Final Report:

Mapping and Building Consensus on HIV Research Priorities for Women and Children

DECEMBER 2009

1. Introduction

Increased HIV investments over the past several years have resulted in substantial increases in access to antiretroviral therapy (ART) for both adult and paediatric populations. The scale-up of ART programmes in resource-limited settings has also drawn attention to a number of outstanding knowledge gaps related to optimal clinical management and ART programme delivery for women and children. This report identifies recommendations for an HIV clinical and operations research agenda for women and children in resource-limited settings, based on a comprehensive research and consensus-building process conducted by the International AIDS Society – Industry Liaison Forum (IAS-ILF).

The recommendations are intended to provide public and private research granting agencies, investigators, clinicians, UN agencies and advocates with consensus guidance on priority HIV clinical and operations research investments for women and children, based on the best available scientific evidence and advice. The IAS is committed to advocating for the implementation of this research agenda, in collaboration with multilateral agencies, research granting agencies and other partners including pharmaceutical and diagnostic companies and is deeply indebted to the many individuals who contributed their time and expertise to this project.

2. Background

The aim of the IAS-ILF, established in 2001, is to provide a multi-stakeholder forum that promotes scientific, intellectual and financial commitments from pharmaceutical and diagnostic companies for HIV research in resource-limited settings. The ILF Advisory Group, which includes representation from independent investigators and academics, multilateral and civil society organizations, as well as pharmaceutical companies with strong commercial and philanthropic interests in HIV/AIDS, sets priorities and provides ongoing strategic direction for the IAS-ILF.

One of the current priorities of IAS-ILF is to strengthen HIV clinical and operations research studies in resource-limited settings that address the needs of women and children. A major initiative was established to address this priority in early 2009: *Mapping and Building Consensus on Clinical and Operations Research Priorities for Women and Children*. An Expert Reference Group (see Annex 1) was established to provide expert advice and guidance for this project, and includes experts in research on paediatrics and women from major research granting agencies and foundations, independent investigators, 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 Expert Reference Group, on priority clinical and operations research questions to address the identified gaps in knowledge.

- A **multi-stakeholder consultation** on the draft recommendations, held in Cape Town on 19 July, in conjunction with the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009).
- A **final report** based on the results of the IAS 2009 consultation and final review by the Expert Reference Group and ILF Advisory group, with a prioritized list of clinical and operations research questions.
- A **consensus statement** to be released by the IAS and its partners, endorsing the recommendations outlined in this report, and advocating for increased commitment and funding to address the identified knowledge gaps.

This is the final report for this project. The environmental scan (which includes an annex of current clinical and operations research trials) and summary report are available online at http://www.iasociety.org/ILF.aspx. The statement is planned for release in early 2010.

3. 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 (ERG) identified and then prioritized a number of research questions aimed at optimizing clinical treatment and ART programme delivery for women and children.

The priority research questions fell into four broad categories:

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

Priority research questions related to the fourth category, operations/implementation research related to PMTCT, including paediatric care, treatment and support, were developed by a parallel initiative led by UNICEF, involving the Elizabeth Glaser Pediatric AIDS Foundation, WHO, UNAIDS and several US agencies. Individuals cross-appointed to the Expert Reference Group and the steering committee for the UNICEF initiative helped to ensure that the development of research questions were closely coordinated between the two initiatives. The five highest-priority recommendations from the UNICEF-led initiative will be included in the IAS statement as part of a comprehensive clinical and operations research agenda for women and children. A complete list of research questions, including information about the methodology used to develop the operations/implementation research agenda related to PMTCT, including paediatric care, treatment and support, will be available at UNCEF website.

A systematic online review was conducted for each research question within the three categories addressed by the IAS-ILF project. The review included relevant scientific and grey literature, focusing on articles and reports published from 2006 onwards. The time frame was

selected both to ensure a focus on the most current literature, to reflect the significant expansion in ART access in resource-limited settings over the past three 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.

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.

Key informant interviews were conducted with experts in the research areas under review, as well as individuals representing organizations which had either made significant investments in these areas or represented populations (HIV-positive women and children) that were the focus of the review. The project team prepared a draft environmental scan, based on the literature reviews and key informant interviews.[1] The IAS-ILF Expert Reference Group provided input on the environmental scan and, in consultation with the IAS-ILF Advisory Group, developed draft recommendations for validation and prioritization at the multi-stakeholder consultation held 19 July in Cape Town, South Africa (in conjunction with IAS 2009).

Consultation participants included a broad range of professionals working in HIV, including independent researchers and clinicians as well as representatives from industry, multilateral agencies, donor agencies and civil society (see Annex 2).

The summary report and draft environmental scan were distributed to confirmed participants in advance of the consultation. Following a plenary presentation by Dr. Lynne Mofenson, consultation participants self-divided into three working groups to review, revise (as necessary) and then prioritize the top five research priorities within each research area. The research recommendations below reflect the results of that exercise and are prefaced by relevant highlights from the environmental scan.

4. Evidence Summary and Research Recommendations

The IAS-ILF Expert Reference Group developed three overarching recommendations relevant to all three research areas, which were validated by consultation participants.

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

[1] A detailed description of the methodology is outlined in the environmental scan, available online at http://www.iasociety.org/Default.aspx?pageId=246.

Recommendation 2: Data from existing operations research studies, programme evaluations and clinical trials should be more broadly shared, reviewed and analyzed to answer some of the specific 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, lost to follow up, and pharmacokinetic (PK) and pharmacodynamic (PD) parameters.

4.1 Clinical Research: Paediatric Treatment

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. Developing paediatric formulations in different formats that allow appropriate paediatric dosage changes are a significant challenge for manufacturers. There are also ethical constraints for paediatric clinical trials, cost and development issues in developing additional pharmokinetic (PK) and pharmacodynamic (PD) studies for paediatric populations, palatability concerns 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 children 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.

Recommendation 4: Invest in innovative drug manufacturing and delivery systems (e.g., dissolvable films, microtablets) to address the urgent need for appropriate paediatric formulations.

Recommendation 5: Evaluate a range of weight-adjusted dosage recommendations and fixed dose combinations (FDCs) for children.

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) or the impact of malnutrition on paediatric ART. ARVs, TB and malaria have been particularly understudied in paediatric populations regarding interactions and contraindications.

Recommendation 6: Invest in innovative TB and HIV diagnostics and monitoring to facilitate early infant diagnosis and treatment.

Recommendation 7: Review currently enrolled clinical trials and conduct necessary clinical studies to evaluate the impact of comorbid conditions and their treatment on drug dosage and toxicity, with priority given to TB, malaria and malnutrition.

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.

A new WHO pharmacovigilance initiative may help address some of the health system shortcomings needed to answer questions related to paediatric adverse events and the need for a coordinated pharmacovigilance system to address outstanding knowledge gaps regarding the short and long-term impact of *in utero* exposure on uninfected children. This includes expanding the existing antiretroviral pregnancy registry to more low and middle-income cohorts.

Recommendation 8: Ensure a more comprehensive pharmacovigilance system by expanding the existing antiretroviral pregnancy registry to include low and middle-income country cohorts/pilots and establishing appropriate follow-up to evaluate the impact of ARV exposure *in utero* or during extended infant prophylaxis on uninfected children in resource-limited settings

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 children over one year of age 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.

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

Recommendation 9: Review existing data and currently enrolled trials to establish optimal treatment strategies for children

4.2 Clinical Research: Treatment for Women

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

Current data, including a recent meta-analysis, suggest sex-based differences in CD4, other surrogate markers and viral level responses do not warrant differential monitoring strategies for men and women, 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.

Recommendation 10: Ensure clinical cohorts and clinical trial data are disaggregated by sex, ethnicity and race to support ongoing analysis of potential differences in PK/PD, treatment outcomes and adverse events in these populations.

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

There are limited data available to answer the question about what, if any, impact that female hormone changes during puberty, pregnancy and menopause have on ART outcomes, and conflicting data regarding to what extent hormone-based contraception may have an impact on disease progression. Sex-based hormones may or may not result in differential treatment outcomes; given the conflicting data, more trials with larger cohorts are required to definitely answer many questions regarding the impact of female hormonal changes during puberty, pregnancy and menopause on treatment outcomes.

Recommendation 11: Establish appropriate studies to answer the questions about the impact and interactions of endogenous and exogenous hormones and ART on health outcomes for women.

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 (sdNVP), although still widely used, is not indicated for PMTCT prophylaxis. There is conflicting evidence regarding the decay of nevirapine resistance after maternal exposure to nevirapine prophylaxis; some studies have suggested it may be a viable component of maternal ART if used not earlier than 12 – 18 months following sdNVP while more recent data suggests that nevirapine should not be used earlier than 24 months following sdNVP exposure. Additional studies are required to confirm the latest findings on resistance and options for nevirapine use following sdNVP exposure. 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 12: Assess the impact of ARV prophylaxis to prevent inter, peri and post-partum HIV transmission on future ART options and health outcomes for women.

4.3 Operations Research: Treatment for Women

Consultation participants recommended that operations research be conducted at the national and sub-national level to ensure context-specificity

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 included sex-disaggregated data and analysis.

Recommendation 13: Conduct retrospective and prospective context-specific studies to identify how to leverage the health care system (primary care, sexual and reproductive health services, PMTCT, harm reduction/opioid substitution programmes) to improve women's access to and retention in health care.

Recommendation 14: Conduct operations research, including programme evaluations, to improve ART access, remove barriers to access and ensure long-term follow-up for sub-populations of adolescent and adult women (e.g., women living in rural settings, single women, sex workers, women who use drugs, transgender and women from different ethnic and socio-economic populations).

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 the environmental scan).

Recommendation 15: Conduct operations research, including programme evaluations, to identify nutritional supplementation interventions (micronutrient and macronutrient) for women that can be integrated into care, treatment and support programmes.

Consultation participants noted that additional clinical trials are required to evaluate the impact of macro and micronutrient supplementation interventions on treatment outcomes for HIV-positive women.

5. Investing in a Social Science Research Agenda

Although social science research was outside the purview of the research agenda developed through this initiative, consultation participants and members of the Expert Reference Group recognize the critical role of social sciences in expanding our understanding of the complex role that gender and other cultural, economic, behavioural and structural variables play in influencing access to HIV interventions and retention in care. The following recommendations were developed to encourage investments in HIV-related social science studies:

- Ensure gender equity analyses address the complexity of social and cultural norms and their impact on differential health-seeking behaviours and other variables that influence access to care, treatment and support
- Establish robust, multidisciplinary social sciences studies to address socio-economic, behavioural, cultural, structural and other factors that have an impact on care, treatment and support outcomes for women and their families

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.

6. Annex 1: Project Team and IAS-ILF Expert Reference Group

Project Team

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7. Annex 2: Participant List – IAS 2009 Consultation

Name	Organization
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