 10 minutes) The work of the ghent group on HIV and infant feeding research	Francois Dabis
	Session 3: Sharing experiences – measurement of infant feeding (Awareness and of the assessment tool for research, experience with the tool or alternative tools)	Chair: Ellen Piwoz
11:40 – 13:00	(Each site: presentation – 15 minutes, discussion – 5 minutes)	
	Botswana	Laura Smeaton
	Kenya	Barbra Richardson
	South Africa	Nigel Rollins
	Simba Study	Elly Hassink
13:00 – 14:00	Lunch	
14:00 – 14:40	(Each site: presentation – 25 minutes, discussion – 15 minutes) Zimbabwe	Ellen Piwoz



Session 4: Discussion – measurement of infant feeding

14:40 – 15:20 Lead discussant: Ellen Piwoz

15:20 – 15:40 Coffee

Session 5: Sharing experiences – measurement of outcomes

(HIV transmission and HIV-free survival; Measured when and how?)

Chair: Marie-Louise Newell

15:40 – 17:10 (Each site: presentation – 10 minutes, discussion – 5 minutes)

Botswana	Laura Smeaton
Kenya	Barbra Richardson
South Africa	Nigel Rollins
Simba study	Elly Hassink
Zimbabwe	Ellen Piwoz

Session 6: Discussion – measurement of outcomes

17:10 – 17:30 Lead discussant: MI Newell

Day 2

Session 7: Sharing experiences – data analysis

(Outline of the plan of analysis, experiences with analysis of sites that have completed data collection)

Chair: Simon Cousens

9:00 – 11:05 (Each site: presentation - 15 minutes, discussion – 10 minutes)

11:05 – 11:30 Coffee

11:30 – 12:15 (presentation – 30 minutes, discussion – 15 minutes)

Botswana	Laura Smeaton
Kenya	Barbra Richardson
South Africa	Nigel Rollins
Simba study	Elly Hassink
Zimbabwe	Ellen Piwoz

12:15 – 13:15 Lunch

Session 8: Identification of key issues in data analysis related to classification of exposure, classification of outcomes, and handling possible confounding and effect-modifiers

13:15 – 14:45 Lead discussant: Simon Cousens

14:45 – 15:15 Coffee



Session 9: Discussion – presentation of results for publication

15:15 – 16:45

Facilitator: Nigel Rollins

Day 3

Session 10: Recommendations – classification of exposure (infant feeding)

9:00 – 10:30

Facilitator: Ellen Piwoz

Session 11: Recommendations – classification of outcomes

(HIV-transmission and HIV-free survival)

10:30 – 11:00

Facilitator: Tim Farley

11:00 – 11:30

Coffee

Session 12: Recommendations – handling possible confounders and effect-modifiers in HIV and infant feeding studies

11:30 – 12:00

Facilitator: Simon Cousens

Session 13: Conclusions – agreement on recommended approaches for analysis and presentation of data

12:00 – 13:30

Facilitator: Rajiv Bahl

13:30 – 14:30

Lunch

Session 14: Future steps

14:30 – 15:00

Facilitator: Peggy Henderson

15:00

Coffee



Studies represented at HIV and infant feeding analysis workshop

Study	Countries	Investigators	Represented by
Mashi (milk) study	Botswana	Botswana-Harvard AIDS Institute Partnership for HIV Research and Education (BHP) <i>Principal Investigator:</i> Myron (Max) Essex; Co-PI (on-site): Ibou Thior <i>Co-Investigators:</i> Jody Heymann, Kenneth McIntosh, Tun-Hou Lee, Richard Marlink <i>Statisticians:</i> Stephen Lagakos, Peter Gilbert, Laura Smeaton <i>Sub-study PIs:</i> Shahin Lockman, Roger Shapiro	Laura Smeaton
CTLs and prevention of breast milk HIV-1 transmission	Kenya	<i>Seattle:</i> Grace John-Stewart (PI), Carey Farquhar, Joan Kreiss, Julie Overbaugh, Barbara Richardson <i>Nairobi:</i> Dorothy Mbori-Ngacha, Ruth Nduati, Rose Bosire, Barbara Lohman <i>Oxford:</i> Sarah Rowland-Jones	Barbara Richardson
Stopping infection from mother-to-child via breastfeeding in Africa (SIMBA) study	Rwanda and Uganda	<i>Mulago Hospital, Kampala (Uganda):</i> F. Mmiro, C. Ndugwa <i>St. Francis Hospital Nsambya, Kampala (Uganda):</i> P. Okong, P. Kituuka <i>Centre Hospitalier de Kigali (Rwanda):</i> J. Vyankandondera, N. Muganga <i>IATEC, Amsterdam (the Netherlands):</i> J. Lange, N. Pakker, S. Luchter, E. Hassink <i>ISS Rome (Italy):</i> S. Vella, M. Giuliano <i>Sponsors:</i> E. Loeliger (GSK), M. Imperiale (BI), A. Beretta (Fondation Jacqueline Beytout)	Elly Hassink
Vertical transmission study	South Africa	Jerry Coovadia, Ruth Bland, Anna Coutsooudis, Michael Bennish, Jan van den Broeck, Nigel Rollins, Marie Louise Newell	Nigel Rollins
Zimbabwe vitamin A for mothers and babies project (ZVITAMBO)	Zimbabwe	Dr. Kusum Nathoo (UZ), Dr. Jean Humphrey (JHU), Dr. Peter Iliff (UZ), Naume Tavengwa, Clare Zunguza (CHD), Dr. Ellen Piwoz (SARA/AED), Dr. Brian Ward (MGH), Dr. Larry Moulton (JHU), and Eddie Marinda (ZVITAMBO study statistician)	Ellen Piwoz
Kesho-Bora (a better future) study	Burkina Faso, Kenya, Rwanda, Tanzania, South Africa	<i>Coordination and partners:</i> WHO, CDC, NIH, ANRS, IRD, ICRH, IATEC, Network for AIDS Researchers in East and South Africa (NARESA), Kilimandjaro Christian Medical Center (KCMC), Centre Muraz, Mombasa Regional Hospital, Belgian Directorate General for International Cooperation, GlaxoSmithKline Foundation.	Tim Farley and Mohammed Ali

Brief description of studies

MASHI (milk) study:

Prevention of milk-borne mother-to-child transmission of HIV-1c in Botswana (3 rural sites - Molepolole, Mochudi, Lobatse, and 1 urban site: Gaborone)

Study design and objectives

2x2 factorial design, sample size of 1200 mother-infant pairs with in-utero and intra-partum intervention (part I) and postpartum intervention (Part II)

~ 6 weeks antenatal AZT (300mg BID) to all women	Breast Feeding for 6 months AZT syrup (4 mg/kg BID) for 6 months	Formula Feeding from birth AZT syrup (4mg/kg) for 1 month
NVP to women at onset of labour -single dose 200mg NVP (6mg) syrup to babies once after birth	GROUP 1	GROUP 2
Matching placebo to women at onset of labour Matching placebo syrup to babies after birth – Original NVP (6mg) syrup to babies once after birth – Revised (13/8/2002)	GROUP 3	GROUP 4

Primary Study Objectives:

- to assess effectiveness of adding single dose NVP to AZT in MTCT;
- to compare breast feeding plus AZT to formula feeding with respect to transmission and HIV-free survival;
- to evaluate safety and tolerance of all interventions.

Sample size of 1200 mother/infant pairs for 80% power to detect 50% decrease in cumulative proportion infected by 7 months (from 14% to 7%) between feeding strategies (among cohort not perinatally infected); or a difference between 24% and 17% from enrolment.

Measurement of infant feeding

Mother/infant pairs are assigned to exclusive breastfeeding or exclusive formula feeding after birth, i.e. mixed feeding is discouraged. Formula is provided by the study and participants are instructed to administer it by cup and spoon. For the group assigned to exclusive breastfeeding, discussion on weaning infants is started at 4 month visit to be completed between 5 and 6 months. Formula is provided to all infants between 6 and 12 months.

Infant feeding information is collected regardless of randomized assignment. An interview by a research nurse/ health educator is conducted every month from 1-7 months and additionally at 9, 12, 15, 18, 21 and 24 months. A breast examination is conducted at every visit during the first year of follow-up postpartum to record evidence of breast milk, mastitis, cracked nipples and to collect breast milk specimens (from those assigned to breastfeeding only).

Women are encouraged to wean at 6 months. Infants are followed to 12 months of age. The key outcome is infant HIV-1 infection after 1 month of age among those infants who are still breastfeeding at 1 month.

Measurement of infant feeding

Questionnaire with several questions regarding breastfeeding, formula feeding, feeding of other foods/liquids, and reasons for stopping breastfeeding is administered at age 2 weeks, one month, and then monthly up to 12 months. One question asks whether the infant is currently breastfeeding. If breastfeeding, questions on frequency are asked, and if stopped breastfeeding, questions on age of stopping and reasons for stopping are asked. Information for all infants on the foods or drinks given in the previous 24 hours is obtained.

Measurement of outcomes

HIV-1 DNA PCR is done on filter paper at birth, 1, 3, 6, 9 and 12 months. Quantitative plasma HIV-1 RNA levels are also used to determine HIV-infection status.

An infant is considered to be HIV-1 infected if HIV-1 DNA or RNA PCR is positive at two consecutive visits or at the last visit. An infant is considered HIV-1 uninfected if no HIV-1 infection criteria are met and HIV-1 PCR is negative at least at two consecutive visits.

Data analysis plan

Issues identified in assessment of the risk and timing of HIV transmission:

- “Event” is ill defined since specificity and sensitivity of testing is <100%. For instance, a filter paper sample is less sensitive than a blood sample, and DNA PCR is less sensitive than RNA PCR. Also, tests remain negative for some time after transmission has occurred.
- Interval censored nature of outcome data, i.e. actual timing of transmission is only known within an interval.
- There is a high potential for informative censoring, i.e. infants negative at last test who die are censored, but these children have a higher likelihood of being infected (quick disease course leading to death).

Possible analysis solutions:

Method	Sensitivity/specificity of test	Interval censored data	Possible informative censoring
KM or Cox PH regression	Assumes perfect detection of event – methods to correct for this available	Have to make assumption of when event occurred (e.g. midpoint of interval) – underestimates variances	Informative censoring due to mortality – underestimates of infection rates
Turnbull	Assumes perfect detection of event – no current methods to correct for this	Allows for interval censoring of time to event	Informative censoring leading to under estimation of infection rates
Estimate bivariate distribution of time to HIV-1 infection (s) and time to death (t) – nonparametric or semi parametric estimation (Hughes and Richardson, JASA, 2000)	Modification for imperfect specificity at birth	Interval censoring taken into account	Informative censoring taken into account through jointly modelling time to HIV-1 infection and time to death

Measurement of outcomes

HIV-1 DNA PCR was conducted at birth, 6, 12, 24 and 72 weeks. HIV-1 RNA PCR was used as a confirmation for those with a positive HIV-1 DNA PCR. The timing of HIV-1 transmission was taken as the midpoint between the last negative and the first positive test.

Data analysis

Transmission was defined as:

- Overall, i.e. from birth to 6 months;
- Intrauterine/peri-partum/early postpartum, i.e. within 4 weeks after birth;
- Late postnatal, i.e. between 4 weeks and 6 months after birth.

Kaplan-Meier estimates for overall and late postnatal HIV-1 transmission, with censoring of deaths were obtained. Kaplan-Meier estimates were also obtained for HIV-1 free survival. Due to low infection rates, it was impossible to assess association with infant feeding patterns; purely descriptive results are therefore presented. Analysis for HIV-1 transmission and HIV-1 free survival up to 18 months of age is still to be done.

Current status of implementation

In February 2004 the last patient had a complete follow up of 18 months in the study. The results as mentioned above are the results of the main study, which had a follow up until 6 months after birth. The study results were presented at the 2nd IAS meeting in Paris (July 2003) and at the ICASA meeting in Nairobi (September 2003). Currently a paper is in preparation.

Vertical transmission study (Hlabisa district and Durban, South Africa)

Objectives

- To determine the effect of infant feeding practices on HIV infection rates of infants at 6 and 22 weeks of age
- To determine the infant survival rate at 24 months of age according to feeding practices and HIV status

Secondary objectives

- To determine the HIV infection rate of infants as measured by a sample collected within 72 hours of birth
- To determine the HIV transmission incidence attributable to the duration of different feeding practices
- To determine the cumulative incidence of vertical transmission in EBF, MBF and EFF infants.
- To determine risk factors other than infant feeding practice, for post-natal transmission of HIV, including maternal and infant morbidity and breast health
- To assess the determinants of transmission in MBF adjusting for exposure factors e.g. type and age of introduction of other food/milk
- To describe the morbidity and growth of infants in relation to feeding practices and HIV status
- To describe adherence rates to EBF following a breastfeeding support intervention

Study design

A non-randomised intervention study to assess the influence of infant feeding practices on postnatal transmission of HIV.

Co-factors in multivariate analysis will include:

- Gestational age (probably <34 and ≥34 weeks)
- Birth weight
- Caesarian section, episiotomy and stitches as dummy variables
- Duration of ruptured membranes
- Nevirapine received: one variable for the mother and one for the child
- Maternal viral load – continuous and categorical variables
- Maternal CD4 %
- Feeding mode in the first week and the second week
- Breast pathology as a dummy variable +/- feeding from that breast
- Age of mother in categories
- Parity of mother
- Maternal education
- Place of delivery

Implementation status

1351 women (863 HIV infected and 488 uninfected) have been enrolled of which 503 have delivered. Publications/reports to date from the study are:

- Bland RM, Rollins NC, Coutsooudis A, Coovadia HM. Breastfeeding practices in an area of high HIV prevalence in rural South Africa. *Acta Paediatr* 2002; 91(6):704-11.
- Rollins NC, Dedicoat M, Danaviah S, Page T, Bishop K, Coovadia HM, Cassol SA. Surveillance of prevalence, incidence and mother-to-child transmission of HIV-1 in rural South Africa. *Lancet* 2002; 360:389.
- Bland RM, Rollins NC, van den Broeck J, Coovadia HM. Maternal recall of exclusive breastfeeding duration. *Arch Dis Child* 2003; 88:778-83.
- Kauchali S, Rollins NC, van den Broeck J. Local beliefs about childhood diarrhoea: potential implications for primary health care and research. Accepted for publication. *J Trop Paediatr*.

Zimbabwe vitamin A for mothers and babies project (ZVITAMBO): Infant feeding component (Harare, Zimbabwe)

Objectives

- To determine the effects of vitamin A supplementation, given to mother and/or their newborn infants within 96 hours of delivery, on infant mortality, MTCT during breastfeeding, and HIV infection among women during the post-partum year. (Primary objective) (All women)
- To evaluate the impact of breastfeeding patterns on postnatal HIV transmission and HIV-free survival at 12 and 18 months. (Secondary objective) (HIV-positive women)
- To evaluate the impact of an education and counseling program about prevention of MTCT and safer breastfeeding practices on knowledge, feeding decisions, safe sex practices, and HIV transmission. (Tertiary objective). (Subset of women)

Study design

ZVITAMBO was a double-blind, placebo-controlled vitamin A supplementation trial with a 2 by 2 factorial design. The vitamin A supplement was a single dose of 400,000 IU for mothers and 50,000 IU for newborns. Mothers were recruited and enrolled in the study within 96 hours of delivery (when the vitamin A intervention was administered) and were followed at 6 weeks, 3 months, and at 3-monthly intervals for up to 24 months.

Baseline data collection included detailed labour and delivery, socio-economic, and nutrition supplement use information. The following data were also collected at baseline and at follow-up visits: detailed feeding information

Infant feeding patterns in the first 3 months were classified using maternal recall of lifetime feeding history at baseline, 6 weeks and 3 months. The classification system was hierarchical, i.e. an infant classified as partially breastfed at 6 weeks and predominantly breastfed at 3 months was considered to have been partially breastfed in the first 3 months of life.

Preliminary results show that the prevalence of exclusive breastfeeding was 4.7%, predominant breastfeeding 31.2% and partial breastfeeding 64.1%. Among infants who were partially breastfed, 1.8% were receiving additional non-human milk only, 10.2% non-human milk and complementary foods, and 52% were receiving only complementary foods but no non-human milk.

The three outcomes that were examined for their association with infant feeding pattern up to 3 months of age were:

- Cumulative infant HIV infection to 6 and 18 months
- HIV transmission due to breastfeeding to 18 months (after 6 weeks)
- HIV transmission or death to 18 months (after 6 weeks)

The potential confounders included in the analysis were birth weight, gestational age, sex, maternal CD4, MUAC, haemoglobin and age, mode of delivery, duration of membrane rupture, breast health (cracked nipples, mastitis), and maternal education and socio-economic status.

Current status of Implementation

The project has been completed. All data have been cleaned, including determination of infant HIV status and timing of infection. Analysis is underway for all study objectives/hypotheses.

14,100 mothers and infants were enrolled in the trial. 4496 were HIV-positive at delivery. 131 HIV-positive mothers were lost to follow-up after recruitment. Follow-up data are available for 4365 HIV-positive mothers. 3196 HIV-positive mothers have feeding data at the 3-month visit. 2753 HIV-positive mothers have feeding data at baseline, 6 weeks, and 3 months.

Papers planned or underway:

- The effect of infant feeding patterns on postnatal HIV transmission and HIV-free survival.
- A methodology paper comparing results and interpretation when different feeding assessment methods are used
- Impact of the education and counselling intervention on knowledge, practices, HIV infection
- Factors influencing feeding decisions by HIV-positive, HIV-negative, and women of unknown HIV status

Impact of HAART on MTCT and mother's health: The Kesho Bora project (World Health Organization, Department of Reproductive Health and Research)

Objectives

The overall goal of the project is to optimise the use of antiretroviral drugs during pregnancy, delivery and breastfeeding to prevent MTCT and to preserve the health of the mother.

The primary objectives of the pilot programme are to provide ARV in the context of pregnancy and lactation for the benefit of both the mother and the child, to carefully monitor the rates of AIDS-free maternal survival and HIV-free

- where a significant proportion ($\geq 50\%$) of HIV-positive mothers still choose to breastfeed their infants despite counselling on infant feeding options and the availability of free or low-cost infant formula; and
- where services for long-term HIV care, including CD4+ cell count monitoring and HAART when needed, are expected to be available within two years after project initiation, in order to care for the Kesho-Bora participants after the end of the programme.

Current status

The project protocol was approved by the WHO Scientific and Ethical Review Groups. Institutional and national approvals are being obtained in each participating site. Site preparation is being undertaken in Kenya (Nairobi and Mombasa), Tanzania (Moshi), Burkina Faso (Bobo Dioulasso) and Rwanda (Kigali). An additional site will be identified.

The project will start in the second half of 2004 in a limited number of sites and will be progressively expanded as more resources become available.

