Beyond "Option B+": Understanding Antiretroviral Therapy (ART) Adherence, Retention in Care and Engagement in ART Services Among Pregnant and Postpartum Women Initiating Therapy in Sub-Saharan Africa

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Background: Several studies from sub-Saharan Africa have highlighted significant challenges in providing antiretroviral therapy (ART) to pregnant and postpartum women, with specific concerns around maintaining optimal levels of adherence to ART and/or retaining women in long-term services. However, there are few conceptual frameworks to help understand nonadherence and non-retention, as well as the drivers of these, among HIV-infected women, particularly in the postpartum period.

Methods: This review provides an overview of the key issues involved in thinking about ART adherence, retention in care and engagement in ART services among pregnant and postpartum women.

Results: The related behaviors of adherence and retention may be understood as components of effective engagement of patients in ART services, which share the goal of achieving and maintaining suppressed maternal viral load on ART. Under this framework, the existing literature indicates that disengagement from care is widespread among postpartum women, with strikingly similar data emerging from ART services around the globe and indications that similar challenges may be encountered by postpartum care services outside the context of HIV. However, the drivers of disengagement require further research, and evidence-based intervention strategies are limited.

Conclusions: The challenges of engaging women in ART services during pregnancy and the postpartum period seem pervasive, although the determinants of these are poorly understood. Looking forward, a host of innovative intervention approaches are needed to help improve women's engagement, and in turn, promote maternal and child health in the context of HIV.

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INTRODUCTION

Over the past decade, the numbers of HIV-infected pregnant and breastfeeding women receiving antiretroviral therapy (ART) have increased dramatically. Expanded access to and uptake of ART during pregnancy has helped to drive significant global reductions in mother-to-child HIV transmission (MTCT).[1] Today, there is robust evidence that effective ART use can almost eliminate MTCT under ideal conditions, and at a programmatic level <2% transmission may be possible in resource-limited settings.[2,3] Most recently, the promulgation in 2013 of policies that call for universal ART use during pregnancy, regardless of HIV disease stage or degree of immunodeficiency [per the World Health Organization's (WHO) "Option B+" policy[4]], laid the foundation for more recent recommendations for universal ART eligibility for all HIV-infected adults and children.[5] Altogether, ART for preventing MTCT and promoting the long-term health of HIV-infected mothers represents one of the most successful examples to date, in both scientific and programmatic terms, of the synergies of ART for HIV treatment and prevention.[6]

Although importance of ART for MTCT and maternal health cannot be understated, significant concerns have been raised around several aspects of "Option B+" programs.[7,8] The benefits of ART use in an HIV-infected individual are due to reductions in viral load,[9] and the goal of effective ART use is rapid and sustained viral suppression. However, multiple investigations have suggested relatively high levels of poor adherence to ART and/or attrition from care [or nonretention/loss to follow-up (LTF)] among women initiating ART in pregnancy.[10,11] This phenomenon has generated global concern, as the potential benefits of ART for reduced MTCT risk and improved long-term maternal health, both based on control of HIV viremia, may be negated by nonadherence and/or nonretention.[12–14] This would see the potential benefits of lifelong ART undermined for both individuals and populations.

With a significant fraction of infant HIV infections occurring during breastfeeding[15] and antiretroviral resistance emerging as a widespread concern,[16] nonadherence and/or nonretention among women initiating ART during pregnancy and breastfeeding have clear implications for maternal and child health in the context of HIV. There is a burgeoning literature on these issues, focusing in particular on populations across sub-Saharan Africa after the roll-out of "Option B+" services. Yet, the insights from this literature may sometimes seem disparate, and there have been few attempts to coalesce thinking to help advance the field. In seeking a vantage over these issues, this piece reviews key concepts in considering adherence and retention behaviors generally, and then highlights aspects of the evidence base related to nonadherence and nonretention in pregnant and postpartum women, including the mechanisms that may be driving these phenomena. Drawing together perspectives from across the field, the piece ends with a discussion of intervention possibilities and research directions to optimize the benefits of ART for pregnant and postpartum women globally.

BEYOND ADHERENCE AND RETENTION: CONSTRUCTS OF ENGAGEMENT

Over the past 20 years, a sizable body of research has accumulated investigating adherence to ART—typically defined as pill-taking behaviors—in different patient populations taking different ART regimens assessed using different measures (recognizing that other terms may be used, *adherence* or *nonadherence* will be used here). Somewhat more recently, issues of attrition and LTF from ART services (or the inverse, *retention in care*) have become recognized as a major concern, particularly in the global scale-up of access to ART; in referring to this, *nonretention* will be used here.

While constructs of adherence and retention are clearly closely linked in the continuum of care—an individual must be retained in health services to access ART as a precursor to ART adherence—the relationships between these remain poorly elucidated. For example, patients who are not retained in ART services are highly likely to be nonadherent to treatment, yet these patients are often missing information regarding their adherence—by virtue of being lost from care, the direct assessment of their adherence becomes more challenging.[17] This paradox, in which individuals who are not retained in care may not be observed to be nonadherent, presents a basic challenge to understanding the real-world effectiveness of ART programs, including for pregnant and postpartum women on ART.

One useful framework for integrating thinking about ART adherence and retention comes from the work of Vrijens and colleagues, whose focus on adherence to medications for chronic conditions recognizes both adherence to treatment and engagement in care along a continuum, from *initiation* of therapy (prescription and ART initiation), to *implementation* of pill-taking (ART adherence or nonadherence) and then *persistence* of therapy (requiring ongoing participation in ART services or discontinuation from care).[18] In this context, disengagement from effective ART care and its sequelae, such as loss of viral control, can result from either nonadherence in patients who are retained in care, or nonretention in ART services and subsequent nonadherence (Fig. 1). Thus. while adherence and retention are separate measures—with different data sources and interpretations—they may be seen in many regards as manifestations of the same underlying phenomenon. Building on previous work, we propose *engagement in ART services* to serve as an umbrella term which involves both retention in care—and with this the ability to access ART and participation/involvement in ART services on an ongoing basis—and adherence to prescribed pill-taking.[19]

Based on this approach, Figure 2 presents a simple schematic linking these constructs for the purposes of this article. With this, we may view studies of ART nonadherence or nonretention in ART services as describing the same underlying issue of disengagement—the deviation of uptake of clinical services and/or actual medication use over time from the standard intended by the health care system to achieve optimal outcomes.[20] These 2 manifestations of disengagement also share consequences: poor viral control—during pregnancy, breastfeeding, and beyond—is an outcome of both nonadherence and nonretention in care.

BEYOND ART INITIATION: KEY INSIGHTS INTO ENGAGEMENT FROM SUB-SAHARAN AFRICA

When viewed in this light, several trends emerge from the existing literature on disengagement from ART services by pregnant and postpartum women. There is ample and growing evidence that even though initial uptake/initiation of ART under Option B+ is very good, women's disengagement from ART services seems unacceptably high during pregnancy and postpartum. For example, programmatic data from Malawi demonstrate high levels of nonretention in women initiating ART under "Option B+" compared with nonpregnant women initiating ART: While the greatest losses were observed in the 2 years after ART initiation, levels of nonretention in women initiating during pregnancy were similar to women initiating outside of pregnancy by the third year of follow-up.[21,22] The evidence demonstrating this is remarkably consistent across countries and health systems settings, with data from both programmatic and research contexts, as similar findings have been documented in Uganda, Rwanda, Cameroon, Mozambique, Zimbabwe, and Ethiopia.[23–28]

Within this literature, 2 specific features frequently characterize women's disengagement from ART services. First, several analyses have suggested that the greatest risk of disengagement may take place immediately after ART initiation—with reduced levels of attrition thereafter. For example, in Malawi, the single greatest losses were observed immediately after ART initiation during pregnancy. Similar findings have been reported in Rwanda and Uganda.[23,24] Whether this finding is universal, and the reasons that may underpin this, remain unclear. One suggestion is that "same day" ART initiation (which in the context of pregnancy care sees ART initiation take place on the day of a woman's first antenatal clinic visit) may contribute to immediate nonretention. Another suggestion is that this early nonretention

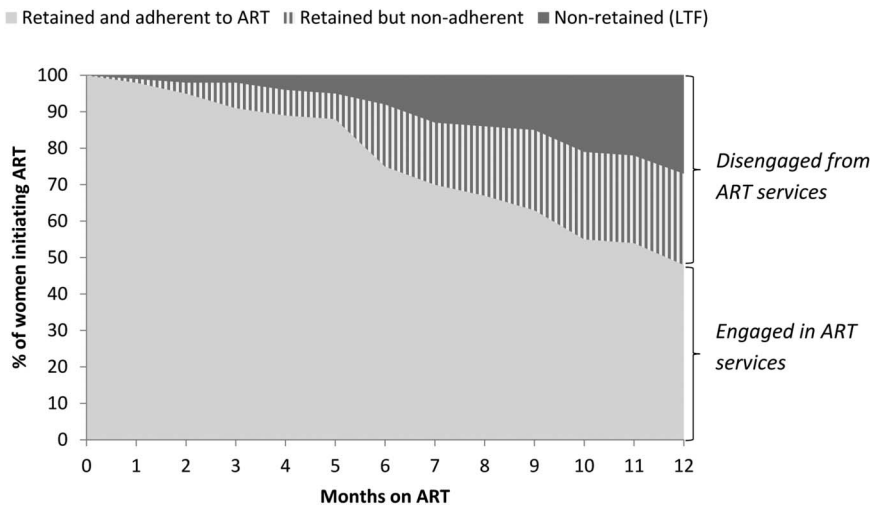

FIGURE 1. Hypothetical depiction of the relationships between adherence and retention in care and engagement in ART services in a cohort of women initiating ART. At initiation (month 0), 100% of women are retained in care and adherent to therapy; disengagement from ART services increases over time in the form of non-retention and nonadherence among women retained in care.[18]

is related to better maternal health status at ART start under Option B+.[22] But, although both these explanations are widely discussed, empirical data are surprisingly sparse and mixed, pointing to an important avenue for future research.

Second, several studies have suggested that engagement in care may worsen in the postpartum period. However, the reasons behind this are poorly elucidated. One likely possibility is related to generalized challenges faced by health services and health systems in providing postpartum care. In the realm of maternal and child health, most health systems globally focus predominantly on the provision of effective antenatal care, with the goal of safe delivery, and services for infants and children, with the goal of promoting child survival.[29] With attention focused on mothers prenatally and children postnatally, the health of postpartum women has received dramatically less attention. At least some of this inattention may be understandable because a healthy mother may have relatively straightforward postnatal health care needs; challenges emerge when ongoing chronic medical care is required in this period. In the case of ART services, the increased volume of HIV-infected postpartum women requiring care under "Option B+" policies may exacerbate these challenges.

Related to this, optimal models of ART service delivery for pregnant and postpartum women are not well described in the literature. Differentiated models of care for ART services have generated substantial interest, but the potential and challenges associated with differentiated care for pregnant and postpartum women have not been explored in depth, and empirical data are few. In addition, in some settings, the transfer of women initiating ART during pregnancy out of the Maternal and Child Health (MCH) setting, either during

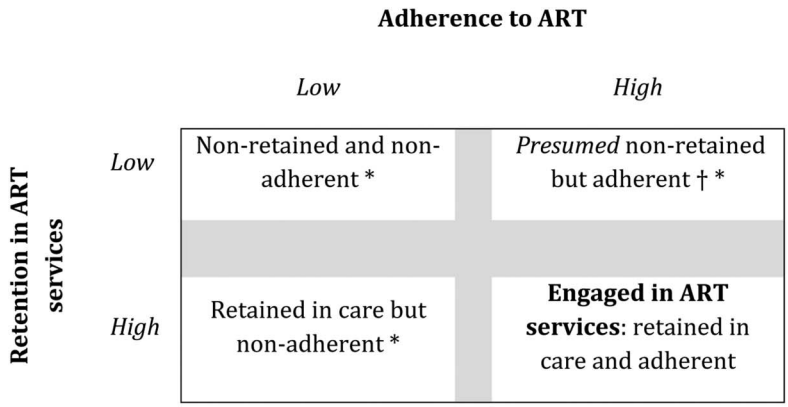

FIGURE 2. Framework for the relationships between ART adherence, retention in care and engagement in ART services. Both adherence and retention are represented here in binary terms, but in reality are continuous phenomena.

** Forms of disengagement from ART services*

† Because retention in ART services is required to access and adhere to ART, being non-retained in services but adherent to ART may not be possible. However this situation could be observed given errors in documenting retention in ART services, including 'silent transfers' of patients between services

pregnancy or postpartum, is commonplace. However, there have been few studies reporting adherence and retention outcomes after transfer of routine ART care with most analyses censoring women at the time of transfer out. Transfer of routine services may be a vulnerable period for women's engagement in care, and understanding adherence and retention during and after women's transfer between ART services will be an important consideration for future research.

Further factors that may contribute to women's disengagement from ART services in the postpartum period include the host of physiological, psychological, social, and/or economic changes that often characterize the time after delivery for many women, and that may also affect women's health-related behaviors.[30,31] The postpartum period is one of rapid change in the lives of women and families, sometimes including geographic mobility; although these changes are not well described in many of the settings where HIV is prevalent, it may be unsurprising that for some women engagement in ART services may suffer amidst these changes.[32,33] Understanding better these phenomena in women's lives generally, and how they may influence HIV-related adherence and care engagement specifically, is an important area for future research.

Most of the literature on this topic from sub-Saharan Africa focuses on women's retention in ART services.[34–36] Data on adherence to treatment during pregnancy and postpartum are less common, although available insights seem to concur.[37] For example, using pharmacy dispensing data, one recent analysis from Malawi suggested that among women retained in care, ART adherence levels were >90% for only 65%–75% of women initiating ART during pregnancy; of note, adherence decreased during the immediate postpartum period, but returned to prenatal levels by 4–6 months postpartum.[38] The reason for the abundance of studies of retention relative to studies of adherence in this population may be attributed primarily to the lack of adherence measures systematically used in routine care. In the same vein, there are very few insights into HIV viral load among women initiating ART in pregnancy. For instance, little is known about how frequently loss of viral control occurs or the factors associated with viremia over time in women on ART. One study from South Africa found that in women initiating ART during pregnancy and achieving viral suppression (<50 copies/mL) by delivery, approximately 30% had a subsequent viral load >1000 copies/mL by 12 months postpartum; the risk of viremic episodes increased with increased time postpartum.[39] Clearly, additional studies are required to understand how disengagement from care, and/or ART nonadherence, may affect risk of HIV transmission and long-term maternal health outcomes.[40]

BEYOND SUB-SAHARAN AFRICA, BEYOND HIV

In seeking to contextualize existing evidence from sub-Saharan Africa, it is apparent that the increased levels of nonadherence and/or nonretention among pregnant and postpartum women on ART are not limited to Africa, and are not limited to low- and middle-income countries.[41–45] Similar challenges have been documented across Europe and North America in both routine service cohorts and research studies. For example, in the UK and Ireland, 27% of women initiating ART in pregnancy experienced viral rebound (>200 copies/mL) by 12 months postpartum.[46] In a US cohort, only 31% and 34% of women receiving ART in pregnancy appeared in care and virally suppressed (<200 copies/mL) by 1 and 2 years after delivery, respectively.[47] Of interest, the ART regimens used across these studies vary widely, in keeping with differential access to antiretrovirals over time across continents; the consistency of findings for women's disengagement may provide indirect evidence that specific antiretroviral agents, or side effects associated with these, are unlikely to be driving this phenomenon in isolation.

There are strong indications that the concerns around engaging women postpartum in long-term health services are not unique to HIV-infected women receiving ART. For example, similar challenges have been well documented across the globe for the postpartum management of diabetes and other chronic conditions in the United States.[48] Furthermore, there is emerging evidence that the postpartum period may receive inadequate attention in non-HIV health services in Africa.[49] These issues have been recognized for at least several decades, and represent a persistent challenge for women's health.[50]

Taken together, these parallels across geographic settings and other chronic conditions help to point toward the possible determinants of ART nonadherence or disengagement from care. Unique local contextual conditions are often important drivers of health-related behaviors including ART adherence;[51] yet, it seems that in this case there may be generalizable factors that (1) are not unique to low- and middle-income countries and that (2) may not be entirely specific to HIV or ART use.

BEYOND RISK FACTORS: UNDERSTANDING THE CAUSES OF DISENGAGEMENT FROM ART SERVICES

Given this evidence, it seems likely that there is no single risk factor that universally drives the observed challenges in women's engagement in ART services during pregnancy and postpartum.[52] Instead, the etiologies of disengagement are likely to be multicausal, with combinations of factors contributing to suboptimal ART adherence and/or retention in care.[53]

Figure 3 presents a basic framework for thinking about the different causes which may contribute to women's disengagement from ART services at a population level, operating at various levels of social and biological organization. This framework recognizes fundamental drivers of disengagement from care among *structural, social, and economic conditions* which are prevalent in many settings where HIV is common. These include poverty, mobility, gender inequalities, food insecurity, and other issues which may play a distal role in a wide range of health behaviors, including ART adherence and retention.[54] *Health systems and services* are closely linked with socioeconomic conditions and warrant separate consideration here. Basic issues of the availability of and access to health services (including

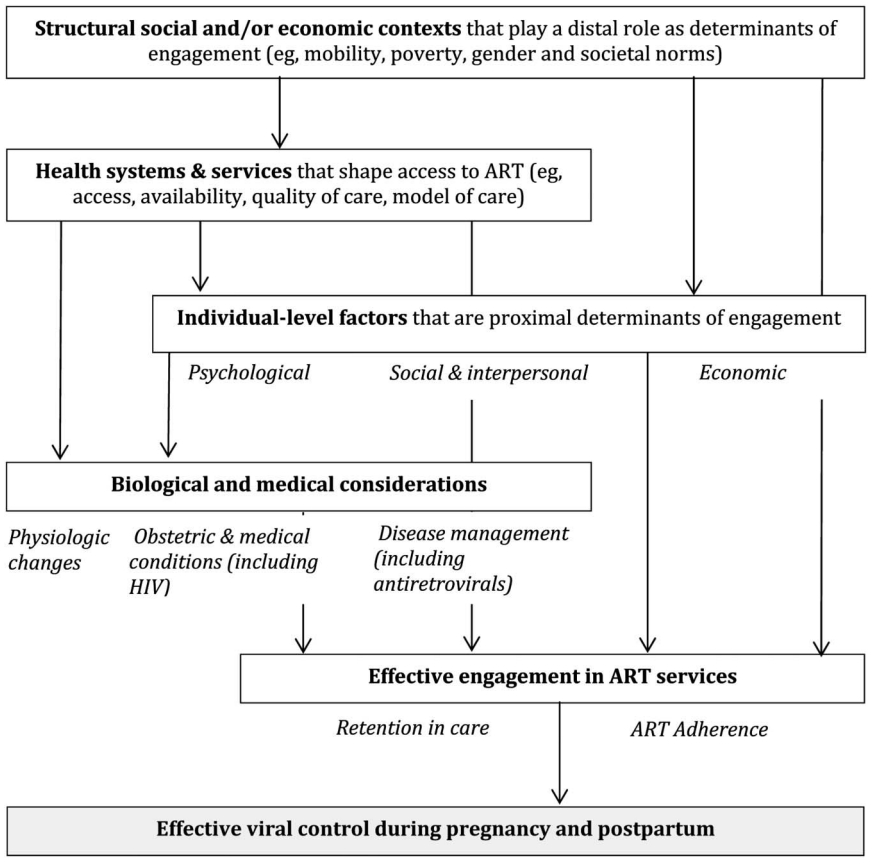

FIGURE 3. Conceptual model for considering determinants of engagement in ART services in pregnant and postpartum women.

antenatal and postnatal care generally and ART services specifically), as well as quality of care and models of service delivery, are likely to be important determinants of retention in ART services and adherence to therapy.[55] *Individual-level factors* are a primary focus in the available literature, including partner and social relationships, the psychology of pregnancy and motherhood, disclosure of HIV status, social support, and/or mental health.[56] And finally, different *biomedical considerations*, including the physiological changes of pregnancy and postpartum as well as HIV- and/or ART-related concerns (such as side effects of antiretroviral drugs) may operate here.[57]

This is not a comprehensive list of all potential risk factors, yet this simple model provides a potentially useful way to think about the drivers of women's engagement in ART services. Importantly, the model does not postulate that specific factors operate in isolation but rather views factors from different levels interacting to shape engagement behaviors in individuals and populations. For example, distance from health services may contribute to disengagement from care for patients who can not afford transport, whereas for individuals and communities with greater economic access the issue of distance from health services may be less important. Similarly, it is possible that ARV side effects may play a major role in nonadherence in health services without functional counseling services, whereas they may be less of a driver in services where counseling addresses issues of common side effects in their messaging. There are many determinants of women's engagement in ART services that may be best understood at the individual level—whether in terms of interpersonal relationships or psychosocial issues—although these types of proximal drivers of engagement are often heavily influenced by structural and/or biomedical conditions. For example, postpartum depression or other mental health concerns may influence women's ability to adhere to ART, recognizing that the determinants of mental health can include both societal conditions and biological processes.

Overall, we may best understand the causes of women's disengagement from ART services during pregnancy and the postpartum period as diverse, multifactorial, and dynamic over time. This complexity raises critical etiologic questions for future research attention. For example, it is plausible that in some contexts the drivers of nonadherence to therapy may be distinct from the factors which increase nonretention in care; this possibility should be tested empirically. Understanding better the range of causes that may operate in different contexts and how different kinds of causes interact represents a major avenue for future research in this field.

BEYOND "QUICK FIXES": STRATEGIES FOR INTERVENTION

Understanding the causes of disengagement from ART services is critical to help identify the most appropriate

interventions to optimize adherence to therapy and retention in care. A number of intervention strategies have been suggested over the past few years, listed in Table 1. Several of these strategies are at a conceptual or pilot testing stage, and few have been subjected to rigorous evaluations in different contexts; those that have been evaluated have encountered mixed results.[58,59]

Though a systematic review of these interventions is beyond the scope of this article, several features of the intervention literature warrant attention. First, the vast majority of interventions target a single factor, or a small host of related issues, that seems to contribute to disengagement from services in a particular setting. While this approach is in keeping with the "risk factor" paradigm that dominates contemporary public health research, our conceptual model above suggests that interventions targeting a single factor may be unlikely to have a profound effect at a population level given the multifactorial etiology of disengagement. Indeed, when evaluations have demonstrated an intervention effect, the effect size has been modest, and the generalizability of the findings is sometimes unclear.[60,61]

Second, the outcomes that have been evaluated to date have focused primarily on retention in care. Very few studies have included markers of ART adherence, and fewer have included viral load measures which are the critical outcome which engagement in services is intended to influence. This focus on retention is understandable, given that retention in care is (1) usually easier to measure in many health systems and (2) likely to be a close correlate of both adherence and viral suppression, based on the concepts of Vrijens and others. However, an exclusive focus on retention outcomes may be problematic for the field for at least several reasons. It is wholly possible that in resource-constrained health systems with increasing patient volumes, the quality of retention data may suffer, leading some patients to be "missed" in routine clinical information systems and thus seem falsely LTF over time.[62] Moreover there is emerging evidence for the phenomenon of "silent transfers": patients who appear LTF from a given ART service, who in fact have transferred (often unofficially) to another service.[63] Similarly, there is the possibility that some patients who appear retained in care are nonadherent to therapy. Both of these issues will result in underestimation of engagement, and in turn, patients who appear to have disengaged from care when they may in fact be in care and virologically suppressed.

Thirdly, most interventions evaluated to date focus on pregnancy and the first few months postpartum. Although this is understandable in the context of prevention of vertical transmission, evaluating the long-term impact of engagement interventions will be an important consideration after initiation of lifelong ART in pregnancy.

Future intervention strategies and evaluations to enhance pregnant and postpartum women's engagement in ART services can address these shortcomings. Multimodal intervention packages are required that seek to address a wide range of issues, ideally simultaneously targeting factors at the level of health systems and individual-level psychological and social factors, at the minimum.[64] The notion of multicomponent intervention packages is well established in the field of HIV prevention, linked closely to the movement toward complex interventions across public health, and these approaches seem to yield more useful results than oversimplified intervention strategies.[65,66] Given the complexity of determinants of women's engagement in ART services during pregnancy and postpartum, this area is ripe for analogous developments.

In addition, the trend toward retention as the most frequently used outcome in this literature is likely to continue for the reasons outlined above. Still, there is an ongoing need to examine the specific data sources and definitions of retention and LTF in much greater detail, and approach retention data with much greater rigor and circumspection[17,67,68]; ultimately, the construct of retention requires the same type of critical attention that is afforded to assessments of ART adherence. In parallel, intervention evaluations which extend longer postpartum and include measures of adherence behaviors will be of critical importance, and viral load measures should be recognized as the gold-standard outcome when available for evaluations of interventions to enhance adherence, retention, or overall engagement in ART services.

TABLE 1. Examples of Intervention Strategies Proposed, Developed, or Evaluated to Enhance Engagement in ART Services by Pregnant and/or Postpartum Women Receiving ART

Enhanced patient education and counseling
Integration of ART and MCH services: antenatal and/or postnatal
Peer support programs and patient navigators
Community health worker/home-based care programs
Family-focused ART services
Male partner involvement
Text reminders and mHealth interventions
Directly observed therapy
Community-based ART delivery and "adherence clubs"
Health systems quality improvement
Conditional cash transfers
Intensive case managers

CONCLUSIONS

With several years' experience of universal eligibility for lifelong ART for both HIV prevention and treatment, prevention of mother-to-child transmission continues to be at the cutting edge of implementation science in HIV. The challenges of engaging women in ART services during pregnancy and the postpartum period seem pervasive, although the determinants of this are poorly understood. Looking forward, a host of innovative intervention approaches require rigorous evaluation to help improve women's engagement, and in turn, promote maternal and child health in the context of HIV. Ultimately, today's learning about optimal strategies to enhance adherence, retention in care and engagement in ART services for pregnant and postpartum women—including the findings of the INSPIRE network[69]—will become tomorrow's conventional wisdom

about providing universal ART for all HIV-infected adults and children.

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