# Summary Report:

# Mapping and Identifying HIV Research Priorities for Women and Children

**DRAFT FOR CONSULTATION**

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# A Introduction

The aim of the International AIDS Society – Industry Liaison Forum (IAS-ILF), established in 2001, is to promote scientific, intellectual and financial commitments from pharmaceutical and diagnostic companies for research in resource-limited settings. The initiative is guided by the ILF Advisory Group, which includes representation from independent investigators and academics, multilateral and civil society organizations, as well as most pharmaceutical companies with strong commercial and philanthropic interests in HIV/AIDS.

One of the strategic priorities of ILF-IAS is to strengthen HIV clinical and operations research projects in resource-limited settings that address the needs of women and children. A major initiative was established to address this priority: *Mapping and Identifying Clinical and Operations Research Priorities for Women and Children*. The initiative is guided by an IAS-ILF Expert Reference Group, which includes experts in research on paediatrics and women from major research granting agencies and foundations, independent investigators and clinicians, and multilateral organizations (UNICEF, WHO and UNAIDS). The initiative includes four major deliverables:

- An **environmental scan**, including grey and scientific literature reviews and key informant interviews, that addresses priority HIV clinical and operations research questions for women and children. These include specific components of preventing mother to child transmission (PMTCT) in order to identify knowledge gaps and research required to improve clinical treatment and programme delivery to these populations.
- A **summary report**, including highlights of key findings from the environmental scan and draft recommendations from the IAS-ILF Expert Reference Group, on priority clinical and operations research questions that would address these knowledge gaps.
- A **multi-stakeholder consultation** on the draft recommendations, to be held in Cape Town on 19 July, in conjunction with the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009).
- A **consensus statement** to be issued by the IAS and supporting partners following the conference, confirming the consensus recommendations from the consultation, and strategic direction on advocacy activities required to fund and implement identified research priorities.

This environmental scan, the first major deliverable of this initiative, provided the foundation for the recommendations and subsequent consultation. It is available as a separate document, including an annex of ongoing clinical and operations research trials.

# B Methodology

There are many potential research questions to explore within clinical and operations research related to PMTCT, women's treatment and paediatric treatment issues. To ensure a manageable scope for the mapping exercise, the IAS-ILF Expert Reference Group identified and then prioritized a number of research questions aimed at optimizing clinical treatment and programme delivery for women and children.

The priority research questions identifying outstanding knowledge gaps fell into three broad categories:

- Clinical research on PMTCT and paediatric treatment
- Clinical research on treatment for women
- Operations research on treatment for women.

Priority research questions in a fourth category, operations and/or implementation research gaps related to PMTCT, including paediatric care, treatment and support, is being addressed by a parallel initiative led by UNICEF, and involving WHO, UNAIDS and several US agencies. The IAS is represented on the steering committee for that initiative, and the IAS-ILF study group is working with George Washington University to coordinate a review of PMTCT and paediatric treatment operations research questions identified as outstanding knowledge gaps by the IAS-ILF Expert Reference Group.

Once the research questions within these categories were finalized, online searches were conducted to identify relevant scientific and grey literature for review. Pub Med Central/Medline and the Cochrane Review Library were used to search for relevant articles in peer-reviewed journals, focusing on articles and reports published from 2006 onwards. That time frame was selected both to ensure a focus on the most current literature, to reflect the significant expansion in antiretroviral therapy (ART) access in resource-limited settings over the past four years, and to ensure the reviewed literature was published subsequent to the 2006 WHO recommendations on scaling up ART using the public health approach.

Articles and reports published before 2006 were considered for review if they provided relevant additional information to research questions in the literature review that were not addressed by more recent publications. PubMed searchers were conducted using the National Library of Sciences' MeSH database, which uses a controlled vocabulary thesaurus (relational database) to include results that may not be specifically identified in the keyword searches. These were supplemented by more focused searches for specific articles, as appropriate.

Websites, databases and other resources for grey literature included those from UNAIDS, UNICEF, WHO, NAM, US National Institutes of Health, US Centers for Disease Prevention and Control, International Community of Women Living with HIV/AIDS, International Council of Research on Women, Global Coalition on Women and AIDS, Elisabeth Glaser Paediatric AIDS Foundation, Global Coalition on Children Affected by AIDS, International Food Policy Reference Institute, and World Food Programme.

Invitations for key informant interviews were sent to individuals who were either well-published experts in the research areas under review, represented organizations which had made significant investments in these areas, or represented populations (HIV-positive women and children) that were the focus of the review. Questions were developed, based on the preliminary results of the literature reviews, and circulated to confirmed interviewees in advance of the interview. Questions were also circulated to industry representatives on the IAS-ILF Advisory Group, the responses to which will be included in the final version of the environmental scan, to be completed following the consultation held in conjunction with IAS 2009.

# C Environmental Scan Highlights and Draft Recommendations

In reviewing the grey and scientific clinical and operations research literature and conducting key informant interviews related to the research questions under review, the project group and IAS-ILF Expert Reference Group identified several issues which are broadly relevant to the HIV research field and should be addressed in future research relevant to women and children.

Recommendation 1: Invest in studies (prospective, retrospective and longitudinal) identified as optimal ways to answer the research questions identified in this report.

Recommendation 2: Data from existing operations research, programme evaluations and clinical studies should be shared more broadly, reviewed and analyzed to answer some of the knowledge gaps identified in this report.

Recommendation 3: Research data should be disaggregated by sex to ensure opportunities for gender-based analysis using a variety of indicators, such as retention in ART programmes, morbidity and mortality, loss to follow up, as well as social science research on issues (e.g., care-giving roles, financial insecurity and HIV stigma) which affect clinical outcomes and programme access for both women and children.

## Clinical Research: PMTCT and Paediatric Care, Treatment and Support

### 1. What is the impact of *in utero* exposure to antiretrovirals (ARVs) on uninfected children?

Some studies address certain aspects of this question (e.g., mitochondrial toxicity), but there are substantial data gaps regarding short- and long-term effects both on cellular processes and on short- and long-term neurocognitive and physical development in uninfected children.

To address gaps in pharmacovigilance (PV) and the need for a coordinated PV system to address outstanding knowledge gaps regarding the short- and long-term impact of *in utero* exposure on uninfected children, the ILF Expert Reference Group noted a new WHO pharmacovigilance initiative that may help address some of the health system shortcomings needed to address questions related to paediatric adverse events reporting. Recommendations of the IAS-ILF Expert Reference Group on this issue are:

Recommendation 4: Establish agreement among key stakeholders on PV indicators for short- and long-term health outcomes, and address the health system shortcomings needed to strengthen paediatric adverse events reporting.

Recommendation 5: Expand the existing antiretroviral pregnancy registry (APR) using existing low- and middle-income country cohorts/pilot settings to ensure a more comprehensive PV/APR system

Recommendation 6: Review existing data and establish additional studies to address specific questions including:

6.1 Risk and/or health impact of mitochondrial toxicities
6.2 Neurological development
6.3 Physical growth and development, including organ development
6.4 Risk of cancers and other diseases into adulthood.

The challenges in addressing outstanding knowledge gaps for this question, as with some of the other questions, will concern controlling for a wide range of variables over time, including time of ART initiation, ART interruptions and discontinuation, and other confounding factors, such as co-infections and malnutrition.

**2. What is the impact of ART on physical and cognitive development into adulthood?**

Most of the available data address the significant benefits of ART on HIV-related morbidity and mortality in paediatric populations. There is little data available on the long-term physical and neurocognitive impacts of ART on this population. As with question 1, this is a complex research area which would need to control for a number of variables, such as age at ART initiation, confounding co-infections, nutritional status and other factors known to affect treatment outcomes. There is an urgent need to identify whether retrospective or longitudinal studies are the best sources to answer specific questions. The recommendation is:

Recommendation 7: Analyze available data from existing clinical cohorts for retrospective information on the impact of ART on children using a variety of data sources.

**3. What are the optimal age-adapted parameters for ART initiation and discontinuation?**

Evidence of the benefits of immediate ART initiation for infants has been established and is reflected in clinical guidance. Data are less clear for older infants and children, as are data on whether treatment interruptions are clinically inadvisable for paediatrics. Additional data is needed to answer a number of questions for post-infant paediatrics to address outstanding knowledge gaps in parameters for ART initiation and discontinuation, ART eligibility, the appropriateness of age-adapted parameters and the impact of structured treatment interruptions on health outcomes. These recommendations are primarily broader population-level/operations research questions, although based on a review of existing clinical studies and necessary bridging studies, and include:

Recommendation 8: Review existing data and currently enrolled trials to establish parameters for defining paediatric ART eligibility and ART initiation for children older than one year of age (including evaluating the appropriateness of existing clinical guidance for children/early adolescents).

Recommendation 9: Review existing evidence and data from currently enrolled paediatric trials regarding drug regimen switching guidance.

Recommendation 10: Assess the impact of structured treatment interruptions on future treatment options and health outcomes for paediatrics.

**4. What is the impact of interventions for co-infections (TB and malaria) and malnutrition on ARV dosage?**

There is some evidence of interactions between some ARVs and rifampicin, including evidence of toxicities, but limited evidence is available for other drug interactions (e.g., malaria drugs) and malnutrition on paediatric ART. ARVs, TB and malaria have been particularly understudied in paediatric populations regarding interactions and contraindications. The impact of malnutrition and TB interventions on paediatric ART and health outcomes was identified as the most pressing priority. Recommendations are:

Recommendation 11: Review currently enrolled clinical trials and establish necessary clinical studies to:

11.1 Assess the impact of isoniazid preventive treatment on paediatric ART and health outcomes.

11.2 Assess TB vaccine (BCG) impact and optimal intervention timing for paediatric populations.

Recommendation 12: Establish studies to assess the potential impact of nutritional or micronutrient supplementation on ART pharmacokinetics (PK) and pharmacodynamics (PD).

**5. What are the barriers to developing paediatric formulations?**

Data suggest that liquid and liquid suspension formulations (particularly those requiring refrigeration) are less suitable for resource-limited settings, although developing paediatric formulations in different formats (such as micro-tablets) that allow appropriate paediatric dosage changes remain a significant challenge for manufacturers. There are also ethical constraints for clinical trials, cost and development issues in developing additional PK and PD studies for paediatric populations, palatability issues and regulatory hurdles for approving paediatric formulations.

There is little evidence available on how best to address these barriers, which represent a significant problem in appropriate clinical management of paediatrics in resource-limited settings. Existing initiatives and mechanisms such as WHO's "Make medicines child size" campaign, PEPFAR's public-private initiative and the IAS-Industry Liaison Forum could be important in addressing some of the non-research barriers to paediatric formulations. Recommendations are:

Recommendation 13: Evaluate a range of drugs and fixed-dose combinations for children, including establishing differential dosage recommendations for age/weight adjusted parameters.

Recommendation 14: Explore and invest in drug manufacturing innovation to address the urgent need for appropriate paediatric formulations for resource-limited settings.

## Clinical Research: Treatment for Women

### 1. What is the impact of periodic ARV exposure via PMTCT prophylaxis on future maternal treatment options?

Nevirapine has been comparatively well studied given its prominence in PMTCT ARV prophylaxis, although it should be noted that single-dose nevirapine, although still widely used, is not indicated for PMTCT prophylaxis. There is conflicting evidence regarding the decay of NVP resistance after maternal exposure of NVP prophylaxis; it may be a viable component of maternal ART if used within 12 to 18 months of initial exposure, although additional studies are required to confirm the latest findings on resistance. There is limited evidence of the impact of other ARVs used in PMTCT prophylaxis (including pre/intra/post-partum interventions and during breastfeeding) on future ART options for women. Recommendations are:

Recommendation 15: Assess the impact of PMTCT ARV prophylaxis use on future treatment options for women, including all drugs currently used as PMTCT ARV prophylaxis either individually, sequentially or in combination (nevirapine, zidovudine and lamivudine).

Recommendation 16: Assess the impact of the timing of PMTCT prophylaxis, including pre-, intra- and post-partum interventions (such as breastfeeding) or maternal ART on future ART options for women.

### 2. What is the impact of sex differences in ART PK/PD and dosage recommendations and treatment outcomes?

Although a number of demonstrated sex-based differences in ARV PKs/PDs are identified in the scientific literature, only efavirenz and nevirapine have resulted in differential clinical guidance for men and women. An upcoming WHO consultation in November 2009 is designed to address strategies for sex-disaggregated PK and PD data and its implications for clinical guidance. Although women are generally well-represented in publicly-funded clinical trials in resource-limited settings, this is not always the case with respect to privately-funded trials, particularly those addressing questions related to ART pharmacokinetics and pharmacodynamics. The recommendations are:

Recommendation 17: Develop strategies to ensure greater representation of women in ARV PK and PD studies

Recommendation 18: Establish what additional studies are required or should be re-analyzed to assess whether sex-based PK/PD differences are clinically relevant

**3. What is the impact of female hormone changes on treatment outcomes?**

There are limited data available to answer this question, and conflicting data regarding to what extent hormone-based contraception may have an impact on disease progression. Although some sex-based hormones may result in differential treatment outcomes, more data are required to definitely answer many questions regarding the impact of female hormonal changes during puberty, pregnancy and menopause on treatment outcomes. Recommendations are:

Recommendation 19: Analyse data from existing studies and establish a longitudinal cohort sufficiently powered to answer the question regarding the impact of hormonal contraception on ART and treatment outcomes for women.

Recommendation 20: Identify relevant studies and observational cohorts which may be able to provide useful data on how hormonal changes and fluctuations during puberty and menopause need to be considered for optimal ART via additional reviews, studies and consensus meetings.

**4. What is the impact of sex-based differences on ART monitoring strategies?**

Current data, including a recent meta-analysis and abstracts from the XII International AIDS Conference, suggest sex-based differences in CD4, other surrogate markers and viral level responses do not warrant differential monitoring strategies, although these findings should be confirmed by follow-up studies. Additional studies are required to definitively address knowledge gaps regarding sex differences among different racial or ethnic groups, which have demonstrated more variation in treatment response and adverse events. The recommendation is:

Recommendation 21: Ensure clinical cohorts are disaggregated by sex, ethnicity and race to ensuring ongoing analysis of potential differences in treatment outcomes and adverse events in these populations.

## Operations Research: Treatment for Women

**1. What are the barriers to ART access for women and what are the best practices in addressing those barriers?**

Data from both programme evaluations and operations research studies and meta-analyses suggest that socio-economic status, financial insecurity, HIV-related stigma (in health care settings, communities and families) and distance from the clinic have a negative impact on

women's access to ART; in most settings this has not translated into disadvantages for women in ART access, retention, adherence or health outcomes compared to men, although it is important to note that most women in PMTCT programmes are not screened for ART eligibility, and that treatment need continues to far outstrip availability for both women and men. The scope of the literature review was limited by the studies and programme evaluations which include sex-disaggregated data and analysis. Recommendations are:

Recommendation 22: A systematic analysis of existing quantitative and qualitative trials is required to evaluate sex-disaggregated data on a range of outcome indicators (such as enrolment, retention and adherence) to identify barriers and potential interventions that will facilitate ART access for women (as well as for men).

Recommendation 23: Retrospective and prospective operations research is required to identify how to leverage existing health system entry points for women (such as sexual and reproductive health services, PMTCT, maternal, child and newborn health services, methadone maintenance programmes and STI clinics) into improved access for HIV counselling, testing and treatment services.

Recommendation 24: Establish trials powered to evaluate access for sub-populations of women (women living in rural settings, single women, sex workers and women who use drugs), using different ethnographic and socio-economic variables to assess ART access issues.

Recommendation 25: Ensure gender equity analyses address the complexity of social and cultural norms of masculinity and femininity and their impact on differential health-seeking behaviours and other variables which have an impact on access to ART for both men and women (including evaluating the impact of gender-based interventions on ART access for women).

Recommendation 26: Establish robust, multidisciplinary social sciences studies to analyze socio-economic, behavioural, ethnographic, structural (e.g., statutory framework) and other factors that have an impact on ART access for women and can be addressed with ART programme interventions.

**2. What are the programmatic issues related to micronutrient, macronutrient and hormonal supplementation for women?**

There are limited operations research on best approaches to integrating nutritional supplements into ART programmes, although recent synthesis guidance, led by a World Bank consultation, will be helpful to the field regarding integrating nutritional status assessments and dietary recommendation into ART programmes. No operations research studies were available for review regarding hormonal supplementation to address changes in female hormones during

puberty, pregnancy or menopause (hormonal contraception is referenced as a related issue in the clinical research section of this report). Recommendations are:

Recommendation 27: Establish operations research and programme evaluations required to identify pilot interventions that work (how best to integrate micronutrient and macronutrient supplementation for women), which can then be scaled up more broadly into ART and care programmes (or that can be incorporated into guidance for people living with HIV to access food programmes, such as the World Food Programme).

Recommendation 28: Evaluate the impact of a range of supplementation interventions on women's health outcomes.

Recommendation 29: Explore how gender-related health issues (e.g., anaemia) have an impact on nutritional support/supplementation requirements for women.

**Nota bene:**

Some of the questions outlined in both the clinical and operations research sections touch on the evidence base required to trigger possible changes in clinical guidance, an issue that may require different processes (as opposed to research), such as expert consultations and the development of clinical and operational consensus on specific issues.

## Annex 1: IAS-ILF Expert Reference Group

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