

WOMEN AND HEALTH INITIATIVE WORKING PAPER SERIES

RESEARCH AND EVALUATION AGENDA FOR MATERNAL HEALTH AND HIV IN SUB-SAHARAN AFRICA



HARVARD | SCHOOL OF PUBLIC HEALTH
Women and Health Initiative



Maternal Health **Task Force**



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Abbreviations and Acronyms

AIDS	Acquired immune-deficiency syndrome
ALPHA	Analyzing Longitudinal Population-based HIV/AIDS data on Africa
ANC	Antenatal care
AOR	Adjusted odds ratio
ART	Antiretroviral therapy
ARV	Antiretroviral (drugs)
CD4	Cluster of differentiation antigen 4
CDC	United States Centers for Disease Control and Prevention
CI	Confidence interval
CVCT	Couple voluntary counseling and testing
DHS	Demographic health survey
EFV	Efavirenz
FP	Family planning
HIV	Human immuno-deficiency virus
HSPH	Harvard School of Public Health
ICAP	International Center for AIDS Care and Treatment Programs
ICD code	International classification of diseases
IMAGE	Intervention with Microfinance for AIDS and Gender Equity
iMMR	Institutional Maternal Mortality Ratio
InterVA	Interpreting Verbal Autopsies
IPTp	Intermittent Preventive Treatment of Malaria in Pregnancy (IPTp)
IPT	Isoniazid preventive therapy
IPV	Intimate partner violence
ITN	Insecticide treated nets
IRIS	Immune Reconstitution Inflammatory Syndrome
IVCT	Individual voluntary counseling and testing
M2M	Mother to mother
MCH	Maternal and child health
MHTF	Maternal Health Task Force
MICS	Multiple Indicator Cluster Survey
MMR	Maternal mortality ratio
MNCH	Maternal, newborn and child health
MTCT-Plus	Mother-to-child-transmission-Plus
NVP	Nevirapine
OR	Odds ratio
PEPFAR	United States President's Emergency Plan for AIDS Relief
PLHIV	People living with HIV
PMTCT	Prevention of mother to child transmission
PrEP	Pre-exposure prophylaxis
RCT	Randomized Controlled Trial
RMC	Respectful maternity care
Sd-NVP	Single dose nevirapine
SEARCH	Sustainable East Africa Research in Community Health

SP	Sulfadoxine-pyrimethamine
STI	Sexually Transmitted Infection
TASO	The AIDS Support Organization
TB	Tuberculosis
UN	United Nations
USAID	United States Agency for International Development
WHO	World Health Organization
ZDV	Zidovudine

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Executive Summary

Objectives

In June 2013, a group of international maternal health and HIV researchers came together in Boston under the auspices of the Maternal Health Task Force (MHTF) at the Harvard School of Public Health, the United States Agency for International Development (USAID), and the Centers for Disease Control and Prevention (CDC) to share emerging evidence, identify promising practices for scale-up, and develop a priority research agenda.¹ Drawing on discussions during the “*Maternal Health, HIV and AIDS: Examining Research Through A Programmatic Lens*” meeting and a comprehensive review of the peer-reviewed literature,² this research and evaluation agenda synthesizes existing knowledge and frames priority research questions that must be answered to improve maternal health in the context of sub-Saharan Africa’s HIV pandemic. The agenda also seeks to provide guidance to researchers, programmers, and policymakers about how to advance research and evaluation relevant for policy, programs, and service delivery in the short- and medium-term.

Maternal Mortality and HIV

Internationally, HIV and complications of childbearing are the top causes of death among women of reproductive age. The research and evaluation agenda focuses on sub-Saharan Africa because in 2011, 90% of pregnant women with HIV resided there and recent estimates suggest that a quarter of deaths during pregnancy and the six week postpartum period in the region are attributable to HIV. Transforming the negative synergies between maternal health and HIV into opportunities to promote the health and well-being of women of reproductive age is necessary to prevent new HIV infections, eliminate AIDS-related deaths, and to end preventable maternal mortality.

Maternal deaths due to non-obstetric causes predominate among women with HIV, and those with advanced disease and least time on antiretroviral therapy (ART) face the highest risk

¹ See Annex 1 for the list of individuals who participated in the June 12 2013 meeting with to develop a research agenda for maternal health and HIV in sub-Saharan Africa

² A comprehensive review of the grey literature was not conducted, however information from presentations made at the meeting and select documents from the grey literature are referenced.

of death. Earlier and more widespread access to ART is expected to reduce maternal morbidity and mortality, but the impact of ART on causes, rates and distribution of maternal morbidity and mortality in low and middle-income countries is not yet well-defined. The need to evaluate the health impacts of new HIV treatment guidelines which recommend earlier initiation of treatment for all adults, the implementation of programs which seek to initiate all pregnant and breastfeeding women on lifelong ART regardless of their immune status (Option B+), and recognition of the potential of “treatment as prevention” provide the context for the identified research priorities.

To date, significant advances have been made towards increasing availability of HIV-testing during pregnancy and provision of ART to prevent mother-to-child transmission (PMTCT) of HIV in many high-burden countries. However, insufficient integration of HIV and Maternal and Child Health (MCH) services persists and opportunities to improve women’s health by addressing tuberculosis, malaria, and reproductive health in HIV and MCH services are missed. Furthermore, rates of uptake, linkage between MCH and HIV care, retention and ART adherence are suboptimal. Reducing HIV-related stigma and gender discrimination, including violence against women, increasing social support for women during pregnancy and the extended postpartum period, and mobilizing communities to promote respectful, high quality HIV and MCH services are promising interventions for creating an enabling environment for women to access and remain in care. Finally, while an exhaustive discussion of human resource needs is beyond the substantive scope of this research and evaluation agenda, there is a clear need to address human resource shortages in the health systems of sub-Saharan Africa and to assess required skills in the context of task-shifting as a prerequisite for improving the coverage and quality of integrated MCH and HIV interventions.

Research Priorities

The third day of the expert meeting was dedicated to developing a consensus research agenda. Meeting participants identified the following three priorities: 1) Improve the evidence base to better ascertain causes of maternal morbidity and mortality among women with HIV and conduct research to assess changes in rates, distribution, and causes of maternal death as ART availability is scaled-up; 2) Implement and evaluate integrated HIV and MCH service delivery and identify how to best incorporate prevention, detection, and treatment of malaria and

tuberculosis and provision of pre-conception counseling and postpartum contraceptives in integrated service delivery models; 3) Determine how best to create an enabling environment for women to enter and remain in HIV and MCH care by reducing violence against women and HIV-related stigma, mobilizing communities to promote respectful, high-quality MCH and HIV services, and increasing social support for women during pregnancy and the extended postpartum period, including by involving male partners.

Moving the Research Agenda Forward

Much of the data needed to answer the key research questions is currently available but needs to be analyzed, or could be generated with reasonable investments to enhance program monitoring, or to implement intervention research and collect complementary data within the context of randomized controlled trials and observational studies. Given the need to optimize scarce resources and generate data relevant for policies and programs in the short-term, opportunities to answer pressing research questions immediately and in the short-term were identified by the meeting participants. Improvement of vital registration, harmonization of data collection and inclusion of key indicators by HIV and maternal health programs in monitoring and evaluation (including maternal death reviews) are essential to advance the evidence base.

Conclusions

Improving maternal health in the context of the sub-Saharan African HIV epidemic requires greater understanding of the relationships between HIV disease and maternal morbidity and mortality, integrated and effective responses by the health system, and a social context which promotes quality care and encourages use of MCH and HIV services. Advancing the proposed research agenda will make an invaluable contribution by generating needed evidence for policy and practice that improves the maternal health of women who are living with HIV, as well as those who are not. Bringing together maternal health and HIV researchers, policy-makers and program implementers to reduce HIV-related maternal morbidity and mortality and improve the HIV response for women represents an opportunity and a challenge. Collaborating on research which addresses HIV and maternal health and capturing key outcomes and variables routinely in program evaluation and monitoring is one way to raise awareness and catalyze the joint responses necessary to improve maternal health in sub-Saharan Africa.

Introduction: Maternal Mortality and HIV

The two top causes of death in women of reproductive age globally are HIV and AIDS (19%) and complications related to childbearing (15%) (WHO 2009). Sub-Saharan Africa is the region with the highest maternal mortality rate globally (596 per 100,000 live births) and where half of maternal deaths occur (Hogan, Foreman et al. 2010). In 2011, 90% of the total number of pregnant women with HIV lived in sub-Saharan Africa (UNAIDS 2012b). The region is home to 69% of the 34 million people living with HIV globally (UNAIDS 2012a). A recent analysis of mortality during pregnancy and the six week postpartum period found that women with HIV were eight times more likely to die than their HIV-negative counterparts and led the researchers to estimate that a quarter of deaths of pregnant and postpartum women in sub-Saharan Africa are attributable to HIV (Zaba, Calvert et al. 2013). Given these findings, the 2012 resolution by the UN Commission on the Status of Women to eliminate preventable maternal mortality will not be achieved unless HIV among women of reproductive age is addressed and care of pregnant women living with HIV is improved (United Nations 2010). Changing the negative synergies between HIV and poor maternal health outcomes into opportunities to promote the health and well-being of women of reproductive age, both those who are living with HIV and those who are not, is an urgent international public health priority.

This document presents priorities for research and evaluation from the meeting *Maternal Health, HIV and AIDS: Examining Research Through A Programmatic Lens* which brought together researchers, programmers and policymakers in Boston, MA June 10-13, 2013 under the auspices of the Maternal Health Task Force (MHTF) at the Harvard School of Public Health, the United States Agency for International Development (USAID), and the Centers for Disease Control and Prevention (CDC). This meeting was one of the first to bring maternal health and HIV experts together to have a substantive discussion of the existing evidence and priority research gaps in the field of maternal health and HIV in sub-Saharan Africa.

The meeting participants identified the following three priorities: 1) Improving cause of death data to better understand relationships between HIV and maternal morbidity and mortality and to assess the impact of scaled-up access to ART on maternal health outcomes; 2) Evaluating models for effectively integrating MCH and HIV care, as well as incorporating malaria,

tuberculosis, preconception counseling and postpartum contraception services; 3) Creating an enabling environment for women to enter and remain in HIV and MCH care.

Many of the research questions are concerned with identifying how best to implement interventions that are known to work (at least in some settings and for some health outcomes) and evaluating their impact on the reduction of maternal mortality and improved maternal health outcomes in the context of HIV. Some questions can be answered by enhancing routine program monitoring and evaluation. Others will require implementation research or the creation of new observational cohorts or adding complementary research components to other studies. Meeting participants emphasized the need to tailor interventions for the country context and to conduct cross-country analysis.

HIV and Maternal Mortality: What Do We Know?

Globally, between 6% and 18% of maternal deaths are attributable to HIV, and women living with HIV in sub-Saharan Africa are six to eight times more likely to die than their HIV-negative counterparts (Hogan, Foreman et al. 2010, Calvert and Ronsmans 2013b, Zaba, Calvert et al. 2013). Maternal deaths among women with HIV are mostly attributed to indirect rather than obstetric causes, particularly non-pregnancy-related infections (Ramogale, Moodley et al. 2007, Menendez, Romagosa et al. 2008, Moodley and Pattison 2012, Ordi, Ismail et al. 2009, Chweneyagae, Delis-Jarrosay et al. 2012). Malaria and tuberculosis pose increased risk of morbidity and mortality in pregnancy and these risks are substantially increased when women are also living with HIV (Brentlinger, Behrens et al. 2006, Khan, Pillay et al. 2001, Gupta, Nayak et al. 2007, ter Kuile, Parise et al. 2004, Ticconi, Mapfumo et al. 2003). Despite the predominance of non-obstetric causes of death, women with HIV experience greater mortality due to puerperal sepsis and obstetric hemorrhage than their HIV-negative peers (Sebitloane 2013, Sebitloane, Moodley et al. 2009). At this time, the available data does not allow for the quantification of maternal mortality among women in low resource settings who are treated with antiretrovirals (ARV) early in pregnancy, nor is it known how increased access to ART will impact the distribution of causes of maternal morbidity and mortality among women living with HIV (Lathrop 2013).

HIV and Maternal Health: Programmatic Progress and Persistent Gaps

Globally, significant progress towards reducing maternal mortality has been made, however much remains to be done especially in sub-Saharan Africa. The number of women estimated to have died each year from causes related to pregnancy or childbirth has dropped substantially from 543,000 deaths in 1990 to around 287,000 deaths in 2010—but eight countries in sub-Saharan Africa with high HIV prevalence have experienced increases in maternal mortality over the past two decades (WHO and UNICEF 2013). Reductions in maternal deaths have largely been attributable to a decline in total fertility rate, increased income per head in Asia and Latin America, improved maternal education in sub-Saharan Africa, and increases in skilled birth attendance (Hogan, Foreman et al. 2010). To eliminate preventable maternal mortality and respond to HIV among women, it is imperative not to miss the opportunities created when women attend health services during the continuum of maternity care (pregnancy, delivery, and postpartum) or when they seek HIV care. There is also a need to continue to improve quality of care and reduce barriers to women attending HIV and MCH services.

To address HIV during pregnancy for the woman's health and for PMTCT, knowledge of women's HIV status is necessary. In 2012, only 38% of pregnant women in low and middle income countries received HIV counseling and testing (WHO, UNICEF et al. 2013: 61). In Africa, 49% of pregnant women were tested for HIV and some sub-Saharan African countries with high burdens of HIV disease made great strides towards universal coverage: Botswana, Mozambique, South Africa and Zambia all provided HIV testing to 95% of pregnant women (WHO, UNICEF et al. 2013: 60). In 2011, more than half of pregnant women with HIV in Africa (58%) received antiretrovirals for PMTCT; in Eastern and Southern Africa the coverage rate was 71%; and some countries prioritized in the Global Plan to Eliminate Mother-to-Child HIV Transmission achieved rates of 80-90% (WHO, UNICEF et al. 2013: 28-30). New treatment guidelines which recommend earlier initiation of ART (at a CD4+ cell count of 500 cells/uL rather than a CD4+ cell count of 350 cells/uL) and the promotion of programs which seek to initiate pregnant and breastfeeding women on lifelong ART independent of women's immune status (Option B+) provide the backdrop for the identified research priorities (WHO 2013a).

Advances in PMTCT contrast with poor progress in implementing other pillars of the needed response to HIV among women and children: preventing new HIV-infections among

women, preventing unintended pregnancies among women with HIV and providing treatment, care, and support to women with HIV and their families (WHO and UNFPA 2006). This research and evaluation agenda prioritizes interventions to improve the reproductive health of women living with HIV and to increase uptake and retention in MCH and HIV services and adherence to ART during pregnancy and beyond.

Rates of unmet need for family planning remain unacceptably high among women in sub-Saharan Africa, including for those living with HIV, even if they are participating in treatment programs (Darroch and Singh 2013, Sarnquist, Rahangdale et al. 2013). The potential for contraceptives to reduce unintended pregnancies among women living with HIV (and thus contribute to PMTCT and reducing maternal morbidity and mortality) is not being realized. Similarly, the game-changing potential of antiretroviral treatment to radically reduce sexual transmission and to increase reproductive options for people living with HIV and their partners needs to be addressed within MCH and HIV care.

Finally, significant programmatic and social barriers must be overcome to ensure that HIV diagnosis during prenatal care translates into access to life-saving ART for women and to promote uptake, retention, and adherence to HIV and MCH care. While progress has been made on the provision of treatment to pregnant women for their own health—jumping from 30% in 2011 to 58% in 2012—estimates indicate that they are still less likely to benefit than other treatment eligible adults (UNAIDS 2012a: 47, UNAIDS 2013: 42). Documented barriers to women beginning HIV treatment for PMTCT and for their own health include: lack of knowledge about the benefits of ART, psychological factors (such as shock, denial, fear of treatment side effects), not having any symptoms of HIV disease, financial constraints and HIV-related stigma, particularly fears about disclosure, and lack of partner and family support (Ferguson, Grant et al. 2012, Gourlay, Birdthistle et al. 2013, Turan and Nyblade 2013). Broader health systems issues such as poor quality of care (inadequate skills and availability of staff, disrespect and abuse, stock-outs, delays in service provision), and geographic and economic barriers are also associated with poor uptake and retention of women in PMTCT and dropping out of the treatment cascade and not accessing HIV services, including ART, for themselves (Ferguson, Grant 2012, Gourlay, Birdthistle et al. 2013).

The focus of this research and evaluation agenda is the health of women living with HIV during pregnancy and the extended postpartum period³, with the understanding that maternal health is an important component of women's health and that high-quality, supportive interactions with the health system during pregnancy and postpartum can have long-term positive consequences for women who are living with HIV as well as those who are not. Infant and child health is considered specifically only with respect to how scale-up of ART and consequent exposure to ART in utero will affect health outcomes. While the focus of this paper is maternal health, the available information strongly suggests that research and evaluation to improve service provision for women living with HIV who are not pregnant and men living with HIV are also important priorities (WHO, UNICEF et al. 2013, Zaba, Calvert et al. 2013).

Priorities for Research and Evaluation

Knowledge about the relationships between HIV and maternal health is rapidly advancing and many aspects of the programmatic response have made impressive progress, but big questions remain. Available evidence suggests that pregnancy does not accelerate HIV disease progression (MacCarthy, Laher et al. 2009). On the other hand, there is evidence that women living with HIV have higher rates of maternal morbidity and mortality (Calvert and Ronsmans 2013a, Zaba, Calvert et al. 2013). However, it is not clear how much HIV in and of itself aggravates pregnancy-related conditions, nor how ART will affect the rates and causes of death among pregnant and postpartum women living with HIV. Questions about the complex interactions between HIV disease, immune status, time on ART, pregnancy and the postpartum period, and the rates, causes and distribution of maternal morbidity and mortality need to be answered. Generating evidence about these relationships in the context of rapid treatment scale-up to provide clinical and programmatic guidance to improve women's health is the focus of *Research Priority 1: Clinical Questions about Maternal Mortality and HIV*.

Second, the available evidence tends to support integration of services as a way to respond to the multiple health needs of pregnant and postpartum women, but questions remain about how to best increase coverage without compromising effectiveness of specific

³ Unless specified as six weeks postpartum, throughout the document postpartum refers to the extended postpartum period which is up to one year postpartum.

interventions or overwhelming already overburdened health systems and health workers. While the clinical effectiveness of PMTCT has been demonstrated in both high and low-income countries, there is surprisingly little evidence about the maternal health outcomes of integrating ART into antenatal and postpartum care even though countries are moving towards integrating HIV with MCH services. Similarly, while some countries have been pioneering integrated approaches, little implementation research has been conducted on the integration of other critical components of care that are needed to promote women's health and reduce maternal morbidity and mortality. *Research Priority 2: Integrating Health Service Delivery to Address Maternal Health and HIV* focuses on evaluating models for effectively integrating MCH and HIV care with malaria, tuberculosis, and broader sexual and reproductive health (SRH) services, particularly preconception counseling and postpartum contraception services.

Third, relatively poor uptake and retention in MCH and HIV services and suboptimal ART adherence, particularly among postpartum women, must be better understood and overcome to promote women's health. To achieve the desired results and truly support the health of women and communities, investments in ART scale-up must appropriately address the realities of women's lives, which include gender discrimination and HIV-related stigma. *Research Priority 3: Transforming the Social Context to Improve Maternal Health* proposes evaluation of interventions which will contribute to an enabling social context and effectively link women to and retain them in care, as well as supporting ART adherence.

Summary of Priority Research and Evaluation Questions

Research Priority 1: Clinical Questions about Maternal Mortality and HIV

Priority Research Questions

- What is the relationship between HIV infection and rates and causes of maternal morbidity and mortality?
- How will rates and causes of morbidity and mortality during pregnancy and the postpartum period be affected by increased availability of antiretroviral treatment for women living with HIV of reproductive age, including provision of lifelong ART to pregnant and postpartum women?

Key Outcomes and Variables⁴

- HIV status, pregnancy/postpartum status, currently on ART, gestational age (or trimester) at initiation or on ART at conception, time on ART, ART regimen, CD4 and viral load (most recent and at treatment initiation), WHO disease stage, cause of death, causes of maternal morbidity, type of delivery (vaginal or cesarean), perinatal outcome (live or stillbirth), cost-benefit and cost-effectiveness

Research Priority 2: Integrating Health Service Delivery to Address Maternal Health and HIV

Priority Research Questions

- What are the most effective models for integrating HIV testing, treatment and care with antenatal, intrapartum, and postpartum services?
- How can additional critical interventions—specifically screening, prophylaxis and treatment for malaria and tuberculosis, postpartum family planning, and preconception counseling—be integrated into the continuum of MCH and HIV services while maintaining quality, effectiveness and coverage?

Key Outcomes and Variables

- Health outcomes: clinical effectiveness of different interventions with integration, maternal morbidity and mortality, pediatric HIV infection, and sexual HIV transmission.
- Health systems: national policies and budget allocation, process indicators to assess coverage and quality of care (including uptake of MCH and HIV services), satisfaction and retention of healthcare workers and service users, human resources needed to delivery interventions (ratio and cadre of providers to service users, skill level), cost-benefit and cost-effectiveness.

⁴ Depending on the intervention to be evaluated and the setting, researchers and programmers will need to select and define specific indicators to measure inputs, process, and outcomes. Validated tools and techniques are mentioned throughout the document for many of the suggested outcomes and variables.

Research Priority 3: Transforming the Social Context to Improve Maternal Health

Priority Research Questions

- What are the effects of programs which reduce HIV-related stigma and discrimination, disrespect and abuse in maternity care, and violence against women on uptake and retention in HIV and MCH services, adherence to ART, disclosure of HIV status, and postpartum depression?
- How does increasing social support for pregnant and postpartum women, including from male partners, and community mobilization to promote respectful, high-quality HIV and MCH services affect maternal health outcomes?

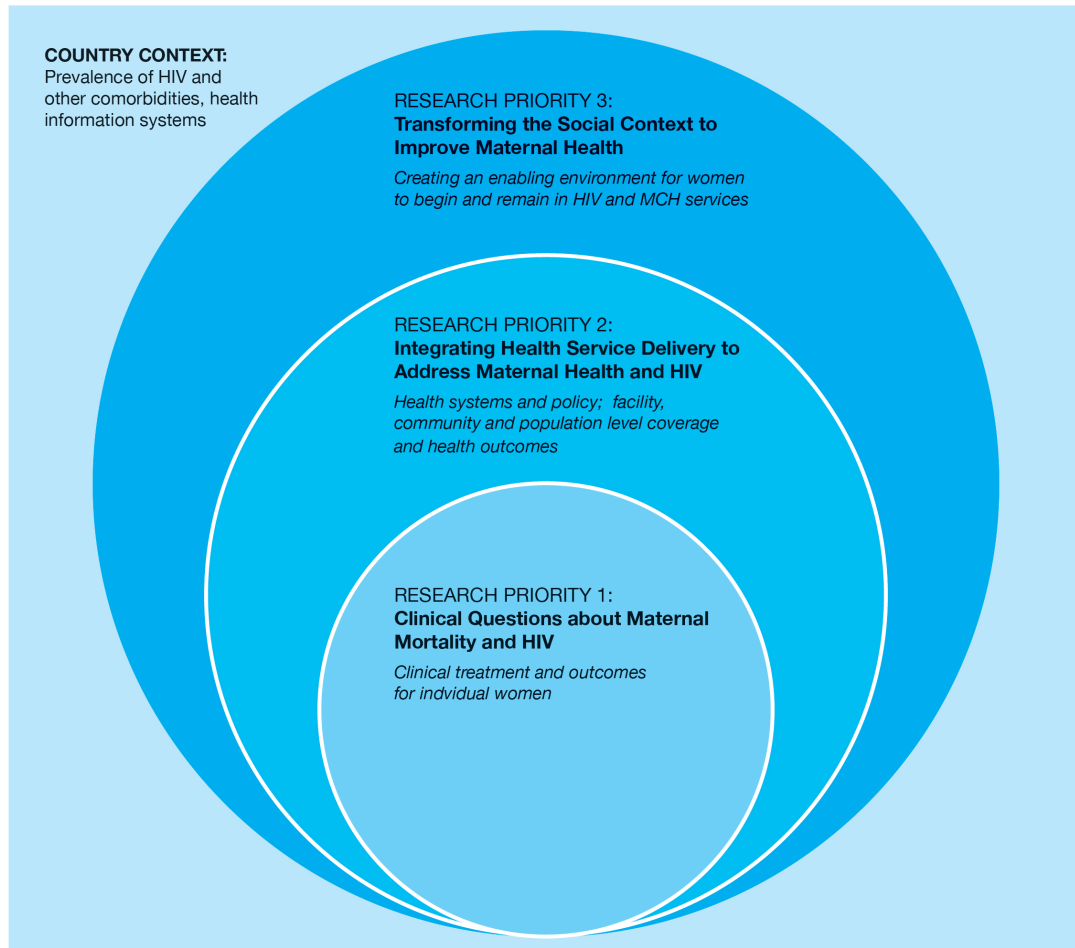
Key outcomes and variables

- Uptake of HIV and MCH services, linkage from HIV diagnosis to treatment, retention in care, antiretroviral adherence, postpartum depression, disclosure of HIV status, HIV-related stigma and discrimination, disrespect and abuse in maternity care, other health-related quality of life measures, cost-benefit and cost-effectiveness.

Conceptual Framework

The three research priorities focus on different levels of the social and programmatic context relevant for HIV and maternal health (see Figure 1): Priority 1 addresses the individual woman and clinical outcomes; Priority 2 considers interactions between pregnant and postpartum women and healthcare providers and the multiple health needs to be addressed within the context of the health system; and Priority 3 seeks to assess how interventions which contribute to transforming social determinants of health and the broader social context affect women's uptake of and retention in health services as well as a range of other social and health outcomes.

FIGURE 1. DIAGRAM OF CONCEPTUAL FRAMEWORK



PRIORITY RESEARCH QUESTIONS

RESEARCH PRIORITY 1:

- What is the relationship between HIV infection and rates and causes of maternal morbidity and mortality?
- How will rates and causes of morbidity and mortality during pregnancy and the postpartum period be affected by increased availability of antiretroviral treatment for women living with HIV of reproductive age, including provision of lifelong ART to pregnant and postpartum women?

RESEARCH PRIORITY 2:

- What are the most effective models for integrating HIV testing, treatment and care with antenatal, intrapartum, and postpartum services?
- How can additional critical interventions—specifically screening, prophylaxis and treatment for malaria and tuberculosis, postpartum family planning, and preconception counseling—be integrated into the continuum of MCH and HIV services while maintaining quality, effectiveness and coverage?

RESEARCH PRIORITY 3:

- What are the effects of programs which reduce HIV-related stigma and discrimination, disrespect and abuse in maternity care, and violence against women on uptake and retention in HIV and MCH services, adherence to ART, disclosure of HIV status, and postpartum depression?
- How does increasing social support for pregnant and postpartum women, including from male partners, and community mobilization to promote respectful, high-quality HIV and MCH services affect maternal health outcomes?

There are mutually influential relationships between the identified Research Priorities and the different levels of the health system and social environment where research will be conducted and programs implemented. Promoting evidence-based policies and programs will resonate positively across all three levels and ultimately improve women's health at the country level. To illustrate, better information about HIV status, antiretroviral regimen and cause of death can guide prioritization of interventions in different country and regional contexts, resource allocation, and inform healthcare provider training. Similarly, community monitoring and social support (which increase demand for and supply of MCH and HIV services) can increase uptake and improve individual ART adherence while acknowledging that individual behavior is shaped by social context. These outcomes contribute to better individual health and also to public health by reducing sexual HIV transmission, preventing MTCT and slowing the development of antiretroviral resistance.

The Need for Consistent Process and Outcome Measures in HIV and MCH Research and Programs

Improved data quality and generation of consistent and comparable indicators in HIV and MCH services are necessary to monitor and evaluate progress toward reducing maternal morbidity, eliminating preventable maternal mortality and addressing the HIV and AIDS pandemic among women of reproductive age. Strengthening vital registration and national health information systems and collecting key indicators in routine program monitoring and evaluation will be essential for generating the needed evidence about maternal health and HIV. At a minimum, the HIV status of pregnant women needs to be known, which is in itself a challenge given that in 2012 just half of pregnant women in Africa were offered HIV testing (WHO, UNICEF et al. 2013). Where possible, disease stage, and markers of immune status (viral load and CD4), time on ART, and treatment regimen would be invaluable information for understanding the relationship between HIV and maternal deaths.

In 2012, the World Health Organization published guidance to facilitate the consistent coding of maternal death certificates (WHO 2012e). The guidance emphasizes identification of a single underlying cause of death and standardization of coding of direct and indirect causes of

maternal death (WHO 2012e). Women living with HIV may die from obstetric causes where HIV-infection or AIDS is not the underlying cause of death. On the other hand, women might die of an HIV- or AIDS-related condition—like pneumocystis pneumonia—that is not related to pregnancy and thus should not be coded as a maternal death. Only if pregnancy contributed to an HIV-related death should HIV be coded as a cause of maternal death (ICD code O98.7) (WHO 2012e: 19). Alternatively, if HIV disease contributed to an obstetric complication that caused a maternal death (e.g. sepsis) it would be listed as a contributing factor.

The causal relationships and interactions between HIV disease, pregnancy, disease progression and maternal deaths are research questions that remain to be answered. Recording all deaths during pregnancy among women with HIV and improving the quality of death certificates will contribute to elucidating these relationships.

However, better death certificates will not solve all problems. Even at tertiary-level hospitals, autopsy studies reveal significant misdiagnoses in cause of maternal death. For example, a study from Mozambique identified major diagnostic errors (mistaken cause of death that resulted in inadequate treatment) in 40% of maternal deaths; for 12 out of 18 women with HIV who died the underlying cause of death was misdiagnosed (Ordi, Ismail et al. 2009). There is a need to conduct more autopsies, expand maternal death audits, and conduct verbal autopsy studies of maternal deaths, particularly where a significant proportion of births take place outside of institutions. Advances in minimally-invasive autopsies that could be carried out in the field, improvements to verbal autopsy tools, and community-based data collection (in some cases facilitated by mobile technologies) are promising avenues for improving the availability and quality of data.

More information is also required about maternal morbidity, which is much more common than mortality, and takes a huge toll on the health and well-being of women internationally. A recent scoping exercise by the WHO found that the existing literature and experts did not share uniform criteria for the identification and classification of maternal morbidity, including severity and time frame (Firoz, Chou et al. 2013). The Maternal Morbidity Working Group is working to develop and validate an assessment tool for measuring maternal morbidity at the community and primary-health-care levels and develop indicators of maternal morbidity for population-level tracking (Firoz, Chou et al. 2013). Meanwhile, identifying severe

cases of maternal morbidity using methodologies such as “near misses” which identify women who experienced serious complications but survived, or calculating the Case Fatality Rate, will generate needed information (Souza, Cecatti et al. 2012).

Program monitoring and evaluation could play an important role in generating evidence needed for improving national and international responses to HIV and maternal morbidity and mortality. However, routine monitoring and evaluation is weak in many countries. There is a paucity of data on actual maternal or neonatal health outcomes in contexts of integrated service delivery and very few studies report on the utilization and/or outcomes based on the HIV-status of pregnant and postpartum women and their children (Nutman, McKee et al. 2013).

The tendency of implementation research to only measure process indicators (utilization and coverage) rather than outcome indicators (health status) or to confine reporting to a single short-term health outcome limits our ability to evaluate program effectiveness and impact on multiple health outcomes (Lindegren, Kennedy et al. 2012). Implementation science, which tracks rare events like maternal mortality over time and takes into account multiple, medium term health outcomes (like incident pregnancy, new HIV and other sexually transmitted infections, malaria, and tuberculosis), is urgently needed. In general, information about the cost of program implementation and cost-effectiveness is lacking.

Finally, while there is increasing recognition that the social determinants of health have an important gender component and there are numerous large-scale initiatives to reduce barriers to care for pregnant women through conditional cash transfer programs, healthcare coverage schemes and financial incentives to attend prenatal and labor and delivery services, less attention has been paid to the effects of intrapersonal quality of care, community engagement and social support (including participation of male partners) on proximate measures (uptake and retention in HIV care, facility delivery, disclosure of HIV-status, postpartum depression, and adherence to antiretroviral treatment) and health outcomes (violence against women, maternal morbidity and mortality, quality of life). Evaluation of community-based, participatory and rights-based interventions and implementation research on programs which aim to create an enabling environment for women to begin and remain in MCH and HIV services are priorities.

In conclusion, better evidence about the relationship between HIV and maternal morbidity and mortality, and how best to implement interventions within and beyond the health

system to improve maternal health outcomes are needed to guide programming and policy. Fortunately, in spite of significant problems with data quality, completeness, and availability, there are opportunities to conduct secondary analyses, draw on data generated through routine monitoring and evaluation, advocate for the inclusion of indicators in routine programming monitoring and periodic population-based studies, improve tools (such as verbal autopsies), and leverage ongoing research and implementation science to answer key questions. Finally, to answer some questions, new research will be needed.

Research Priority 1: Clinical Questions about Maternal Mortality and HIV

Women with HIV in sub-Saharan Africa are six to eight times more likely to die during pregnancy and the six week postpartum period than are their HIV-negative counterparts (Calvert and Ronsmans 2013a, Zaba, Calvert et al. 2013). Research is needed to determine whether pregnancy has an independent effect on mortality among women living with HIV and how risk of morbidity and mortality interacts with immune parameters and time on ART. Several studies and reviews have found that pregnancy does not seem to accelerate HIV disease progression or time to death either before or after the availability of antiretroviral treatment, however high rates of loss to follow-up may have contributed to underestimation of mortality (Tai, Udoji et al. 2007, MacCarthy, Laher et al. 2009, Westreich, Maskew et al. 2013). A recent prospective cohort study of women initiating ART in Uganda found no significant differences when comparing crude mortality rates between women who had a pregnancy and those who did not, however when pregnancy and the one-year postpartum period was treated as a time-dependent risk factor, significantly higher pregnancy-related mortality was identified (Matthews, Kaida et al. 2013). These findings should be interpreted cautiously as only five deaths of pregnant and postpartum women occurred (Matthews, Kaida et al. 2013).

Questions related to the impact of pregnancy on HIV progression and, conversely, the impact of HIV and pregnancy on infections such as TB and malaria, are complicated by the “healthy pregnancy effect”. Fertility is reduced as HIV disease progresses, thus women living with HIV who become pregnant tend to be healthier than women who do not become pregnant. The healthy pregnancy effect complicates comparisons of rates of morbidity and mortality between pregnant and non-pregnant women living with HIV, and requires more research which controls for immune parameters and treatment status.

How increased availability of ART in low-resource settings will change the causes and patterns of maternal and neonatal morbidity and mortality remains to be determined. As countries implement the new World Health Organization Guidelines for ART during pregnancy, initiate treatment earlier (at CD4+ cell count of 500 cells/uL rather than a CD4+ cell count of 350 cells/uL), and offer pregnant, breastfeeding and postpartum women lifelong ART independent of immune system parameters (Option B+), many more women of reproductive age

will be on ART continuously (WHO 2013a). Understanding the impact of increased use of ART at conception, during pregnancy, and postpartum for women and children's health is a research priority. Finally, there are outstanding clinical questions about how to best manage pregnant and postpartum women with HIV to reduce morbidity and mortality.

Priority Research Questions

- What is the relationship between HIV-infection and rates and causes of maternal morbidity and mortality?
- How will rates and causes of morbidity and mortality during pregnancy and the postpartum period be affected by increased availability of ART for women of reproductive age living with HIV, including provision of Option B+?
- Does pregnancy influence the progression of HIV disease?
- What research designs are most appropriate for adjusting for the healthy pregnancy effect and ensuring valid comparisons between groups of pregnant and postpartum women living with HIV as well as those who are not pregnant?

Key Outcomes and Variables:

HIV status, pregnancy/postpartum status, currently on ART, gestational age (or trimester) at initiation or on ART at conception, time on ART, ART regimen, CD4 and viral load (most recent and at treatment initiation), WHO disease stage, cause of death, causes of maternal morbidity, type of delivery (vaginal or cesarean), perinatal outcome (live or stillbirth), cost-benefit and cost-effectiveness.

Cause of Death among Pregnant and Postpartum Women with HIV

The majority of maternal deaths in women with HIV are attributed to non-pregnancy related infections. For example, an autopsy study of maternal deaths among women with HIV found HIV or AIDS related conditions to be the most common cause of death, followed by tuberculosis, bacterial pneumonia, and severe malaria, while the main obstetric causes of death were puerperal septicemia and eclampsia (Menendez, Romagosa et al. 2008) . In South Africa, the top causes of maternal death among women with HIV between 2008 and 2010 were: non-

pregnancy related infections (cause specific Institutional Maternal Mortality Ratio iMMR 267.3 per 100, 000 live births vs. 6.6 among HIV-negative); obstetric hemorrhage (iMMR 38.4 HIV+ vs. 17.1 HIV-); hypertension (iMMR 27.4 HIV+ vs. 18.8 HIV-); sepsis (iMMR 24.2 HIV+ vs. 4.1 HIV-); and medical and surgical disorders (iMMR 24.2 HIV+ vs. 11.5 HIV-) (Sebitloane 2013). Between 2008 and 2010, two-thirds of South African women with AIDS who died during pregnancy or six weeks postpartum had respiratory complications, namely TB (26.9%), pneumocystis pneumonia (13.3%) and other non-specified pneumonia (26.7%); the second most common contributing cause of death in women with AIDS was meningitis (12.9%) (Moodley and Pattison 2012). In Nigeria, between 2005 and 2009, 62% of maternal deaths among women with HIV were from indirect causes, specifically cerebral infections, tuberculosis, pneumonia and AIDS (Danel 2013). The expert meeting convened by the CDC, USAID and the MHTF in June 2013 prioritized the following contributors to and causes of maternal death for future research: sepsis, obstetric hemorrhage, hypertension, anemia, malaria, pneumonia, and tuberculosis.

Research Questions

- What is the impact of ART on maternal morbidity and mortality caused by or associated with: sepsis, obstetric hemorrhage, hypertension, anemia, malaria, pneumonia, and tuberculosis?
- How are maternal morbidity and mortality related to: women's immune status (CD4 and viral load); time on treatment and timing of treatment initiation in relation to conception and gestation; treatment regimen?

Sepsis

Women living with HIV are more likely to experience puerperal sepsis than their HIV-negative counterparts, particularly if they are immunocompromised (CD4+ cell count under 200 cells/uL), and are more likely to die as a consequence. For instance, in South Africa, in the period between 2008 and 2010, the iMMR from puerperal sepsis was six times higher among women with HIV than HIV-negative women (24.2 per 100,000 live births vs. 4.1 per 100,000 live births) (Chweneyagae, Delis-Jarrosay et al. 2012). A US study comparing pregnancy outcomes of women with HIV with those of HIV-negative women in the era of ART and which

included women who had both vaginal and cesarean deliveries found that women with HIV were more than twice as likely to experience puerperal sepsis (AOR 2.27) (Bansil, Jamieson et al. 2007). A US study which compared women living with HIV and HIV-negative women who had a cesarean section between 1999 and 2002 found women living with HIV to have 6 times the rates of puerperal sepsis (AOR 6.2) (Louis, Landon et al. 2007). A recent systematic review of obstetric complications and HIV-status reinforced findings that women with HIV are more likely to experience puerperal sepsis and that cesarean delivery greatly increases women's risk. Meta-analysis found that women living with HIV were more likely to experience puerperal sepsis (OR 3.43) and that when women delivered by cesarean section the risk of puerperal sepsis was almost six times greater than among HIV-negative women (OR 5.81) (Calvert and Ronsmans 2013a, see also Bjorklund, Mutyaba et al. 2005, van den Akker, de Vroome et al. 2011). It is also known that in South Africa, women with HIV bear a disproportionate burden of maternal deaths due to abortion—from 2005 to 2007, for deaths for which women's HIV status was known, 89% of deaths related to abortion were among women with HIV (Moran and Moodley 2012).

Compromised immune status is also associated with a higher rate of sepsis among women with HIV who give birth vaginally. In a South African study women with a CD4+ cell count of <200 cells/uL had much higher rates of infectious morbidity than HIV-negative women while women with CD4+ cell count above 200 cells/uL were no more likely than HIV-negative women to experience infectious morbidity (incident rate ratio 0.69) (Sebitloane, Moodley et al. 2009). Factors which significantly increased puerperal infections among women with HIV and HIV-negative women were episiotomy ($p<0.001$), the number of vaginal examinations after rupture of membranes ($p<0.026$), and CD4+ cell counts below 200 cells/uL among women living with HIV (Sebitloane, Moodley et al. 2009). Results of the impact of providing prophylactic antibiotics to women with HIV prior or during delivery have been mixed, with one South African Randomized Controlled Trial (RCT) finding a significant reduction in sepsis and endometritis with antibiotics compared to placebo, and a multisite RCT in Malawi, Tanzania and Zambia finding no difference in puerperal sepsis between pregnant women with HIV given prophylactic antibiotics when compared to placebo (Sebitloane, Moodley et al. 2008, Aboud, Msamanga et al. 2009). Further research is needed on sepsis prevention among women with HIV during labor and

delivery and as part of postpartum and post-abortion care, as well as on the relationship between sepsis, immune status, and ART.

Research Questions

- Will earlier initiation of ART eradicate differences in maternal morbidity and mortality related to sepsis between women with HIV and HIV-negative women?
- Are different prophylaxis and clinical management of sepsis indicated for women living with HIV during post-abortion and labor and delivery care (particularly caesarean section)?
- What are the relative outcomes of giving antibiotics prophylactically or therapeutically on rates of sepsis?

Obstetric Hemorrhage

Obstetric hemorrhage may not be more common among women living with HIV than HIV-negative women, but it may have more serious consequences. A meta-analysis found that women living with HIV had double the odds of antepartum hemorrhage (OR 2.06) compared to HIV-negative women but no evidence that HIV increases the odds of postpartum hemorrhage (Calvert and Ronsmans 2013a). A study conducted between April and August 2012 in four South African hospitals found that overall obstetric hemorrhage rates were 2.5% and there was no significant difference between women living with HIV (2.68%) and HIV-negative (2.35%) women. Nevertheless, the incidence of anemia at admission ($p < 0.0001$) and blood transfusion among women living with HIV (OR 1.53) were both significantly higher than among HIV-negative women, though units of blood transfused did not differ between women with HIV and other women (Bloch, Crookes et al. 2013).⁵ The South African Maternal Death Review estimated that the iMMR for obstetric hemorrhage was 38.4 for women living with HIV as opposed to 17.1 for HIV-negative women in the period between 2008 and 2010 (Sebitloane 2013). The effect of antiretroviral treatment on blood vessels, the myometrium, and possible contribution to obstetric

⁵ 81.5% of the HIV-positive women were on ART at the time of delivery.

hemorrhage is unknown. The question of whether women with HIV experience treatment delays or substandard care because of HIV-related stigma and providers' fear of HIV transmission remains to be answered.

Research Questions

- Is hemorrhage more severe among women with HIV than HIV-negative women after controlling for the presence of anemia?
- Does ART increase or mitigate the incidence of morbidity and mortality associated with maternal hemorrhage?
- Do women living with HIV experience longer delays in receiving care for obstetric hemorrhage than other women?
- Are interventions to prevent and manage hemorrhage as effective among women living with HIV as among other women?

Anemia

Pregnancy, HIV infection, HIV treatment, and other infections such as tuberculosis and malaria can all contribute to women developing anemia. The causes of anemia in women with HIV include anemia of chronic disease, immune mediated red cell destruction, bone marrow infections, neoplasms, malnutrition and malabsorption related to HIV infection, as well as adverse effects of antiretroviral treatment, particularly zidovudine (ZDV). Several studies from sub-Saharan Africa have reported very high rates of anemia among pregnant women living with HIV who were not taking antiretroviral treatment: 78% in Burkina Faso (Meda, Dao et al. 1998), 82% in Tanzania (Villamor, Dreyfuss et al. 2004) , 83% in Cote d'Ivoire (Ramon, Sawadogo et al. 1999), and 73% in an analysis of a multicenter trial conducted in Tanzania, Zambia and Malawi (Mehta, Manji et al. 2008). In a longitudinal Tanzanian study of pregnant women with HIV where 87% of women developed incident anemia over the two year period postpartum, infections with malaria and pathogenic protozoa were associated with a two-fold increase in the risk of developing anemia, as were lower CD4 counts (Finkelstein, Mehta et al. 2012).

In the context of HIV, anemia has been shown to have negative impacts on maternal and child health. Anemia has been associated with disease progression among women living with HIV (Levine, Berhane et al. 2001). A study of maternal death, anemia and HIV in rural Malawi

before availability of ART showed that HIV and anemia were both associated with maternal and non-maternal deaths, though the association with maternal deaths was no longer statistically significant in multivariate analysis (McDermott, Slutsker et al. 1996). A multicenter PMTCT study (using SD-NVP) in Tanzania, Zambia and Malawi associated severe anemia with stillbirth, preterm birth, low birth weight, and mother-to-child transmission of HIV at birth and in the six week postpartum period (Mehta, Manji et al. 2008). A recent Nigerian study from an urban hospital where women had access to ART associated anemia in pregnant women living with HIV with shorter time between pregnancies, presence of other opportunistic infections, lower CD4 count, and taking a ZDV containing regimen (Ezechi, Kalejaiye et al. 2013). Despite the association between ZDV and anemia, the study also found that beginning ART before pregnancy was protective against anemia (Ezechi, Kalejaiye et al. 2013).

Controversies about Iron Supplementation during Pregnancy in Women Infected with or who have a High Risk of Acquiring HIV, Tuberculosis, or Malaria

There is some controversy about how to address anemia in pregnant women who are infected with or have a high risk of acquiring HIV, tuberculosis or malaria. Iron supplementation is the only specific treatment for iron deficiency but in the presence of chronic infections such as malaria, HIV and tuberculosis there is concern that excess iron may increase the replication of infectious agents. In a study of postpartum women living with HIV in Zimbabwe, elevated iron stores were associated with higher viral load and HIV-related maternal mortality during the subsequent year; this effect was only found among non-anemic women which led the authors to posit that iron is being prioritized for red blood cell production in anemic women and is thus not available for viral replication (Rawat, Humphrey et al. 2009). Results from studies of antenatal iron supplementation on malaria outcomes are contradictory, with some studies finding increased prevalence of malaria in pregnant women after supplementation and others not finding this association (Oppenheimer, Macfarlane et al. 1986, Menendez, Todd et al. 1994, Nacher, McGready et al. 2003, Haider, Olofin et al. 2013). There is a lack of evidence about how best to treat anemia among people living with HIV (Marti-Carvajal, Sola et al. 2011). WHO does not vary the recommendation for prevention and treatment of anemia among pregnant women based

on HIV-status⁶ but notes that more research is needed on the use of iron supplementation in pregnant women living with HIV (WHO 2003:8-9).

Research Questions

- Will rates of anemia continue to be elevated among pregnant women living with HIV if ART is begun earlier and ZDV-containing regimens are used less frequently?
- Will timely diagnosis and treatment of malaria and tuberculosis reduce prevalence and severity of anemia among pregnant and postpartum women living with HIV?
- Is routine iron supplementation without verifying the presence of anemia warranted for pregnant women in areas where there is a high prevalence of both malaria and HIV?
- Does ART modify any effects of iron supplementations on HIV and malarial replication, obviating concerns about its use?

Malaria⁷

Approximately one million pregnancies are complicated by both malaria and HIV infection in sub-Saharan Africa annually (Brentlinger, Behrens et al. 2006). Both infections have been associated with maternal, as well as infant, morbidity and mortality (Brentlinger, Behrens et al. 2006). Pregnant women with HIV are at increased risk of malaria because of HIV and pregnancy-related depression of immune response, and have a higher incidence and density of malaria parasites than uninfected pregnant women (ter Kuile, Parise et al. 2004, Alban and Andersen 2007, Briand, Badaut et al. 2009, De Beaudrap, Turyakira et al. 2013). Pregnant women with HIV who are co-infected with malaria experience greater rates of febrile illnesses and adverse birth outcomes such as low birth weight, prematurity, and intrauterine growth restriction (ter Kuile, Parise et al. 2004). Co-infection with HIV and malaria is also associated with developing anemia and increased risk of severe anemia during pregnancy (Ayisi, van Eijk et

⁶ 400 mg of folate and 60 mg of iron daily to prevent anemia and double that dose to treat severe anemia (WHO 2003: 8).

⁷ Malaria prevention is discussed in Research Priority 2: Integrating Health Service Delivery to Address Maternal Health and HIV

al. 2003, Finkelstein, Mehta et al. 2012). Women with HIV who also have malaria are at increased risk of maternal death (OR 5.05, CI 2.12-12.04) (Ticconi, Mapfumo et al. 2003). Antimalarial treatment on the basis of clinical suspicion of malaria (without parasitological confirmation if unavailable) is recommended for pregnant women in stable high-transmission settings where there is a high prevalence of HIV (WHO 2010a: 12).

Treating HIV and malaria co-infection in pregnant women presents several challenges. There are known drug interactions between antiretrovirals, cotrimoxazole used for prophylaxis in immunocompromised women with HIV (which is also preventive treatment for malaria), and other antimalarial drugs. There is limited information at present on how HIV infection modifies the therapeutic responses to the preferred and more effective artemisinin-based combination therapy (ACTs) or on interactions between antimalarial medicines and antiretrovirals for the general population living with HIV (WHO 2010a: 32). In their review of adverse effects of antiretroviral and antimalarials commonly used during pregnancy in developing countries, Bretlinger and colleagues recommend cautious use of sulfadoxine-pyrimethamine (SP) (a less effective antimalarial agent) in women who are concurrently receiving daily NVP and/or ZDV and avoiding SP if women are taking daily cotrimoxazole because of increased toxicity and adverse effects and because cotrimoxazole provides prophylaxis for malaria (Brentlinger, Behrens et al. 2006). In fact, one study found cotrimoxazole to be more effective than Intermittent Preventive Treatment of Malaria in Pregnancy (IPTp) with SP among pregnant women with HIV (Kapito-Tembo, Meshnick et al. 2011). This raises the question of whether women living with HIV in malaria endemic areas should remain on cotrimoxazole after their CD4+ cell count goes above 350 cells/uL (Kamya, Byakika-Kibwika et al. 2012).⁸ There are no reported drug interactions between SP and the fixed-dosed once a day combination that is being recommended by the World Health Organization for pregnant women and women of reproductive age (Atripla: Efavirenz, Emtricitabine, Tenofovir) (WHO 2013a). Co-administration of antiretroviral and antimalarial drugs creates the potential for pharmacokinetic

⁸ In settings with a high prevalence of bacterial infections or malaria the 2013 WHO Antiretroviral Treatment Guidelines recommend ongoing treatment with cotrimoxazole or waiting until CD4+ cell count is above 350 cells/uL and the person with HIV has been on ART for 6 months (WHO 2013a: 157).

drug interactions that may increase (causing enhancement of malaria treatment efficacy and post-treatment prophylaxis and/or unanticipated toxicity) or reduce drug exposure (creating risk for treatment failure). Further studies are needed to elucidate the clinical implications of potentially important pharmacokinetic interactions between commonly used antimalarials, ARV, and cotrimoxazole (Kamya, Byakika-Kibwika et al. 2012).

The pregnancy specific immunity to malaria seen in HIV-negative women is diminished in women living with HIV and response to IPTp is impaired (Flateau, Le Loup et al. 2011). More doses of SP may improve outcomes among pregnant women with HIV and their infants, as well as among pregnant women in general (WHO 2013b). Two randomized trials (one in Malawi and one in Zambia) comparing monthly SP to the standard 2-dose regimen found that for pregnant women living with HIV, monthly SP reduced maternal and placental parasitaemia at delivery, maternal anemia, and the number of low birth weight babies (Mathanga, Uthman et al. 2011). New WHO guidelines on IPTp with SP recommends giving a directly observed dose of SP to every pregnant woman at each scheduled ANC visit, provided that the doses are given at least one month apart; SP should not be given during the first trimester but can be administered up to the time of delivery without safety concerns (WHO 2013b).

Women in second and third trimesters of pregnancy are more likely to develop severe malaria than other adults, and in this scenario, maternal mortality is approximately 50% (WHO 2010a: 47). To treat severe malaria during the second and third trimester of pregnancy, WHO recommends parenteral artesunate over quinine because about 50% of women with severe malaria treated with quinine late in pregnancy experience hypoglycemia (WHO 2010a: 47, 91). However, there is also the recommendation that people with HIV who are receiving ZDV or EFV should, if possible, avoid amodiaquine containing artemisinin-based combinations because of risk of neutropaenia with ZDV and hepatotoxicity with EFV; recommendations for treating pregnant women with severe malaria on ART are not specified (WHO 2013a: 167).

Research Questions

- What combinations of prophylactic agents like cotrimoxazole, ARV and drugs to prevent and treat uncomplicated malaria are safest and most efficacious for pregnant women with HIV?

- What is the optimal clinical protocol for treating pregnant women with HIV who also have severe malaria, including in the context of labor and delivery?
- What are the effects of first trimester exposure to artemisinin on neonatal health?

Pneumonia

Pneumonia is a leading cause of maternal death among women with HIV in sub-Saharan Africa (Moodley and Pattison 2012, Sebitloane 2013). Between 2008 and 2010 in South Africa, 13% of maternal deaths among women with AIDS were caused by pneumocystis pneumonia and 27% by non-specified pneumonia (Moodley and Pattison, 2012). A US review of 22 cases of pneumocystis pneumonia in pregnant women living with HIV who had a mean CD4+ cell count of 98 cells/uL when ART was not available found that half of the women died—a much higher mortality rate than reported for people with HIV due to pneumocystis pneumonia at that time (Ahmad, Mehta et al. 2001). Even in high-income, well-resourced settings, late diagnosis with HIV and pneumonia during pregnancy can be fatal (Parisaie, Hemelaar et al. 2010). The burden of pneumonia deaths among pregnant women with HIV highlights the importance of HIV-testing in early pregnancy, prompt access to ART, and cotrimoxazole prophylaxis for those with CD4+ cell counts below 350 cells/uL.

Research Questions

- What are the specific microbial causes of pneumonia mortality in pregnant women with HIV?
- After how much time on ART and at what CD4 counts does the incidence of pneumonia among pregnant women living with HIV approximate the baseline rates of pregnant women who do not have HIV?
- What are the optimal clinical protocols for identifying and treating pneumonia among pregnant and postpartum women living with HIV?

Tuberculosis⁹

The risk of developing TB is between 21 and 34 times greater in people living with HIV than among HIV-negative individuals (Sculier and Getahun 2011). TB remains the leading cause of death among people with HIV in sub-Saharan Africa; a review of autopsy studies done between 1993 and 2010 in 12 African countries identified TB as the cause of death in 32-45% of cases (Cox, Lukande et al. 2010). Women living with HIV who have TB disease have a two to threefold higher risk of maternal mortality two to three fold as compared to pregnant women with TB disease who are HIV-negative (Khan, Pillay et al. 2001, Gupta, Nayak et al. 2007). Immune suppression during pregnancy may mask symptoms of TB while increasing susceptibility to the development of TB disease. A large study recently found that during the first six months postpartum, women were twice as likely to develop TB disease as women who had not had a pregnancy (Zenner, Kruijshaar et al. 2012). HIV infection further increases the probability of developing TB disease. A South African study found that pregnant women living with HIV had a tenfold higher risk of developing active TB than HIV-negative pregnant women (Pillay, Khan et al. 2001). Rates of active TB disease range from 0.7% to 7.9% among women living with HIV in high-burden countries (Mathad and Gupta 2012). Latent TB is highly dependent on the underlying population prevalence. One indicator of the importance of screening for and providing prophylaxis to pregnant women in countries with high burden of HIV are reports of latent TB prevalence as high as 49% among women living with HIV in South Africa (Nachega, Coetzee et al. 2003). TB infection of the placenta can increase HIV placental viral load and increase mother-to-child transmission (Ezechi, Odberg Petterson et al. 2012).

Despite the devastating interactions between HIV, TB and pregnancy, optimism can be drawn from a recent meta-analysis which found that ART reduces opportunistic infections in low and middle-income countries, including both pulmonary and extra-pulmonary TB (Low, Gavriilidis et al. 2013). ART reduced the risk of TB by up to 65%, even in people with high CD4 cell counts suggesting that earlier initiation of ART may be a key strategy for reducing HIV-

⁹ Screening and prophylactic treatment are addressed in Research Priority 2: Integrating Health Service Delivery to Address Maternal Health and HIV.

associated TB (Suthar, Lawn et al. 2012). Isoniazid Preventive Therapy (IPT) for 6 months and early initiation of ART are the mainstays of tuberculosis prevention among pregnant women living with HIV. Isoniazid is not teratogenic even when used in the first trimester which implies that it can be given at any stage of pregnancy (Getahun, Granich et al. 2010). WHO recommends initiation of IPT in people with HIV who are unlikely to have active TB, even in the absence of a tuberculin skin test because IPT does not increase risk of developing isoniazid resistant TB; past history of TB and current pregnancy are not contraindications for initiating IPT (WHO 2013a: 160-161). A recent randomized placebo-controlled study from Botswana which examined a sub-sample of women living with HIV who became pregnant while taking IPT provided reassuring findings for both maternal and infant health. None of the 103 women exposed to isoniazid during pregnancy or the immediate postpartum period experienced severe hepatitis or rash and isoniazid exposure was not associated with adverse outcomes among infants (Taylor, Mosimaneotsile et al. 2013). Studies conducted in Brazil and South Africa have shown up to 90% reduction in the risk of contracting TB among people living with HIV who received both ART and IPT. Whether pregnant women experience a similar additive benefit from ART and IPT remains to be assessed (Getahun, Granich et al. 2010).

The World Health Organization recommends a six month rifampicin containing regimen to treat TB disease in people living with HIV (WHO 2013a). While rifampicin is contraindicated with nevirapine and protease inhibitors, it is compatible with the EFV containing once daily regimen that is recommended as first-line treatment for all adults, including pregnant women (WHO 2013a). Data assessing the safety, tolerability, and long-term treatment outcomes of pregnant women living with HIV and postpartum women on ART with TB disease are scarce (Mathad and Gupta 2012). One of the very few studies to report on clinical outcomes of concurrent TB treatment with rifampicin and ART among 33 pregnant women living with HIV from the MTCT-Plus cohort found one death and elevated rates of pregnancy loss among women who were treated for TB compared with pregnant women who took ART alone (15.2% vs. 5.9%) (Toro, Schneider et al. 2011). However, in this study, there was significant heterogeneity in the ART regimens taken by women with 33% receiving a nevirapine-containing regimen (which was contraindicated) and 33% receiving the abacavir-containing regimen which was recommended for concurrent treatment of HIV and TB disease at that time (Toro, Schneider et

al. 2011). Existing studies suggest that EFV-based ART is safe with rifampicin, with no significant differences in EFV levels, HIV virologic suppression, or six-week mother-to-child HIV transmission rates as compared to HIV-positive women without TB (McIlleron, Martinson et al. 2012).

The following medications for treating tuberculosis are contraindicated in pregnant women: streptomycin, kanamycin, amikacin, capreomycin and fluoroquinolones (CDC 2011, WHO 2010c). Pregnant women who are being treated for drug resistant TB disease should be counseled concerning risks to the fetus because of known and unknown risks of second-line tuberculosis medications (CDC 2011). Despite these concerns, treatment of TB disease among pregnant women living with HIV is crucial and women should be treated for both HIV and TB (Mathad and Gupta 2012).

Studies funded by the National Institutes of Health (NIH) are underway to assess optimal timing of isoniazid for women living with HIV (IMPAACT P1078), pharmacology of TB treatment in pregnant and postpartum women (both those who are HIV-negative and living with HIV) (IMPAACT P1026s), and outcomes of pregnant women with TB (RO1HD06435). A TB pregnancy register, similar to the ART Pregnancy Registry or the WHO Pregnancy Registry Database should be developed to collect safety and outcome data from pregnant women taking treatment for TB. There is a need for research which includes pregnant and postpartum women living with HIV who are on ART to determine the safety and optimal timing for active and multidrug resistant TB treatment (Mathad and Gupta 2012).

Research Questions

- What is the impact of early ART initiation on the prevalence of tuberculosis among pregnant women with HIV?
- Does early initiation of ART and provision of IPT to pregnant women with HIV offer the same additive protective effect against development of TB as has been observed in other populations of people living with HIV (PLHIV)?
- What treatment regimens for active TB and multi-drug resistant TB are safe and effective for pregnant women taking ART?

Hypertension

Hypertensive disorders during pregnancy are an important cause of maternal death internationally and are the cause of an estimated 9% of maternal deaths in Africa (Khan, Wojdyla et al. 2006). The role of ART in the pathogenesis of hypertension is not well understood, however ART is linked to a series of metabolic abnormalities associated with hypertension, including insulin resistance, diabetes, and elevated cholesterol and triglyceride levels (Falutz 2007). As ART is introduced in low-income settings and HIV becomes a chronic rather than acute condition, greater frequency of metabolic complications can be expected. Single hospital studies from South Africa and from Ethiopia found hypertension rates of 19% and 35%, respectively, among patients who had been on ART for at least one year (Julius, Basu et al. 2011). An observational US study which compared women living with HIV to HIV-negative women found pregnancy to be protective against hypertension ($p < 0.04$). In this cohort, hypertension was associated with being African American, older, and overweight; these associations did not vary by HIV status. For women living with HIV, hypertension was not associated with differences in CD4 count, viral load or antiretroviral regimen (Khalsa, Karim et al. 2007). In contrast, a study conducted in Botswana found that pregnant women living with HIV on ART were significantly more likely to have placental pathology consistent with chronic hypertension than their peers who were not taking ART (65% vs. 28% $p = 0.003$) (Shapiro, Souda et al. 2012). The birth outcomes from this study independently associated maternal hypertension with increased risk for pre-term delivery, babies small for gestational age, and stillbirth (Chen, Ribauda et al. 2012).

Pre-eclampsia and eclampsia are major causes of maternal morbidity and mortality (WHO 2011b). Pre-eclampsia research with women living with HIV has been limited. Some studies from both high and low-income settings suggest that pregnant women living with HIV who are not taking ART are less likely to develop pre-eclampsia than HIV-negative pregnant women (Kalumba, Moodley et al. 2013, Suy, Martinez et al. 2006). Studies in high-income settings have reported conflicting findings about the relationship between ART and pre-eclampsia, with some studies reporting an increase in pre-eclampsia with ART and others showing no difference in rates of pre-eclampsia between pregnant women living with HIV on ART and HIV-negative women (Kourtis, Bansil et al. 2006, Suy, Martinez et al. 2006). In the

Mma Bana study in Botswana, only having a high viral load was significantly associated with pre-eclampsia, though there was a trend towards developing pre-eclampsia with a CD4+ count of less than 200 cells/uL and depending on the type of ART regimen (Powis, McElrath et al. 2013). The rate of stillbirths among pre-eclamptic women living with HIV was 64% as opposed to 2% in the total cohort (Powis, McElrath et al. 2013) . As ART is scaled-up in low and middle-income countries, larger studies and more research are needed to clarify the relationships between ART, immune status, the hypertensive disorders of pregnancy with a focus on pre-eclampsia and eclampsia, and maternal and infant outcomes.

Research Questions

- What are the interactions between ART, pregnancy and hypertension?
- Will provision of ART result in increased rates of pre-eclampsia and eclampsia among women with HIV?
- What are the associations between ART, hypertension and adverse infant outcomes such as pre-term delivery, infants that are small for gestational age, and stillbirth?

Impact of Antiretroviral Treatment on Maternal and Neonatal Health

Several prospective and retrospective studies from sub-Saharan Africa which assessed ART during pregnancy and in the postpartum period have found lower mortality in the group of women with HIV who received ART as compared to those who did not receive ART, suggesting both that there is maternal benefit to extended use of ART postpartum and that being on ART for a longer period during pregnancy has benefit for maternal survival (Kuhn, Semrau et al. 2009 , Marazzi, Palombi et al. 2011, Jamieson, Chasela et al. 2012). A prospective analysis of deaths during pregnancy and one-year postpartum among women initiating ART in Uganda found that the pregnancy-associated risk of mortality was greatest in the first year of ART with a steady decline over time and that by the second year on treatment women who became pregnant had no greater risk of death (Matthews, Kaida et al. 2013). However, caution should be exercised in drawing conclusions from these studies because they were not specifically designed to assess

reductions in maternal mortality associated with ART, and in some cases the findings are based on small numbers of participants.

A recent systematic review from the London School of Hygiene and Tropical Medicine found no reduction in the risk of mortality during pregnancy and up to one year postpartum period when women took ART, but the available studies were undertaken when treatment availability was scarce and the treatment guidelines of most countries recommended beginning treatment at CD4+ cell count of 200 cells/uL (Calvert and Ronsmans 2013b). Another analysis using data from the Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network of demographic surveillance sites in eastern and southern Africa found a large drop in the mortality ratio post-ART as compared with pre-ART among women who were not pregnant or postpartum (RR 0.42 $p < 0.0001$), and a smaller reduction among women who were pregnant and up to six weeks postpartum (RR 0.70, $p = 0.205$). Again, the small reduction in the maternal mortality ratio (MMR) is probably due in part to the relationship between being in good health and becoming pregnant (“healthy pregnancy effect”) and in part to the fact that throughout most of the period under study, ART was not widely available and the treatment regimen given to prevent mother-to-child HIV transmission was single-dose Nevirapine (Sd-NVP) which does not confer health benefits to the mother (Zaba, Calvert et al. 2013).

Preliminary data from South Africa indicate a 13% drop in the MMR among women with HIV when the Ministry of Health switched from Sd-NVP to NVP-based ART for PMTCT and increased the threshold for initiating ART from CD4+ cell count of 200 cells/uL to a CD4+ cell count of 350 cells/uL (Sebitloane 2013, Chweneyagae, Delis-Jarrosay et al. 2012). Even if triple therapy is not provided beyond breastfeeding, the provision of ART during the antenatal period and breastfeeding is likely to improve women’s health. In Mozambique, Marazzi and colleagues showed a clear “dose effect” between a longer period of exposure to antenatal ART and reductions in maternal mortality; MMR was 10-fold higher in women with no treatment before delivery compared to women with 90 days or more of ART prior to birth (Marazzi, Palombi et al. 2011). Immune system preservation and reconstitution through earlier and sustained access to ART can be expected to reduce maternal morbidity and mortality among women living with HIV. Thus, early initiation of ART (at between a CD4+ cell count of 350 cells/uL and 500 cells/uL rather than below a CD4+ cell count below 350 cells/uL) and an

increasing number of women continuing on lifelong ART after pregnancy, as per new international guidelines (WHO 2013a), should lead to declines in morbidity and mortality during pregnancy and in the extended postpartum period.

Notwithstanding, data from South Africa show higher mortality rates among pregnant women living with HIV compared to HIV-negative pregnant women even when they are receiving ART (Moodley and Pattinson 2012)¹⁰. However, late presentation and delayed initiation of treatment could be the underlying cause for the persistently elevated rate of deaths among pregnant and postpartum women living with HIV in the context of antiretroviral availability. More studies are needed to tease out the relationships between pregnancy, time on ART, immune status, and maternal morbidity and mortality. Cohort studies which allow valid comparisons by controlling for the health status of different groups of pregnant and postpartum women living with HIV, and that permit comparisons between women living with HIV and HIV-negative women can make a significant contribution to the evidence base.

Finally, ART is not without health risks for women and infants. In the 2008-2010 South African Maternal Death Confidential enquiries, over a three-year period, 73 women died of side-effects of ART, increasing from 6.5% of the cause of death of women taking ART in 2008 to 11.6% in 2010. Most of the deaths were due to liver toxicity and Steven-Johnson syndrome associated with the NVP-based ART regimen and coincided with starting pregnant women on ART at a CD4+ cell count of 350 cells/uL rather than a CD4+ cell count of 200 cells/uL (Chweneyagae, Delis-Jarrosay et al. 2012).

Similarly, while ART during pregnancy has impressive health benefits for the infant—dramatically reducing the risk of HIV transmission during gestation, labor and delivery, and breastfeeding from about 45% to 5% (De Cock, Fowler et al. 2000, Volmink, Siegfried et al. 2007)—ART has also been associated with higher rates of pre-term delivery and low birth weight among infants (Coutsoudis 2013, Newell and Bunders 2013). One large observational study from Botswana found that preterm delivery, low birth weight, and stillbirth increased among women living with HIV who were taking ART from before conception relative to women

¹⁰ The report covers the period from 2008-2010; before December 2009, ART was initiated at a CD4+ cell count of <200 cells/uL and from January 2010 forward at a CD4+ cell count of <350 cells/uL.

taking ART only during pregnancy and women who were not on ART (Chen, Ribaudó et al. 2012).

Monitoring neonatal outcomes in the context of more widespread ART use is important to improve the evidence base about possible relationships between in utero exposure to ARVs and other drugs used to treat and prevent opportunistic infections in people living with HIV and adverse birth outcomes such as birth defects, stillbirth, low birth weight, and prematurity. Early gestational exposure, the developmentally sensitive period when major organ systems are formed is of special concern, and can be adequately assessed only when large numbers of women are on ART around the time of conception. With many sub-Saharan African and other countries scaling up ART for pregnant and breastfeeding women and providing lifelong ART (Option B+), the number of children conceived while their mothers are taking ART will increase substantially, especially where fertility is high.

Based on analysis of the existing evidence on efficacy and toxicity as well as the need to simplify drug procurement and service delivery in the context of ART scale-up and to promote individual adherence, the World Health Organization recommends a once daily fixed dose combination for all people living with HIV beginning ART, regardless of pregnancy or breastfeeding status (WHO 2012d, WHO 2013a). This 3-drug regimen contains Efavirenz, Lamivudine or Emtricitibine and Tenofovir. While case reports and some small prospective observational studies have raised concerns about EFV, international meta-analyses have found that there are no significant associations between first trimester EFV use and elevated rates of birth defects as compared to the general population (Ford, Mofenson et al. 2010, Ford Calmy et al. 2011; Knapp, Brogly et al. 2012). Concerns about the effects of Tenofovir on fetal bone development based on animal studies require further monitoring (WHO 2013a).

Ongoing monitoring is needed to clarify relationships between ART exposure and adverse as well as beneficial neonatal and maternal health outcomes. The World Health Organization, the United States National Institutes of Health, the United States Centers for Disease Control and Prevention, and the US Department of State, Office of the Global AIDS Coordinator through the President's Emergency Plan for AIDS Relief are supporting efforts to establish ARV pregnancy registries and to implement birth defects surveillance in sentinel sites in Malawi, South Africa and Uganda (WHO 2013a). Research and monitoring that increases

understanding of the impact of ART on maternal and child health can guide clinical practice and prepare health systems to mitigate any adverse effects of treatment scale up.

Research Questions

- What is the impact of ART on maternal morbidity and mortality in different country contexts? Some of the specific contextual variables to be explored include: ART regimen offered to women of reproductive age; initiation and duration of treatment (CD4 count, lifelong treatment post-pregnancy or based on immune status, prevalence of co-infections such as malaria and tuberculosis).
- Does the distribution and rate of maternal death among women with HIV change with large-scale introduction of ART?
- How do treatment regimen, timing of initiation of treatment, and time on ART affect maternal morbidity and mortality?
- Are ART-related adverse events more common or severe during pregnancy? Is the experience of side effects associated with reduced ART adherence among pregnant women?
- How does ART from before conception and throughout gestation impact on stillbirth, preterm delivery, low birth weight, and birth defects among ART-exposed children?

Research Priority 1: Moving the Research and Evaluation Agenda Forward

There are opportunities to conduct secondary analysis and improve data collection to answer questions about the causes, rates, and distribution of maternal deaths and morbidity in the era of ART scale-up, as well as a need to conduct new research.

Secondary Analysis

- Conduct secondary analysis using data from Observational Treatment Cohorts (prospective and retrospective) and household and community surveys that have collected HIV status and other information related to HIV. The population-based survey conducted by and housed at the Africa Centre in South Africa, the body of data being generated by the ALPHA network, and the TASO cohort in Uganda are only a few of the existing data repositories which are being used to conduct relevant research.
 - The ALPHA Network brings together data from ten community-based longitudinal HIV studies in sub-Saharan Africa. All of the sites are phasing in information about ART (ever prescribed, ever on or off ART, when started or stopped) in verbal autopsy studies. Additionally, seven of the sites can link clinic data generated by the studies' own clinics or by using unique identifiers or other variations to match records. Zaba et al. estimated that a quarter of deaths among women during pregnancy and up to six weeks in sub-Saharan Africa are attributable to HIV. This estimate was drawn from data generated through the ALPHA Network (Zaba, Calvert, et al. 2013).
 - The Africa Center Demographic Information System (ACDIS), housed at the Africa Centre for Health and Population Studies at the University of Kwazulu-Natal, collects longitudinal demographic data (e.g. mortality, fertility, migration) and since 2003 has conducted HIV testing. An example of the high quality research it is possible to conduct using population-based household surveys that collect HIV-status is the Tanser et al. (2013) publication which demonstrated that an individual in a South African community with high ART coverage (30-40% of all infected individuals on ART) was 38% less likely to acquire HIV than someone living in a community where ART coverage was below 10%. A similar study estimating rates of maternal mortality and cause of death in communities with differential rates of ART coverage would make a significant contribution to the literature.
- Other key opportunities for conducting secondary analysis to generate better information on maternal morbidity and mortality in the context of HIV are country level maternal and pediatric death reviews where HIV status is available. Different countries offer comparative advantages for answering different research questions based on disease

epidemiology, programmatic context (for example ART coverage and type of regimen), and existing data collection and management systems.

Improving the Evidence Base and Synergistic Knowledge Generation with Ongoing Research or Programs

- Advocate for the inclusion of indicators that will permit analysis of the relationship between HIV and maternal health (HIV status, pregnancy/postpartum status, on or off ART, time on ART, measures of immune status such as CD4 and viral load) in national and international routine and periodic monitoring
 - Nationally, data collection opportunities include Maternal Death Reviews, program monitoring of HIV treatment programs, vital statistics, facility and community-based pregnancy outcome data, antenatal and postpartum care data
- Expand and strengthen pregnancy registries, birth defects surveillance, and post-consumer pharmacosurveillance to identify adverse outcomes of ART on maternal and neonatal health
- Improve and validate verbal autopsy tools and promote the use of validated methods and virtual platforms (such as INTERVA) for verbal autopsies of maternal deaths
- Include nested studies on maternal health within large scale intervention studies, including in the context of implementation science funded by PEPFAR.
 - Include verbal autopsies of maternal deaths in the context of other studies. e.g in the context of large-scale community clustered randomized controlled trials which are exploring the impacts of widespread HIV-testing and early initiation of ART.
 - For instance a nested study on maternal health within the SEARCH (Sustainable East Africa Research in Community Health) Study being implemented in 50 communities in Kenya and Uganda and which includes extensive documentation of all deaths.
 - Inclusion of questions on pregnancy status and maternal morbidity and mortality in facility and community-based surveys would generate valuable information about the relationships between timing of treatment initiation, ART and maternal health.
 - Adding autopsies and verbal autopsies of maternal deaths in a selection of intervention communities could generate improved cause of death data.
- Advocate for the inclusion of measures of maternal health, including calculations of maternal morbidity, in periodic population-based studies and other research addressing HIV and maternal health.

New Research

To better understand the consequences of increased availability of antiretroviral treatment for women living with HIV of reproductive age and further elucidate relationships between HIV status and maternal health, the expert meeting proposed a multicenter network study which would include both urban and rural facilities and allocate sufficient resources for outreach workers in order to reduce loss to follow-up of pregnant and postpartum women, both those living with HIV and those who are not. The study would use a common data collection tool and include detailed death investigation. This research could also provide a forum to improve verbal autopsy tools by using autopsy or minimally invasive autopsy to validate results and to generate and validate new questions and algorithms. In addition, cohort studies that include pregnant women who are both living with HIV and HIV-negative and studies that use a stepped wedge design as different options for providing ART are rolled out can help address some of the unanswered questions about HIV disease progression during pregnancy, effects of HIV on pregnancy, and impact of ART on maternal health and pregnancy outcomes.

Research Priority 2: Integrating Health Service Delivery to Address Maternal Health and HIV

Integration is a process that occurs at different levels of the health system (national, regional, district, health facility) and in relation to key health system functions (e.g. governance, financing, planning, service delivery, monitoring and evaluation, demand generation) (WHO 2008, Atun, Lazarus et al. 2010). Research Priority 2 considers integration at the service delivery level. The focus is operational integration of critical components of MCH and HIV services, preferably by providing a single point of access or adding a priority component to an existing service rather than partial integration through referrals to other services even if they are located at the same facility. The promise of integrated service delivery is that meeting women's multiple health needs at a single point-of-care, possibly during a single visit and potentially by the same providers, could optimize women's contact with the health system and more effectively utilize scarce human and financial resources. The danger of integration is that providing additional services could prove to be an excessive burden on already under-resourced health systems. In addition, integration should not dilute the specialised skills needed to deliver each health care component. While, as discussed in greater depth below, research suggests some benefit to MCH and HIV service integration and different countries have significant experience with service integration, there is surprisingly little high quality data to guide policy and practice. Studies on the impact of adding *another* component to integrated MCH and HIV service delivery are even more limited. This situation presents both a need for and an opportunity to conduct high quality implementation research and evaluation.

As well as recommending program evaluation and intervention research on provision of integrated MCH and HIV services, the expert meeting prioritized the following interventions for research and evaluation: prevention and treatment of malaria; diagnosis and treatment of tuberculosis; and two reproductive health services—preconception counseling and postpartum contraception for women living with HIV. Implementation science is urgently needed. It can be employed to test how these program components can be integrated with HIV and MCH services and assess i) the impact on human resource needs and measures of coverage and proximate outcomes (for instance uptake and retention in care for women, retention of health workers, and

satisfaction of both service users and providers); and ii) the effect on intermediate health outcomes (such as prevention of unintended pregnancy and maternal morbidity and mortality).

Priority Research Questions

- What are the most effective models for integrating HIV testing, treatment and care with antenatal, intrapartum, and postpartum services?
- How can additional critical interventions—specifically screening, prophylaxis and treatment for malaria and tuberculosis, postpartum family planning, and preconception counseling—be integrated into the continuum of MCH and HIV services while maintaining quality, effectiveness and coverage?

Key Outcomes and Variables

- Health outcomes: clinical effectiveness of different interventions with integration, maternal morbidity and mortality, pediatric HIV infection, and sexual HIV transmission.
- Health systems: national policies and budget allocation, process indicators to assess coverage and quality of care (including uptake of MCH and HIV services), satisfaction and retention of healthcare workers and service users, human resources needed to delivery interventions (ratio and cadre of providers to service users, skill level), cost-benefit and cost-effectiveness.

Integrated HIV and MCH Service Delivery

A systematic review of integrating HIV services into MCH, neonatal, nutrition, and family planning care found that integration generally improved health outcomes, as well as coverage and quality of services (Lindegren, Kennedy et al. 2012). Another systematic review which looked only at the impact of implementation or intensification of PMTCT programs on the provision of other MCH services found generally positive results. There were beneficial synergies in terms of increased STI prevention (including syphilis screening and treatment) and early childhood immunization (Nutman, McKee et al. 2013). Depending on the study, offering PMTCT was reported to have positive and negative results for the provision of antenatal, intrapartum, delivery care, family planning and nutritional supplementation (Nutman, McKee et al. 2013). For instance, of twelve studies of the effect of implementation of PMTCT on antenatal care attendance, ten studies reported increased attendance and two reported decreases in the number of care visits (Nutman, McKee et al. 2013). Similarly, of four studies of implementation of nutritional counseling and provision of supplements, three found improvements and one found negative effects of implementation of PMTCT. Study settings and designs are heterogeneous so

it is not possible to draw definitive conclusions, but in general it seems that implementing PMTCT tended to strengthen delivery of other maternal and child health services (Nutman, McKee et al. 2013). However, the impact of providing additional HIV-related services in MCH care needs to be closely monitored. A case in point comes from a recently published Tanzanian study which found that adding HIV-diagnosis and referral for mothers and children during routine immunization visits resulted in stable or increased rates of immunizations at urban clinics but was associated with an important decline in the number of immunizations performed at rural sites (Goodson, Finkbeiner et al. 2013).

With respect to the provision of ART in MCH services, there is relatively little information in the peer reviewed literature about how integrated vs. stand-alone provision of PMTCT services impacts on coverage of ART or health outcomes (Tudor Car, van-Velthoven et al. 2011, Azman Firdaus, Spaulding et al. 2013). One Zambian study compared provision of CD4 testing and ART for PMTCT in the ANC clinic versus urgent referral to the HIV clinic located in the same building. The offer of CD4 testing and ART in ANC doubled the proportion of treatment-eligible women initiating ART for their own health during pregnancy, but rates were still low with only 33% of the women at the integrated site and 14% of the women who were referred initiating treatment; there was no difference in rates of retention in treatment at 90 days (Killam, Tambatamba et al. 2010). A cross-sectional South African study which brought HIV providers to ANC clinics to provide ART and CD4 counseling reduced delays from the time of HIV diagnosis to treatment initiation from a median of 56 days to 37 days (van der Merwe, Chersich et al. 2006).

While not a comparative study, Malawi's Option B+ Program integrated ART into ANC services and began initiating all pregnant and breastfeeding women living with HIV on ART without CD4 testing, which resulted in a 748% increase in the number of pregnant and postpartum women beginning ART; over a fourteen month period, pregnant and postpartum women went from 5% to 35% of all new ART initiations (Chimbwandira, Mhango et al. 2013). Offering point-of-care CD4 testing alongside HIV testing in antenatal care may result in similarly positive outcomes. A pilot program in South Africa which offered point-of-care CD4 testing at an antenatal clinic captured all pregnant women who tested positive for HIV and 97%

of treatment eligible women began ART, with 91% of them beginning ART the same day they had the point-of-care testing (Myer, Zulliger et al. 2012).

A 2013 review of integration of provision of ART in ANC or MCH settings showed positive impacts on adherence to ART during pregnancy, improved ART initiation, and retention in care; no statistically significant effects were found for mortality, morbidity, immunologic response, uptake of infant HIV testing, number of infants testing positive for HIV, or satisfaction with care (Azman Firdaus, Spaulding et al. 2013). Delivery of ART in ANC services increases uptake, but most studies have not reported specifically on morbidity and mortality outcomes for pregnant and postpartum women or long-term retention in care.

Research in the peer reviewed literature about how to best integrate other interventions, such as postpartum contraception or TB screening and treatment, into services that are already providing some aspect of integrated HIV care for pregnant and postpartum women is almost nonexistent (Tudor Car, van-Velthoven et al. 2011). Research which evaluates the effectiveness, costs, and satisfaction of users and healthcare workers with integrated service delivery is urgently needed.

Research Questions

- What are the advantages and disadvantages of integrating services, in terms of the quality of care, clinical effectiveness, and coverage of each of the specific health services (e.g. contraception counseling and provision; safer conception counseling; malaria screening and treatment, tuberculosis screening and treatment)?
- What is the optimal setting (point on the continuum of care) to deliver each service?
- How does service integration impact the uptake, linkage and retention of pregnant and postpartum women in HIV, MCH and related services?
- What human resources are needed to effectively and safely deliver the intervention to pregnant women and women of reproductive age in areas of high HIV prevalence?
- What is the effect of providing integrated services on maternal morbidity and mortality, unintended pregnancy postpartum, new pediatric HIV infections and sexual HIV transmission?

- What are the costs and cost-effectiveness of integrated services? Are there efficiency gains for both the woman and the health system that would improve uptake and sustainability?

Prevention and Treatment of Malaria

Implementation of the interventions to prevent malaria among pregnant women— Intermittent Preventive Treatment of Malaria in Pregnancy (IPTp) and insecticide treated bednets (ITN) are insufficient in sub-Saharan Africa. Review of national survey data from 27 countries (2009-2011) found that even though the median coverage for at least two ANC visits was 85%, the median coverage of two doses of SP for IPTp was 25% (Hill, Hoyt et al. 2013). Similarly, despite national policy commitments to provide ITNs to pregnant women in all malaria-endemic countries, data from 37 countries reported a median bednet use of 35% (personal communication with A.M. van Eijk cited in Hill, Hoyt et al. 2013). A recent study from Kenya found that 59% of women who attended ANC and were not taking cotrimaxole received a single dose of SP, and of the 90% who returned for at least one more prenatal visit, 57% received a second dose, only 9% reported receiving a third dose; coverage with bed nets, which were mostly provided through the ANC was 89%. No differences in SP use or bed net coverage were reported by HIV-status (Hill, Dellicour et al. 2013). Low levels of implementation of multiple doses of SP may be particularly deleterious for pregnant women living with HIV as a recent Cochrane review found that women with HIV can benefit from monthly SP (Mathanga, Uthman et al. 2011). Key barriers to the provision of IPTp and ITN during pregnancy in sub-Saharan Africa include unclear policy and guidance; healthcare system issues (for example stock-outs and user fees); and barriers related to the health facility and health workers, including poor organization and confusion about dosing (Hill, Hoyt et al. 2013).

Information about the integration of prevention and treatment for malaria with HIV treatment and care is scarce. A study of PEPFAR-funded programs in six Ministry of Health primary care clinics in Uganda found that implementation of the HIV treatment program increased testing for malaria, though specific results for pregnant women were not reported (Matsubayashi, Manabe et al. 2011). A study on the acceptability and feasibility of integrated malaria and HIV prevention services for pregnant women in Uganda found that women in the lowest wealth quintile were less likely to receive HIV testing and preventive treatment for

malaria and that midwives working in the public and private sector need increased support in terms of provision of medications, training, and supervision if they are to provide these services routinely (Mbonye, Hansen et al. 2010).

Research Questions

- How does the offer of monthly SP to pregnant women living with HIV in prenatal care affect coverage of IPTp for HIV-negative pregnant women?
- Is monthly SP or cotrimoxazole more effective and safer for IPTp among pregnant women living with HIV?
- What are the most effective models for harmonization of policy and programmatic guidelines which integrate HIV and malaria prevention, diagnosis, and treatment in antenatal care?

Diagnosis and Treatment of Tuberculosis:

The WHO recommends a four-part symptom screening algorithm to identify TB among HIV-infected people, including pregnant women. However, doubts about the sensitivity and specificity of this screening tool among women living with HIV are being raised. A study of 1451 pregnant women living with HIV in Soweto that compared the screening questions to the gold standard of liquid sputum culture found that 73% of the women who were culture positive did not report any of the symptoms identified in the WHO four-part symptom screen (Hoffmann, Variava et al. 2013). Further healthcare provider training in diagnosis and management of tuberculosis that may be unmasked as a consequence of antiretroviral treatment and closer monitoring of pregnant women starting ART for Immune Reconstitution Inflammatory Syndrome (IRIS) may be indicated until improved screening techniques are available. Screening techniques with improved sensitivity and lower cost diagnostic tests are urgently needed to identify TB among HIV-infected pregnant women in resource limited settings (Mathad and Gupta 2012, Hoffmann, Variava et al. 2013). Cost-reductions in new diagnostic technology (Expert MTB-RIF) that can provide confirmation of tuberculosis within two hours at the point of care, including identifying multidrug resistant TB, could make a significant contribution to improving diagnosis, confirmation and effective treatment of drug resistant TB.

Technical challenges for TB diagnosis among pregnant women living with HIV are compounded by health systems challenges. In South Africa, where TB screening is recommended as a routine part of prenatal care, uptake and provision of preventive treatment has been suboptimal. For instance, only 66% of pregnant women living with HIV accepted screening for TB in the context of PMTCT during a 2003 study in two Soweto clinics (Kali, Gray et al. 2006). A follow-up study which recruited women living with HIV and HIV-negative women at six antenatal clinics which were also providing PMTCT was only able to screen 45% for TB; nurses did not investigate 15% of suspected TB cases (Gounder, Wada et al. 2011). In 2008, the province of KwaZulu-Natal reported that 55% of pregnant women living with HIV were screened for TB symptoms, but none were provided preventive treatment (Uwimana, Jackson et al. 2012).

Pregnant women may be reluctant to undergo another screening test and face diagnosis with tuberculosis, particularly if they have been recently diagnosed with HIV (Kali, Gray et al. 2006). Poor morale among healthcare providers and resistance to taking on new responsibilities without additional payment in antenatal clinics that are already providing PMTCT was identified as a barrier to integrating TB screening in Soweto, South Africa (Gounder, Wada et al. 2011). In KwaZulu-Natal, stakeholders stated that the legacy of vertical programs (financing, targets, hierarchy), different ideas about how to integrate services, and human resource limitations (in terms of staffing levels, skills, and scope of practice) were barriers to providing integrated TB/HIV/PMTCT services (Uwimana, Jackson et al. 2012). An acceptability study of TB screening and treatment as part of ANC in Malawi found that clients and healthcare providers were concerned that providing integrated services would negatively affect staff workloads and waiting times (Sangala, Briggs et al. 2006). To date there is little evidence on the quality of care before and after introduction of TB screening into ANC/PMTCT services, quantitative measures of the impact on workload, or maternal mortality or morbidity (Tudor Car, van-Velthoven et al. 2011).

Research Questions

- What are the best screening questions and diagnostic methods for improving detection of TB or excluding active TB in pregnant women?

- How do educational programs for healthcare providers and counseling for pregnant women to inform them about the safety of IPT during pregnancy impact on coverage?
- What are the barriers to acceptance of TB screening among women with a recent HIV-diagnosis?
- Does training providers working in prenatal care to identify and manage IRIS improve clinical outcomes in areas with a high prevalence of HIV/TB co-infection?

Reproductive Health of Women with HIV: Pre-Conception Counseling and Postpartum Contraceptives for HIV-Positive Women

Meeting unmet need for family planning in sub-Saharan Africa could make an important contribution to improving maternal health. In 2008, the estimated maternal mortality ratio in sub-Saharan Africa was 596 per 100,000 live births, contraceptive prevalence was 22% and the proportion of maternal deaths averted by contraceptive use was estimated at 32%. In contrast, among low- and middle-income countries as a group, the maternal mortality ratio was 273, contraceptive prevalence was 63%, and 44% of maternal deaths were estimated to be averted by contraceptive use (Ahmed, Li et al. 2012). In 2012 it was estimated that in sub-Saharan Africa 53 million women who wanted to avoid pregnancy were not using a contraceptive method, i.e. had unmet need for modern contraceptive methods (Darroch and Singh 2013). Maternal mortality is affected by multiple social, economic, and health systems factors beyond contraceptive access and use, yet these estimates suggest that important gains in eliminating preventable maternal mortality could be achieved if more women used modern contraceptives. For women living with HIV, preventing unintended pregnancies will promote women's health and is also a cost-effective way to prevent new pediatric HIV infections (Reynolds, Janowitz et al. 2008). In fact, modeling studies suggest that it will not be possible to reach the 2015 targets for reducing new pediatric HIV infections in high-burden countries unless unmet need for family planning among women living with HIV is eliminated (Mahy, Stover et al. 2010).¹¹ Yet, unmet need for

¹¹ The target is to reduce new pediatric HIV infections 90% by 2015 in 25 high-burden African countries. Modeling suggests that to reduce new pediatric HIV infections 73%, in addition to providing 90% of HIV-positive pregnant women with ART, new HIV infections among women of reproductive age must be halved and unmet need for family planning eliminated.

contraception among women living with HIV in sub-Saharan Africa is high, with 66-92% of women reporting not wanting another child (now or ever), but only 20-43% using contraception (Sarnquist, Rahangdale et al. 2013).

Reports about the influence of HIV status on reproductive desires vary, with some studies showing no difference in reproductive intentions between people with HIV and the general population, and others finding that women living with HIV are less likely to desire more children than their HIV-negative counterparts (Nattabi, Li et al. 2009). There is evidence that 20% to 50% of people with HIV desire more children after the diagnosis (Matthews, Crankshaw et al. 2013). A recent meta-analysis which mostly drew data from studies conducted in sub-Saharan Africa associated wanting more children with not having a child and being under thirty years of age (Berhan and Berhan 2013). In addition to these two factors, being a man, having fewer children, good (self-reported) health status, and broader cultural, spousal and familial norms and expectations about reproduction and family size have all been associated with desiring children following an HIV diagnosis (Nattabi, Li et al. 2009).

Better health status associated with ART use can be expected to increase the biological capacity of women living with HIV to become pregnant, and may also increase their desire to have more children. Being on ART has been associated with increased fertility desires (Myer, Rebe et al. 2007, Cooper, Harries et al. 2007, Cooper, Moodley et al. 2009) and initiating ART has been associated with a higher incidence of pregnancy (Myer, Carter et al. 2010, Kaida, Matthews et al. 2013). Whether these pregnancies are intended or unintended, significant numbers of women in HIV treatment programs become pregnant (Cooper, Moodley et al. 2009, Homsy, Bunnell et al. 2009, Kaida, Laher et al. 2010, Kaida, Matthews et al. 2013). For instance, in the context of the multi-country MTCT-Plus initiative, which provided women living with HIV with contraceptives but did not have a special reproductive health counseling protocol, the incident pregnancy rate was 7.8 per 100 person years [range 3.3 in South Africa to 21.7 in Rwanda]; using condoms for contraception was associated with a higher pregnancy rate than using non-barrier modern contraception (Myer, Carter et al. 2010). Women with HIV require health services to prevent unwanted pregnancies and to permit safe conception, healthy pregnancy, and safe delivery. There is an urgent need to integrate both safe conception

counseling and pregnancy prevention services for women living with HIV into MCH and HIV services.

Preconception Counseling and Safe Conception for Women Living with HIV

People with HIV often desire a child or more children (Kaida, Laher et al. 2011, Matthews, Crankshaw et al. 2013, Cooper, Moodley et al. 2009) and 20-60% have an HIV-negative partner (Anderson 2013). In sub-Saharan Africa, women are the HIV-positive person in about half of discordant partnerships (Eyawo, de Walque et al. 2010). In this context, it is difficult to overstate the revolutionary potential of “treatment as prevention”—the capacity of ART to suppress viral load and radically reduce sexual and mother-to-child transmission—for the reproductive lives of women living with HIV in sub-Saharan Africa (Volmink, Siegfried et al. 2007, Attia, Egger et al. 2009, Cohen, Chen et al. 2011). The WHO recommendation that people with HIV who have serodiscordant partners be given the option of immediately beginning ART to reduce sexual transmission can facilitate safe conception for serodiscordant couples and will contribute to preventing new HIV infections among men and women (WHO 2013).

Women and men with HIV in resource constrained settings can conceive a child while reducing transmission risks to an HIV-negative partner by diagnosing and treating other sexually transmitted infections (STIs), the person with HIV adhering to their ART regimen and having an undetectable viral load and reducing the instances of unprotected sex through timed intercourse or home-based insemination (Chadwick, Mantell et al. 2011, Matthews, Smit et al. 2012). It is reasonable to conclude that the HIV-negative partner taking pre- or post-exposure prophylaxis can further reduce the risk of HIV transmission, but more research is needed (Bekker, Black et al. 2011, Vernazza, Graf et al. 2011). Two studies of “natural conception” in high-income settings among serodiscordant couples in which the person with HIV had an undetectable viral load recorded no instances of transmission to the HIV-negative partner in a total of 129 pregnancies and only one instance of MTCT (Vernazza, Graf et al. 2011, Barreiro, del Romero et al. 2006). Nevertheless, these findings should be interpreted cautiously as the numbers were small and because HIV has been identified in the semen, follicular fluid and endometrial lining of men and women with full viral suppression, indicating that while HIV transmission is very

unlikely under these circumstances, it remains a possibility (Bekker, Black et al. 2011, Mounzer and DiNubile 2013).

To enable people with HIV to make informed choices and benefit from “treatment as prevention” for reproductive ends, healthcare providers must know about these interventions and communicate clearly with people with HIV. The track record of HIV services in both rich and resource-constrained countries for providing a supportive, non-stigmatizing environment for women living with HIV to make reproductive decisions has been middling at best. Most women living with HIV do not broach the issue of reproduction with providers before getting pregnant. If providers do not initiate a non-stigmatizing conversation about reproductive intentions, this communication between provider and client tends not to happen at all (Cooper, Harries et al. 2007, Cooper, Moodley et al. 2009, Squires, Hodder et al. 2011, Finocchiaro-Kessler, Bastos et al. 2012, Finocchiaro-Kessler, Mabachi et al. 2012). Research about healthcare providers’ and PLHIV’s knowledge and communication about “treatment as prevention” and associated reproductive intentions, behaviors, and outcomes is just beginning. A qualitative study with men and women living with HIV in Durban South Africa found that most couples did not know how to reduce the risk of sexual HIV transmission and still become pregnant (Matthews, Crankshaw et al. 2013).

Implementation research is urgently needed about i) how to integrate pre-conception counseling interventions into HIV care (including information about knowledge, attitudes and practices of PLHIV and providers); ii) the acceptability and evaluation of guidelines for safer conception; iii) how best to provide pre-exposure prophylaxis (PREP) to support safe conception; and iv) the health outcomes associated with provision of these interventions—specifically rates of intended and unintended pregnancy, new pediatric HIV infections, and seroconversion of HIV-negative partners.

Research Questions

Recognition that ART allows safer conception for people living with HIV and their sexual partners is relatively recent. Formative and implementation research is needed on models of care for preconception counseling. There are multiple outstanding research questions, such as:

- What is the efficacy and acceptability of biomedically safer conception methods including treatment as prevention, pre-exposure prophylaxis, and male circumcision in the context of desired conception?
- What safer conception policies and guidelines are feasible to introduce into policy, programs and services for serodiscordant and concordant couples living with HIV?
- What are the most effective means of engaging policy-makers and other key stakeholders to move towards implementation of what is currently feasible?
- What do people with HIV and health care providers know and communicate about serodiscordance and safer conception methods, including treatment as prevention?
- What is the best mix of providers and program models for providing to preconception counseling?
- When and where should preconception counseling be offered?
- What counseling and support services (such as peer support groups and networks of people with HIV) are feasible and support safe conception and pregnancy among serodiscordant couples in resource-constrained settings?
- How will knowledge about treatment as prevention and pre-exposure prophylaxis, and information provided during preconception counseling, affect reproductive desires, intentions and behaviors?

Integrated Provision of Contraceptives for Women Living with HIV

Integration of family planning and HIV services and behavioral interventions to promote contraceptive use among women living with HIV has had generally positive results. While the evidence-base is not abundant, uptake of contraceptives, condom use, measures of service quality, and health outcomes—measured by incident pregnancies and sexually transmitted infections—have all been positively affected by integration (Brou, Viho et al. 2009, Ngunjiri, Heffron et al. 2009, Spaulding, Brickley et al. 2009, McCarragher, Vance et al. 2011, Lopez, Hilgenberg et al. 2013, Wilcher, Hoke et al. 2013). That information and access fuels demand for contraceptives among people living with HIV is suggested by the 99% of couples adopting a modern method in a Zambian study of contraceptive use (Wall, Vwalika et al. 2013). The feasibility and positive impact of increasing information and access has been identified in several African studies which found that strengthening referrals from HIV clinics resulted in increased attendance at Family Planning (FP) clinics (Wilcher, Hoke et al. 2013). For instance relatively small program modifications in monitoring and evaluation and training in the context of a national PEPFAR program boosted referrals to FP clinics in Ghana (Chabikuli, Awi et al. 2009). Providing contraceptive counseling and methods to women in HIV services has been shown to be even more effective. A Kenyan clinical trial which trained HIV staff on FP and provided couple counseling and free methods onsite rather than referring to FP services observed a substantial increase in use of non-condom contraception by women with HIV (OR 6.4) (Ngunjiri, Heffron et al. 2009). In this study, reported condom use was 88% at last sex and overall pregnancy incidence declined (Ngunjiri, Heffron et al. 2009). A more recent cluster-randomized trial in Kenya which compared provision of effective contraceptive methods within HIV services at the twelve intervention sites with referral to family planning services at the six control sites found that women in the intervention clinics were significantly more likely to use effective contraceptive methods (OR 1.81) and the decrease in condom use at intervention sites was non-significant (OR 0.64) (Grossman, Onono et al. 2013). The intervention was found to be a cost-efficient way to provide contraceptives to women living with HIV (Shade, Kevaney et al. 2013).

As this brief review illustrates, most interventions have focused on strengthening referrals from HIV clinics or providing contraceptive methods within HIV clinics. Integration of family

planning counseling and contraceptives into postpartum services for women with HIV is a relatively neglected area of research.

Additional research is also needed on the safest and most acceptable contraceptive methods for women living with HIV. The World Health Organization recommends a full range of contraceptive methods for women with HIV (depending on immune status and ART regimen) (WHO 2012a).¹² The weight of available evidence suggests that hormonal contraceptives do not hasten disease progression among women with HIV (Heffron, Mugo et al. 2013, Phillips, Curtis et al. 2013). However, evidence suggesting that there may be increased risk of female-to-male transmission when women use progestin-only injectable contraceptives remains a concern, and more research is needed (Heffron, Donnell et al. 2012, Polis, Phillips et al. 2013, McCoy, Zheng et al. 2013). More clinical research on the best contraceptives for women with HIV, including long acting reversible contraceptive methods (LARC) other than injectable contraceptives, is needed. Several studies on LARC are planned or underway.

Equally important is implementation research to assess attitudes and acceptability of currently available and new contraceptive methods among women with HIV (both those who are taking ART and those who are not), their intimate partners and health service providers, and to demonstrate how to optimally provide contraceptives to women living with HIV, particularly during the postpartum period. While recent reviews provide reassurance about the use of hormonal contraceptives and disease progression, concerns about HIV acquisition and injectable contraceptives, drug interactions between some hormonal contraceptives, medications to treat tuberculosis and antiretroviral treatment (WHO 2010b) and the resulting complexity of choosing the best contraceptive method has caused worry and confusion among healthcare providers, community networks, and women living with HIV (Athena 2012). Similarly, more information about why women living with HIV do and do not adopt dual protection (condom + another contraceptive method) and evaluation of models of service delivery that are effective at increasing use of dual protection are needed.

¹²There is continued uncertainty about whether or not the use of progestin-only injectable contraceptives increase women's risk for HIV acquisition, with some studies finding an association and others not (Heffron, Donnell et al. 2012, Polis and Curtis 2013). High quality counseling and promotion of dual method use are crucial for all women.

International research also documents that women living with HIV continue to experience reproductive rights abuses which range from omission of information and services to coercive sterilization and abortion (Ahmed, Roseman et al. 2012, Kendall 2009, Kendall 2013, Landolt, Phanuphak, et al. 2012, Mallet and Kalambi 2008). Implementation research on stigma-reduction for healthcare providers and rights-based approaches to ensure women with HIV have the needed information and access to services to make and implement informed, autonomous contraceptive choices is a priority.

While modeling studies have found that preventing unintended pregnancies among women with HIV is a highly cost-effective means to prevent new pediatric HIV infections, little information is available about the cost and relative cost effectiveness or cost benefits of integration of contraception into HIV programs in the postpartum period, or comparative assessment of health outcomes such as incident pregnancies, HIV or other STIs (Spaulding, Brickley et al. 2009, Lopez, Hilgenberg et al. 2013). Nevertheless, it is heartening that a recent cluster-randomized trial in Kenya found integration of contraceptives into HIV clinic services to be cost-efficient (Shade, Kevaney et al. 2013). Many of the studies available were conducted in the context of clinical trials and thus do not address the mix and level of human resources needed to provide integrated services in the context of routine care. Wilcher and colleagues note that the effects of integration of contraceptive referral and provision into public sector clinics has been more modest than for interventions which took place in the context of clinical trials, emphasizing the need for implementation research (Wilcher, Hoke et al. 2013). Impact of the provision of contraceptives in the postpartum period on subsequent maternal morbidity and mortality among women living with HIV was not described in any of the studies reviewed.

Research Questions

- What models of counseling and service delivery increase accessibility and uptake of contraceptive methods by women with HIV, and simultaneously ensure respect for reproductive rights?
- What is the role of community and community-facility collaborations in expanding access and uptake of contraceptives among women living with HIV?
- How can contraceptives be most effectively provided in PMTCT and MCH settings and within HIV care and treatment?
- What contraceptives are most effective and safest for women living with HIV who are taking ART?
- What are the possibilities of expanding LARC other than hormonal injectable contraceptives for use among women living with HIV? What is the status of their approval (e.g. implants) and availability in different country contexts?
- What are the attitudes of women with HIV, male partners and healthcare providers toward currently available and alternative longer term contraceptive methods?
- How can dual method use (condom + contraceptive) be increased among women living with HIV and their sexual partners?
- How do we increase postpartum and post-abortion contraceptive uptake and retention?
- Are postpartum immunization visits an optimal time for providing family planning counseling for women with HIV?

Human Resources Shortages and Workload

There are critical human resource shortages in all areas of health care throughout Africa. Absolute shortages are compounded by inequitable distribution between urban and rural areas, as well as heavy workloads, insufficient training, weak management and low staffing ratios which increase stress and burn-out for health workers, contributing to poor quality care (Kieffer and Kiragu 2012). The lack of human resources available to provide HIV care and PMTCT are illustrative of the severity and consequences of these shortages which are also present in other areas of MCH service provision and across the health system. For instance, an estimation of the human resources needed to deliver universal coverage of ART in sub-Saharan Africa by 2017 found that this could only be achieved if the population of health workers doubled each year over a decade and factors such as out-migration were kept to a minimum (Barnighausen, Bloom et al. 2007). A modelling study which looked at the financial and human resources needed to provide recommended interventions for maternal and child health in the context of PMTCT¹³ in seven sub-Saharan African countries found that only three countries had sufficient funds (mostly from foreign aid) and only one (Zambia) had sufficient human resources to scale up the interventions by 2010 and sustain them to 2015 (Nakakeeto and Kumaranayake 2009). In 2012 the United Nations Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children stated bluntly that at the present time there are simply not enough health workers in the 22 countries with the highest burden of mother-to-child HIV transmission to meet the goals of the Global Plan for the Elimination of Mother-to-Child Transmission of HIV and Keeping Their Mothers Alive (Kieffer and Kiragu 2012).¹⁴

¹³ HIV testing and counselling of pregnant women in ANC, provision of antiretroviral and cotrimoxazole prophylaxis to HIV-infected women, cotrimoxazole prophylaxis to HIV-exposed infants, and provision of family planning to people with HIV.

¹⁴ The goals are to reduce the number of new HIV infections among children by 90% and the number of AIDS-related maternal deaths by 50% with the following actions: reducing HIV incidence among women, eliminating unmet need for family planning among women with HIV, providing antiretroviral prophylaxis to 90% of women living with HIV during pregnancy and breastfeeding, and ensuring that 90% of women who need it stay on antiretroviral therapy (UNAIDS 2011).

There is some evidence that the lack of adequate numbers of healthcare providers with the needed skills constrains the successful implementation of PMTCT. For example, a study of PMTCT in 15 sub-Saharan African countries associated moderate ANC activity (30-100 women attending ANC services per month) with lower coverage of Sd-NVP. The authors suggest that it may be more difficult for medium-sized facilities to adjust to the increased workload demanded by PMTCT (Audureau, Kahn et al. 2013). Likewise, a qualitative study which tracked implementation of PMTCT in four South African clinics identified missed opportunities for testing of pregnant women because one nurse was usually responsible for providing all counseling and related HIV services in PMTCT, as well as performing their regular duties. Nurses tried to control their workload by only providing a certain number of HIV counseling sessions per day and/or only working a certain number of hours on HIV counseling. Pregnant women coming to the clinic in the evening or on weekends would not be counselled and tested; if the “PMTCT nurse” was ill or absent, no services were provided (Sprague, Chersich et al. 2011).

In the case of task shifting to lay counselors, irregular payment and consequent absenteeism limited effectiveness (Sprague, Chersich et al. 2011). Similarly, in Uganda, qualitative interviews found that nurses and midwives providing HIV testing to pregnant women in ANC perceived that their workload was too heavy and many had other duties (medical histories, physical exams, postpartum care, and family planning counseling). To cope, midwife-counselors employed the following strategies: not taking lunch or breaks, streamlining counseling for HIV-negative women to have more time with women living with HIV, or including post-test information in the group pretest session in order to shorten individual post-test counseling sessions (Medley and Kennedy 2010). In short, these findings suggest, not surprisingly, that the quality of antenatal counseling for both women living with HIV and HIV-negative women was negatively impacted by limited human resources. Finally, while a study of 39 facilities in Zambia found that coverage of key services like ANC, childhood immunization, and family planning increased as ART provision and PMTCT were scaled up, they also found that provision of HIV services increased workloads and that the few available staff were taking on additional work, especially in small rural health facilities (Brugha, Simbaya et al. 2010, Walsh, Ndubani et al. 2010).

This discussion of challenges related to human resources associated with the provision of HIV testing and treatment in the context of prenatal, intrapartum and postnatal care exemplifies some of the considerations which must be taken into account when contemplating integration of HIV and MCH services, and the inclusion of additional program components such as screening and treatment for malaria and tuberculosis and preconception counseling and family planning for women with HIV.

Task Shifting to address Human Resource Shortages and Workload Issues

For all of the health interventions identified by the expert group as priorities for integration, there are studies which suggest that task shifting may be a promising strategy to address human resource shortages and workload issues: provision of ART (Mdege, Chindove et al. 2013), screening and treatment of tuberculosis (Gabriel and Mercado 2011, Zwarenstein, Fairall et al. 2011, Park, Magut et al. 2012), prevention and treatment of malaria (Rao, Schellenberg et al. 2013), and delivery of family planning services (Malarcher, Meirik et al. 2011, Janowitz, Stanback et al. 2012). Indeed, many countries are already implementing task shifting strategies for a variety of functions. Checklists, standardized patient record forms, other job aids, use of mobile technologies, and continued training, support and supervision are needed components for successful task shifting. Care must be taken to avoid intolerable additional work pressure on some categories of health workers due to task shifting. Attention is needed to additional human resource needs which result from increased number of people with HIV accessing treatment and care in response to a lower CD4 threshold for beginning ARTs and the implementation of Option B+. Further, while the available evidence on task shifting is promising it does not specifically refer to pregnant and postpartum women living with HIV. The skill level and optimal provider mix needed to deliver the possible permutations of the needed interventions safely and effectively remains an important research gap. Provision of integrated services may require a team approach. The World Health Organization has recently released guidance on the recommended skill-level for health workers providing contraceptives, antenatal, intrapartum, postpartum and neonatal care (WHO 2012c). Similar guidance on the requisite skills and staffing levels for the provision of integrated MCH and HIV services which address malaria,

tuberculosis, and the reproductive health of women with HIV during pregnancy and postpartum would assist policymakers and administrators.

Research Questions

- What skills, optimal provider mix, and staffing levels are needed to deliver health services which integrate MCH and HIV care, particularly in the antenatal and postpartum period?
- What human resources are required to provide other crucial services such as prevention, diagnosis and treatment of malaria and tuberculosis and provision of reproductive health services using the platform of antenatal, intrapartum, and postpartum care?
- What is the effect of task shifting on uptake and quality of care?
- What is the effect of integrated service delivery on client and provider satisfaction and retention?

Research Priority 2: Moving the Research and Evaluation Agenda Forward

Secondary Analysis

- Conduct retrospective or prospective, ecological analysis of countries that have created integrated policy guidance and/or implemented integrated service delivery.
- Examine what types of integration have occurred, at what levels of the health system, and what models have proved successful.

Improving the Evidence Base and Synergistic Knowledge Generation with Ongoing Research or Programs

- Advocate for key indicators to be included in the routine program monitoring of relevant programs (the Global Fund, STOP TB, PEPFAR, and Saving Mothers Giving Lives, among others). For example, PEPFAR reporting could be extremely useful for assessing program outcomes if pregnancy/postpartum status of women were available for regularly collected indicators. To illustrate, PEPFAR collects HIV and treatment status of pregnant women, and monitors TB/HIV integration. If the “pregnant/postpartum” variable were available in the standard monitoring of TB programs, coverage could be assessed. The reasons for collection of current and additional indicator data need to be explained to and accepted by health service managers and providers and their use understood and appreciated for effective and complete data gathering to be achieved.
- Promote inclusion of HIV and ARV treatment status in periodic, large-scale surveys (MICS, DHS)
- Promote stepped wedge design where an intervention is rolled-out sequentially (either as individuals or clusters of individuals) at different points in time. For example, if resources do not permit universal program implementation, purposive, prospective roll-out in randomized, community samples with data collection from control communities can allow rigorous evaluation. Evaluation is a valuable input for decision-making and, if results are positive, can generate significant impetus and support for scale-up among decision-makers.

New Research

The critical interventions to be evaluated for integration into the continuum of MCH and HIV services are dependent on the country epidemiological, policy context and structure of MCH and HIV services. The first step for intervention studies would be to conduct a situation analysis to determine the priority of different critical interventions (tuberculosis, malaria, reproductive health services), existing policy framework, and the extent to which HIV testing

and treatment are currently integrated into antenatal, intrapartum and postpartum care (and vice versa). Subsequently, assessment of infrastructure, training and staffing needs and optimal point for integration along the continuum of care would be determined. After conducting baseline research and pilot testing the interventions, a multi-arm research design comparing various models for integrated care vs. each other and/or the standard of care would allow the identification of preferred integrated models for service delivery. Similarly, a stepped wedge design could be used to evaluate integrated models of service delivery. Research should also document process measures, such as uptake of HIV and MCH services, retention in care, coverage, and satisfaction with integrated service delivery models.

Research Priority 3: Transforming the Social Context to Improve Maternal Health

In addition to providing an opportunity for PMTCT, diagnosis during pregnancy must support women's access to treatment for their own health (WHO and UNFPA 2006). Unfortunately, pregnant women are less likely to access treatment for their own health than other adults. In 2012 only 58% of eligible pregnant women received ART for their own health as compared to 65% of the adult population (UNAIDS 2013: 42). This is a promising development given that in 2011 only 30% of pregnant women who were estimated to need ART for their own health received it, as compared to 54% of the adult population (UNAIDS 2012a: 47). Attention is needed to ensure that women who choose to begin treatment remain in care and are supported to adhere to treatment. A meta-analysis of adherence during pregnancy and postpartum found that while 74% of pregnant women adhered adequately to ART during pregnancy (taking more than 80% of their ARV doses), only 53% did so in the postpartum period (Nachega, Uthman et al. 2012). Ensuring uptake and retention in care and adherence to antiretroviral treatment is crucial to ensure maximum health benefits of increasing availability of antiretroviral treatment for women, their children, and their sexual partners. At the community and national level uptake, retention and ART adherence will prevent new HIV infections and delay the development of resistance, thereby extending the utility of existing treatment options for individuals and contributing to the sustainability of expanded treatment access for national health systems.

Structural interventions may facilitate women's uptake and retention in care and directly improve health outcomes by modifying social determinants of health. Examples of structural interventions include improving women's socioeconomic status through large-scale poverty alleviation programs, for example the Millennium Development Villages and programs of conditional and unconditional cash transfers which target women. There are also important initiatives to expand healthcare insurance in many low and middle-income countries and provide financial incentives for healthcare providers and healthcare users to increase both supply and demand of HIV and MCH care. These programs should be evaluated for their impact on pregnancy-related morbidity and mortality among women living with HIV and HIV-negative women. At the health facility and community level, UNAIDS has identified a series of promising practices for retaining people living with HIV in care and promoting adherence, such as

provision of cotrimoxazole prophylaxis free of charge, ensuring shorter waiting times at HIV clinics, point-of-care CD4 testing, decentralization of services and various forms of adherence support (peer groups and community adherence clubs, mobile-phone text reminders, diary cards and food rations) (WHO, UNICEF et al. 2013: 11).

While noting the relevance of the initiatives and strategies mentioned above, the expert meeting chose to prioritize evaluation of existing interventions that have been shown to modify gender norms (reducing gender violence and increasing supportive male involvement), mobilize the community to promote maternal health, and increase social support for pregnant and postpartum women. The interventions described below have reduced gender violence or improved clinical outcomes in maternity care including adherence to PMTCT. Some also show promise for improving uptake, coverage, and technical and intrapersonal quality of care through greater community oversight and reduction of HIV-related stigma and disrespect and abuse. The interventions share a common mechanism of action in that they seek to empower women using participatory methodologies and to change the social context by engaging the broader community to transform social norms that undermine women's health. These programs have been shown to change individual behaviors, as well as promote policy frameworks and institutional practices that support women's rights and dignity. Research on the impact of human-rights based approaches in maternal and child health is urgently needed (Bustreo, Hunt et al. 2013, Ferguson and Halliday 2013, Tarantola, Unnithan et al. 2013).

Priority Research Questions

- Which community mobilization, peer support, and male engagement interventions improve uptake of and retention in HIV and MCH services and promote improved maternal health outcomes?
- Do interventions which reduce gender violence, HIV-related stigma and discrimination, and disrespect and abuse in maternity care reduce maternal morbidity and mortality?
- Do these interventions affect proximate outcomes like uptake of HIV and MCH services, linkage from diagnosis to ART, retention in care, adherence to ART or disclosure of HIV-status? Do they reduce postpartum depression?

Key Outcomes and Variables

- Key outcomes to be measured include: uptake of HIV and MCH services, linkage from HIV diagnosis to treatment, retention in care, antiretroviral adherence, postpartum depression, disclosure of HIV status, HIV-related stigma and discrimination, disrespect and abuse in maternity care, other health-related quality of life measures, cost-benefit and cost-effectiveness.

Validated measures exist for many of these outcomes. For instance, it is recommended that ART adherence be measured through a combination of self-report and pharmacy refill data, if possible. For self-report, there are different validated measures such as count based measures (for example the frequently used recall portion of the AIDS Clinical Trials Group questionnaire) or estimation measures such as visual analog scales (where patients mark their estimated adherence during a specific time period—for example during the last month), the Swiss Cohort Study Adherence Questionnaire, or the Case Adherence Index Questionnaire (Williams, Amico et al. 2013). There are several tools to measure post-partum depression, including the Edinburgh Postnatal Depression Scale (EPDS) and the Postpartum Depression Screening Scale (PDSS). These screening tools have shown sensitivity and specificity, though cultural context and the socioeconomic situation must be considered (Zubaran, Schumacher et al. 2010). Health-related quality of life measures have been adapted specifically for PLHIV, for example the Medical Outcomes Study (MOS-HIV) and Functional Assessment of HIV Infection (FAHI) survey which have both been used extensively (Clayson, Wild et al. 2006). Several tools to identify HIV-related stigma that have been used extensively (see for example The People with HIV Stigma Index www.stigmaindex.org). Finally, efforts are underway to define and validate measures for disrespect and abuse during maternity care

Reduce Violence Against Women

The WHO Multi-country study on domestic violence identified that among ever-partnered women in 15 sites from ten countries, 15 to 71% had experienced physical, sexual or both forms of violence from an intimate partner during their lifetime (Garcia-Moreno, Jansen et al. 2006). Experiencing sexual and physical violence from an intimate partner has been associated with higher HIV prevalence among women attending ANC in South Africa (Dunkle, Jewkes et al. 2004). Intimate partner violence (IPV) has been associated with higher rates of unintended pregnancy and abortion, both of which put women at risk of maternal morbidity and mortality (Pallitto, Garcia-Moreno et al. 2013), especially in contexts where abortion is illegal or access is very restricted. Experiencing IPV has been associated with lower rates of skilled birth attendance among women in Kenya (Goo and Harlow 2012), pregnancy complications (sepsis, bleeding, eclampsia) among Nigerian women (Andersson, Omer et al. 2011), and pregnancy loss and induced abortion in Tanzania (Stockl, Filippi et al. 2012). No studies on the relationship between experiencing IPV and ART adherence in Africa were identified, but in the United States, IPV has been associated with reduced adherence to ART and detectable viral load among women living with HIV (Lopez, Jones et al. 2010, Trimble, Nava et al. 2013). Both the IMAGE project and the Stepping Stones project were found to reduce IPV, and other risk behaviors for HIV transmission and negative gender norms which are drivers of both the HIV and gender violence pandemics.

The IMAGE project implemented in Southern Africa provided micro-finance to the poorest women in different communities alongside a participatory curriculum of gender and HIV education for the women and other community members. While the intervention was not found to significantly reduce unprotected sex with non-spousal partners or HIV incidence, it did reduce women's experience of IPV by half (Pronyk, Hargreaves et al. 2006). At follow-up, levels of IPV were maintained at less than half of the baseline in all four intervention villages while they stayed the same or increased in the four control villages. The intervention also increased the economic well-being of the household, improved measures of women's empowerment, and contributed to better communication about sexuality and more supportive partner relationships (Kim, Watts et al. 2007). Women in the intervention villages were also more likely to join (and

lead) social groups and to take part in collective action than women in the control villages (Kim, Watts et al. 2007).

The *Stepping Stones* program, which was originally developed in Uganda and has now been implemented in more than forty countries in Africa, Asia, and Latin America, takes a participatory gender transformative approach involving critical reflection on gender inequality as a means of encouraging safer sexual practices. Peer groups (stratified by age and gender) work separately and then together to analyze factors that affect their lives and behavior, and to define how they could implement positive change to reduce HIV and AIDS vulnerability in their life and community. Program evaluations from India, Gambia, South Africa, Ethiopia, Angola, Tanzania, Uganda and Fiji involving 14,630 people have also shown varied but generally positive results with reduction in IPV and other behavioral risk factors for HIV acquisition such as abusing alcohol and having multiple sexual partners (Skevington, Sovetkina et al. 2013). Participation in the Stepping Stones program has also been correlated with increases in HIV knowledge and measures of gender equity and reductions in HIV-related stigma (Skevington, Sovetkina et al. 2013). The South African randomized controlled trial of the *Stepping Stones* program, which measured biological outcomes, had a number of interesting findings. First, the study identified a statistically significant reduction in herpes infections among the intervention group. Second, while not statistically significant, there were 15% fewer new HIV infections among young women in the intervention group (Jewkes, Nduna et al. 2008).

The interventions mentioned have not been evaluated for their impact on maternal health outcomes in areas of high HIV prevalence.

Research Questions

- Do interventions which transform gender norms and reduce gender-based violence reduce maternal morbidity and mortality, increase uptake of MCH or HIV services, or improve retention in care, maternal and child health outcomes and quality of life measures?

Engage Men in HIV and MCH Services

Male involvement in PMTCT—either by accompanying women to antenatal visits, because the woman has shared information about PMTCT and her HIV status with her male partner, or because the man has participated in individual and/or couple-testing for HIV—supports women to successfully complete PMTCT interventions, as measured by facility delivery, infant dosing with ARV, and exclusive infant feeding (Farquhar, Kiarie et al. 2004, Conkling, Shutes et al. 2010, Peltzer, Mlambo et al. 2010, Peltzer, Sikwane et al. 2011, Kalembo, Zgambo et al. 2013). However, the finding that male involvement improves PMTCT outcomes may arise in relationships where men are already supportive of women’s health. Promoting men’s engagement through intervention studies has had mixed results.

An intervention which randomized pregnant women to individual voluntary counseling and testing (IVCT) for HIV or couple voluntary counseling and testing (CVCT) in Tanzania is a cautionary tale about the potentially negative impacts of certain ways of promoting male involvement on women’s uptake of services. Half of the women randomized to CVCT did not return to the clinic, only 16% completed CVCT, and only 43% of the women randomized to CVCT completed HIV testing during pregnancy (either alone or with their male partners) as compared to 78% of the women in the IVCT group (Becker, Mlay et al. 2010). Clearly, women’s concerns about disclosure of HIV status to male partners needs to be addressed and options for confidentiality considered carefully in efforts to promote male engagement. Not requiring male involvement as a condition of service provision is critical given that, in many communities in sub-Saharan Africa, a significant proportion of pregnant women are single. Finally, interventions which seek to involve men must ensure that women’s autonomy, safety and choices are respected.

Identifying the most effective models for engaging men in HIV and MCH services to promote their own and their female partners’ health is an important research priority. Disappointingly, most efforts to involve men in PMTCT have focused narrowly on male HIV testing (Sherr and Croome 2012). A wider range of interventions to involve men in pregnancy and HIV prevention and care, and which treat men as clients and respond to their reproductive and HIV-related health needs as well promoting women’s health, are needed (Brusamento, Ghanotakis et al. 2012, Sherr and Croome 2012). One of the interventions which has been

successful at engaging men and obtaining high rates of treatment uptake and retention for men, women and children is the MTCT-Plus model of “family-focused care” which aims to enroll the pregnant woman and other HIV-infected family members. In a cohort from the Ivory Coast, 95% of the eligible women began treatment and, of those, 98% were still in care two-years later. Additionally, 78% of those living with HIV and more than half of the HIV-negative male partners participated in the program and 95% of the male partners on ART and 100% of the HIV-positive and HIV-negative children, as well as the HIV negative male partners were still in the program at the two year follow-up (Tonwe-Gold, Ekouevi et al. 2009).

Women’s choice not to disclose their HIV status to male partners can be a barrier to male involvement if disclosure is or is perceived to be a condition of participation. However, programs can be designed to involve men without requiring disclosure of HIV status. For example, an HIV prevention intervention implemented in the context of prenatal care that consisted of educational discussions and skills building around pregnancy, PMTCT, and HIV prevention and involved women who were living with HIV and women who were not, as well as their male partners, was not successful at increasing accurate disclosure of HIV status. Nevertheless, among couples randomized to the intervention group there was increased male HIV-testing, greater condom use, fewer women seroconverting, reduced IPV, greater adherence to HIV medication for infants, and fewer infant infections (Jones, Peltzer et al. 2013, Weiss, Peltzer et al. 2013).

Multiple positive synergies may exist between stigma reduction, promotion of respectful maternity care, and male engagement. If self-stigma and community level stigma are reduced and dominant gender norms which support IPV challenged, women may feel safer disclosing HIV status to their male partners. Further, given that men object to HIV stigma and abuse of women during maternity care, reducing HIV-related stigma and discrimination and promoting respectful maternity care may also make services more welcoming for men (WHO 2012b: 11).

Research Questions

- What are the most promising interventions for engaging men in MCH and HIV care beyond antenatal HIV testing and HIV couple counseling and testing?

- How can pregnant and postpartum women and service providers enlist men as allies in promoting high quality maternity care and reducing HIV-related stigma and disrespect and abuse?
- What are the best models for involving male partners to support women's health and promote their own health, while also ensuring that women's autonomy, safety and choices are respected?
- Male involvement has been seen to improve PMTCT outcomes. Will male involvement also improve other outcomes, such as maternal morbidity and mortality? What are the pathways by which male involvement improves maternal health outcomes in the context of HIV?

Reduce HIV-Related Stigma and Discrimination and Promote Respectful Maternity Care (RMC)

Efforts to reduce HIV-related stigma and discrimination and promote Respectful Maternity Care (RMC) are rooted in a human rights paradigm which defends the dignity of people living with HIV and of women during pregnancy and childbirth. HIV-related stigma and discrimination and disrespect and abuse discourage women from seeking health services and can cause them to drop-out of care (Bowser and Hill 2010, Ratcliffe 2013, Turan and Nyblade 2013). Anticipation of discrimination, internalized stigma, and having stigmatizing attitudes towards people living with HIV are associated with: refusing HIV testing in ANC, not returning for post-test counseling, not delivering in a facility, reduced adherence to antiretroviral treatment for PMTCT, and not enrolling in HIV treatment services (Turan and Nyblade 2013). Similarly, despite expressing a preference for a facility-based delivery, many sub-Saharan African women choose to deliver at home because of previous experiences (their own or a relative's/friend's) of inadequate, low quality, and/or disrespectful care in facilities (Ratcliffe 2013). While intervention research on reduction of HIV-related stigma in the context of maternity care and RMC intervention research are still in their infancy, rights-based approaches to community mobilization and social support are promising (WHO 2011a, Yamin 2013).

Reducing HIV-related stigma and discrimination and promoting respectful maternity care will involve working at multiple levels: with individual women and healthcare providers, with institutions, with the community, and at the level of national and international policy (Nyblade,

Stangl et al. 2009, Ratcliffe 2013). Gender discrimination, stereotypes about HIV, and other sources of social vulnerability, such as class and ethnicity, frequently cause HIV-related stigma and discrimination and abuse of women during maternity care to be rendered invisible (Parker and Aggleton 2003, Bowser and Hill 2010). Challenging “business as usual” and creating awareness that many ubiquitous, taken-for-granted acts violate women’s rights and the rights of people living with HIV is crucial. Embedding principles of non-discrimination and equality in national policy and legislative frameworks and facility-level “bills of rights” for patients, for example adoption of the White Ribbon Alliance’s Respectful Maternal Care Charter which describes the universal rights of childbearing women, can be important steps towards creating awareness and increasing accountability (Bustreo, Hunt et al. 2013, Yamin 2013).

After a policy framework is established, steps must be taken to promote changes in service delivery. Healthcare provider training combined with participatory planning and quality improvement processes and community monitoring and evaluation are effective mechanisms for changing institutional practices.

Healthcare worker training that combines information about HIV, skills-building, and contact with PLHIV improves knowledge about HIV and the importance of confidentiality and universal precautions, and increases willingness to treat PLHIV (Brown, Macintyre et al. 2003). At the facility level, providing the means to implement universal precautions, conducting facility level research to identify stigma, involving all workers (not only healthcare providers) in planning to address stigma, and using participatory processes which include PLHIV are promising practices (Nyblade, Stangl et al. 2009).

Monitoring and evaluation of HIV-related stigma and disrespect and abuse are also needed to promote institutional cultures of non-discrimination towards PLHIV and dignity during maternity care. Inclusion of validated RMC and stigma measures into quality improvement models would ensure that these issues are regularly evaluated as a central component of the day-to-day work of individuals and institutions. Some of the models that could be adapted to include measures of RMC and stigma are EngenderHealth’s Client-Oriented, Provider-Efficient Services, JHPIEGO’s Standards-Based Management and Recognition and USAID’s Health Care Improvement Collaborative model (Franco, Marquez et al. 2009, Ratcliffe 2013).

Research Questions

- Do different interventions focused on reducing HIV-related stigma and discrimination and promoting Respectful Maternity Care (RMC) (for example healthcare provider training, patient rights charters, and quality improvement models) have an impact on rates of maternal morbidity and mortality, uptake of MCH or HIV services, retention in care, maternal and child health outcomes and quality of life measures?

Increase Community and Peer Support for Pregnant and Postpartum Women

Community monitoring and accountability mechanisms can generate political will for better service quality, demand for services, and improve health outcomes (Stoffregen, Andión et al. 2010, Barnes, Deshmukh et al. 2011). In the field of HIV, community program monitoring has been shown to increase the supply of PMTCT services while participatory approaches to generating local solutions and peer involvement increases demand for services among pregnant women (Ackerman Gulaid and Kiragu 2012). More broadly in the field of maternal and child health, participatory women's groups that identified problems, developed locally-feasible plans to address the priority issues, implemented, and then assessed the results of their actions were shown to dramatically improve health outcomes (Prost, Colbourn et al. 2013). Meta-analysis of program results from seven randomized controlled trials in four countries found that women's groups resulted in a 37% reduction of maternal mortality; if more than 30% of pregnant women in the community participated in a women's group, the impact on women's and children's health was estimated to be even larger—55% reduction in maternal mortality and 33% reduction in neonatal deaths (Prost, Colbourn et al. 2013). The authors hypothesized that maternal mortality was reduced through improved uptake of ANC, better hygiene during and after delivery, and small changes in the rapidity of response and care-seeking which contributed to maternal survival (Prost, Colbourn et al. 2013). The Malawian study correlated establishing a women's group in the community with a 74% reduction in the maternal mortality rate and a 28% reduction in the infant mortality rate (Lewycka, Mwansambo et al. 2013).

Social support provided by peers has a long history in HIV treatment and care programs, and has been formalized in models such as Mothers to Mothers (M2M) and Mentor Mothers which focus on pregnancy and the post-natal period. While not consistent across studies, HIV-

positive pregnant women participating in these programs have reported earlier and more frequent disclosure of HIV status and better psychosocial well-being (Baek, Mathambo et al. 2007) and have been more likely to bring infants for follow-up care (Futterman, Shea et al. 2010). Recently, a randomized cluster community trial in Malawi associated volunteer peer counseling with the community infant mortality rate falling 36% and overall infant morbidity falling 42% (Lewycka, Mwansambo et al. 2013). There is a need to determine how peer support interventions influence the uptake and use of services among pregnant and postpartum women, both those who are living with HIV and those who are not, and to evaluate impact on health outcomes. Data from a South African study suggests that antenatal and postpartum visits by trained peer mothers benefit women living with HIV and HIV-negative women. Women living with HIV who were visited by a peer mother were significantly less likely to have birth-related medical complications and more likely to administer infant antiretrovirals, practice exclusive infant feeding, and have infants with healthy height-for-age scores (le Roux, Tomlinson et al. 2013). Both women living with HIV and HIV-negative women who received visits from peer mothers during pregnancy and in the postpartum period were more likely to use condoms, breastfeed for longer, and exclusively breastfeed than women who did not receive this social support (le Roux, Tomlinson et al. 2013).

Based on the disparate but overwhelmingly positive evidence for the impact of women's groups and peer support scale-up and evaluation seem warranted. While information about the cost-effectiveness of such interventions is limited, a Malawian study reported that both participatory women's groups and peer support during pregnancy and postpartum were highly cost-effective (Lewycka, Mwansambo et al. 2013).

Research Questions

- Do the myriad programs which provide social support to women living with HIV in the context of PMTCT and postpartum: i) increase safe disclosure of HIV status and/or ii) improve mental health postpartum and/or iii) improve antiretroviral adherence postpartum?
- How do different iterations of programs to provide social support for pregnant and postpartum women influence uptake of health services, linkage between MCH and HIV

services, retention in care, quality of life measures, and maternal and child health outcomes?

- Do community monitoring and accountability mechanisms reduce maternal morbidity and mortality and improve quality of life and maternal health for women living with HIV and HIV-negative women?

Research Priority 3: Moving the Research and Evaluation Agenda Forward

Secondary Analysis

- Conduct retrospective, or prospective, ecological analysis in areas where prioritized interventions have sufficient coverage

Improving the Evidence Base and Synergistic Knowledge Generation with Ongoing Research or Programs

- Include measures of disrespect and abuse during maternity care and HIV-related stigma and discrimination in models used for institutional quality improvement.
- Promote and evaluate community engagement in data collection. Community involvement in data collection is an area which requires research and evaluation to establish how data quality and sustainability can be ensured and community generated results integrated into health information systems. While community involvement in data collection is not a panacea and requires significant planning and investments in supervision and support to ensure high quality data, it also has multiple advantages. First, it is feasible for community data collection to take place more frequently than traditional household surveys such as DHS or MICS, thereby providing information about the impact of interventions to improve maternal health at shorter intervals. Second, involving community members in data collection may provide both evidence and impetus for action, increasing accountability. Community involvement in data collection increases ownership of those involved and could be an important adjunct to the social support interventions mentioned as priorities for evaluation. The involvement of networks of women living with HIV and organizations that support women's rights and health will be critical to such efforts.

New Research

Evaluation of the socially transformative interventions described above would focus on proximate measures such as uptake and retention in HIV and MCH services, and effects on maternal health outcomes. Potential research designs include comparing outcomes before and after intervention and community cluster trials. Experts emphasized the need to extend evaluation of interventions which aim to create an enabling environment for women beyond pregnancy and the immediate postpartum period, and to look between physical health outcomes to quality of life measures.

Conclusions

Implications for Policy and Practice

The evidence presented in this document can be immediately useful for policy and practice. Some of the key take away messages are summarized below.

Clinical Questions about Maternal Mortality and HIV

Women living with HIV in sub-Saharan Africa are six to eight times more likely to die during pregnancy and the immediate postpartum period than are HIV-negative women. To begin to address the intersections between HIV and maternal morbidity and mortality, there is an urgent need to ensure that the half of pregnant African women who aren't currently learning their HIV status during pregnancy have an opportunity to do so. Several countries in the region have shown it is possible to reach 80% or more of women with HIV testing during pregnancy. To guide clinical practice and answer research questions about the relationships between HIV and maternal health, women must not only be tested, but test results must also be recorded and linked to other clinical and sociodemographic data in ways that are useful for making clinical and programmatic decisions. Clinical questions about how to treat women living with HIV during pregnancy and the postpartum period, and the impact that expanded access to ART will have on causes, rates, and distribution of maternal morbidity and mortality, need to be answered.

To generate the needed information, vital registration and health information systems need to be strengthened. Cause of maternal death data must be improved, as must availability of facility-based information on pregnancy outcomes that includes HIV status, ART use, maternal morbidities and neonatal health. Implementation of the guidance for coding deaths during pregnancy, childbirth and puerperium (ICD-MM) promoted by the World Health Organization, wider use of autopsies and minimally invasive autopsies, improvement of verbal autopsy tools, and wider pharmacosurveillance which involves pregnant women will all contribute to improving the knowledge base.

Integrating Health Service Delivery to Address Maternal Health and HIV

In general, efforts to integrate HIV testing and provision of ART with antenatal and postpartum care and to provide reproductive health services to women living with HIV have shown positive results. However, there is surprisingly little peer-reviewed research about HIV/MCH integration and an almost complete dearth of information about providing screening,

prevention, and treatment of malaria and tuberculosis in environments that provide components of integrated MCH/HIV care. The literature shows that while service integration has had generally positive results, significant health systems challenges persist. Assessing and addressing human resource needs will be crucial for delivering high quality, integrated services. Task-shifting and job aids (such as checklists, mobile technologies etc.) show promise in some instances, but guidance is needed on the skills and staffing levels necessary to safely and effectively deliver critical services to pregnant and postpartum women living with HIV. The impact of service integration on medium-term health outcomes is generally not reported, and the influence of integrated HIV and MCH service delivery on maternal morbidity and mortality is unknown.

Transforming the Social Context to Improve Maternal Health

A range of interventions that modify gender norms, reduce HIV-related stigma, mobilize communities to promote maternal health, and increase social support for pregnant and postpartum women have been shown to positively influence the policy context and demand for and delivery of PMTCT and maternal health services. There is also evidence that these interventions can improve service utilization, ART adherence and maternal health outcomes. The interventions prioritized for evaluation share a common mechanism of action: they seek to empower women using participatory methodologies and to change the social context by engaging the broader community to transform social norms that undermine women's health. To overcome poor rates of uptake and retention in MCH and HIV services and improve adherence, adoption of interventions which promote an enabling environment for women to use health services should be routinely considered by policymakers and practitioners working in maternal health and HIV.

Moving the Research Agenda Forward

Research and evaluation on maternal health and HIV can contribute to increased interaction between the maternal health and HIV communities. Integrating key outcomes measures and the variables needed to answer priority questions into routine program monitoring and collaborating on nested studies are places to begin. Conducting joint research can provide a powerful impetus for dialogue, resulting in strengthened political constituencies and communities of practice. The investments being made to reduce maternal mortality and increase access to HIV treatment in sub-Saharan Africa are significant. The scope of these investments should be reflected in support for research and evaluation that fills priority knowledge gaps and assesses the impact of these investments on health outcomes.

Priority Research Questions

While all of the knowledge gaps and research questions identified in this research agenda are important for reducing HIV-related maternal morbidity and mortality and improving health outcomes, the advisory working group prioritized the following research questions based on: 1) the immediate relevance for clinical practice or programs; 2) the expected public health benefits; and 3) the feasibility of conducting the research or evaluation in the short-term, particularly if it is possible to do so by improving existing monitoring and evaluation tools, strengthening data collection, conducting secondary analyses, or nesting research within on-going studies.

Research Priority 1: Clinical Questions about Maternal Mortality and HIV

Greater accuracy and completeness of vital records is crucial for better ascertainment of causes of maternal death in women with HIV, and for tracking changes in health outcomes as ART availability is scaled-up. More research on cause of maternal death which uses autopsy and minimally invasive autopsy, and validates and improves verbal autopsy tools, is needed to generate better cause of maternal death data.

Prospective observational evaluations of the rates and distribution of causes of maternal morbidity and mortality are needed to assess the impact of larger numbers of pregnant and postpartum women accessing and remaining on ART. Researchers with experience conducting prospective and retrospective analyses within HIV treatment cohorts and community-based longitudinal studies emphasized the need to allocate adequate resources to reduce the number of women lost to follow up. Ideally, a rigorous cohort design that follows all pregnant women in a

defined geographical area as ART access is scaled-up will provide compelling answers to questions about the relationship between HIV status, maternal morbidity, mortality, and access to ART. This cohort should include women living with HIV as well as those who are not, and women who attend facilities for delivery as well as those who give birth in the community. The need to track maternal deaths outside facilities will depend upon the proportion of women delivering in facilities in a given community or at the national level. Better identification of causes of maternal death among women with HIV will allow the subsequent prioritization of causes of death to be addressed in clinical intervention studies.

Research Priority 2: Integrating Health Service Delivery to Address Maternal Health and HIV

Successful delivery of integrated MCH and HIV services requires further health system strengthening. One crucial aspect is to identify and guarantee the needed mix of skills and staffing levels when implementing and evaluating integrated models of service delivery. More research and evaluation of integrated models that are already functioning to understand how HIV testing and treatment during antenatal, labor and delivery, and postpartum care can be delivered in ways that improve uptake, retention in services and linkage to antiretroviral treatment, and the effects on maternal morbidity and mortality is needed. Tuberculosis, unmet need for contraceptives, and in some settings, malaria, are important contributors to and causes of maternal deaths in sub-Saharan Africa, including among women with HIV. Thus, implementation research on how to successfully incorporate screening and treatment for tuberculosis and malaria, preconception counseling, and postpartum contraception within HIV and MCH services is called for. Disease burden, causes of maternal deaths at the community and country level, and the national policy context need to be considered when identifying which of the prioritized interventions will be the object of implementation science.

Research Priority 3: Transforming the Social Context to Improve Maternal Health

There is an increasing body of compelling evidence about the social and psychosocial barriers women living with HIV face to seeking and remaining in MCH and HIV care, but there is less information available about how to overcome these barriers. Reducing HIV-related stigma and gender discrimination, including violence against women, increasing social support for pregnant and postpartum women, and mobilizing communities to promote respectful, high quality HIV and MCH services are promising interventions for creating an enabling environment

for women to access and remain in care. Engaging with men to support women's health, especially during pregnancy and the postpartum period, is an urgent need. However, interventions aiming to increase male involvement need to ensure autonomy and informed choice about disclosure to mitigate unintended negative consequences and promote the health and well-being of women and men. Ideally, interventions that seek to create an enabling environment will address multiple social barriers to care and treatment simultaneously. Several of the interventions discussed have been seen to act synergistically, for example reducing both violence against women and HIV related stigma. The gender transformative interventions identified in this paper should be evaluated for their effects on proximate outcomes such as postpartum depression, antiretroviral adherence, and uptake and retention in health services, as well as HIV-related stigma, measures of social support and well-being, and health outcomes.

Summary

Improving maternal health in the context of the sub-Saharan African HIV epidemic requires greater understanding of the relationships between HIV disease and maternal morbidity and mortality, integrated and effective responses by the health system, and a social context which promotes quality care and encourages use of MCH and HIV services. Advancing the proposed research agenda will make an invaluable contribution by generating needed evidence for policy and practice that improves the health of pregnant and postpartum women who are living with HIV, as well as those who are not. Collaborating on research which addresses HIV and maternal health and harmonizing aspects of program evaluation and routine monitoring is one way to raise awareness and catalyze the joint responses necessary to improve maternal health and eliminate preventable maternal mortality in sub-Saharan Africa.

Appendix I

Participant List

Meeting to Develop a Research Agenda for Maternal Health and HIV in Sub-Saharan Africa

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