Environmental Scan: Mapping HIV Research Priorities for Women and Children

DRAFT FOR CONSULTATION

July 2009

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ACRONYMS

APR	Antiretroviral Pregnancy Registry
ART	Antiretroviral therapy
ARVs	Antiretrovirals
AZT	Zidovudine
CDC	Centers for Disease Prevention and Control
CHER	Children with HIV Early Antiretroviral Therapy
d4t	Stavudine
DMPA	Depomedroxyprogesterone acetate
EMEA	European Medicines Agency
FDA	US Food and Drug Administration
HAART	Highly active antiretroviral therapy
HBC	Hepatitis C virus
IAS 2009	5th IAS Conference on HIV Pathogenesis, Treatment and Prevention
IAS-ILF	International AIDS Society – Industry Liaison Forum
ICW	International Community of Women Living with HIV/AIDS
IPT	Isoniazid prevention therapy
IRIS	Immune reconstitution inflammatory syndrome
IT	Intracellular triphosphate
KIDS-ART-LINC	Kids' Antiretroviral Treatment in Lower-Income Countries
MDR-TB	Multidrug-resistant TB
MSF	Médecins Sans Frontières
mtDNA	Mitochondrial DNA
MTCT	Mother to child transmission
NIH	National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OCPs	Oral contraceptive pills
PACT	Pediatric AIDS Clinical Trials Group
PI	Protease inhibitor
PMTCT	Prevention of mother to child transmission
sdNVP	Single-dose nevirapine
SMART	Strategies for Management of Antiretroviral Therapy
TB	Tuberculosis
VL	Viral load
WITS	Women and Infants Transmission Study

1 Introduction

In 2008, the International AIDS Society – Industry Liaison Forum (IAS-ILF) determined its strategic priorities for 2008-2011. The aim of the 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 the 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, funded through IAS-ILF, 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).[1] The initiative includes four major deliverables:

- An **environmental scan/mapping** (including grey and scientific literature reviews and key informant interviews) that address priority HIV clinical and operations research questions for women and children (including specific components of prevention of 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 **draft report**, including a summary 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** issued by the IAS and supporting partners in early September 2009, confirming the consensus recommendations from the consultation, and strategic direction on advocacy and other activities required to fund and implement identified research priorities.

This environmental scan, the first major deliverable of this initiative, will provide the foundation for the recommendations and subsequent consultation and consensus statement. It is organized into the following sections:

- Methodology
- Literature Review: Clinical Research on PMTCT and Paediatric Treatment
- Literature Review: Clinical Research focused on Treatment for Women
- Key Informant Interviews: Clinical Research – PMTCT, Paediatric Treatment and Treatment for Women
- Literature review: Operations Research focused on Treatment for Women

[1] The ILF Expert Reference Group membership is appended as Annex 1.

- Key Informant Interviews: Operations Research focused on Treatment for Women.

2 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 reviewed a broad list of research questions and identified and prioritized research areas that would optimize clinical treatment and service delivery for women and children.

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

- Clinical research on PMTCT, including paediatric treatment
- Clinical research on treatment for women
- Operations research on treatment for women.

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.

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 and to reflect the substantial increases in HIV investments and the significant expansion in antiretroviral therapy (ART) access in resource-limited settings over the past four years. In 2006, WHO published its recommendations on how to most effectively scale up ART programmes in resource-limited settings using the public health approach, an approach which – following its experience with the '3 by 5' initiative – has guided ART expansion in low and middle-income countries (1).

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 (NIH), US Centers for Disease Prevention and Control (CDC), International Community of Women Living with HIV/AIDS (ICW), International Council of Research on Women (ICRW), 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.

3 Literature Review: Clinical Research – PMTCT and Paediatric Treatment

3.1 Introduction

The most recent estimates from UNAIDS report two million children living with HIV, 370,000 of whom were infected in 2007, mostly through mother to child transmission (MTCT) (2). The number of children on antiretroviral treatment increased from 75,000 in 2005 to almost 200,000 in 2007(3). Despite the substantial increase, coverage remains low relative to the number of infants who are diagnosed with HIV infection and who should be immediately placed on ART. ART coverage of women receiving ARVs for PMTCT was 33% in low- and middle-income countries, although a substantial proportion are still receiving the suboptimal single-dose nevirapine (sdNVP) regimen (4).

While there is consensus about the urgent need to scale up counselling, care and treatment services, there are still a number of important clinical questions related to PMTCT and paediatric treatment that need to be answered.

The ILF-IAS Expert Reference Group identified the following questions as priorities in this research area:

- What are the short- and long-term effects of *in utero* exposure to antiretrovirals (ARVs) in uninfected infants?
- What are the optimal age-adapted parameters for ART initiation and discontinuation among infants and children?
- What is the impact of ART on childhood development (physical growth and/or cognitive development) and additional impact into adulthood?
- Do interventions for malnutrition, TB or malaria have an impact on ART dosage recommendations for paediatrics?
- What are the barriers to developing paediatric formulations of approved and/or recommended drugs?

3.2 Methodology

Authors searched PubMed/Medline to address the above five questions on paediatric treatment issues (searches were limited to articles published from 2006 onwards which were related to children and adolescents, aged 0-18 years).

The following search terms were used regarding the question about short- and long-term effects of *in utero* exposure to ART: “Anti-Retroviral Agents” and “Prenatal Exposure Delayed Effects”. Keywords for optimal age-adapted parameters for ART initiation and discontinuation among infants and children included: “Start”, “Initiation”, “Interruption”, “Infant”, “Child”, “Child, Preschool”, “Antiretroviral Therapy, Highly Active” and “Anti-Retroviral Agents”.

Keywords regarding the question about the impact of ART on childhood development (physical growth and/or cognitive development) included: “Antiretroviral Therapy”, “Anti-Retroviral Agents”, “Adolescent Development”, “Child Development”, “Psychosexual Development”, “Personality Development”, “Language Development”, and “Developmental Disabilities”.

Keywords for the question on whether interventions for malnutrition, TB or malaria have an impact on ART dosage recommendations for paediatrics included: “Antiretroviral Therapy, Highly Active”, “Anti-Retroviral Agents”, “Malnutrition”, “Malaria”, and “Tuberculosis”.

Keywords on the question about the barriers to developing paediatric formulations of approved and/or recommended drugs included: “Antiretroviral Therapy, Highly Active”, “Anti-Retroviral Agents”, “drug development”. Additional literature was found through reviewing the references of these articles.

3.3 Findings

What are the short and long-term effects of *in utero* exposure to ARVs in uninfected infants?

Since the introduction of PMTCT, the incidence of vertical transmission has fallen from 25% to below 2% in settings where optimal (multi-drug prophylaxis) regimens are available. The benefits of PMTCT in reducing the number of infants born HIV infected are indisputable. However, questions remain regarding the effects of *in utero* exposure to ARVs on the uninfected child (5-7).

The Antiretroviral Pregnancy Registry (APR) is a prospective registry that aims to record any teratogenic effects in women exposed to ARVs during pregnancy. It shows that the prevalence of birth defects among women exposed to ARVs at any time during their pregnancy does not appear to be higher than that of the general population. Additional information, including a January 2009 report on all currently available ARVs, is available on the APR website at: http://www.apregistry.com.

The focus of this question is not teratogenicity *per se*, but on all potential clinical impacts of *in utero* exposure on uninfected infants. Data are available regarding the risk for malformations for children who are exposed to ARVs during pregnancy, and there have also been some discussions regarding various pregnancy-related disabilities (8).

The section is grouped into several key sub-headings, based on data from reported scientific literature.

Premature Delivery

Data from the National Study of HIV in Pregnancy and Childhood in the UK and Ireland include 5,009 pregnancies. Of the 3,384 women on highly active antiretroviral treatment (HAART) – defined as a regimen of at least three ARVs, including at least two drug classes – there was an increased risk of premature delivery associated with ART compared to women on mono/dual ART. An increased risk of premature delivery (defined as early than 35 weeks) was also strongly associated with HAART compared to mono/dual ART.

No differences were seen between HAART that included a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). In comparison with exposure to mono/dual therapy, exposure to HAART was associated with lower birth weight, standardized for gestational age (P<0.001), and an increased risk of stillbirth (AOR=2.27; 95% CI, 0.96-5.41; P=0.063) (9).

Mitochondrial Toxicity

Mitochondria are structures found in most human cells that are essential for energy production. Mitochondrial toxicity is a class-wide effect of nucleoside reverse transcriptase inhibitors (NRTIs), associated most strongly with zalcitabine, didanosine, stavudine (d4t) and zidovudine (AZT). The proposed mechanisms of NRTI-associated mitochondrial toxicity include the impairment of mitochondrial DNA (mtDNA) replication and acquisition of mtDNA point mutations leading to altered mitochondrial replication and dysfunction (14).

Clinically relevant symptoms of mitochondrial toxicity include lactic acidosis, peripheral neuropathy, myopathy, cardiomyopathy, hepatic steatosis and pancreatitis.

The impact of mitochondrial toxicity upon HIV-positive infants and children exposed to NRTIs following birth has been previously described (10; 11): the impact of mitochondrial dysfunction related to NRTI exposure in perinatally exposed infants is unclear (13). Although NRTIs have the potential to damage the mitochondrial and nuclear DNA of the foetus, a case report of symptoms similar to mitochondrial toxicity in HIV-negative infants has also been published (12). A review by Kamemoto describes case reports from various authors of neonatal NRTI-associated mitochondrial toxicities (13).

Mitochondrial toxicity has been reported in seven out of 2,644 ART-exposed but uninfected children in the French Perinatal Cohort Study Group, with a further five cases identified through a register. All 12 infants presented with neurological symptoms and seven were also found to have hyperlactataemia. At 18 months, incidence of symptoms compatible with mitochondrial toxicity in the cohort was 0.26% in the ART-exposed but uninfected group (95% confidence interval, 0.10-0.54) compared to 0.01% in the general population (14).

The Women and Infants Transmission Study (WITS) published data on infants born to HIV-negative mothers (n=30), and HIV-negative infants (n=20) born to HIV-positive mothers who received either no ARV therapy (n=10) or zidovudine during pregnancy (n= 10). Zidovudine exposure is known to cause persistent depletion of mtDNA. The study found that children of

HIV-positive mothers exposed to zidovudine had a significantly higher risk for mitochondrial damage than children of non-zidovudine-exposed mothers (15).

However, Pediatric AIDS Clinical Trials Group (PACT) protocols 219/219C that included 1,037 ARV-exposed but HIV-uninfected children did not observe any significant association between overall *in utero* ARV exposure and mitochondrial dysfunction. Nevertheless, in unadjusted models, children with symptoms suggestive of mitochondrial dysfunction were more likely to have been exposed to lamivudine or zidovudine/lamivudine in the third trimester compared to children without signs of mitochondrial dysfunction (16).

Haematological effects

Anaemia is a well-described side effect in children and adults receiving zidovudine-containing HAART; however, data are conflicting regarding zidovudine-induced anaemia in exposed but uninfected children.

A small retrospective long-term follow-up review of 43 infants born to HIV-positive mothers found no increased risk of neonatal illness in children exposed to ARVs *in utero*. No significant differences between median neutrophil counts or haemoglobin were observed between children who received zidovudine in the neonatal period and those who did not. In addition, no significant differences were observed between ARV-exposed and non-exposed children during long-term follow-up at four to seven years of age (17).

However, in a longitudinal study of more than 4,000 children aged between 0 and 18 months, haemoglobin levels were found to be reduced in zidovudine-exposed children up to the age of 18 months (18).

PACT protocol 219/076 published data from a prospective study that included 234 HIV-children (122 of whom were exposed to zidovudine, with 112 receiving placebos). No adverse effects were observed in the HIV-uninfected children with *in utero* and neonatal exposure to zidovudine followed up for as long as 5.6 years; similar data have been published from PACT protocol 076 (19).

WITS compared haematologic values in 1,820 uninfected HIV-exposed and ARV-exposed children with 351 children who were not exposed to ARVs. Infants exposed to ARVs were observed to have small but significant differences in several haematologic parameters for the first 24 months of life (20).

A nested cohort study within a randomized clinical trial (the Mashi study) compared laboratory toxicities among children born to women on HAART during pregnancy with those of women who received zidovudine and a single dose of nevirapine in labour for prevention of MTCT. Exposure to maternal HAART *in utero* increased the risk for infant neutropenia compared to infants exposed to zidovudine up to one month of age; the study also found a significant positive correlation between neutropenia and additional exposure to HAART during breastfeeding (21).

Metabolic, cardiovascular, and cancer risks

A small prospective study of 57 women (20 on zidovudine monotherapy, 25 on HAART and 12 ART unexposed) found that use of HAART during pregnancy induced a significant decrease in serum levels of neonatal insulin compared with the control group (22).

Discussions around the potential toxicity of HAART on cardiovascular disease in uninfected, exposed infants, including the risk of cardiomyopathy, are ongoing (23). Other concerns related to *in utero* exposure to ARVs are an increased risk of infectious diseases in the newborn and malignancies later in life (24; 25).

A prospective study that included 69 HIV-positive pregnant women (compared with a control group of 284 HIV-negative women) showed higher prevalence of haemangioma among infants with prenatal exposure to HAART, but due to the small sample size, no significant difference was seen (26).

A small French study found effects of heterochromatin domains in peripheral blood leukocytes of HIV-uninfected children after perinatal exposure to zidovudine. The relevance of these data is not clear, although these defects could lead to increased risk of cancer and haematopoiesis defects (27).

Data from the PACT 219/219C cohorts that included 1,859 HIV-uninfected children exposed to any ART (of whom 1,847 were exposed to an NRTI) and 184 HIV-uninfected children not exposed to ART found no increase in the occurrence of early childhood cancer (28).

Low birth weight, growth and development

A prospective study from Canada of 39 HAART-exposed, uninfected children observed no significant differences compared to a control group of 24 children born to HIV-negative mothers regarding the neurodevelopment of the exposed children. However, the authors discussed the need to use more precise measures of development and behaviour to better assess the effects of HAART on the developing child (29).

The European Collaborative Study published data from a cohort of 1,912 children: 1,304 of the children were not ARV exposed (987); 317 were exposed to zidovudine monotherapy; and 608 were exposed to two or more antiretrovirals. Although the study found a lack of association between zidovudine monotherapy exposure and growth in uninfected children up to 18 months of age, a small adverse effect on growth on children exposed to combination therapy was observed, although the subsequent clinical implications of this finding are unclear (30).

A prospective study of 32 HIV-negative infants exposed to maternal zidovudine (20 of whom were zidovudine-exposed and 12 of whom were not exposed to ARVs) found no differences in growth in the infants exposed to zidovudine compared with their zidovudine-unexposed counterparts at 18 months. However, the authors note that all of the infants in the study did not develop, in terms of weight and length, as fast as infants with HIV-negative mothers (31).

Data from the ANRS French Perinatal Cohort consisting of 8,192 mothers and exposed, uninfected children found no difference in the incidence of underdevelopment of weight and length for gestational age when comparing children exposed to zidovudine with those exposed to HAART. However, the number of low-birth-weight neonates in this cohort was about twice as that seen in the general population (32).

A study that followed a cohort of 999 women who received either monotherapy (n=492), non-PI HAART (n=373) or PI-containing HAART (n=134) during pregnancy found no differences between the three arms in terms of low birthweight or stillbirth. However PI-containing HAART led to a higher risk of pre-term delivery (33). Another study, from the Côte D'Ivoire (ANRS Ditrame Plus and the MTCTPlus projects), however, did find an association between HAART and low birth weight (34).

What are the optimal age-adapted parameters for ART initiation and discontinuation among infants and children?

The excellent response of infants and children to ART is well documented and thanks to increasing ART scale up and coverage, AIDS diagnoses in children are declining (35). Paediatric ART centres have been established at multiple sites in low- and middle-income countries, and have proven feasible and successful (36-44). Overall, ART responses have been found to be similar among infants and children in high- and low-income countries.

Although consensus has been reached regarding initiating ART in infants younger than 12 months as early as possible (45; 46), with such guidance incorporated into the most recent WHO paediatric treatment guidelines (47; 48), data to ascertain the optimal age-adapted parameters for ART initiation are still lacking, and the debate over when to start treatment in children older than one year of age continues (43).

The Children with HIV Early Antiretroviral Therapy (CHER) study randomized 125 infants to defer therapy until an infant's CD4 cell percentage declined below 25 or they developed clinical symptoms of HIV disease and 252 to receive immediate therapy lasting until the infant's first birthday. The Data and Safety Monitoring Board halted the study after 20 infants in the deferred therapy group (16%) died compared to 10 (4%) infants in the immediate therapy group (49). The European Collaborative Study had published data in 2006 about the advantages of initiating treatment early (50).

Results from the PACT 356 study further confirmed the benefits of early initiation of treatment. This multicentre open-label phase I-II trial compared three different ART regimens. Children were stratified according to age: either three months or younger (early therapy) or older than three months (delayed therapy). The results showed that compared with those who started treatment early, fewer infants in the delayed-treatment group (which delayed treatment until week 200) reached viral loads below 400 copies per millilitre (51).

The Kids' Antiretroviral Treatment in Lower-Income Countries (KIDS-ART-LINC) Collaboration, a network of paediatric HIV treatment programmes in sub-Saharan Africa found that not only HIV/AIDS clinical staging, but also nutritional status and baseline

anaemia, were essential indicators for survival rates among HIV-infected children whose median age was five years (52). Advantages of early treatment have also been shown to be beneficial after six years of follow up (53).

A meta-analysis for predicting mortality in 2,510 untreated HIV-infected children found that CD4 counts are the most important indicator of mortality. It also found that weight-for-age and haemoglobin levels need to be taken into account when determining the optimal time to initiate treatment (54).

An analysis of 766 perinatally-infected children from the PACT 219C cohort group born before 2004 found that the risk of switching treatment was higher in children who initiated ART at a CD4 percentage of less than 15% and/or with higher age at initiation. The analysis also found that children treated with regimens inconsistent with clinical guidance had a higher risk of switching (55).

The results of the Strategies for Management of Antiretroviral Therapy (SMART) study, published in 2006, provided good evidence that CD4-count guided, structured treatment interruptions were an inferior strategy compared with continual treatment in adults (56) (57). However, structured treatment interruption trials in children are still in progress, and include CHER and BANA 2 (Botswana). A pilot study by the PENTA (PENTA 11) group is due to be published soon.

Observational, unplanned treatment interruption studies in children and adolescents have found that unplanned treatment interruptions are associated with disease progression (58). The Collaborative HIV Paediatric Study analyzed data from 71 children undertaking 82 unplanned interruptions. The rate of CD4 percentage decline was found to be 6.2% annually, and the decline was found not to be age dependant (59).

A small cohort of 26 HIV-infected children found that partial treatment interruption (by discontinuing the PI in PI-based HAART regimens) did not result in CDC-classified disease progression and no significant changes in viral loads were observed although a significant decrease in CD4 percentage was seen (60).

There is ongoing work at identifying the risks and benefits of structured treatment interruptions among paediatric populations, including an intriguing study that found a decrease of viraemia in a subset of children undertaking increasingly longer cycles of treatment interruptions (starting at three days, and increasing by two days in length for each cycle), which appears to be due to increased interferon gamma production (61).

What is the impact of ART on childhood development (physical growth and/or cognitive development) and additional impact into adulthood?

Few studies have examined the impact of ART on childhood development, and those that have suggest an overwhelmingly positive role compared with untreated HIV infection. However, there is a paucity of data regarding the long-term effects of individual drugs on childhood development.

The metabolic side effects of HAART are well described in adults. These include insulin resistance, dyslipidaemia, hyperlactataemia and osteopenia. Although a recent study from a high-income setting found that these side effects also affect children, the increased risk of coronary artery disease associated with many of HAART's metabolic effects may only be of concern when they reach adulthood (62; 63).

The impact of HAART on psychiatric and psychological disorders has been described in HIV-infected children: psychiatric morbidity seems to be higher in HIV-infected treatment-naive children compared to uninfected children (64). Impacts on neurocognitive development may depend partly on the effects of HIV on the brain and partly on HAART (65). Neurodevelopmental outcomes were observed in 62 children under three years of age in a high-income setting, of which 22% had abnormal neurological signs consistent with HIV encephalopathy and 40% exhibited significant developmental delay (66). Progressive HIV encephalopathy in children has been observed to respond well to HAART (67).

The PACTG 219C study team has published data showing significantly lower mean mental and motor scores in HIV-positive infants under one year of age compared to their HIV-negative counterparts; improvements were observed in infants who started a PI-containing regimen (68).

Bone mineral density in 37 HIV-positive children (81% of whom were taking HAART) has been shown to be lower than in HIV-negative children, although no negative association with HAART was observed. (69).

Do interventions for malnutrition, tuberculosis or malaria have an impact on ART dosage recommendations for paediatrics?

Tuberculosis

The impact of HIV on the spread of tuberculosis (TB) is well documented, with children representing 15% to 20% of the global TB burden: children also represent a substantial number of individuals co-infected with HIV and TB (70)(71). HIV-infected children are at a 20-fold higher risk for contracting TB than HIV-negative children (72).

As with the adult HIV-positive population, TB is one of the biggest challenges for successful management of children with HIV. The incidence of childhood TB in a community in Cape Town was 407 cases/100,000 population per year (73). Diagnosis and management of childhood TB is difficult even in the absence of HIV, and becomes more complicated when there is co-infection with HIV (74; 75). The effectiveness of HAART in reducing morbidity and mortality among co-infected children is clear (76; 77).

In a review, Marais *et al* describe the main challenges for the management of childhood TB in HIV-infected children (78). Recommendations for treatment in HIV-infected children are similar to treatment in uninfected children. In many countries, thambutol has replaced thiacetacone, which has been associated with Stevens-Johnson syndrome; ethambutol appears to be safe in children (79).

Treatment outcomes in HIV-infected children are poorer than their HIV-negative counterparts due to a variety of factors: higher incidence of co-infections; poorer absorption leading to lower levels of anti-TB drugs; misdiagnosis of TB; poor penetration of TB drugs into the fibrotic area; poor adherence to treatment; and advanced immune suppression.

Drug interactions, such as the well-documented interaction between rifampicin and NNRTIs and PIs, are also of major concern. Induction of cytochrome P450 by rifampicin lowers plasma concentrations of protease inhibitors. Lopinavir concentration is reduced by rifampicin. A study from South Africa that included 30 children aged between seven months and 3.9 years showed that reductions in the plasma levels of lopinavir can be attenuated by using a higher dose of ritonavir (lopinavir/ritonavir ratio of 1:1) (80).

In the ACTG 22513 study of 15 HIV-negative subjects, atazanavir levels did not maintain therapeutic levels in combination with rifampicin (81). A study from Thailand of seven adult patients suggests that nevirapine dosing should be increased when co-administrated with rifampicin (82).

In order to measure such interactions, therapeutic drug monitoring is possible in high-income countries, but due to its cost, this is unrealistic for most middle- and low-income countries (83).

Another challenge in many settings is the lack of approved fixed drug combinations for children for the treatment of HIV and TB, which leads to a high pill burden (84).

BCG vaccination is recommended for HIV-positive children. However, 25 case reports of BCG vaccine-induced disease have been published. Treatment outcomes of distant BCG disease have been poor (85). A retrospective study of 352 children has also found BCG complications – mainly local or regional immune reconstitution inflammatory syndrome (IRIS) – in 6% of the children after starting HAART. Independent risk factors for adverse effects in this study were a high baseline viral load and younger age (86).

An important option for preventing childhood TB is isoniazid prevention therapy (IPT), which has led to a marked reduction in TB cases in high-prevalence areas (87; 88).

The situation regarding HIV/TB co-infection is complicated by the emergence of multidrug-resistant TB (MDR-TB) strains. Treating MDR-TB requires administration of a minimum of four effective drugs. Overlapping toxicities with HAART have been well established, and drug interactions are also a concern (89).

Common adverse effects include: nausea (associated with didanosine, zidovudine, ritonavir, pyrazinamide); peripheral neuropathy (stavudine, didanosine, isoniazid); rash (nevirapine, abacavir, isoniazid); and hepatitis (rifampicin, nevirapine, PIs) (90).

Malaria

Like TB, malaria is a highly prevalent disease in countries with a high burden of HIV. However, our search strategy on ART and malaria in children provided just one article. This

article, from Uganda, describes a high risk of neutropenia when artesunate/amodiaquine (the first-line treatment for malaria in 15 African countries) was administered to HIV-positive children. The highest risk for neutropenia was in children on ART. The clinical significance of this finding was an increased risk of pneumonia during episodes of neutropenia (91).

Malnutrition

Malnutrition contributes to 5.6 million of the 10 million deaths in children per year. The Blantyre working group collectively cares for more than 100,000 severely malnourished children per year. In their 2008 *Lancet* viewpoint commentary, they describe the lack of knowledge of pharmacokinetics, particularly complex drug interactions, as it relates to ART/TB and malnutrition (92).

What are the barriers to developing paediatric formulations of approved and/or recommended drugs?

Despite many challenges, antiretroviral treatment has been effective in low-income settings (93). However, an unmet challenge remains: to make paediatric fixed-dose combinations available in resource-limited settings (92). ART with a low pill burden has been proven possible for children, and successful use of a once-daily fixed-dose combination of nevirapine, stavudine and lamivudine has been described in Zambia (94; 95).

In December 2007, WHO spearheaded the launch of a global campaign, “Make Medicine Child Size”, to accelerate access to paediatric drugs. The campaign is endorsed by UNICEF, UNITAID, Médecins Sans Frontières (MSF), Save the Children, the African Medical and Research Foundation, the National Institute of Child Health & Human Development, the International Alliance for Better Medicines for Children, the International Pediatric Association, the International Federation of Pharmaceutical Manufacturers & Associations, and others (96).

One of the challenges facing the development and manufacture of paediatric formulations is the imperative that drugs should be assessed for side effects that may impact upon child development. Formulations must be adapted for weight or age and may need to be available in liquid formulations for newborns and infants. However, the Committee on Paediatric AIDS argues that liquid formulations for children might be problematic. Liquid formulations often need special storage, such as refrigeration, which is not always available. Often, children do not like the taste of the liquid formulation, and the content additives may not be suitable for children. They suggest better options might be small tablets; tablets which can easily be divided into halves or quarters; or tablets that can be crushed or dissolved in water (97).

In a 2007 review, Dunne examines the myriad challenges facing the development of antiretroviral agents for children (98).

These include:

- Assessing the influence of age and weight on dosing.

- Correlating measures of efficacy with drug exposure, independent of the assessments in adults, given the significant variability in pharmacokinetic parameters in children.
- Ensuring that drugs within a co-formulated product are dose-adjusted for each component.
- Running additional assessments of pharmaceutical quality, such as stability and dissolution testing, which can be especially complicated with reconstituted oral suspensions.
- Potentially rerunning full clinical programmes due to difficulties in basing the suitability of new product formulations on bioequivalence studies.
- The scarcity of sites equipped to run paediatric pharmacokinetic studies efficiently.
- The ethical constraints in obtaining informed consent and assent in children for paediatric pharmacokinetic studies.
- The additional resources and expertise required to comply with requirements for registration of paediatric formulations beyond that of an adult programme.
- The need to acknowledge regional constraints in choosing a formulation, for example, the lack of access to clean water as a mitigating factor in the use of liquid suspension.
- The difficulty in extrapolating taste preferences in adults to children.
- The difficulty in obtaining certain safety tests, such as electrocardiograms, in children, and the limits on the amount of blood taken for testing.

3.4 Analysis

Short- and long-term effects of *in utero* exposure

The review of the literature regarding effects of maternal ART on children as part of PMTCT prophylaxis indicates that there are still many areas where clarification is urgently needed; even some of the areas that have been studied have resulted in conflicting findings, depending on the study. For example, mitochondrial toxicities in uninfected children with *in utero* exposure to ARVs were observed in the French Perinatal Cohort Group, but not in the PACTG studies.

Limited data are available in establishing the risk of cancer, metabolic and cardiovascular health or neurodevelopmental challenges in exposed but uninfected children. It is also unclear to what extent exposure to combination therapy during pregnancy impacts on infant growth and development.

Optimal age-adapted parameters for ART initiation and discontinuation

Studies have demonstrated the benefits of starting ART immediately after diagnosis for HIV-infected children under one year of age, independent of immunological or virological parameters. In the absence of treatment, there is a high risk of impaired immune development leading to an increased risk of morbidity and mortality in children. Although there are clear guidelines regarding when to start ART in children under one year of age, less data are available to provide guidance for children over one year of age.

The early discontinuation of the SMART trial demonstrated the negative impact of CD4 count-guided structured treatment interruptions among adults. There are currently no data

on structured treatment interruptions in children. However, studies are underway (CHER; BANA 2) and a pilot study involving shorter on-off treatment cycling strategies warrants further attention. Data on the safety and effectiveness of novel approaches to treatment interruption strategies are urgently needed for children.

Impact of ART on childhood development

The impact of ART on childhood development has been studied, but the focus has primarily been on the advantages of starting HAART in HIV-positive children. Consequently, data regarding the beneficial effect of HAART are more readily available than potential side effects of individual drugs on growth and childhood development.

Interventions for co-infections and their impact on ART dosage recommendations

The impact of interventions for malnutrition, TB or malaria on ART dosage also requires further research. Although interactions between rifampicin and PIs have been well studied, and the potential for similar toxicities are well described, there have been few paediatric studies.

Lack of knowledge about the impact of malaria treatment and treatment for malnutrition on HIV treatment is a challenge, particularly given the huge burden for both diseases in low- and middle-income countries.

Barriers to developing paediatric formulations

There are a number of barriers to developing paediatric formulations of antiretroviral drugs for use in resource-limited settings, such as the unsuitability of liquid formulations used in high-income countries for these settings. Especially during the first year of life, adjustment of the dose to body weight is a challenge and drugs must be adapted to this. In order to make HIV medicine child size, the pharmaceutical industry, donors and international agencies must work together to overcome these barriers and make paediatric treatment a priority (99).

3.5 Conclusions

What are the short- and long-term effects of *in utero* exposure to ARVs on uninfected infants?

The literature review clearly shows the necessity of monitoring short- and long-term effects of ART exposure during pregnancy and delivery on the uninfected child.

Cohorts must be established to follow up ARV-exposed, uninfected children in order to monitor the long-term effects of drug exposure. The focus should not only be on mitochondrial toxicity, but also on the risk of other metabolic effects and cancer. Adverse pregnancy effects and perinatal outcomes must be documented, with a special focus on pre-term labour for women on HAART. Drug regimens with a lower genotoxic risk must be identified, and a comparative evaluation is essential.

What are the optimal age-adapted parameters for ART initiation and discontinuation among infants and children?

Knowledge regarding optimal treatments for children is improving, and newer, better antiretrovirals for children are becoming available. However, several major questions are still not fully answered:

- What are the best parameters to define eligibility for treatment in children?
- How must these parameters be adapted to age?
- Is there an urgent need for initiation of children older than one year?
- When is there a need to switch treatment?
- What, if any, strategies for treatment interruptions in children are possible?

What is the impact of ART on childhood development (physical growth and/or cognitive development) and additional impact into adulthood?

Few data are published on this topic. Longitudinal studies are needed to understand the impact of ART on childhood development.

Do interventions for malnutrition, TB or malaria have an impact on ART dosage recommendations for paediatrics?

Isonazid prevention therapy (IPT) has proven to be effective in preventing TB in children who are not on HAART. Studies are required to understand the effect of IPT in children on antiretrovirals. There are no data regarding whether IPT should be considered in countries with a low prevalence of TB.

Data on interactions between TB drugs and ARVs in childhood are limited, and most data are extrapolated from adults: more paediatric studies are needed to determine interactions in children.

No data are available regarding safe and effective malaria treatment for children on HAART. Studies answering questions about the best first-line malaria treatment in children on ARVs are needed.

Malnutrition and HAART is not well studied. There is a lack of knowledge concerning when to start treatment in malnourished children, and little is known regarding the pharmacokinetics of ART and TB drugs in malnourished children.

What are the barriers to developing paediatric formulations of approved and/or recommended drugs?

Although many barriers have been identified, the will is there. How, then, can the international community and all stakeholders make paediatric formulations available as early as possible after efficacy has been proved for adults?

4 Literature Review: Clinical Research on Women

4.1 Introduction

The biological and social vulnerability that women face with respect to HIV infection is well described (100). However, in most countries, ART coverage for women is equal to or higher than that for men. This is likely to be due to two different entry points for treatment: one through regular clinics, and one through antenatal care.

However, women are still poorly represented in clinical trials, and there is a great need to address outstanding knowledge gaps in clinical issues that are unique to women. The ILF-IAS Expert Reference Group identified the following questions as priorities in this research area:

1. What is the impact of periodic treatment (due to PMTCT ARV interventions) on future treatment options for women?
2. Are there differences between men and women in ART pharmacokinetics and pharmacodynamics, and do/should these differences have an impact on dosage recommendations and treatment outcomes?
3. What is the impact of female hormone fluctuations during adolescence, pregnancy and peri- or post-menopause on treatment outcomes (e.g., pharmacodynamics)?
4. Are there sex differences (based on CD4+ and viral load) that are unique to women and which might have an impact on ART initiation and monitoring (i.e., should women be stratified for ART initiation and monitored differently based on viral load/CD4)?

4.2 Methodology

PubMed keywords related to the impact of periodic treatment (due to PMTCT ARV interventions) on future treatment options for women included: “Subsequent Pregnancy”, “Antiretroviral Therapy, Highly Active” and “Anti-Retroviral Agents”.

Keywords related to the questions about sex- based differences in ART pharmacokinetics and pharmacodynamics, whether these differences will have an impact on dosage recommendations, treatment outcomes, ART initiation and monitoring strategies included: “HIV”, “Antiretroviral Therapy, Highly Active”, “Anti-Retroviral Agents”, “Gender Identity”, “Sex” and “Sex Characteristics”.

Keywords related to the impact of female hormone fluctuations during adolescence, pregnancy, or post-menonpause on treatment outcomes (e.g., pharmacodynamics) included: “Female Hormones”, “HIV”, “Antiretroviral Therapy, Highly Active” and “Anti-Retroviral Agents”. Additional literature was identified by reviewing the references of these articles.

4.3 Findings

What is the impact of periodic treatment (due to PMTCT ARV interventions) on future treatment options for women?

HAART has reduced the risk of mother to child transmission to between 1% and 2%. In settings where HAART is not available or there is no indication for starting HAART, simpler antiretroviral regimens are offered for a defined period of time (5). A major breakthrough was the study from the PACTG 076 group, which showed that AZT for the mother ante- and intra-partum and for the newborn for six week reduces the risk of HIV transmission by two thirds (6). The focus of this intervention is the prevention of HIV transmission to the child.

After AZT, single dose nevirapine (sdNVP) has been established as another drug for preventing mother to child transmission of HIV. Although studies have found that NNRTI-resistant virus can emerge following sdNVP, compromising the mother's future treatment options, a study from Lusaka has shown that the reuse of sdNVP in a subsequent pregnancy did not appear to influence the risk of mother to child transmission (101).

Although sdNVP strategies appear to be efficient for preventing mother to child transmission, available data regarding the consequences for the mother are scarce. There is an ongoing debate focusing on the use of sdNVP during pregnancy to protect the child and the potential for the emergence of nevirapine resistance on the mother's health (102).

In resource-limited settings, where nevirapine is the most commonly used third HAART drug, the impact of resistance to nevirapine is a major concern. In a study from South Africa that examined the impact of sdNVP on 67 women exposed to the drug for the first time, 52.3% of DNA samples and 87.1% of RNA samples showed presence of K103N mutation six weeks after receiving sdNVP. A significant decline in the prevalence of the mutation was observed in the RNA samples after three months (65.4%), seven months (38.9%) and 12 months (11.3%).

In the DNA samples, K103N prevalence declined to 4.2% after 12 months. The authors conclude that K103N resistance might not persist in the long term, and should not be of major concern if nevirapine is not prescribed again during the following 12 months. The study did not measure other potential NNRTI mutations (103). However, in a smaller study of 22 women, nevirapine-resistant mutants persisted for more than one year in 23% of the sample (104).

A meta-analysis examining the prevalence of nevirapine resistance four to eight weeks after delivery found a prevalence of resistance in 35.7% of women receiving sdNVP without postpartum treatment, compared to 4.5% of women who received sdNVP plus postpartum ART (105). These data suggest that the risk of nevirapine resistance can be substantially reduced if supplemental postpartum treatment is prescribed. The rationale behind this is that ART will suppress viral load, thus avoiding selection of nevirapine-resistant viruses (106).

Data from the Perinatal HIV Prevention Trial Group showed that women exposed to nevirapine had a less favourable treatment outcome compared to women without prior experience of sdNVP when treated with nevirapine-based HAART. This was observed even in women where nevirapine resistance was not found (107). In a study with 218 women in Botswana, this finding was confirmed when treatment was started within six months after

receiving sdNVP, with no significant difference between women receiving placebos and sdNVP (108).

HIVNET 012 evaluated data from 44 Ugandan women who were re-exposed to sdNVP in a subsequent pregnancy. The number of women in whom the K103N mutation was detected two years after the second dose was similar to that seen two years after the first dose. Three years after re-exposure to sdNVP, K103N was not observed in 92.3% of the women (109).

Are there differences between men and women in ART pharmacokinetics and pharmacodynamics, and do/should these differences have an impact on dosage recommendations and treatment outcomes?

The role that sex plays regarding differences in ARV side effects has been well established. For example, nevirapine is not indicated for women with a CD4 count above 250 cells/mm³ (46). In 2004, nevirapine's manufacturer, Boehringer Ingelheim, issued a warning about the increased risk of hepatotoxicity in women with a CD4 count >250 cells/mm³ (110). In 2006, the US Food and Drug Administration (FDA) issued a warning to not initiate nevirapine in women with a CD4 count >250 cells/mm³ and men with a CD4 count >400 cells/mm³ (111). A small study comparing 11 women and men had previously shown statistically significant differences in the plasma concentrations of nevirapine (112).

Efavirenz levels and toxicity are also affected by sex differences. A 2006 study, following a cohort of 255 patients using the Therapeutic Drug Monitoring Service in the Netherlands, found that mean plasma efavirenz levels were significantly higher in females compared to males (4.0mg/l versus 2.8mg/l). This difference was seen independently of body weight, height, body surface, and contraceptive use (113). Although an analysis of sex differences between 96 women and 337 men attending London's Royal Free Hospital on efavirenz-containing first-line HAART found similar virological and immunological responses, women were more likely to discontinue treatment. However, this difference was not found to be statistically significant (114).

Rotger points out the following in a 2005 review about genetic, ethnic and sex differences in antiretroviral pharmacokinetics (115):

- Indinavir: two population-based studies found an apparent decrease in drug clearance and an increase in drug levels in female compared with male patients, after adjustment for body weight, but other studies have found similar pharmacokinetic values in women and men.
- Saquinavir (alone or boosted with ritonavir): women appear to have higher exposure in terms of maximum and trough concentrations, as well as a 50% reduction in clearing the drug from the body via the kidneys.
- NNRTIs: no conclusive results have been found in several studies.

Nevertheless, some studies have described an increase in the observation of adverse effects of NRTIs in women, such as a higher rate of rash in nevirapine-containing regimens, as well as higher rates of side effects in PI-containing treatments (116).

Data are unclear regarding sex differences in the efficacy and side effect profile of NRTIs. Intracellular triphosphate (TP) concentrations have been reported to be higher in women than in men by 2.3 and 1.6 fold for zidovudine and lamivudine respectively (117). Conversely, a study from the NIAID AIDS Clinical Trials Group found that zidovudine TP concentrations were significantly higher in men than in women (118). Reasons for sex differences could be body weight and composition, renal clearance and P-Glykoprotein activity (119).

An analysis of 53 women and 60 men with undetectable viral loads 24 weeks after initiating treatment found a significant difference regarding changes in CD4 counts: the mean CD4 count change in women was 170 cells/mm³ compared to 100 cells/mm³ in men (120).

In contrast, the EuroSIDA group found no significant differences in its cohort regarding clinical, virologic or immunologic outcomes (203 males and 511 females were included in the analysis) (121). The EuroSIDA analysis, however, confirmed results of other studies which had found that women have a higher CD4 count than men (approximately 100 cells/mm³) early in HIV infection. This has not been proven to result in better treatment outcomes, suggesting that there might be different "normal" CD4 ranges for men and women.

What is the impact of female hormone fluctuations: adolescence, pregnancy/peri- or post-menopause on treatment outcomes (e.g., pharmacodynamics)?

The role of hormonal contraception with regard to the risk of acquiring HIV infection, as well as the effect of hormonal contraception on disease progression, remains unclear.

A prospective cohort of 1,206 Kenyan women attending a sexual health clinic found an increased risk for HIV infection among women with hormonal contraception compared to those without (122). However, a multicentre study of 6,109 women attending family planning clinics in Uganda, Zimbabwe and Thailand found no increased risk of HIV infection for women who used hormonal contraceptives (123). A South African study of 4,200 women enrolled in a cervical cancer screening trial also found no increased risk of HIV infection when using hormonal contraception (124).

A recent report from a Zambian trial that included 595 women not on ART at time of hormonal contraception initiation, where 190 used depomedroxyprogesterone acetate (DMPA) and 112 used oral contraceptive pills (OCPs), found that women on either DMPA or OCPs were more likely to become eligible for ART or experience disease progression compared with the women in the study using a non-hormonal contraceptive method, the intrauterine device (125).
Hormonal contraceptive therapy has not been shown to have an effect on AZT pharmacokinetics, and maraviroc had no effect on the oral contraceptives, ethinyloestradiol and levonorgestrel (126).

ACTG A5093 found no significant changes in nelfinavir, efavirenz or nevirapine plasma levels during co-administration with DMPA. Similarly, DMPA levels were not affected by antiretroviral treatment (127; 128).

There is some evidence that HIV-infected women may experience earlier onset of menopause, depending on CD4 count and whether or not they are on treatment. No significant differences in menopause onset have been observed in women with a CD4 count above 500 cells/mm³ or for those on HAART (129).

An analysis of 263 Müllerian inhibiting substance samples from participants in the Women's Interagency HIV study found no effect of HIV on ovarian aging (130).

Our review found no studies to address the question on treatment outcomes related to female hormone fluctuations.

Are there sex differences (based on CD4+ count and viral load) that are unique to women and which might have an impact on ART initiation and monitoring (i.e., should women be stratified for ART initiation and monitored differently based on viral load (VL)/CD4)?

The current guidelines do not differentiate between men and women when it comes to monitoring and initiation, with the exception of pregnant women, and nevirapine initiation, which is not recommended for women with CD4 counts above 250cells/mm³ (131)(46).

Two studies published in April 2009 found that starting treatment at higher CD4 counts results in better outcomes in adult patients (male and female): starting treatment at CD4 counts below 500cells/mm³ was associated with a higher risk of AIDS and/or mortality (132; 133). However, neither study was a randomized clinical trial and current recommendations to start treatment at 350 cells/mm³, based on best possible evidence, are reflected in the IAS-USA treatment recommendations (134).

Data from one of the studies, NA-ACCORD, found an increased risk of death in women. However, this risk was not significant after adjusting for injecting drug use or hepatitis C virus (HCV) infection (135). Overall, there is little evidence that the response to treatment in HIV-positive women is different than in men (135). Consequently, no data produced so far provides any evidence for differences in monitoring or treatment initiation for women.

4.4 Analysis

Impact of periodic ARV exposure on future treatment options for women

The impact of periodic treatment on future treatment options in women has been studied with respect to single dose nevirapine; emerging resistance has been demonstrated, although some studies suggest that such resistance does not play a significant role as long as nevirapine is not included as part of the maternal treatment regimen in the first year after nevirapine PMTCT prophylaxis exposure. There are insufficient data regarding the effect of other ARVs used during pregnancy on future treatment options for women.

Sex-related differences in pharmacokinetics and pharmacodynamics

There is clear evidence that pharmacokinetics and pharmacodynamics are different in men and women for a number of ARVs. The most obvious and clinically relevant example is that initiation with nevirapine is contraindicated in women with a CD4 count >250 cells/mm³, while men can be started on nevirapine with a CD4 count >400 cells/mm³. However, none of the findings of different pharmacokinetics and pharmacodynamics have been found to be relevant enough to be reflected in treatment guidelines.

The impact of female hormonal fluctuations on treatment outcomes

This review was unable to identify any relevant data on hormone fluctuations during pregnancy and adolescence and their potential impact on ARVs. One recent study did address the effect of hormonal contraception on disease progression, suggesting a higher risk for women using either oral or DMPA contraception.

Studies indicate that there are no major drug interactions between hormonal contraceptives and the tested ARVs.

There may be sex differences regarding treatment responses on ART, although the one published paper addressing this issue was not powered to demonstrate that sex-differentiated clinical guidance is required. Most important is the evidence that both men and women need to be started earlier in disease progression and that deferred treatment is – for both sexes – associated with negative treatment outcomes.

4.5 Conclusions

What is the impact of periodic treatment (due to PMTCT ARV interventions) on future treatment options for women?

Nevirapine is a well-established drug in the prevention of mother to child transmission. The drug's positive effect of reducing infection in newborns is not questioned.

The consequences for women of using nevirapine, however, are less clear. While some data suggest that exposure to single dose nevirapine does not affect women's treatment outcomes if the drug is not re-used within six to 12 months, there is some evidence that resistance to nevirapine – whether or not it is detected – may adversely affect women's treatment choices and outcomes.

More research is needed on the effects of sdNVP on women, as well as other regimens that are used for PMTCT purposes. This should include using HAART during pregnancy and stopping it after delivery or after breastfeeding.

Are there differences between men and women in ART pharmacokinetics and pharmacodynamics, and do/should these differences have an impact on dosage recommendations and treatment outcomes?

There is some evidence that ART may have different pharmacokinetics and pharmacodynamics in men and women, which may have consequences for treatment regimens.

There needs to be a greater number of clinical trials which analyse treatment response data according to sex, although to be adequately powered, this requires more participation by women in trials.

What is the impact of female hormone fluctuations: adolescence, pregnancy/peri or post-menopause on treatment outcomes (e.g., pharmacodynamics)?

There are insufficient data to answer this question. Some published data suggest an impact of hormonal contraception on disease progression. There is an urgent need to address this issue.

Are there sex differences (based on CD4+ and viral load) that are unique to women which might have an impact on ART initiation and monitoring (i.e., should women be stratified for ART initiation and monitored differently based on VL/CD4)?

To date, there is no evidence to support differential ART treatment strategies or ART monitoring between men and women. However, the number of women taking part in clinical trials that would answer these questions, and the overall number of these trials, is still too low to definitively answer these questions.

5 Key Informant Interviews: Clinical Research Priorities – PMTCT, Paediatrics and Women

5.1 Methodology

We conducted telephone interviews with four experts in the field of women and children: **Jintanat Ananworanich**, Clinical Trials Coordinator, HIV-NAT Bangkok; **Myrto Schaefer**, Paediatric Advisor, MSF Australia; **Agnès Saint Raymond,** Head of Scientific Advice & Orphan Drugs Sector, Paediatric Medicinal Products, European Medicines Agency (EMEA); and **Nigel Rollins**, Department of Child and Adolescent Health and Development, WHO .

The nine questions addressed in the literature review we have described were sent to the experts beforehand. At the beginning of the phone call, the interviewees were informed about the aim of the interview and of the entire project.

The focus during each interview was on the following three questions, which guided discussions on all nine topic areas:

1) What is your idea about the particular question?
2) What are the main sources (articles, grey literature and/or policy statements) to address this particular question?
3) What specific research question needs to be answered in the above discussed topic?

The duration of the interviews was between 30 and 60 minutes.

5.2 Findings

What are the short- and long-term effects of *in utero* exposure to ARVs on uninfected infants?

The interviewees pointed out that very little information is available on this topic. One of the problems closely related to this question is to the desire to provide the most efficient drugs for reducing mother to child transmission. MSF would like WHO to recommend the use of HAART rather than sdNVP; however, the benefits and trade offs for both mother and child must be clarified.

New drug regimens for PMTCT are called for and need to be tested, the interviewees noted. Some agents, such as tenofovir, are currently being used, but are not registered for use in infants or during pregnancy.

More information is also needed about the effects of exposure of the children to ARVs through breastfeeding.

Data regarding the metabolic consequences of drugs used for PMTCT are not conclusive; there is a need for better understanding of the risks for the uninfected children. However, in their experience, the key informants have not observed many adverse effects.

Teratogenetic effects in children have been described for efavirenz, but most of the other ARVs used for PMTCT appear to be fairly safe.

The key informants urged for the study of the short- and long-term effects of newer drugs, such as ritonavir-boosted lopinavir and tenofovir, on the uninfected infant exposed *in utero* in order to have more, and potentially better, options available. This should be done with the support of the pharmaceutical industry. It is also important to establish networks for pharmacovigilance. The EMEA noted that some European centres are already interested in establishing or participating in such networks.

What are the optimal age-adapted parameters for ART initiation and discontinuation among infants and children?

Early initiation of infants <12 months of age is a standard of care and is adopted in guidelines. One interviewee asked whether the evidence for initiating at < 12 months was good enough or whether guidelines should include children up to the age of 15 months?

Another question posed was whether children, who were not infected perinatally, but through breastfeeding, should also be initiated on ART as early as possible? There may well be a differentiate between children infected perinatally and through breastfeeding. For example, children infected via breastfeeding may acquire immunological competence, which may help them to survive for longer without treatment.

Hopefully, some of the questions for children aged between one and eight years will be answered by the PREDICT study: results should be available early next year. One concern is that although CD4 count may not be the best parameter to establish the optimal timing for treatment initiation, the more appropriate measure, CD4 percentage, is not universally available.

A more difficult question may be when to initiate ART in adolescents. Studies in Uganda and Zimbabwe are currently underway. Two of the experts stated that preliminary data from these studies suggest that adolescents seem to do quite well without HAART and the optimal time to initiate treatment in this sub-population still needs to be defined.

The interviewees were divided over treatment interruption and whether more studies were required. While some said that the results from SMART should set the standard for children, others said that results from paediatric studies were needed to fully answer this question.

What is the impact of ART on childhood development (physical growth and/or cognitive development) and additional impact into adulthood?

To answer this question, monitoring is needed and networks must be established.

All experts pointed out the positive effect of HAART on infected children. Evidence of restored head circumference, as evidence of normal growth, in children started on treatment was mentioned. They also pointed out that when children no longer have stunted growth, there are also psychological benefits and many contextual issues, which are influenced by the care environment (family, orphanage or community environment).

Do interventions for malnutrition, TB or malaria have an impact on ART dosage recommendations for paediatrics?

Malnutrition

One important research question is whether ART should be initiated as soon as malnourished children are diagnosed as HIV positive or whether is better to wait until physical rehabilitation. At the moment, malnourished children are receiving the same per-kg ARV dosages as children who are not malnourished. However, renal perfusion and cardiac output is reduced by up to 40% (this is known as "reductive adaptation") in malnourished children. It is also known that malnourished children use just 0.5g proteins per kg the day before, and 6-7g proteins per kg the day after they are treated for malnutrition. These dramatic differences may have consequences for the metabolism of ART. However, in resource-limited settings, drug levels are not often measured.

As well as the challenge of malnutrition, treating children with HAART is leading to concerns around metabolic problems, such as hyperlipidaemia and hyperglycaemia. Currently, no drugs to treat metabolic problems are approved for children.

Tuberculosis

Children aged three or younger are the most vulnerable to TB infection, but are also the most difficult to diagnose. Understanding how to treat children co-infected with HIV and TB must also focus on how to improve TB diagnosis.

Using TB treatment concurrently with a second-line HIV treatment is a major challenge: it is currently unknown what treatment is best if a protease inhibitor is used and little information is available regarding interactions with rifampicin/rifabutin and protease inhibitors in children.

It is also thought that there may also be some racial differences (for example, Asian versus African patients may respond differently to treatment) and the genetic determinants of such disparities may even be more relevant in children. The operational question is this: how do we evaluate correct dosage as children grow in the absence of access to therapeutic drug level monitoring in most settings?

Malaria

The interviewees considered the effects of malaria treatment on ART dosage to be important, but not as important as the previous two topics. However, they pointed out that more information regarding drug interactions between ARVs and antimalarials was required.

What are the barriers to developing paediatric formulations of approved and/or recommended drugs?

The financial cost of drug development was considered to be the main barrier to developing new paediatric formulations. The interviewees also highlighted the risks of developing paediatric formulations of older drugs that might not be used in the future due to newer and/or better treatment being developed for adults. However, more money would solve most of these problems. The WHO initiative, "Make Medicine Child Size", which aims to develop more and better fixed-drug combinations is an important step for better treatment for children.

The interviewees noted that a range of fixed-dose combinations was necessary, especially for small children since not all drugs were proportional to weight. Reducing the size of tablets is also essential to make them easier to swallow. Although liquid formulations are commonly available in Europe, solid options might be the better option in settings where water quality is an issue.

The main challenge, however, is treatment for children younger than two years old due to their rapidly changing height and weight, which requires many different dosages. The interviewees highlighted that tablets should be easy to swallow, taste good and several fixed-dose combinations should be available to choose from. They also noted, however, the disadvantage of fixed-dose combinations: changing just one drug was not possible.

Although some drugs, e.g., lopinavir/r, are very difficult to manufacture for pharmacological reasons, the interviewees stressed that innovation was essential, and that what was expensive today might be cheap tomorrow.

However, a major barrier to such developments is changes in guidelines and recommendations. The experience of MSF was that the pharmaceutical industry was reluctant to invest in developing fixed-dose combinations because recommended components may change within a year or two.

They also noted that more evidence was needed regarding pharmacokinetics and dosing recommendation in children. Dosage may differ according to ethnicity. For example, Thai children's PI plasma concentrations have been shown to be different than that of caucasian children, requiring lower doses. In order to understand appropriate dosing for different ethnic populations, PK studies are needed with different populations.

Research Area 2: Treatment Issues: Women

What is the impact of periodic treatment (due to PMTCT ARV interventions) on future treatment options for women?

The drug agenda is moving very quickly, and there is little justification for single dose nevirapine (sdNVP): the minimum standard of care is now sdNVP plus AZT. However, most data presented on periodic treatment are about sdNVP, which, while no longer a standard of care, is still used in many low- and middle-income countries. More data are needed on other PMTCT strategies, such as the risk of resistance for sdNVP plus AZT/3TC postpartum.

Studies are underway and partial datasets may be presented soon regarding HAART for PMTCT which is stopped after delivery or breastfeeding.

Highest on the agenda is the issue of resistance. More information is needed regarding the risk of resistance due to breastfeeding since resistance may develop in breastfed children due to ARVs being passed to the child through breast milk.

Are there differences between men and women in ART pharmacokinetics and pharmacodynamics, and do/should these differences have an impact on dosage recommendations and treatment outcomes?

The experts agreed that there was a knowledge gap regarding pharmacokinetics and/or pharmacodynamics in men and women. However, there was a difference of opinion about the importance of this topic. While some thought that this was an important issue for research, others said that differences in pharmacokinetics might be related to weight or ethnicity/race rather than sex. For example, Asian men have higher PI plasma levels than women.

What is the impact of female hormone fluctuations: adolescence, pregnancy and/or peri or post-menopause on treatment outcomes (e.g., pharmacodynamics)?

The impact of female hormone fluctuations on treatment outcomes was judged to be important by all the experts. A higher priority, however, was to produce more information regarding the effects of hormonal contraception on treatment outcomes, they said.

One interviewee mentioned the need to better understand which hormonal contraception was best, and that having a fixed-dose combination that included both ARVs and hormonal contraception would be ideal. This will become increasingly more relevant as the number of girls on HAART requiring hormonal contraception increases.

Aside from hormonal contraception, the experts agreed that the research focus should be on hormonal fluctuations experienced during puberty and their potential impact on HAART. This was considered to be more important than hormonal fluctuations during menopause and the impact of HAART.

Are there sex differences (based on CD4+ and viral load) that are unique to women and might have an impact on ART initiation and monitoring (i.e., should women be stratified for ART initiation and monitored differently based on VL/CD4)?

The experts stressed that there were obvious knowledge gaps regarding sex differences that might have an impact upon treatment.

Two interviewees mentioned the well-known effect of haemodilution during pregnancy: CD4 counts can be low during pregnancy due to pregnancy-related haemodilution and up to 30% of women may not fulfil immunological criteria for treatment eligibility. This issue will

become even more critical if WHO treatment guidelines recommend initiating ART at 350 cells/mm³ rather than the currently recommended 200 cells/mm^3.

Although the interviewees did not mention any other important differences regarding sex differences, one noted that human rights activists were recommending that specific resources should be allocated for women. However, this was related to different needs and socio-economic disadvantages, than than to clinical parameters.

5.3 Analysis

The short- and long-term effects of *in utero* exposure to ARVs on uninfected children has been rated as a very high priority. Studies must include newer drugs, such as lopinavir/r or tenofovir. Another question that needs to be addressed is the short- and long-term effects of drug exposure on the uninfected infant through breastfeeding.

Although the question regarding initiation of treatment in infants under the age of one has been answered, it is unclear whether initiation could be delayed if the child was infected during breastfeeding due to the possible development of immunological competence compared to an infant infected *in utero*. The PREDICT study may provide answers regarding initiation of children between the ages of one and eight years, and more studies are underway in adolescents.

Monitoring the impact of ART on childhood development is essential. This includes understanding potential drug resistance issues if infected through breastfeeding. Although the benefits of ART on children are obvious, the potential negative impacts on individual drugs require further study.

Understanding the timing of initiation, and the impact of ART dosage in the context of malnutrition, is also a major priority. Far more resources are needed to address this highly complex and understudied area. There are also unanswered questions regarding the pharmacokinetics and pharmacodynamics of antiretrovirals in malnourished children.

The impact of TB on ART dosing is also seen as a topic for further study: drug interactions between treatments for HIV and TB need to be much better understood.

The impact of malaria treatment on HIV treatment is also an important area for study particularly in Africa where both diseases play a major role. Many questions are still unanswered regarding drug interactions between HIV and antimalarial drugs.

There are also many challenges regarding the development of paediatric formulations, notably fixed-drug combinations that are acceptable to children under the age of two; in this age group, dosages may change regularly due to rapid weight and height variations. An added barrier to fixed-dose combination development is the concern that WHO recommendations for ART in children may change, making it more difficult for the pharmaceutical drug companies to deliver fixed-dose combinations.

Experts agree that simplification of treatment is essential. Once-daily regimens or, even better, one pill taken just a few days a week, using extended release compounds, must be developed for children.

The impact of periodic treatment due to PMTCT ARV interventions on future treatment options is an important research area. Single dose nevirapine should not longer be the focus of research and more studies are required regarding HAART taken for the duration of pregnancy, breast-feeding and/or consecutive pregnancies. These studies focus equally on the prevention of mother to child transmission and on the potential risks of resistance.

The experts had differing views regarding the importance of further study of sex differences in ARV pharmacokinetics and/or pharmacodynamics. Nevertheless, they agreed that more research regarding the role of ethnicity and/or race was needed in this area.

The most relevant questions regarding hormone fluctuations and ART concerned the impact of hormonal contraception on treatment, as well as on disease progression. An ideal drug development opportunity would be to combine ARVs and hormonal contraception in a fixed-dose combination tablet. This was considered to be more important than the discussion around hormonal fluctuations during adolescence, pregnancy or in pre- and postmenopausal women.

Although more research into sex differences for treatment monitoring was not considered to be a top priority, further research into the impact of sex differences on treatment initiation is warranted, mainly due to concern about the effect of CD4 counts due to haemodilution in pregnancy.

5.4 Conclusions

All nine topic areas identified by the ILF-IAS Expert Reference Group were considered to be important areas for further research by the experts interviewed.

The experts stressed that research must not only raise further questions, but also find answers that can be easily implemented in resource-limited settings. In other words, research outcomes should preferably not lead to new obstacles. This concern was raised regarding potential new WHO treatment guidelines, which, it was hoped, would not create new barriers, i.e., through establishing new laboratory parameters that are not easily available in low- and middle-income countries.

They also pointed out that research questions focusing on paediatric ART must always consider that implementation would always require a multidisciplinary approach model that included, for example, psychosocial support. In other words, it just not just pharmacokinetics that are important for successful interventions, but also knowledge about how to deal holistically with HIV and ART in infants, children and adolescents.

Some of the questions raised – such as the effects of exposure to ARVs in pregnancies, pharmacokinetic and/or pharmacodynamic studies with children, or the effect of ART on different ethnicities – could perhaps be answered through collaborations that link existing

multi-site studies, such as the European Collaborative Study, with sites in low- and middle-income countries.

6 Literature Review: Operations Research – Delivering Treatment to Women

6.1 Introduction

Although the ratio of males to females infected with HIV globally has remained stable at approximately 50/50 since 2002, this varies between regions, with women in sub-Saharan Africa comprising more than 60% of people living with HIV, and young women (aged between 15 and 24 years) at the greatest risk of infection (2).

The structural impacts of gender inequity on women and girls as it relates to HIV/AIDS, and particularly on access to HIV care, treatment and support services, has been the subject of a number of reports and peer-reviewed scientific literature over the past several years. Consistent themes regarding the potential impact of gender inequity on women and girls include: differential access to ART and other health services compared to men; HIV-related stigma and discrimination (both on an individual and community level); fear of losing their partner or of domestic violence as a result of HIV disclosure or taking antiretroviral medications; and financial insecurity (136-138).

Two questions were identified for this review of the operations research literature (including programme evaluations):

1. What are the barriers that women face in access to ART, and what are the best approaches to delivering ART to women?
2. What are the programmatic issues related to supplementation (e.g., micronutrient, nutritional and hormonal) for women on ART regarding what types of supplementation should be provided and how they should be integrated in ART programmes?

6.2 Methodology

For the question related to barriers to ART access for women, and best practices and/or approaches related to addressing those barriers, the following search terms using the Pub Med MeSH (relational) dbase were used: “Health Care Quality, Access, and Evaluation”, “Anti-HIV Agents” and “Women”.

As the search resulted in only a small number of articles, the search parameters were expanded to include only the first and second terms. This search resulted in an extensive list of articles which were reviewed for potential inclusion in the scientific literature review. Articles considered for inclusion covered programme evaluations and related operations research studies, including those focusing on patient retention, adherence, barriers to access and health equity analyses. Studies which were not primarily focused on identifying barriers to access for women were, at a minimum, required to include data on women as a variable within the broader qualitative or quantitative analysis.

For the question on programmatic and/or implementation issues related to nutritional or hormonal supplementation, the following MeSH search terms were used: “Pregnant Women”, “Women”, “Female”, “Micronutrients”, “Micronutrients "Pharmacological Action”, “Trace Elements”, “Nutrition Processes”, “Nutritional Sciences”, “Nutrition Therapy”, “Gonadal Hormones”, “Maternal Nutritional Physiological Phenomena”, “Dietary Supplements”, “Nutrition Policy”, “Nutrition Assessment”, “Nutritional Status”, “Nutrition Surveys” AND “HIV”, “Anti-Retroviral Agents”, and “Antiretroviral Therapy, Highly Active”.

We used the following criteria as a guide for evaluating grey literature for inclusion:

- Reports or publications that address operations research questions related to the above questions, but which do not reference peer-reviewed studies (qualitative or quantitative) are referenced as contextual information if directly relevant, but are not included in the formal literature review.
- Primary research reports or papers must identify a clear methodology and report on findings of not less than 40 participants in the focus groups and/or study population to be included in the review.
- Publications and reports that are not primary research reports must cite peer-reviewed publications or grey literature research reports that meet the above criteria (i.e., clear methodology and an aggregate participant cohort of 40) to be included.

6.3 Findings

A cross-sectional survey of knowledge, attitudes and practices among 1,667 HIV-positive adults (of which 31% were women) attending six public and private clinics in India found that women were underrepresented in private fee-for-service clinics in India when compared to local epidemiology (139). The survey indicated that access to ART overall was low, particularly among patients attending public clinics, and that while private clinic attendees were four times more likely to be on ART, they were also more likely to be male and live a distance of less than five miles from the clinic.

This is consistent with other studies indicating that ART programmes that charge user fees or other levies present barriers to both enrolment and retention (of women?) (140; 141). A qualitative study of barriers and facilitators to ART access in India among 60 individuals (49 men and 11 women) identified cost of ART as a primary barrier, with other themes, such as the impact of HIV-related stigma and confidentiality concerns, also identified as important factors across demographic groups (142).

The impact of gender inequity as it relates to socio-economic status was highlighted in a 2007 report on women and HIV/AIDS in Botswana and Swaziland (143). Of the 1,268 men and women surveyed in Botswana (52% of whom were women) and 588 men and women from Swaziland (50% of whom were women), more women than men reported food insufficiency, lower incomes, greater likelihood of unemployment and having at least one dependent, with men reporting higher levels of poor health and substantially fewer visits to a doctor. The report noted that in Botswana, on the basis of purchasing power parity, female gross domestic product per capita was US$5,322, while the equivalent for a male was US$14,748.

This report (which included follow-up interviews with 24 people living with HIV in Botswana, of which 21 were women, and 58 in Swaziland, of which 45 were women) was also one of the few studies reviewed which provided sex-disaggregated analysis of the data. The diffuse effects of HIV-related stigma was identified in both countries, as were very high levels of gender discriminatory beliefs (95% of women and 90% of men held at least one gender discriminatory belief, with the majority holding at least two).

The Swaziland survey cohort (both men and women) reflected community-level beliefs that HIV stigma and poor treatment fell disproportionately on women. In interviews, both men and women reported similar levels of fear of abandonment and other negative reactions by their partner, as well as gender inequality and insufficient food as barriers to treatment access.

A May 2009 community-based research report based on interviews and focus groups in six countries identified HIV-related stigma, discrimination and violence against women as barriers in the uptake of HIV services (1). Although this report focused on access to PMTCT, it noted that globally, only 12% of women accessing PMTCT services were assessed for treatment eligibility, and it underscored that the lack of integration of PMTCT with treatment services aimed at post-partum maternal health was a significant barrier to ART access for women.

The need to scale up maternal ART-eligibility assessment for their own health, involve male partners in testing, counselling and ART-eligibility assessment (referred to as "family-centred longitudinal care"), and better integrate PMTCT with other health services (such as sexual and reproductive health services and maternal, newborn and child health services) is also reflected in recent WHO guidance on scaling up PMTCT (144).

Adherence and retention in ART programmes are important indicators in determining whether women have meaningful access to ART beyond initial enrolment, particularly given the high aggregate attrition rate reported in the literature (141). Some reports have suggested that, while women may not necessarily be disadvantaged compared to men in ART access, they face unique challenges in adherence due to fear of the negative reactions of disclosure that taking daily mediations would likely entail; these ranged from losing their male partners (and therefore a key source of financial security), fear of physical violence from their partners and social ostracism from their communities due to HIV-related stigma (138; 145).

A qualitative study of women participating in the Zambia Exclusive Breastfeeding Study cohort posed two questions to HIV-positive women: Why had treatment-eligible women refused ART; and why had women who were initially enrolled in the ART programme discontinued taking ART (n=47 and 45 respectively) (146)? Responses for both questions were categorized and developed into four themes, which were then used as a basis for key informant interviews (n=33). The highest number of responses to both initial questions related to negative associations with ART and the side effects associated with taking medications (93.6% and 55.5% respectively), as well as concerns related to HIV stigma, such as the impact on interpersonal relationships (including fear of negative reactions from male

partners or family members) or how they would be perceived in the community if their serostatus became known. One of the major themes noted by study investigators was unfamiliarity with the implications of having a chronic, potentially fatal disease, as well as the complex impact of HIV stigma on interpersonal relationships and cultural frameworks that have an impact on enrolment and adherence.

A recent qualitative research study of the Kisesa cohort in rural Tanzania analyzed determinants of access given high attrition rates from the ART programme. The first study (42 in-depth interviews and four sex-specific and residence-specific focus group discussions; 64% of participants were women) were coded and grouped into major elements of the Health Belief Model, which was used to conceptualize individual and social determinants of access.

Barriers to clinic attendance included health system factors, such as distance to the clinic or lengthy clinic waiting times, as well as HIV-related stigma, such as actual or anticipated conflicts with family members and social standing in the community. Of note in both this and a follow-up qualitative study from the same cohort, which used a framework guided by socio-ecological data analysis, was the extent to which beliefs in the efficacy of God or traditional healers to cure HIV negatively informed their perceptions of ART efficacy (147; 148).

In order to fully explore gender equity issues as it relates to ART access for women, the author also reviewed quantitative reports and studies to assess how well-recognized structural inequities between men and women identified in grey and scientific literature translate into uptake, adherence and retention in ART programmes. The most recent published data from UNAIDS and WHO indicates that when country-level epidemiological data are compared to demographic characteristics of individuals enrolled in treatment programmes, women both globally and in sub-Saharan Africa (where women account for more than 60% of people living with HIV/AIDS and which accounts for about 60% of the global epidemic) have equal or greater access to ART compared to men (149; 2).

A large longitudinal study of women and men receiving ART in the ART-LINC Collaboration (33,164 individuals, of whom 19,989 or 60.3% were women) found that, of 22 centres in sub-Saharan African, the proportion of women receiving ART were similar to UNAIDS epidemiological estimates in eight centres, overrepresented in 13 centres and underrepresented in one centre (150).

Evaluation data from a Médecins sans Frontières (MSF) programme in a Nairobi clinic (women represented 60% of this programme's 7,100 clients and 60% of the 4,700 individuals enrolled on ART) and an equity analysis of Malawi's national treatment programme (using gender as a variable to analyze data on 85,168 individuals who had ever enrolled in ART programmes, of which 61% were women) also revealed women's access to ART was proportionally consistent to, or higher than, their prevalence in the population would suggest (151; 152).

A systematic review of the gender distribution of adult patients accessing ART in South Africa indicated that proportionally more females were on HIV antiretroviral treatment than

men, even when higher HIV infection prevalence in females was accounted for (153). These data have been explained (at least in part) by the attendance of pregnant women at antenatal clinics, which represent an important entry point to HIV testing, counselling and treatment services for women (154). However, when the previously cited large-scale ART-LINC Collaboration study reviewed the 16 centres where women were overrepresented, it found that nine were antenatal clinics, six were general public clinics and one was a research cohort, suggesting that while attendance at antenatal clinics is a factor in increasing ART access for women, other socio-behavioural variables may also be contributing.

Gender inequity, of course, has implications for men as well as women, and several studies and papers have suggested that traditional masculine gender roles – what has been referred to as the "ideology of masculinity" – result in differential health-seeking behaviours that result in men presenting older and later in disease progression to ART programmes. These factors have been reported in the scientific literature and are known to contribute to increased morbidity and mortality (150; 136; 155).

A study of patient retention in the ART-LINC collaboration (5,491 adult patients, of which 2,519 or 46% were women) found that men were less likely to return to the clinic than women (140). An evaluation of Malawi's national ART scale up programme found that women were, on average, 10 years younger than men upon enrolment (out of 6,791 patients enrolled, of whom 60% were female) (152). A Ugandan study of ART programme retention and lost to follow up rates (n=399) found that men and people with advanced disease at baseline were more likely to be lost to follow up and die (156).

A number of methodologically robust research studies and meta-analyses were reviewed, but could not be included because sex-disaggregated data were not included or were not analyzed as a separate variable to assess potential differences between men and women with respect to reported barriers to access, adherence, retention and/or health outcomes.

A recent systematic review of barriers to adherence in both developed and developing world HIV-positive populations, for example, included 37 qualitative studies, 47 studies using a quantitative methodology (surveys) and 72 studies (35 qualitative) in developed nations, while the remaining 12 (two qualitative) were conducted in developing nations. Reported barriers in both economic settings included fear of disclosure, forgetfulness, suspicions of treatment, regimens that are too complicated, number of pills required, decreased quality of life, work and family responsibilities, falling asleep, and access to medication (157). However, the review did not disaggregate the findings based on sex to assess whether specific barriers were particularly problematic for women.

What are the programmatic issues related to supplementation (e.g., micronutrient, nutritional and hormonal) for women on ART regarding what types of supplementation should be provided and how they should be integrated into ART programmes?

Malnutrition (most commonly, the result of inadequate protein and energy intake) and micronutrient deficiencies are common in sub-Saharan Africa and are often more pronounced in people living with HIV (158; 159). Although ensuring food security in low-

and middle-income countries is an important factor in addressing nutritional requirements for people living with HIV, this review is more narrowly focused on nutritional and micronutrient supplementation as a component within the broader issue of food and food security. Micronutrients play an important role in maintaining immune function and neutralizing oxidants produced as part of the body's inflammatory response to HIV infection; some studies have also suggested some micronutrients (e.g., selenium) down-regulate HIV expression and reduce viral load through non-specified immunostimulatory effects (160-162). Also, energy demands for HIV-positive individuals are increased by 10% to 30% compared to uninfected adults, and this requires compensatory nutrition (163; 164).

Two Cochrane Reviews address micronutrient supplementation in children and adults with HIV infection (published in 2005) and nutritional (macronutrient) interventions for reducing morbidity and mortality in people living with HIV (published in 2007) respectively (165; 166). Only randomized control trials were included in the reviews, within which only the micronutrient review reported sex-specific data. A Tanzanian trial assessed daily multivitamin supplementation (mainly vitamins B complex, C, and E at doses of up to 22 times the recommended daily allowances) in pregnant and lactating women; it found a reduction in AIDS-related maternal mortality over four years and a lower risk of progression to WHO Stage 4 disease (167).

A number of clinical trials have evaluated a range of micronutrient, macronutrient and hormonal supplementation. These include: a Thai trial that demonstrated significant reductions in mortality among men and women receiving multivitamin (B complex, C and E) supplementation; and a recent study of multivitamin supplementation in HIV-positive pregnant women, which demonstrated protective effects on depression for those receiving B complex, C and E and the efficacy of iron supplementation to treat anaemia among women (168)(169).

Most of the clinical literature which addresses micronutrient and malnutrition issues among HIV-positive women focus on pregnant and lactating women, where maternal requirements for protein, iron, folate, niacin, zinc, iron and iodine are 30% to 50% higher than before pregnancy (170). Some micronutrient supplementation, such as Vitamin A, have received mixed results in populations of pregnant women, with some trials reporting increased risk of mother to child transmission, while others report no discernible effects on vertical transmission and benefits to the infant in terms of reducing the proportion of low birth weight babies (161; 171).

Anaemia is a well-recognized problem among pregnant women; a recent study of the effect of selenium supplementation on haemoglobin and morbidity in a cohort of 915 pregnant Tanzanian women found it had no impact on haemoglobin increases, but it did reduce diarrhoeal morbidity by 40% (172).

Operations research studies have demonstrated the positive impact of nutritional support and food supplementation on men and women living with HIV. A Zambian pilot study (n=636; 414 of which were women) demonstrated improved ART adherence among those receiving food supplementation (with no statistically significant differences related to sex). The Academic Model Providing Access to Healthcare HIV care programme in Western Kenya

recently published an evaluation of the nutritional support component of its programme (N=133,192 assessed, of which 75% were women; 9,623 were enrolled into the nutritional support programme following assessment).

The evaluation suggested that there were clinical and immunological benefits to food supplementation, although clinical data were not included in the study parameters. The major finding of this evaluation was that nutritional supplementation could be effectively and sustainably integrated into clinical care programmes through an innovative approach that included food production, donation and a food distribution network (173; 174).

However, although there is increased programmatic focus on the need to address nutritional and micronutrient deficits as part of ART programme scale up (particularly within the President's Emergency Plan For AIDS Relief, which has issued several reports on the issue), there are limited operations research or programme evaluation data to identify the most effective way of integrating nutritional and micronutrient supplementation for women in ART programmes, outside of pregnancy (175; 176). One report noted that:

> More evidence is needed about: the relationship between malnutrition or nutritional interventions and HIV progression; the impact of therapeutic feeding on drug adherence; the effects of nutritional intervention on drug efficacy; and interactions between alternative nutritional or herbal therapies and ARVs. There are also numerous questions surrounding food security, such as how to transition clients from food aid into food security and livelihood assistance programs, and how food and nutrition interventions should be adapted (in terms of ration size or composition) in order to better serve HIV-infected and affected clients (175).

A WHO consultation on HIV and nutrition in pregnant and lactating women noted a number of operations research gaps, including how best to deliver appropriate levels of energy and micronutrients (pill versus fortified food product), appropriate recommendations for frequency and amount of locally available food to optimize maternal nutritional status, the means to monitor body mass index, and evidence-based algorithms to trigger nutrition intervention (177).

Recent WHO guidance on scaling up PMTCT for women recommends integrating nutrition support as part of a package of services for rolling out ART and establishing a baseline nutrition and dietary assessment as a routine component of the package of care for women living with HIV and their children in all antenatal, childbirth and postpartum care settings (144).

A recent synthesis of international guidance on HIV/AIDS, nutrition and food security, led by the World Bank, provides operational guidance on nutritional and food supplementation issues based on the best available evidence to date, with a specific section on pregnant and lactating women (178).

6.4 Analysis

Data suggest that women's disadvantaged economic status result in reduced access to ART compared to men in private, fee-for-service ART programmes, where cost was negatively associated with being on ART. Although the majority of ART programmes in low- and middle-income countries are free, individuals accessing programmes often cite transportation costs, other service fees (including bribing health care workers in order to access treatment services) and loss of earnings due to time spent travelling or waiting in clinics as barriers to access and adherence.

All of the qualitative studies, regardless of methodology and sample size, reflect the multifactoral ways in with HIV stigma is a significant barrier for women in enrolment, adherence and retention in ART programmes. Although HIV stigma has a profound impact for both men and women at both the individual and structural level, data suggest some qualitative differences between how HIV stigma is perceived and experienced by men compared to women. At the interpersonal level, for example, some studies suggest that while both men and women fear being abandoned by their partners as a result of accessing ART, women articulated concerns about the impact that such negative reactions would have on their financial security and personal safety, in addition to concerns about community-level response.

Both women and men identified food and nutritional issues as having a significant impact on ART access, and in at least one study, the impact was greater on women than men.

Inadequate or inaccurate knowledge about the benefits of ART, and negative experiences with health care providers and the health care system was identified in a number of studies as barriers to access for women; this had a significant impact on perceptions of self-agency as it relates to physical health and disease management. Poor integration of ART programmes with other components of the health system accessed by women (including PMTCT programmes, sexual health and reproductive services and maternal, newborn and child health services and primary care) has also been identified as a barrier to ART access.

Despite the wide gap in socio-economic status between women and men in middle- and low-income countries, this has not translated into differential access to ART which favours men, a result which reinforces the complex relationship between gender inequity, health-seeking behaviour and uptake of HIV services, such as ART programmes.

Despite significant attention to gender inequity as a factor in access to HIV treatment services, many potentially useful studies either do not include sex-disaggregated data or do not include gender analyses of their research findings that would identify some of the unique barriers faced by women. Some papers proposed defining more clearly the differences between biological "sex" and socially constructed "gender" as analytical tools in health research, proposing a more nuanced approach to gender equity issues as it relates to ART access. Research that demonstrates the complex and culturally specific ways in which gender inequity has an impact on health-seeking behaviours for both women and men will be important in driving improvements in ART programme delivery (155; 179).

Data from a number of studies reinforce the multifactoral ways in which gender inequity disadvantages women in terms of decision-making power with male partners and broader

family structures, socio-economic status, self-agency, and their experience of HIV stigma, as well as fundamental issues of personal safety and financial insecurity. Based on the most current global data and studies in a number of settings (primarily from sub-Saharan Africa and India), this has not translated into lower levels of ART access compared to men, although it is important to note the ongoing and substantial gap between treatment need and access for both men and women in low- and middle-income countries (2).

Some studies, which reported data relevant to this review, could not be used due to gaps in methodological or sampling size information. A series of papers issued by the International Community of Women Living with HIV (ICW), which mapped the experiences of HIV-positive women in Tanzania, Namibia and Kenya (using both mixed-sex and women-only focus groups) were not included in the review because a denominator was either not identified or identified as an approximate figure; nor were figures regarding the relative proportion of men and women participating in the various focus groups included within these studies (138).

Important gaps in the research and analyses of the grey and scientific literature reviewed for this scan include whether sex workers – as a sub-population of women – are disadvantaged in ART access compared to other women (or men), and the extent to which a number of other factors (such as geography, class, ethnicity, race and other ethnographic variables) affect access to ART (and other HIV services) for women.

What are the programmatic issues related to supplementation (e.g., micronutrient, nutritional and hormonal) for women on ART regarding what types of supplementation should be provided and how they should be integrated into ART programmes?

A number of clinical studies have demonstrated the importance of adequate nutrition and micronutrient levels to strengthen the body's immunological response to HIV infection, which places increased demands on the unique role of nutrition and micronutrients; nutritional support, including micronutrient supplementation, is an important adjunct to optimizing both adherence and therapeutic outcomes. However, there are relatively few operations research studies or programme evaluations that evaluate different strategies for integrating such supplementation strategies into ART programme scale up.

6.5 Conclusions

Methodologically rigorous operations research that includes both quantitative and qualitative analyses is required to better identify the multiple individual and structural barriers women face in accessing ART and to inform programmatic interventions. Disaggregating data by sex and deploying gender equity analyses to assess outcomes in programme enrolment, retention and ART adherence will help provide a more detailed evidence base of ART access issues for women.

Operations research and programme evaluations are required to identify how to leverage existing entry points to health care systems (such as antenatal care or sexual and reproductive health services) into increased ART coverage for women, consistent with recommendations of two recent publications (one of which analyzed gender policies of the

three major AIDS financing mechanisms: the Global Fund to fight AIDS, Tuberculosis and Malaria; the World Bank; and the US President's Emergency Plan for AIDS Relief) (180; 1).

Ethnographic, anthropological, political science and other social science research can provide more nuanced analyses of the complex range of social, economic, cultural and behavioural factors that affect ART access for both men and women. Quantitative and qualitative analyses of ART access should also address sub-populations of women (e.g., sex workers and childless women) to inform programme delivery.

Operations research and programme evaluation data is required to determine the optimal approach for implementing nutritional and micronutrient supplementation for women into ART programmes.

7 Key Informant Interviews: Operations Research Priorities – Delivering Treatment to Women

7.1 Introduction

Key informant interviews were conducted with five individuals in May and June 2009: Alejandra Trossero (Planned Parenthood Federation; former board member, ICW), Robert Oerlichs (the World Bank), Marco Vittoria (WHO), Berri Hull (International Community of Women Living with HIV) and Nokhwezi Hoboyi (Treatment Action Campaign). Approaches were also made to several independent operations research investigators without success.

7.2 Methodology

Questions were developed based on the two operations research questions from this review: barriers to ART access for women and programmatic issues related to nutritional, micronutrient and hormonal supplementation relevant to women. Upon confirmation of availability, interviewees were provided with background information on the initiative and a list of questions which was used to guide discussion.

The questions were:

1. What do you think are the most significant barriers for women in accessing ART programmes?
2. What, if any, operations and/or implementation research questions need to be answered in order to address those barriers?
3. What do you think are the most urgent outstanding questions regarding how gender inequity has an impact on women's access to ART programmes?
4. Our literature review suggests that very limited operations research has been conducted regarding what supplementation (micronutrient, macronutrient and hormonal) would help optimize treatment and/or health outcomes for HIV-positive women enrolled in ART programmes. What do you think are the most important operations research priorities regarding supplementation to address nutritional deficiencies or ART-related toxicities unique to women?

5. Please identify any additional urgent operations and/or implementation research questions, unique to treating women, that have not been addressed to date.

After completing all interviews, responses to each question were analyzed for consistent themes and are presented below.

7.3 Findings

Barriers to ART access for women

All of the interviewees referenced aspects of the health care system, including shortages of health care workers, as a barrier to access for women (noting that this is not a barrier only for women). Four of the five interviewees emphasized a lack of integration between ART programmes and other components of the health care system, such as sexual and reproductive health services, antenatal services (including PMTCT), maternal, child and newborn health services, and primary care. Two interviewees also noted the lack of drugs and diagnostics (e.g., drug stock outs) as ongoing barriers to access, with one noting that scale-up efforts remain primarily doctor driven and focused on urban populations, with ART programmes underutilizing nursing staff and community-based health workers to expand ART access.

Socio-economic barriers were identified by four of the five, with interviewees also referencing HIV stigma as a barrier to ART access, both in terms of the negative experiences that some HIV-positive women have with health care providers and as a concern regarding actual or potentially negative responses from their family or community; one interviewee noted this was particularly a problem in rural areas. Cost (e.g., transportation and laboratory tests) was also cited.

Other issues included distance to clinic, presentation late in disease progression, and lack of knowledge about ART (which was identified as a particular problem in rural areas).

Operations and/or implementation research needed to address barriers

All interviewees identified research into the most effective service delivery models (including retention strategies) for ART programme delivery and integration with other health services as the most urgent operations research priority; this included developing strategies for training and retaining health care workers in resource-limited settings, ensuring quality care, and assessing alternative, community-based models of care.

Related to the issue of service delivery and integration was a suggestion for more research into differences in health-seeking behaviours to explain why women access health care more than men, and where those entry points can be leveraged for greater access to ART.

Two interviewees identified research into the impact of HIV stigma on access to ART as important, with one noting that this was a particularly challenging issue for HIV-positive health care workers.

Another interviewee noted the need to establish the evidence base for ART as prevention, suggesting large cohorts of sero-discordant couples in sub-Saharan Africa could provide the evidence base for a broader rollout of ART.

The need for operations research on ART access among sub-populations of women (.e.g, sex workers or women from different socioeconomic backgrounds) was also noted as a priority.

Impact of gender inequity on ART access for women

This question elicited a diverse response from interviewees, with no single issue or theme emerging, with the exception of two interviewees who suggested that the impact of gender inequity could vary among sub-populations of women (e.g., women who inject drugs, are sex workers, or come from different socio-economic backgrounds) in terms of access to care, and that this was an issue that had not been well explored to date.

Other responses included: exploring the impact of individual and social expectations of fertility and childbearing on women; evaluating programme retention issues with a view to optimizing women's entry points to the health care system; and evaluating gender rights education programmes to determine whether they were having an impact on ART access for women. The impact of circumcision scale-up efforts on women, their role as primary caregivers within families, fears related to HIV disclosure and their lack of control in decision making (and its impact on self-agency and autonomy) were also referenced as having potential impacts on ART access. One interviewee also noted a surprising lack of research attention on how best to engage men and boys in addressing gender equity issues.

Operations research priorities on supplementation for women

Three interviewees suggested that the role of micronutrient and nutritional supplementation on women living with HIV, including interactions of supplements with ARVs and their potential health risk and benefits, needed to be better understood, along with the potential impact of incorporating supplementation into ART programmes.

One interviewee suggested assessing different models of nutritional and micronutrient support into ART programmes, citing a Kenyan project that addresses nutritional support as part of a broader attempt to build social capital and empowerment. In this pilot, the ART programme conducts nutritional assessments, purchases seeds for enrolees to develop gardens, and provides opportunities to buy and sell products from each other, with the overall goal of establishing a self-sustaining community-based initiative that addresses both practical nutritional requirements within a broader context of community development.

Two interviewers suggested exploring the role of nutritional support and food security on community resilience and social capital. The impact of the global recession on food insecurity (e.g., the capacity of the community to support women to adhere to ART in a context of food insecurity) was also referenced as an important operations research question. Other questions suggested by interviewees included the need to better understand the role of other complementary therapies (including their impact on

therapeutic drug levels) and how the use of these therapies may have an impact on beliefs about the efficacy of ART.

Additional urgent operations/and/or implementation research questions

Additional questions suggested by interviewees included: evaluating treatment access for women in a concentrated epidemic (including access to opioid substitution therapy and harm-reduction interventions); access to diagnostics, such as pap smears; assessing whether biological and pharmacological differences between women and men (including different ARV toxicity profiles) have an impact on clinical guidance and access; and the impact of their role as caregivers on ART access.

7.4 Analysis

Barriers to ART access for women

Although the sample size is small, several themes emerged in key informant interviews. The most common theme was the multiple ways in which the health care system presented barriers to ART access for women, from a lack of integration between ART programmes and other health services (ranging from sexual and reproductive health services and PMTCT to harm-reduction services for female injecting drug users) to the availability of drugs and diagnostics.

There was significant consensus among interviewees regarding the urgent need for operations research to identify ART programme delivery models (including more community-based care approaches) in resource-limited settings that better leverage various health care entry points into greater ART access for women. Related to this was the need for research on the health-seeking behaviours to inform ART programme delivery.

The complex and multifaceted role of HIV stigma – at the levels of individual, community and health system – was the most common socio-behavioural issue identified by interviewees as a barrier to ART access for women. Research in this area could inform programmatic strategies to strengthen enrolment, adherence and retention. Other social determinants of health, such as caregiving roles and decision-making autonomy, were also referenced as important areas of research that could inform programme delivery.

The need for research to evaluate ART access (and other health services such as OST) among sub-populations of women was also raised by several interviewees.

Programmatic issues related to supplementation

Although interviewees agreed on the need for research on how best to incorporate micronutrient and nutritional support (including dietary and/or nutritional evaluations) into ART programmes, some suggested operations research should be broadly defined and include clinical research on the impact and potential interactions of various supplements (including complementary therapies) on ARVs and the health and treatment outcomes of people living with HIV.

Research questions related to how integrating nutritional support and supplementation into ART programmes could help strengthen social capital and community resilience in the face of food insecurity was an intriguing theme, particularly in the context of the current global recession. There are many unanswered questions regarding how best to deliver such support and whether dietary variations in different regions of the world will have an impact on the type of nutritional or micronutrient supplementation required.

7.5 Conclusions

Key informant interviews reflect a growing emphasis in the HIV field on the need for operations research to inform ART programme delivery models that ensure improved ART access for women, including analysis of treatment access for sub-populations of women, and an approach to ART delivery that is integrated with other components of the health care system.

Research on the multifaceted impact of HIV stigma on ART access for women is required to develop appropriate programmatic interventions, including the need to address HIV stigma within the health care system.

There are significant knowledge gaps regarding the potential role of micronutrient and nutritional supplementation in ART programmes, despite chronic food insecurity among many high-burden countries. Both the efficacy of specific types of supplementation for women and how best to deliver such supplementation as part of ART programmes need to be better understood. The potential of such programmes on both food insecurity and community development could be significant.

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9 Annex 1: IAS-ILF Expert Reference Group

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10 Annex 2: Current Clinical and Operational Trials

There are currently a number of clinical and operations research studies that address various aspects of the questions identified as urgent priorities for the purposes of this mapping exercise. Below is a summary table of trials currently know to the authors of this report.

CLINICAL RESEARCH TRIALS

1.1 What are the short and long-term effects of in-utero exposure to ARVs on uninfected infants?

Table 1. Ongoing clinical trials: HIV and in utero exposure to ARVs

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start / estimated completion date
NCT00146380	**A phase II open label clinical trial of maternal zidovudine/lamivudine and either nevirapine or nelfinavir for maximal reduction of mother-to-child HIV transmission in resource-limited settings among breastfeeding populations**	To demonstrate that a regimen using highly active antiretroviral therapy (HAART) to maximally suppress maternal viral load in the late antenatal period and during the first six months of lactation is safe, effective and can be implemented in resource-poor settings in order to reduce the risk of HIV transmission to the infant	CDC	Kenya	520 (female, 15 years and older)	July 2003/ January 2009
NCT00753324	**Routine use of antiretroviral therapy to prevent mother-to-child HIV transmission in the Kafue District of Zambia (Impact of HAART to prevent pediatric AIDS in rural**	To better understand the incremental benefits (e.g., reduction in HIV transmission, improvements in HIV-free survival) and risks (e.g., drug toxicities) of the routine HAART strategy.	CIDRZ	Zambia	320 (female)	December 2008/ December 2010

	Zambia)					
NCT00069004	**Prevalence of morphologic and metabolic abnormalities in vertically HIV-infected and uninfected children and youth**	To assess the prevalence of metabolic and physical abnormalities in HIV infected (via mother to child transmission) and uninfected children and youth.	University of Alabama at Birmingham, University of Florida	USA	450 (7 to 25 years old)	Not specified (ongoing, but not recruiting)
NCT00647803	**Surveillance monitoring for ART toxicities study in HIV uninfected children born to HIV infected women (SMARTT)**	To continue to try to find out what these and other problems might be, how often they happen, and if there are ways we can prevent these problems for babies in the future.	University of Alabama at Birmingham	USA	1,600 (0 to 11 years old)	May 2007/ August 2010
NCT00146380	**A phase II open label clinical trial of maternal zidovudine/lamivudine and either nevirapine or nelfinavir for maximal reduction of mother-to-child HIV transmission in resource-limited settings among breastfeeding populations**	To demonstrate that a regimen using HAART to maximally suppress maternal viral load in the late antenatal period and during the first six months of lactation is safe, effective and can be implemented in resource poor settings in order to reduce the risk of HIV transmission to the infant. To evaluate infant and maternal safety, and tolerance of ZDV/3TC and Nevirapine (NVP) or Nelfinavir given to HIV-infected pregnant women from 34 weeks gestation to six months postpartum.	CDC	Kenya	520 (female, 15 years and older)	July 2003/ January 2009
NCT00100867 ACTG A5190-	**Assessment of safety and toxicity among**	To determine the safety, toxicity, and potential side	University of California, Los	Botswana, Brazil,	410 (infants born to HIV-infected	June 2006/ June 2010

P1054, ACTG A5190, PACTG P1054	**infants born to HIV-1-infected women enrolled in antiretroviral treatment protocols in diverse areas of the world**	effects of maternal anti-HIV treatment on infants born to these HIV-infected women.	Angeles	Malawi, Peru, South Africa, Thailand, Zimbabwe	women)	
NCT00640263	**Double blind randomised placebo-controlled trial of the efficacy and safety of infant peri-exposure prophylaxis with lamivudine to prevent HIV-1 transmission by breastfeeding**	To measure the efficacy of PEP with 3TC once daily from day seven until four weeks after cessation of BF (maximum duration of prophylaxis: 38 weeks for a maximum duration of breastfeeding of 34 weeks) on the risk of postnatal HIV-1 acquisition between seven days and 38 weeks of age. To assess the safety of long-term prophylaxis with 3TC (including adverse events, resistance to lamivudine and growth) until 38 weeks and at one year of age.	ANRS, University of Montpellier	Burkina Faso, South Africa, Uganda, Zambia	1,500 (0 to 9 days old)	January 2009/ December 2012

1.2 What are the optimal age-adapted parameters for ART initiation and discontinuation among infants and children?

Table 2. Ongoing clinical trials: initiation and discontinuation

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start / Estimated completion date
NCT00427297 (30200-D, 2 RO1 HD023412-16;, 06-1886-D 02)	**Optimizing pediatric HIV-1 treatment in infants with prophylactic exposure to nevirapine, Nairobi, Kenya (6-12 month RCT)**	To compare response to therapy (viral levels, CD4, growth, and morbidity) in infants without detectable NVP-resistance on population-based sequencing who are randomized to NVP-containing versus NVP-sparing HAART. To develop methods to detect and quantify NVP resistance mutations present at low frequency in the virus population in order to examine the relationship between the copy number of such variants and virologic failure of infants treated with nevirapine-containing HAART.	University of Washington	Kenya	100 (6 to 18 months of age at enrolment)	September 2007/ December 2010
NCT00234091	**An open label, randomized study to compare antiretroviral therapy (ART) initiation when CD4 is between 15% to 24% to ART initiation when CD4 falls below 15% in children with HIV infection and moderate immune suppression**	To determine when HIV infected children should begin taking anti-HIV medications in order to improve both patient quality of life and survival	University of Bangkok	Thailand	300 (1 to 12 years old)	March 2006/ September 2011

NCT00016783	**Intensification of HIV-specific CD4 and CD8 activity by cycling highly active antiretroviral therapy (HAART) in pediatric/adolescent patients with less than 50 HIV RNA Copies/ml**	To determine if short periods of stopping HAART increase the activity of CD8 and CD4 cells (cells of the immune system that fight infection), if repeated stopping of these drugs for longer periods of time and restarting them will increase effectiveness of HAART, and if the increased immune system activity as a result of stopping treatment leads to lower levels of HIV over time.	NY University Medical Center	USA	39 (2 to 21 years old)	Not specified (ongoing, but not recruiting)
NCT00039741 PENTA 9/ PACTG 390, PENPACT-1B	**A phase II/III randomized, open-label study of combination antiretroviral regimens and treatment-switching strategies in HIV-1-infected antiretroviral naive children between 30 Days and 18 years of age**	To compare the combination of two nucleoside reverse transcriptase inhibitor (NRTI) plus a protease inhibitor (PI) versus 2 NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) as initial therapy, followed by second-line therapy if virologic failure occurs, in terms of their effects on a long-term virologic endpoint; to compare two different viral load criteria for switching from first-line to second-line therapy.	Duke University	USA, Bahamas, Brazil, Puerto Rico	256 (0 to 18 years old)	October 2005/ October 2013
NCT00102960 CIPRA-ZA Project 2, CHER, 5R01AI062512-02, CIPRA-SA Project 2	**A phase III, randomized, open-label trial to evaluate strategies for providing antiretroviral therapy to infants shortly after primary infection in a**	To evaluate the efficacy of three different short-course ART strategies in HIV infected infants from South Africa. 1) ART deferred until it is clinically needed; 2) immediate initiation of ART for	University of the Witwatersrand	South Africa	451 (6 weeks to 12 weeks old)	July 2005/ May 2009

	resource poor setting	approximately 40 weeks until their first birthday; 3) immediate initiation of ART for approximately 96 weeks until their second birthdays.				
iTHEMBA	**Pediatric early HAART and structured treatment interruptions**	To determine the feasibility of implementing a simple structured treatment interruption protocol in a sub-Saharan African setting initiated in infected infants.	Philip Goulder	South Africa	63	Not available
NCT00307151 IMPAACT P1060, PACTG P1060	**Phase II, parallel, randomized, clinical trial comparing the responses to initiation of NNRTI-based versus PI-based antiretroviral therapy in HIV infected infants who have and have not previously received single dose nevirapine for prevention of mother-to-child HIV transmission**	To compare rates of treatment failure at 24 weeks in subjects receiving a NVP-based HAART regimen (Group 1) versus a LPV/r-based HAART regimen. To compare rates of treatment failure at 24 weeks in subjects receiving a NVP-based HAART regimen (Group 3) versus a LPV/r-based HAART regimen. To compare rates of treatment failure at 24 weeks in NVP-exposed versus NVP-unexposed subjects receiving a NVP-based HAART regimen (Group 1 versus Group 3) and NVP-exposed versus NVP-unexposed subjects receiving a LPV/r-based HAART regimen (Group 2 versus Group 4).	Dartmouth-Hitchcock Medical Center	India, Malawi, Tanzania, Zambia	576 (6 months to 35 months old)	September 2006/ October 2009
BANA 2	**A randomized, comparative trial of continuous versus intermittent highly-active antiretroviral**	To compare the two treatment strategies (continuous versus intermittent) with respect to rates of drug-associated toxicity or intolerance and HIV	Princess Marina Hospital, Baylor College of Medicine,	Botswana	600	Not available

	therapy In Hiv-infected infants and children in Botswana	disease progression (growth failure, changes in neurodevelopmental status, development of two or more new or recurrent AIDS-defining opportunistic infections, development of clinically significant conditions, or death) in HIV-infected infants and children. To compare the rates of emergence of antiretroviral drug resistance in the two treatment arms. To compare rates of emergence of viral resistance in two treatment strategies. To compare the cost of two antiretroviral treatment strategies.	Texas Children's Hospital			
PENTA 11 ISRCTN36694210	**A randomized phase II trial to determine whether children are disadvantaged clinically, immunologically or virologically by planned treatment interruptions**	To determine whether children with chronic HIV infection undergoing planned antiretroviral (ART) treatment interruptions are disadvantaged clinically, immunologically or virologically by periods of time off ART. To assess HIV-specific immune responses during and after interruptions of ART, compared with continuous ART, in an immunology/virology substudy.	MRC Clinical Trials Unit, UK: INSERM SC10, France; Program for HIV Prevention and Treatment (PHPT), Thailand and Westat, USA	France, Germany, Italy, Poland, Spain, Switzerland, Thailand, UK, USA	100 (2 to 15 years old)	Not available (ongoing but not recruiting)
ISRCTN24791	**Antiretroviral research**	The key objectives are to	Medical	Uganda,	1,200	October

884	**for Watoto**	determine: 1. Will clinically driven monitoring have a similar outcome in terms of disease progression or death as routine laboratory and clinical monitoring for toxicity (haematology/biochemistry) and efficacy (CD4)? 2. Will induction with four drugs (two antiretroviral therapy classes) followed by maintenance with three drugs after 36 weeks be more effective than a continuous NNRTI-based triple drug regimen in terms of CD4 and clinical outcome?	Research Council (UK)	Zimbabwe		2006 / October 2011
NCT00038480 PACTG 1030	**A phase I/II study of lopinavir/ritonavir in HIV-1 infected infants less than 6 months of age**	To find out if the drug, lopinavir/ritonavir, is safe and well tolerated in HIV infected infants. This study will also determine the most effective dose of the drug for infants	Children's Memorial Hospital, Universidade Federal de Minas Gerais	USA, Brazil, Puerto Rico	26 (0 to 6 months year old)	Not mentioned/ September 2007 (ongoing but not recruiting)
NCT00084058 PACTG 1038	**A phase I/II safety, tolerability, and pharmacokinetic study of high dose lopinavir/ritonavir with or without saquinavir in HIV-infected pediatric subjects previously treated with protease inhibitors**	To determine the effect of increased doses of lopinavir/ritonavir and saquinavir in HIV-infected children who are failing their current antiretroviral regimen	Medical College of Wisconsin	USA, Puerto Rico	48 (2 to 17 years old)	Not mentioned/ December 2006 (ongoing but not recruiting)
NCT00626301	**Simplifying**	To evaluate the efficacy	HIV-NAT,	Thailand	40 (2 to 18 years	November

	antiretroviral treatment in virally suppressed children by switching from double boosted protease inhibitors to lopinavir/ritonavir monotherapy	(clinical, immunological, virological outcome), pharmacokinetics and safety of lopinavir/ritonavir monotherapy maintenance in Thai children after viral load suppression with double boosted protease inhibitors .	Chulalongkorn University, Khon Kaen University		old)	2007/ June 2011
-	**Lopinavir exposure, efficacy, safety and toxicity in children receiving the new lower-strength tablet of Kaletra® (lopinavir/ritonavir 100/25 mg) dosed according to the WHO weight band dosing guideline**	To establish the pharmacokinetics of lopinavir/ritonavir when dosed according to the WHO weight band dosing schedule n HIV-infected infants and children and determine the resulting frequency of sub-optimal lopinavir exposures. To establish the short-term tolerance and safety of lopinavir/ritonavir when administered as the heat stable pediatric Kaletra® or Alluvia® tablet or the liquid Kaletra® formulation as part of a combination antiretroviral regimen in HIV-infected infants and children.	Jorge Pinto	IMPAACT domestic and internationa l sites	85 (able to swallow tablets, 3 to 25 kg)	Not available

1.3 What is the impact of ART on childhood development (physical growth/cognitive development) and additional impact into adulthood?

Table 3. Ongoing clinical trials: impact of ART on development

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start/ Estimated completion date
NCT00476606	**Treatment outcome of children with HIV infection**	To evaluate clinical and immunological outcome of children treated with HAART. **Outcomes**: To collect clinical and immunologic data of children treated with HAART 2. To collect clinical outcome data on children with HIV infection 3. To provide the best possible care to children with HIV infection.	HIV-NAT	Thailand	200 (0 to 20 years old)	March 2003/ December 2013
NCT00110331	**A study of central nervous system disease in pediatric HIV in the HAART era**	To examine how HIV affects the brain and nervous system, learning, and behaviour in children on HAART.	NCI	USA	40	March 2005/ March 2006 (currently recruiting)
NCT00428116	**Optimizing pediatric HIV-1 treatment, Nairobi, Kenya (0-4.5 month RCT)**	To compare growth and morbidity in infants (who initiated HAART during primary infection at less than or equal to four months of age with subsequently normalized CD4% and growth following 24 months of HAART) randomized to deferred versus continuous therapy and followed for an additional 18 months.	University of Nairobi, University of Washington	Kenya	150 (0 to 4 months old, of which 100 are expected to be eligible)	September 2007/ June 2012
NCT00908284	**Atherosclerotic risk**	To assess cardiovascular risk	University of	USA	80 (0 to 25 years	December

	and response to exercise intervention in HIV+ children	factors in children infected with HIV who receive HAART medications and to determine the effectiveness of an exercise programme on cardiovascular outcomes in these children.	Miami		old)	2008/ June 2011
NCT00197587	**Prevention, randomized, open label, placebo control, factorial assignment**	To confirm the safety and tolerance of one dose of NVP given to mothers and infants. To evaluate the safety and tolerance of AZT given to infants for up to six months. To determine the association between. assigned infant feeding strategy and maternal morbidity and mortality 4. To determine the rates of virologic response to NNRTI-containing HAART at 26 and 52 weeks after initiating treatment, among HIV-positive women who previously received single-dose NVP versus placebo during labour.	Harvard School of Public Health	Botswana	1,200 (female 15 to 45 years old)	Not specified, (ongoing, but not recruiting)

1.4 Do interventions for malnutrition, TB or malaria have an impact on ART dosage recommendations for paediatrics?

Table 4. Ongoing clinical trials: malnutrition, TB, malaria

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start / Estimated completion date
-	**Evaluation of the steady state pharmacokinetics of syrup formulations of zidovudine (AZT) lamuvidine(3TC), stavudine (d4T), nevirapine (NVP) and sprinkle lopinavir / ritonavir (Kaletra) in severely malnourished HIV infected children initiating HAART in Kampala, Uganda**	In severely malnourished HIV-infected children: to determine the intensive PK of AZT, 3TC, d4T, NVP, and Kaletra; to compare the C trough of NVP and Kaletra after initiation of HAART; and to determine the demographic and biochemical characteristics that influence PK of AZT, 3TC, d4T, NVP, and kaletra.	Makarere University	Uganda	60 (6 months to 59 months old)	Not available
-	**Body composition changes in a cohort of HIV infected children receiving antiretroviral therapy in a population where background malnutrition is prevalent**	Assess change in body composition measure by stable isotopes and DEXA in HIV-infected children starting on PI-based ARV regimen in a subset of patients.	Wits Paediatric HIV Unit	Soweto	38 (9 to 36 months)	Not available
NCT00330304	**Isoniazid prophylaxis With concomitant cotrimoxazole in HIV-infected children**	To investigate the efficacy, safety and tolerability of INH and CTX as prophylactic strategies for HIV-infected children in a high tuberculosis prevalence area.	University of Cape Town, Stellenbosch University	South Africa	450 (8 weeks-15 years old)	January 2003/ May 2006 (currently recruiting)

NCT00802802 IMPAACT P1070	**Dose-finding and pharmacogenetic study of efavirenz in HIV-infected and HIV/TB co-infected infants and children 3 months to less than 36 months of age**	To dose requirements of EFV. To determine 24-week safety and tolerance of EFV-based HAART. To explore genetic polymorphisms in children in low- and middle-income countries.	UAB, University of Zimbabwe, Northwestern University Feinberg School of Medicine	Africa	100 (3 months to 35 months old)	December 2009/ December 2010
-	**Doubling the dose of lopinavir/ ritonavir as an approach to using Kaletra® in TB/HIV-infected patients receiving rifampicin-based antitubercular treatment; paediatric study**	To compare trough (pre-dose) LPV concentrations in children established on RIF-based TB treatment and a HAART regimen including double-dose kaletra.	University of Cape Town, Stellenbosch University	South Africa	160	Not available
-	**The concentrations of efavirenz in South African HIV-infected children with and without rifampicin-based TB treatment**	To compare estimated EFV trough concentrations in children established on a rifampicin-base regimen (for TB or BCG'osis) and an ART regimen including EFV to the estimated EFV trough concentrations in children without concomitant rifampicin who are receiving EFV as part of their ART	University of Cape Town, Stellenbosch University	South Africa	86	Not available
NCT00108862	**A strategy study of immediate versus deferred initiation of antiretroviral therapy for HIV infected persons treated for tuberculosis with CD4 less than 200**	To determine the best time to begin anti-HIV treatment in individuals who have HIV and TB.	San Francisco General Hospital and University of California, San Francisco	Brazil, India, Malawi, Peru, South Africa, South Africa, South	800 (13 years and older)	August 2006/ July 2013

	cells/mm3			America USA		
NCT00078247 1R01AI051219-01A2, 1 R01 AI051219-01A2	**Delaying HIV disease progression with punctuated antiretroviral therapy in HIV-associated tuberculosis**	To determine whether six months of anti-HIV drugs given along with TB treatment will delay the onset of AIDS in HIV-infected African patients.	Case Western Reserve University, Makarere University, University of California, San Francisco	Uganda	350 (13 years and older)	October 2004/ not available

1.5 What are the barriers to developing paediatric formulations of approved / recommended drugs?

Table 5. Ongoing clinical trials: paediatric formulations

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start / Estimated completion date
NCT00006604 IMPAACT P1020A	**Atazanavir used in combination with other anti-HIV drugs in HIV infected infants, children, and adolescents**	To try to find safe and tolerable doses of ATV with or without low-dose RTV boost in infants, children, and adolescents.	Children's Hospital of Philadelphia, Children's Hospital of Los Angeles, Baylor College of Medicine	USA	157 (3 months to 21 years old)	July 2005/ January 2010
NCT00122538	**Once-daily highly active antiretroviral treatment regimen administration in HIV-1 infected children in Burkina Faso (ANRS 12103 BURKINAME)**	To try a known antiretroviral combination in HIV-infected children with only one intake a day, in order to simplify the prescription and improve adherence to treatment. To study the tolerance of drugs in that mode of prescription of the triple combination.	French National Agency for Research on AIDS and Viral Hepatitis (ANRS) – Institut de Recherche et Développement (IRD) and CHU Sanou Souro	Burkina Faso	52 (30 months to 15 years old)	February 2006/ May 2009
NCT00672412 IMPAACT P1069	**A phase I / II comparative pharmacokinetic study of the fixed-dose combination (FDC) of aidovudine (ZDV), lamivudine (3TC), and nevirapine (NVP) as**	To compare the bioavailability of ZDV, 3TC and NVP in the GPO-VIR® Z30 tablet with the individual liquid formulations and estimate the population average exposure to NVP delivered in the GPO-VIR® Z30 tablet.	Mahidol University, CMRC Children's Memorial Hospital	Thailand	48 (5 months to 12 years old)	October 2009/ October 2010

	GPO-Vir Z30 pediatric tablets versus the individual liquid formulations in HIV-infected children greater than or equal to five months and less than 13 years of age in Thailand					
NCT00766597 IMPAACT P1071	**Phase I/II open-label study to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of vicriviroc (SCH-417690) a novel CCR5 antagonist in combination regimens in HIV-infected antiretroviral therapy experienced children and adolescents**	To test the effectiveness and safety of Vivriviroc, an HIV entry inhibitor and CCR5 co-receptor antagonist	University of California	USA, Puerto Rico	280 (2 to 18 years old)	December 2008/ December 2009
NCT00364793 AI266-922	**An open-label study of liquid and sprinkled formulations of efavirenz administered in combination with didanosine and emtricitabine in HIV-infected infants and children 3 months to 6 years of age**	To study pharmokinetics of efavirenz for young children and to study the safety and how the medication is tolerated.	BMS	Argentina, Mexico, Panama	32 (3 months to 6 years old)	February 2007/ September 2016

NCT00623597	**An open label study of the pharmacokinetics, safety and antiviral activity of invirase boosted with witonavir in HIV-infected infants and children 4 months to <6 years old**	To assess the pharmacokinetics, safety and activity of saquinavir (Invirase hard gel capsules, film-coated tablets or opened capsules) boosted by combination with ritonavir, in HIV-1 infected infants and children between the ages of four months and six years.	Hoffmann-La Roche	Argentina, Spain, Thailand	19 (4 months to 6 years old)	June 2008/ August 2010
NCT00076999	**Multiple-dose, open-label, randomized, safety and pharmacokinetic study of tipranavir in combination with low-dose ritonavir in HIV-infected pediatric patients**	The primary objective of this study is to assess the safety and tolerability of tipranavir oral formulation and soft gelatin capsules together with low-dose ritonavir in HIV-infected children and adolescents, to provide information concerning the pharmacokinetic characteristics of tipranavir and ritonavir in this age group, and to determine the relative bioavailability of the TPV liquid formulation and TPV SEDDS capsule formulation in adolescents switching from liquid to capsule.	Boerhinger-Ingelheim	Argentina, Brazil, Canada, France, Germany, Italy, Mexico, Puerto Rico, Spain, Thailand	115 (2 to 18 years old)	November 2003/ December 2009
NCT00750542 TMC-125-TiDP35-C213	**A phase 2, open-label trial to evaluate the safety, tolerability, and antiviral activity of TMC 125 in antiretroviral experienced HIV-1 infected children and**	A research study with a new drug called TMC 125 to be used in the treatment of HIV-infected children and adolescents.	University of South Alabama, Tibotec Pharmaceutical Limited	Not specified	Not specified (6 to 17 years old)	Not specified

	adolescents					
NCT00665847	**A phase II, open-label trial, to evaluate the safety, tolerability and antiviral activity of TMC125 in antiretroviral experienced HIV-1 infected children and adolescents**	To determine the safety and antiviral activity of etravirine in treatment-experienced HIV-infected children and adolescents.	Tibotec Pharmaceutical Limited	Argentina, Belgium, Brazil, Canada, France, Germany, Netherlands, Portugal, Puerto Rico, Romania, Spain, UK, USA	100 (6 to 17 years old)	July 2008/April 2010
NCT00006604 IMPAACT P1020A, PACTG P1020-A, ACTG P1020-A	**Phase I/II, open-Label, pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, Atazanavir, ATV, ReyatazTM) in Combination Regimens in Antiretroviral Therapy (ART)-Naive and -Experienced HIV-Infected Infants, Children, and Adolescents**	To find a safe and tolerable dose of the protease inhibitor (PI) atazanavir (ATV, also known as BMS-232632 or ReyatazTM), with or without a low-dose boost of the PI ritonavir (RTV), when taken with other anti-HIV drugs in HIV infected infants, children, and adolescents.	Children's Hospital of Philadelphia, Children's Hospital Los Angeles, Baylor College of Medicine	USA, Puerto Rico	157 (3 months to 21 years old)	July 2005/ January 2010
NCT00485264 IMPAACT P1066, PACTG P1066	**A Phase I/II, Multicenter, Open-Label, Noncomparative Study of the International Maternal,**	To determine the safety and effectiveness of raltegravir in treatment-experienced HIV-infected children and adolescents.	State University of New York at Stony Brook, Albert Einstein	Botswana, USA	140 (2 to 18 years old)	September 2007/ August 2009

	Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress, MK-0518) in HIV-1 Infected Children and Adolescents		College of Medicine			
-	**Population Pharmacokinetic and Pharmacodynamic study of Efavirenz in HIV-1 infected children treated with First Line Antiretroviral Therapy in South Africa**	To establish a large data base for population pharmacokinetic parameters of efavirenz in children who are being treated with the first line regimen (two NRTIs + efavirenz) and not on TB co-treatment.	University of the Witwatersrand	South Africa	68 (3 to 16 years old)	Not available
NCT00017992	**An Open-Label Study of a Once Daily Dose of Emtricitabine in Combination With Other Antiretroviral Agents in HIV-Infected Pediatric Patients**	To see if emtricitabine is safe in children infected with HIV and to determine the best dose.	Triangle Pharmaceuticals	Argentina, Mexico, Panama, Puerto Rico, South Africa, USA	100 (3 months to 17 years old)	June 2001/ June 2005 (currently recruiting)
NCT00089583	**48-Week Study Of GW433908 And Ritonavir Or GW433908 Alone, Twice Daily In Pediatric Patients With**	To evaluate safety, tolerability, pharmacokinetics and antiviral activity an investigational medicine in patients, ages 2-18 years old with HIV infection.	GSK	Belgium, Canada, Romania, Russian Fedaration, South	78 (2 to 18 years old)	July 2004/ December 2012

	HIV Infection (Lexiva)			Africa, Spain, USA		

WOMEN

2.1 What is the impact of periodic treatment (due to PMTCT ARV interventions) on future treatment options for women?

Table 6. Ongoing clinical trials on women: periodic treatment

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start / Estimated completion date
NCT00424814	**Prevention of HIV1 Mother to Child Transmission Without Nucleoside Analogue Reverse Transcriptase Inhibitors in the Pre-Partum Phase. ANRS 135 Primeva**	To assess the safety and efficacy use of a boosted protease inhibitor without nucleoside analogue during the pre-partum phase for women with no indication of antiretroviral therapy for their own.	Hopital Pitie Salpetriere, INSERM, Abbott	France	150 (female, 18 years and older)	March 2007/ September 2011
NCT00753324	**Routine Use of Antiretroviral Therapy to Prevent Mother-to-Child HIV Transmission in the Kafue District of Zambia (Impact of HAART to Prevent Pediatric AIDS in Rural Zambia)**	To better understand the incremental benefits (e.g., reduction in HIV transmission, improvements in HIV-free survival) and risks (e.g., drug toxicities) of the routine HAART strategy	CIDRZ	Zambia	320 (female)	December 2008/ December 2010
NCT00872872	**Nevirapine Plasma Level After Discontinuation of Short-Term Antiretroviral Treatment for the Prevention of Mother-to-Child Transmission of HIV and Development of Drug**	Explore how fast NVP is eliminated from women after delivery and to see if given zidovudine/lamivudine (AZT/3TC) for 1 or 2 weeks after NVP discontinuation can help reduce the development of NVP-resistant virus.	Thai Red Cross AIDS Research Center	Thailand	30 (female, 18 to 45 years old)	May 2008/ April 2010

	Resistant HIV-1 Variants With 1 or 2 Weeks Continuation of Zidovudine/Lamivudine in Women After Delivery)					
NCT00028145	**Prenatal and Postnatal Studies of Interventions for Prevention of Mother-To-Child Transmission**	To collect and study clinical and laboratory information about a pregnant or new mother and her medical care that will increase our knowledge of the best care for HIV-infected pregnant women and their children.	Brigham and Women's Hospital University of Miami	USA	3,200 (female, 14 years and older)	October 2002/not specified (currently recruiting)
NCT00334256	**Phase II Trial, Multicentre, Opened Label Evaluating the Pharmacokinetics and the Safety and Toxicity of the Tenofovir-Emtricitabine Combination in Pregnant Women and Infants in Africa and Asia**	To study the pharmacokinetic properties, safety and viral resistance pattern of the combination of tenofovir disoproxil fumarate and emtricitabine in HIV-1-infected pregnant women and their newborns, with a view to prevention of mother to child transmission of HIV-1 in Africa and Asia. **Secondary outcome:** Frequency of viral resistance to tenofovir and emtricitabine in the mothers and in the infected children.	ANRS	Côte d'Ivoire, Cambodia, South Africa	72 (female 18 years and older)	October 2006/ December 2009
NCT00346567	**Clinical Trial: Backup With Combivir (AZT/3TC) or Single Dose (sd) Truvada (FTC/TDF) in Order to Avoid NNRTI**	To find short course alternatives to single-dose NVP for the prevention of mother to child HIV transmission with the same or better degree of transmission protection than	University of Copenhagen	Tanzania	450 (female 18 to 55 years old)	June 2006/ November 2010

	Resistance After sd Nevirapine for the Prevention of Mother-to-Child Transmission	single-dose NVP but with less NNRTI resistance development. **Outcome**: Frequency of NNRTI resistance development.				
NCT00099632 ACTG A5207	**Maintaining Options for Mothers Study (MOMS): A Phase II Randomized Comparison of Three Antiretroviral Strategies Administered for 7 or 21 Days to Reduce the Emergence of Nevirapine Resistant HIV-1 Following a Single Intrapartum Dose of Nevirapine**	To determine which of three anti-HIV drug regimens most effectively reduces the development of maternal NVP resistance in HIV infected pregnant women.	Les Centres GHESKIO, University of Washington Medical Center, University of Pittsburgh	Haiti, India, Malawi, South Africa	420 (female 13 years and older)	January 2007/ January 2010
NCT00089505 ACTG A5208, OCTANE	**Optimal Combination Therapy After Nevirapine Exposure**	To compare the effectiveness of NNRTI- and PI-based regimens in women who have taken NVP for prevention of MTCT of HIV. To compare regimens including an NNRTI with regimens including a PI in women who have never taken NVP.	Harvard School of Public Health, The Walter Reed Project/WRAIR	Botswana, Kenya, Malawi, South Africa, Zambia, Zimbabwe	740 (female 13 years and older)	October 2005/ October 2009
NCT00117728 5R01HD47177	**Clinical Relevance of Nevirapine Resistance**	To evaluate a possible strategy to preserve NVP as a component of treatment regimens for young children when exposure to NVP as a part of a PMTCT prophylaxis regimen has already occurred	Columbia University	South Africa	340 (0 to 24 months old)	April 2005/ September 2010

		to test among NVP-exposed, HIV-infected children less than 24 months of age whether an induction period using a protease-inhibitor (PI) based treatment regimen (Lopinavir-Ritonavir/Lamivudine/Stavudine) can safely allow a formulation switch to an NNRTI-based treatment regimen (NVP/Lamivudine/Stavudine) once viral suppression (<400 copies/ml) has been achieved				

2.2 Are there differences between men and women in ART pharmacokinetics and pharmacodynamics, and do/should these differences have an impact on dosage recommendations and treatment outcomes?

Table 7. Ongoing clinical trials on women: differences in pharmokinetics and pharmacodynamics

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start/ Estimated completion date
NCT00433979	**Predictors of Antiretroviral Pharmacokinetics in HIV-Infected Women With Virologic Suppression on Combination Antiretroviral Therapy**	To demonstrate that levels of PIs and NNRTIs are significantly higher in our female population as compared to the mean drug levels in the historical general population (which is primarily men). To determine the association between PI and NNRTI minimum concentration (Cmin) and body weight in our female population.	Women's College Hospital	Canada	80 (female 18 to 65 years old)	February 2007/ March 2009
NCT00326716	**A Study of the Pharmacokinetics of Atazanavir (ATV)/Ritonavir(RTV) Administered as Part of HAART Therapy in HIV-1 Infected Pregnant Women**	To determine what dosing regimen of ATV/RTV produces adequate drug exposure during pregnancy compared to drug exposure in historical data in HIV-infected subjects.	BMS	USA, South Africa	42 (female, 18 years and older)	June 2006/ August 2009

2.3 What is the impact of female hormone fluctuations during adolescence, pregnancy and peri or post-menopause on treatment outcomes (e.g., pharmacodynamics)?

Table 8. Ongoing clinical trials on women: female hormone fluctuations

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start / Estimated completion date
NCT00666055	**Sex, Aging and Antiretroviral Pharmacokinetics**	To learn about levels of antiretroviral drug levels and response to HIV virus in the genital tract of women who are post-menopausal.	The University of North Carolina at Chapel Hill	USA	42 (female, 19 years and older)	March 2008/ May 2010

2.4. Are there sex differences (based on CD4+ and viral load) that are unique to women and which might have an impact on ART initiation and monitoring (i.e., should women be stratified for ART initiation and monitored differently based on viral load/CD4)?

Table 9. Ongoing clinical trials on women: sex differences impact on ART initiation and monitoring

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start / Estimated completion date
NCT00339430	**HLA and KIR Associations With Infectious Viral Agents in an HIV Cohort of Women (WIHS)**	To examine the role of HLA and killer immunolobulin-like receptors (KIR) in the natural history of HPV, HCV, and HBV in HIV-positive and HIV-negative women.	NIH	USA	3,500 (female)	July 2002/ December 2005 (still recruiting)

OPERATIONAL RESEARCH TRIALS

3.1 What are the barriers to ART access faced by women, and what are the best approaches to delivering ART to women?
3.2 What are the programmatic issues related to supplementation (e.g., micronutrient, nutritional, hormonal) for women on ART regarding what types of supplementation should be provided and how they should be integrated in ART programmes?

Table 10. Ongoing trials: operations research on women

Trial number	Trial name	Objectives related to our research questions	Principal investigator	Location	Number of participants (additional characteristics)	Start / Estimated completion date
NCT00383669	**Trial of Vitamins in HIV Progression and Transmission (A Trial of Vitamins and HAART in HIV Disease Progression)**	To examine the effects of multivitamins (including B, C, and E) on HIV disease progression among HIV-positive Tanzanian adult men and women taking HAART.	Muhimbili University College of Health Sciences and Harvard School of Public Health	Tanzania	4,000 (18 years and older)	November 2006/ September 2011
NCT00480350	**RiSolubles™, the Soluble Fraction of Rice Bran for HIV-Infected Patients**	To demonstrate the efficacy of food supplementation versus a flavoured-dextrose supplement with respect to increment of patient CD4+ cell count from baseline at 24 weeks, or virological response defined as lowering of plasma HIV-1 RNA and immunologic response.	Hadassah Medical Organization	Israel	140 (18 to 80 years old)	September 2007/ January 2009
NCT00860769	**Asha HIV Health Promotion Intervention in India**	Plan an intervention designed to support women who are receiving treatment and care for HIV and TB, and to help promote their adjustment to illness and improve their health as it relates to their coping and behavioural responses and physical health	The Regents of the University of California	India	70 women (16 to 45 years old)	September 2008/ June 2011

		outcomes. This intervention, delivered by specially trained village women, will then be tested with women living with HIV to assess how acceptable and effective the intervention might be compared to WLH who receive usual care.				

Penta 15 ISRCTN38147516	**Plasma pharmacokinetic study of once versus twice daily abacavir as part of combination antiretroviral therapy in children with HIV-1 infection aged 3 months to <36 months**	To assess the pharmacokinetics, feasibility and acceptability of dosing ABC or ABC in combination with 3TC once daily in children aged three months to <36 months.	PENTA	France, Germany, Italy, Spain, United Kingdom	18 (3 to 36 months years old)	January 2006/June 2008 – completed