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Optimizing Antiretroviral Therapy (ART) for Maternal and Child Health (MCH): Rationale and Design of the MCH-ART Study

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Background: Prevention of mother-to-child transmission of HIV implementation faces significant challenges globally, particularly in the context of universal lifelong antiretroviral therapy (ART) for all HIV-infected pregnant women.

Methods: We describe the rationale and methods of the Maternal and Child Health-Antiretroviral Therapy (MCH-ART) study, an implementation science project examining strategies for providing HIV care and treatment to HIV-infected women who initiate ART during pregnancy and their HIV-exposed infants.

Results: MCH-ART is composed of 3 interrelated study designs across the antenatal and postnatal periods. Phase 1 is a cross-sectional evaluation of consecutive HIV-infected pregnant women seeking antenatal care; phase 2 is an observational cohort of all women from phase 1 who are eligible for initiation of ART following local guidelines; and phase 3 is a randomized trial of strategies for delivering ART to breastfeeding women from phase 2 during the postpartum period. During each phase, a set of study measurement visits is carried out separately from antenatal care and ART services; a maximum of 9 visits takes place from the beginning of antenatal care through 12 months postpartum. In parallel, in-depth interviews are used to examine issues of ART adherence and retention qualitatively, and costs and cost-effectiveness of models of care are examined. Separate substudies examine health outcomes in HIV-uninfected women and their HIV-unexposed infants, and the role of the adherence club model for long-term adherence and retention.

Discussion: Combining observational and experimental components, the MCH-ART study presents a novel approach to understand and optimize ART delivery for MCH.

Key Words: HIV, antiretroviral therapy, PMTCT, integration, adherence, retention

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BACKGROUND

Over the last 2 decades, there have been unprecedented advances globally in prevention of mother-to-child transmission of HIV (PMTCT). Studies have demonstrated highly efficacious approaches to prevent vertical transmission using combination antiretroviral therapy (ART) during pregnancy, delivery, and breastfeeding.[1–3] Meanwhile, increased access to ART within PMTCT services has resulted in substantial population-level reductions in new pediatric infections in South Africa and across Sub-Saharan Africa.[4,5]

Although the successes to date in PMTCT are encouraging, current approaches to implementation face significant challenges.[6] There is growing concern that in many settings women's adherence to ART, both during pregnancy and the postpartum period, may be suboptimal.[7–9] Retaining women in ART services is necessary for treatment adherence, and with mounting evidence that failure to retain patients in care is the most widespread form of treatment nonadherence, disengagement of women on ART from care is a major concern.[10,11]

Although nonadherence and nonretention are widespread concerns in adult and paediatric ART care, these are particularly problematic in pregnancy as nonadherence and failure to suppress HIV viral load increase the risk of transmission. In addition, retention in ART services and long-term adherence are also critical to sustaining maternal health over time.

Multiple impediments to providing ART to pregnant and postpartum women have been described across Sub-Saharan Africa. These include both health systems concerns [eg, multiple appointments in different services and settings for maternal and child health (MCH) care and ART] and patient-level barriers (including patient readiness for ART initiation, HIV-related stigma and disclosure, transport and other costs).[12] There have been recent advances that help address some of these factors during the antenatal period, including the integration of ART into antenatal care rather than through referral to separate ART services, and more recently, the shift to universal initiation of lifelong ART in all HIV-infected pregnant women, which removed CD4-based ART eligibility criteria.[13] Critical threats to adherence and retention remain, however, with important questions about the optimal location of ART care during the postpartum period, and when and how to transfer postpartum women to routine adult ART services after ART initiation in the MCH setting during pregnancy.[14,15]

Given the concerns around ART adherence and retention in PMTCT services during the postpartum period, there is a need for greater attention to services and outcomes that include the complete PMTCT cascade, from entry into services through determination of infants' HIV status and maternal engagement in adult services, to identify feasible and effective interventions to eliminate new pediatric infections and keep mothers healthy.[16] This is the overarching purpose of the MCH-ART study.

METHODS

The principal aim of the MCH-ART study (ClinicalTrials.gov NCT01933477) is to evaluate strategies for delivering HIV care and treatment services during the postpartum period to eligible HIV-infected women who initiate ART during pregnancy and their HIV-exposed infants. The primary objective is to compare an MCH-focused ART service to general adult ART services during the postpartum period on the composite outcomes of (1) maternal HIV viral suppression and (2) maternal retention in ART services by 12 months postpartum. Secondary objectives focus on understanding how MCH-focused ART services may differ from general adult ART services on other MCH outcomes [eg, breastfeeding practices, infant health, mother-to-child transmission (MTCT)], examining the feasibility, acceptability and cost-effectiveness of the MCH-focused ART service, characterizing the PMTCT cascade from the first antenatal visit through the cessation of breastfeeding, and describing patterns and predictors of ART adherence and retention in care antenatally and postpartum.

Setting

The study took place at the Midwife-Obstetric Unit (MOU) at the Gugulethu Community Health Centre in Cape Town, South Africa. The MOU sees >4000 women annually for primary care antenatal, obstetric, and postpartum services. The service is operated by nurse-midwives with obstetrician support twice weekly on site and through referral to a secondary-level obstetric hospital. The local antenatal HIV prevalence is high (~26%), and the MTCT rate is estimated at 2%–4% based on HIV-exposed infant HIV polymerase chain reaction testing at 6 weeks. PMTCT services have been offered at the Gugulethu MOU since 2001, with ART integrated into PMTCT services since 2012.

Study Design

The design of MCH-ART is composed of 3 interrelated phases with observational and experimental elements, in which HIV-infected pregnant women are followed up during the antenatal and postnatal periods (Fig. 1). Throughout, participants attend study measurement visits conducted separately from routine ART service appointments.

Phase 1 is a cross-sectional evaluation of consecutively enrolled HIV-infected pregnant women seeking antenatal care. This phase of the study allows characterization of the health status of the population of HIV-infected pregnant women seeking care at the Gugulethu MOU and the services they receive. Phase 2 of the study is an observational cohort of all women in phase 1 who are eligible for initiation of ART (following local public sector guidelines), from their second antenatal clinic visit until their first postpartum clinic visit (conducted within 7 days postpartum). This phase of the study provides detailed description of ART initiation and antenatal follow-up in the population of women who will be involved in the postnatal component of the study.

Phase 3 of the study is a randomized trial of strategies for delivering ART to women during the postpartum period. Women enrolled in phase 2 who are breastfeeding their infants (regardless of infant HIV status) are approached to participate in the trial at the first routine postpartum clinic visit. Consenting eligible women are randomized to 1 of 2 approaches to providing ART:

- Referral to general adult ART services from approximately 4–8 weeks postpartum (the local standard of care), or,
- Continued receipt of ART in the antenatal clinic, as part of an MCH-focused ART service that only refers women to general adult ART services after the end of breastfeeding.

Women participating in phase 3 are asked to return for 5 additional study visits at approximately 6 weeks, 3, 6, 9, and 12 months postpartum. The primary outcomes are assessed through 12 months postpartum, and further follow-up of the cohort through 18 months postpartum is planned to assess long-term maternal retention in care after transfer to general adult ART services.

The sample sizes for each phase are shown in Figure 1. An estimated 480 women are required in phase 3 to detect a 15% absolute difference in the combined endpoint of maternal viral suppression and retention in care through 12 months postpartum. To achieve this sample size, we anticipated enrolling up to 600 women in phase 2, and for this, a maximum of 1600 women were enrolled into phase 1. Ethical approval for the study, including the informed consent

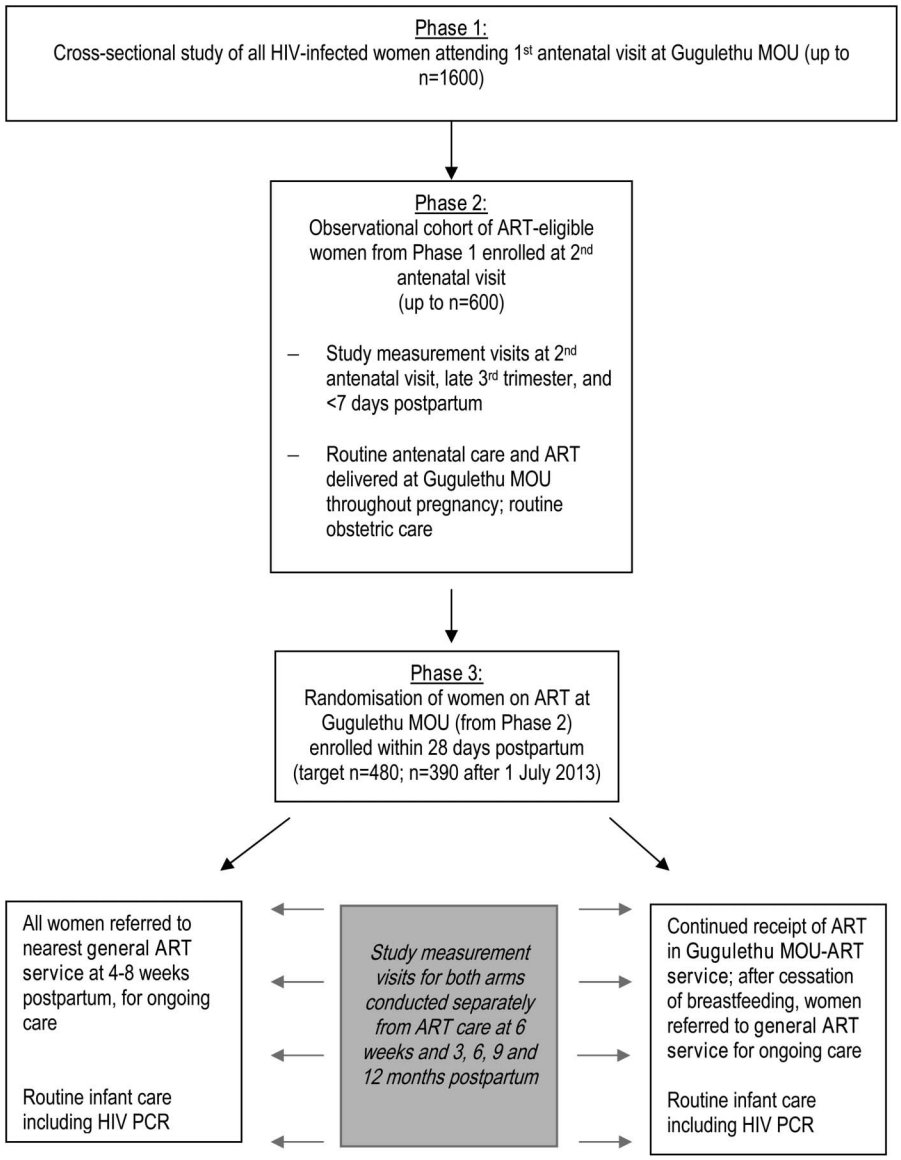

FIGURE 1. Overall design of the MCH-ART study.

process, was provided by the Human Research Ethics Committee of the University of Cape Town, Faculty of Health Sciences and the Columbia University Medical Centre Institutional Review Board.

Postpartum ART Services

Postpartum women randomized to the MCH-focused ART management strategy are retained in the MOU ART service, along with their infants, throughout the period of breastfeeding. After the end of breastfeeding, the women are referred to their nearest adult ART clinic. ART visits are scheduled every 1–2 months throughout this period. The package of services delivered in MCH-focused ART services are identical to those provided through the standard of care for both HIV-infected mothers and their infants (Table 1). The key difference between the study arms is the location of care: in the MCH-ART arm, these services are co-located at the Gugulethu MOU, whereas under the standard of care, mothers are referred to general adult ART services and their infants receive care at their nearest routine "well baby" clinic (including polymerase chain reaction testing for early infant diagnosis).

Postpartum women and infants randomized to the standard of care ART management strategy are referred from the MOU ART service to their nearest adult ART clinic at their first postpartum ART clinic visit, at around 4 weeks postpartum. The precise timing of this referral depends on the scheduling of women's ART visits, and in practice takes place approximately 2 and 8 weeks after delivery. Infants in this arm are referred for routine "well baby" care to local primary care clinics that operate separately from adult ART services, following practice in this setting.

The specific facility to which women are referred is determined by their area of residence. After transfer to routine

TABLE 1. Key Features of MCH-Focused ART Service Versus Standard of Care Control for Providing Postpartum Care in Phase 3 of the MCH-ART Study

	MCH-Focused ART Service (Intervention)	Standard of Care (Control)	
Service	Maternal ART and Child Health services (integrated)	Maternal ART services	Child health services
Location of service	Midwife Obstetric Unit (integrated maternal and child service)	General adult ART services	"Well baby" primary care clinics
Transfer into service postdelivery	No transfer—continuation of antenatal ART initiation and follow-up at the Midwife Obstetric Unit	Transfer out of Midwife Obstetric Unit 4–8 wk postpartum	Transfer out of Midwife Obstetric Unit 4–8 wk postpartum
Ongoing ART clinical and counseling services based on local protocols	X	X	
Routine infant health care (including infant weight monitoring, vaccination, and early infant HIV diagnosis) based on local protocols	X		X
Duration of service	Until cessation of breastfeeding	Ongoing care	Ongoing care
Transfer out of service	Transfer to general adult ART services and "well baby" clinics after cessation of breastfeeding	No transfer—continuation of general adult ART service	No transfer—continuation of routine "well baby" care

ART care, postpartum women are incorporated into the general population of adults receiving ART, including transfers from other ART services. Throughout the study, all clinical care is provided according to the South African national protocols and using the same record-keeping systems. Briefly, routine public sector adult ART services (outside of the context of the study) that dispense ART 2-monthly include viral load and CD4 monitoring after 6 and 12 months on ART, then annually thereafter, with serum creatinine measures for patients on tenofovir-containing regimens.

Measurements

During each phase of MCH-ART, a set of study measurement visits is carried out separately from antenatal care and ART services. A maximum of 9 visits takes place from the beginning of antenatal care through 12 months postpartum. The schedule of study measurement visits is shown in Table 2, including data collected on mothers and infants. Viral load testing at study measurement visits is separate from routine clinical monitoring, with batch testing by the South African National Health Laboratory Services using the Abbott Realtime HIV-1 assay (Abbott Laboratories, Waltham, MA). Questionnaire data include demographics, HIV testing and other medical history, disclosure of HIV status, and a range of measures of ART adherence. Further quantitative process evaluation measures are collected over time including patient–provider relationships and breastfeeding practices. The separation of study measurement visits from routine care services is important to allow participants to engage in study procedures independent of their site of care and to assist in masking study personnel to the routine services attended by study participants.

Of note, a series of behavioral, mental health and psychosocial measures, drawing on social action theory,[17] are examined during the study as potential mediators or modifiers of the intervention's effect and are also of interest as independent factors, which may influence adherence-related behaviors. These include assessments of HIV knowledge, treatment knowledge, and medication-related beliefs, and measures of depression, alcohol and substance use, psychological distress, intimate partner violence, adherence self-efficacy, availability of social support, and HIV-related stigma.

Additional measures for the study come from the review of routine medical records. Specifically, we abstract data from local health-care services on participants' (1) antenatal and obstetric care, (2) ART initiation and follow-up in routine care, and (3) infant health and health care. The primary endpoint of phase 3 of the study is measured at 12 months postpartum based on the combination of viral load measures (from study measurement visits) and evidence of maternal retention in ART services (from routine medical record review).

Qualitative in-Depth Interviews

In addition to the quantitative study measurements, a parallel qualitative investigation is used to understand how the MCH-focused ART service may influence adherence and retention outcomes in the broader context of factors influencing these behaviors during the postpartum period. Qualitative in-depth interviews are conducted with a random subset of participants by a trained isiXhosa-speaking research assistant using an interview guide to examine experiences including: ART adherence and its determinants, postpartum experience of clinical services, and transitions to routine adult ART care. These interviews provide an additional "process evaluation" of the MCH-focused ART service and how and why it may be different from general adult ART services for postpartum women and their infants.

TABLE 2. Schedule of Study Measurements in the MCH-ART Study

Study Phase	Phase 1	Phase 2			Phase 3				
Study Population	Consecutive HIV+ Pregnant Women	All HIV+ Pregnant Women From Phase 1 Eligible for ART			All Women From Phase 2 on ART and Breastfeeding				
Timing of Study Visit	First Antenatal Visit	Second Antenatal Visit	Late Third Trimester	<7 d Postpartum	6 wk Postpartum	3 mo Postpartum	6 mo Postpartum	9 mo Postpartum	12 mo Postpartum
Questionnaire-based measures									
Demographics and medical history	X								
Intercurrent maternal medical history		X	X	X	X	X	X	X	X
Maternal adherence to ART	X	X	X	X	X	X	X	X	X
Alcohol/substance use screen		X	X				X		X
Trauma/abuse assessment		X		X					X
Unplanned pregnancy assessment	X								
Family planning and future pregnancies	X			X	X		X	X	X
Patient–provider relationship scale			X	X	X		X	X	X
HIV knowledge, HIV treatment knowledge, ART beliefs inventories	X	X			X			X	
Adherence self-efficacy	X	X	X				X		X
Mental health assessments		X			X				X
Social impact and stigma scale		X			X				X
Availability of social support scale		X	X				X		X
Infant demographics and medical history				X	X	X	X	X	X
Infant feeding intentions/practices			X	X	X	X	X	X	X
Infant adherence to chemoprophylaxis				X	X	X	X	X	X
Child grants					X		X		X
Food security									X
Patient resource utilization interview							X		X
Laboratory and clinical measures									
Maternal and infant anthropometry					X	X	X	X	X
Infant neurodevelopmental assessment									X
Batched HIV viral load	X	X	X	X	X	X	X	X	X
Infant HIV polymerase chain reaction testing									X
Infant rapid antibody test									X

(*continued on next page*)

TABLE 2. (*Continued*) Schedule of Study Measurements in the MCH-ART Study

Study Phase	Phase 1	Phase 2			Phase 3				
Study Population	Consecutive HIV+ Pregnant Women	All HIV+ Pregnant Women From Phase 1 Eligible for ART			All Women From Phase 2 on ART and Breastfeeding				
Timing of Study Visit	First Antenatal Visit	Second Antenatal Visit	Late Third Trimester	<7 d Postpartum	6 wk Postpartum	3 mo Postpartum	6 mo Postpartum	9 mo Postpartum	12 mo Postpartum
Clinical data abstraction measures									
ART initiation and follow-up		X	X	X	X	X	X		X
Antenatal and obstetric information	X	X	X	X					
Pharmacy ART dispensing records		X	X	X	X	X	X	X	X
Maternal laboratory test results	X	X		X			X		X
Infant health-care services received				X	X	X	X	X	X
Infant HIV polymerase chain reaction test results					X		X		
Health services utilization and costs		X	X	X	X	X	X	X	X

Cost-Effectiveness Analysis

Costing data are being used alongside findings on clinical outcomes to understand the costs and cost-effectiveness of the 2 strategies for maternal ART and infant care services during the postpartum period. We collect detailed data on health-care resource utilization for mothers and infants during the study period, defined as (1) from start of ANC through delivery and then (2) from delivery through 12 months postpartum. Resources include health services visits for mothers and infants, laboratory investigations, and antiretroviral costs and the program-level costs (eg, patient education and adherence support materials) for each study group. Calculations follow standard methods, with total costs as quantities of resources used multiplied by unit costs; we measure costs from both health system and patient perspectives. These costs are used as data inputs into a detailed simulation model of MTCT, pediatric HIV, and adult HIV, and the Cost-effectiveness of Preventing AIDS Complications model. This allows us to project short-term and long-term clinical outcomes and costs for both mothers and infants and to estimate the cost-effectiveness of the integrated care strategy compared with standard of care.[18,19]

Substudies

Two substudies to MCH-ART are underway, which build on the implementation science platform. The first is a cohort study of HIV-negative women and their infants, the HIV-unexposed, uninfected (HU2) study. The main purpose of the HU2 study is to provide an HIV-unexposed comparison group to assist in interpreting key MCH-ART findings, particularly related to infant health outcomes. This study is enrolling up to 600 HIV-negative pregnant women from their first antenatal clinic visit and following up on them through delivery until 12 months postpartum. The schedule of study visits is identical to that of the MCH-ART cohort, and the panel of measures is adapted from MCH-ART for HIV-negative women and their HIV-unexposed infants.

In addition, there is growing interest in the role of community-based models of chronic ART care for HIV-infected individuals in resource-limited settings, most notably the "adherence club" (AC) model.[20] Given the large numbers of women initiating ART in pregnancy, adherence clubs may be particularly well suited to postpartum women. The Postpartum Adherence Clubs to Enhance Retention (PACER) study seeks to describe AC uptake and key programmatic outcomes in a group of women referred to ACs in the postpartum period and to examine the acceptability and cost-effectiveness of ACs to manage postpartum HIV-infected women on ART. The design is a cohort study, enrolling women immediately postpartum and following them for up to 12 months, with a schedule of measures identical to those used in MCH-ART. PACER is intended to provide preliminary insights into how ACs may assist in the management of women on ART in the postpartum period and to provide a valuable comparator to the MCH-focused and standard of care services examined in the parent study.

STUDY PROGRESS

MCH-ART commenced enrolment into phase 1 in March 2013, the final deliveries from phase 2 were in December 2014, and the final follow-up visits are being completed in early 2016. The final sample sizes are: 1554 women enrolled into phase 1, 628 women initiating ART

from phase 1 enrolled into phase 2, and 471 breastfeeding women enrolled postpartum from phase 2 into phase 3.

Although follow-up of phase 3 is ongoing, analyses from phases 1 and 2 have already yielded important insights into the PMTCT cascade. An analysis of all HIV-infected women making their first antenatal clinic visit as part of phase 1 highlighted both the sizable number of HIV-infected pregnant women who conceive on ART in this setting and the relatively high levels of nonsuppressed viral loads in this group.[21] Phase 1 data also demonstrated the discordance between depressed CD4 cell count and elevated viral loads in women not yet on ART—with a substantial proportion of women with viral load >10,000 copies per milliliter despite CD4 cell counts >350 cells per microliter—an important finding that speaks to the limitations of CD4-based ART eligibility for PMTCT programs. Other analyses have shown high levels of unintended pregnancy,[22] intimate partner violence,[23] and mental health problems among HIV+ women in this setting,[24] raising important concerns for long-term PMTCT outcomes.

Among women enrolled into phase 2, the vast majority initiated the local standard of care regimen of tenofovir 300 mg + emtracitabine or lamivudine 300 mg + efavirenz 600 mg once daily, provided as a fixed-dose combination. The follow-up of women initiating ART in pregnancy as part of phase 2 has demonstrated rapid declines in viral load immediately after ART initiation (median gestation at initiation, 20 weeks), with >90% of women achieving viral loads <1000 copies per milliliter before delivery. However, approximately one-quarter of women had detectable viral loads at the time of delivery, and viremia at delivery was a direct function of pretreatment viral load and duration of ART before delivery. The overall risk of MTCT in the cohort was 1.3% (95% confidence interval: 0.5% to 2.6%) by 56 days postpartum. This transmission was strongly associated with viral loads at the time of delivery, with risks of 0.25%, 2.0%, and 8.5% among women with viral loads <50, 50–1000, and >1000 copies per milliliter, respectively, at delivery ($P < 0.001$).[25]

Additional analyses from phase 2 of the study have also shown the high burden of side effects among women initiating ART in this setting, with >95% of women reporting at least one class of side effect before delivery. Interestingly, although no single type of side effect was independently associated with missed ART doses in pregnancy, the total number of side effects experienced was a strong predictor of nonadherence. Although it is difficult to distinguish ART side effects from symptoms of HIV disease and/or "normal" physiologic changes in pregnancy, this finding has important implications for adherence counseling under Option B+.[26]

Key Features of MCH-ART

The approach of the MCH-ART study features several noteworthy design elements that position it to help advance knowledge around optimal implementation of ART services for pregnant and postpartum women.

Integration of Multiple Study Designs

Rather than a single study addressing a single step in the PMTCT cascade, each phase of MCH-ART uses a different design to address interrelated implementation questions with nested study populations across the PMTCT cascade. This approach, with different designs within a program of research used to approach a single issue from different perspectives, can help maximize the knowledge generated by investments in PMTCT implementation science.

Multidisciplinary Measures

Within each phase of MCH-ART, study questions are investigated through different study designs using a multidisciplinary set of measures that include virologic, psychological, behavioral, interpersonal, and social and economic considerations. This diversity of approaches and measures within a single conceptual framework is unusual in PMTCT implementation science and allows the study to examine an array of factors shaping PMTCT outcomes.

Collaborations Across Disciplines

Increasingly, the key questions facing PMTCT services extend beyond the efficacy of specific antiretroviral interventions to encompass the factors that determine programmatic effectiveness and implementation at scale. Implementation science frequently draws on multidisciplinary collaborations to help address these broader issues, and in the case of MCH-ART, the study team draws input from clinical disciplines (including pediatrics, obstetrics, and HIV medicine), epidemiology, psychology, health economics, virology, biostatistics, and health systems research. This diversity has exciting potential but is not uncomplicated, as bringing together wide-ranging disciplinary traditions and perspectives to focus on a specific set of implementation questions can be challenging. We have found that having a "core" set of investigators providing constant scientific oversight, and then coordinating the inputs from different disciplines and substudies, can be an effective approach to managing multidisciplinary collaborations.

Choice of Outcomes in PMTCT Implementation Science

To date, a wide range of endpoints have been used in PMTCT implementation science, with studies drawing on varying behavioral and health service outcomes focused on specific steps of the PMTCT cascade. This diversity is understandable, but may diffuse the impact of implementation science on policy and programs. We use maternal HIV viral load over time—a robust biological endpoint—as a unifying outcome to measure effective implementation of PMTCT services across all 3 phases of MCH-ART. Viral load is the most appropriate outcome in this context as it encompasses health service functioning, patient and provider behaviors, and the real-world effectiveness of treatments. In the phase 3 trial, MCH-ART uses a composite endpoint of maternal viral load coupled with retention in care to capture the ultimate goal of ART use within PMTCT services: to keep HIV-infected mothers engaged in care and virologically suppressed

to maximize the benefits of ART for both treatment and prevention.

Generalizability

The external validity of implementation science findings—their generalizability to different settings and broader populations—is an ongoing major concern for the field that requires careful and constant consideration. One facet of generalizability affecting MCH-ART centers on the patient populations, burden of HIV disease, and health-care systems contexts where research takes place. The setting of the MCH-ART study in a public sector, primary health-care system in Cape Town may facilitate the generalization of results to other urban, high-burden settings, in South Africa and other resource-limited settings. However, the questions at the center of MCH-ART—issues of women's retention in care, adherence to ART and viral suppression, and how these may be influenced by the integration of health-care services—are clearly of importance across countries where HIV is prevalent.

SUMMARY

The emerging challenges of delivering ART effectively in the context of PMTCT services—particularly engaging HIV-infected mothers and their children across the full cascade of care—require robust implementation science to document critical problems and the interventions to address these. Combining observational and experimental components, the MCH-ART study presents one approach to understand the optimization of ART delivery for MCH. Key features of the study design have the potential to add novel insights in the field, and the study's progress to date suggests that the MCH-ART study will make an important contribution towards maximizing the benefits of universal initiation of lifelong ART for HIV-infected women.

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