Title

Implementation Research for the Prevention of Mother-to-Child HIV Transmission in Sub-Saharan Africa: Existing Evidence, Current Gaps, and New Opportunities

Journal

Current HIV/AIDS Reports, 12(2)

ISSN

1548-3568

Authors

Bhardwaj, Sanjana
Carter, Bryan
Aarons, Gregory A
et al.

Publication Date

2015-06-01

DOI

10.1007/s11904-015-0260-1

Peer reviewed

HHS Public Access

Author manuscript

Curr HIV/AIDS Rep. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Curr HIV/AIDS Rep. 2015 June ; 12(2): 246–255. doi:10.1007/s11904-015-0260-1.

Implementation Research for the Prevention of Mother-to-Child HIV Transmission in Sub-Saharan Africa: Existing Evidence, Current Gaps, and New Opportunities

Sanjana Bhardwaj, MD, MPH[1], **Bryan Carter, BA**[2], **Gregory A. Aarons, PhD**[3], and **Benjamin H. Chi, MD, MSc**[4]

[1]UNICEF, Pretoria, South Africa

[2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[3]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

[4]Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract

Tremendous gains have been made in the prevention of mother-to-child HIV transmission (PMTCT) in sub-Saharan Africa. Ambitious goals for the “virtual elimination” of pediatric HIV appear increasingly feasible, driven by new scientific advances, forward-thinking health policy, and substantial donor investment. To fulfill this promise, however, rapid and effective implementation of evidence-based practices must be brought to scale across a diversity of settings. The discipline of implementation research can facilitate this translation from policy into practice; however, to date, its core principles and frameworks have been inconsistently applied in the field. We reviewed the recent developments in implementation research across each of the four “prongs” of a comprehensive PMTCT approach. While significant progress continues to be made, a greater emphasis on context, fidelity, and scalability – in the design and dissemination of study results – would greatly enhance current efforts and provide the necessary foundation for future evidence-based programs.

Keywords

HIV; implementation research; prevention of mother-to-child HIV transmission; PMTCT; Africa

Corresponding Author: Dr. Ben Chi, Campus Box 7577, 3004 Old Clinic Building, Chapel Hill, NC 27590; Tel 919-966-5281; bchi@med.unc.edu.

Compliance with Ethics Guidelines

Conflict of Interest Sanjana Bhardwaj, Bryan Carter, Gregory A. Aarons, and Benjamin H. Chi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Considerable advances have been made to prevent mother-to-child transmission of HIV (PMTCT). Unlike in North America and Europe, where vertical transmission of HIV is now exceedingly low, progress has lagged in sub-Saharan Africa due to numerous contextual factors. However, new developments in clinical research, policy, and program expansion have led to a renewed hope about the dramatic reduction of pediatric AIDS. Numerous clinical trials, for example, have demonstrated the efficacy of maternal antiretroviral therapy (ART) through pregnancy, delivery, and breastfeeding [1]. The World Health Organization and other international donors have strongly endorsed the "Option B+" strategy to provide lifelong ART to all HIV-infected pregnant and breastfeeding women [2], a policy that seeks to reduce key bottlenecks by making treatment universal. Joint investments in PMTCT – from international donors and local governments – have made considerable resources available to "virtually eliminate" pediatric AIDS and reduce maternal deaths worldwide [3, 4].

Over the past decade, there has been growing recognition that scientific discovery and translational research alone will not result in the public health gains sought by local governments and international agencies [5]. For any particular health problem, there may exist a number of proven clinical interventions; however, their potential is often unrealized because of poor implementation, poor access through health systems, and incomplete uptake by health systems, care providers, or individuals in need [6]. To address this gap, the field of implementation research has emerged as a priority area. This is certainly true in the field of HIV, where greater efforts have been made to articulate and address the "know-do" gap across prevention, care, and treatment [7–9]. Despite its growing prominence, however, the approaches and frameworks of implementation research are often misunderstood outside of the discipline [10]; as a result, concerted efforts have been made to better define and disseminate its foundational principles [11**, 12]. The traditional view of research has been linear, with strong emphasis on discovery and translation. More recent efforts have recast this paradigm as cyclical, with bidirectional interplay between each phase. Key steps have been articulated beyond the "translational" clinical trials that support development of applied clinical interventions (T2): implementation strategies designed to optimize uptake of guidelines and clinical interventions (T3) and measurement of the resulting population impact (T4) [11**].

In this report, we reviewed published articles and conference abstracts in the medical literature focused on PMTCT implementation research over the past three years. We framed our discussion according to the four "prongs" of PMTCT articulated by the United Nations: (1) primary prevention of HIV among women of childbearing age, (2) prevention of unintended pregnancies among HIV-infected women, (3) prevention of mother-to-child transmission among HIV-infected women, and (4) linkage of HIV-infected women and children to long-term HIV care and treatment.

Preventing incident HIV infection among women of childbearing age

Significant advances have been made in the area of HIV prevention over the past decade. There now exists a growing body of evidence that biomedical and behavioral interventions used in combination can dramatically reduce incident HIV infection at a population level. A number of review articles have been published over the past several years, which together provide a comprehensive survey of the field [13–15]. Here, we emphasize three areas of particular relevance to women of childbearing age.

Pregnancy and breastfeeding are windows of elevated risk for maternal HIV acquisition. Drake and colleagues showed that the overall incidence during pregnancy/postpartum was 3.8/100 person-years (95%CI: 3.0–4.6) in a recent meta-analysis, with higher rates during pregnancy (4.7/100 person-years) than afterwards (2.9/100 person-years; p=0.18). Perhaps most relevant to this review are the high mother-to-child transmission rates observed among incident cases during pregnancy. Pooled transmission rates were estimated at nearly 23%, at rates two- to threefold higher than those observed with chronic HIV infection [16*]. Tailored prevention interventions are needed for this population, ones that incorporate both biomedical and behavioral components. Partner HIV testing, for example, can help to identify serodiscordant couples that may be eligible for intensive counseling and “treatment for prevention” modalities. Pre-exposure prophylaxis during the pregnancy/breastfeeding period may also be promising, though the risks and benefits of antiretroviral drug exposure to otherwise healthy HIV-uninfected mother-infant pairs must be carefully weighed [17].

Controversy persists regarding the association between hormonal contraception and HIV acquisition. A pair of recently published meta-analyses – conducted by Ralph et al [18] and Morrison et al [19] – contribute meaningfully to the ongoing debate. In these studies, depot-medroxyprogesterone acetate was associated with elevated risk for HIV acquisition (hazard ratios of 1.40 [95%CI: 1.16–1.69] and 1.50 [95%CI: 1.24–1.83], respectively); however, similar associations were not observed with other forms of hormonal contraception (i.e., combination oral contraceptives, neorethisterone enanthate). Given the widespread use of depot-medroxyprogesterone acetate, there is also need to weigh these risks against the broader benefits in maternal health and mother-to-child HIV transmission [20]. The potential for residual confounding in these analyses is an ongoing concern, particularly given the potential for misclassification around exposure status [21]. A large randomized trial is currently planned and should provide important insight to this complex public health issue [22].

Adolescence is a period of elevated risk for HIV acquisition, particularly for girls, and this has been an area of increased emphasis in programs and research. While many studies have focused on engagement into care [23, 24], including the positive impact of parent involvement [25], broader approaches are needed to address the behavioral, social, and environmental complexities individuals face during this transitional period [26, 27]. Structural interventions may hold promise. Epidemiologic data from the Rakai Community Cohort Study demonstrated significant declines in HIV incidence and reported HIV risk behaviors from 1999 to 2011, encouraging trends that coincided with increases in school enrollment and decline in adolescent marriage, among other factors [28]. The “SHAZ!”

(Shaping the Health of Adolescents in Zimbabwe) trial, for example, provided feasibility data about a combination package that included life-skills and health education, vocational training, micro-grants, and social support. The pilot intervention was effective in modifying risk-related behaviors, including lower risk for transactional sex, higher likelihood of using a condom, and fewer unintended pregnancies [29]. The HIV Prevention Trials Network (HPTN) Protocol 068 is examining the impact of conditional cash transfers for school attendance on HIV incidence among adolescent girls in South Africa. One of the largest of its kind, this study is currently in follow-up, with primary results are anticipated in the coming year.

Preventing unintended pregnancies among HIV-infected women

Prevention of unintended pregnancies among HIV-infected women is a core component to PMTCT efforts globally; however, unmet need for contraception in sub-Saharan Africa remains high [30]. In most settings, this gap reflects a misalignment of patient needs and available services, which can in turn translate into poor uptake of and adherence to family planning services. Several recent studies demonstrate how increased patient engagement may lead to higher utilization rates. In cohort of HIV-serodiscordant and -seroconcordant couples from Zambia and Rwanda, fertility goal-based counseling resulted in significant increases in uptake for intrauterine device and hormonal implants [31]. Similarly, participation in video-based intervention describing family planning methods was associated with decreased incident pregnancy rates, with lower rates observed among women already on contraception [32]. Multiple studies have shown the important association between partner opinion and contraceptive use [33–36], highlighting a role for active male engagement within effective family planning services. In South Africa, researchers also demonstrated higher rates of contraception use as women advanced further along the HIV treatment cascade, a marker of healthcare engagement. Reported use increased from less than 40% among HIV-infected women who did not yet know their status to over 70% among women who were already on ART for several years [37].

While interventions to increase patient-provider interaction may generate demand for family planning, in order to increase uptake, this demand must be met with adequate supply. The availability and accessibility of family planning services are thus critical. Integration of family planning services, within the context of PMTCT or HIV care, has been studied in different settings. Most rigorous has been an 18-site cluster-randomized trial in the Nyanza Province of Kenya. Women seen at integrated sites were more likely to use more effective contraceptive methods (OR: 1.81, 95%CI: 1.24–2.63) but less likely to use condoms (OR: 0.64, 95%CI: 0.35–1.19), though this latter finding was not significant. Pregnancy rates at one year did not differ between the two study arms (OR: 0.90; 95%CI: 0.68–1.20) but, as the authors note, the time was likely insufficient for this outcome [38*]. Community-based approaches for contraception can also extend the reach of traditional facility-based services. Numerous programs have integrated trained community workers into the health workforce, allowing them to distribute oral contraceptive pills and condoms and administer injections [39]. Community pharmacies and drug distribution points could also decongest busy clinics and promote long-term adherence [40]. Even with expanded access, however, it is important to acknowledge the role of the underlying health system for provision of quality family

planning services. Targeted implementation strategies to improve supply chain, health infrastructure, or human resources are urgently needed in many African settings.

Preventing mother-to-child transmission of HIV

First developed and implemented in Malawi [41], the so-called Option B+ strategy to provide universal lifelong ART to pregnant and breastfeeding women has now been adopted in many African countries [42]. A key rationale for Option B+ among policymakers has been the simplification of PMTCT strategies and better alignment to adult treatment guidelines [43]. Formative work by Ngarina, et al. suggests that patients share similar preferences. In qualitative interviews and focus group discussions of Tanzanian mothers, universal maternal ART was preferred over daily continuous infant nevirapine prophylaxis during breastfeeding because of the potential for reduced stigma and enhanced adherence [44]. As combination antiretroviral regimens become the sole standard of care for PMTCT in many settings, however, there may be unanticipated consequences to this streamlined public health approach. Researchers have identified a significant proportion – up to 15% in some studies [45] – who decline maternal combination regimens outright; another group silently defaults from care [46]. Without viable alternatives, these women may not receive any antiretroviral interventions to reduce HIV transmission to their infants. In Botswana, researchers found a significant increase in ART uptake following the introduction of universal maternal combination regimens for PMTCT (adjusted odds ratio [OR]: 2.59, 95%CI: 2.25–2.98), but this was accompanied by a twofold for receiving no PMTCT intervention at all (adjusted OR: 2.10, 95%CI: 1.74–2.53). The net result was a projected increase in mother-to-child transmission at 6 months of age at the population level, from 3.8% to 4.7% [47].

The rapid adoption of Option B+ into policy has presented unique implementation challenges. Because its introduction has been relatively recent, few published studies to date have examined the contextual issues (e.g., health infrastructure, community characteristics, stigma) related directly to the strategy. Nevertheless, lessons can be adopted from the broader PMTCT literature. Despite significant investments in community-based HIV education and sensitization, for example, stigma persists. A systematic review by Gourlay and colleagues highlighted the critical role of stigma and fear of status disclosure as major barriers to health-seeking behaviors for PMTCT [48**]. Work by Kohler, et al. demonstrated the high levels of stigma and discrimination in Kenya, with most HIV-positive women (89%) reporting blame or judgment of people with HIV. Feelings of shame were significantly associated with decreased likelihood of maternal HIV testing, completing courses of antiretroviral prophylaxis, and infant HIV testing [49]. In Tanzania, patients reported a lack of supportive communication around PMTCT and, for some, healthcare providers were viewed as potentially breaching confidentiality around HIV status [50]. Interventions designed to address these problems – and their community perceptions – are needed to improve uptake of PMTCT services.

Research on supply-side interventions provides additional insight. Several themes emerge from the recent medical literature. A holistic view of the PMTCT continuum of care is needed in order to realize the full potential of Option B+ at a population level. While there

has been great emphasis on the initiation of and adherence to ART, earlier steps in the "PMTCT cascade" – e.g., entry into antenatal care, consent to HIV testing – can also have significant downstream impact on reducing pediatric HIV [51]. For example, although pregnancy is increasingly recognized as a high-risk period for HIV acquisition [16], repeat maternal HIV testing to identify new infections during pregnancy and breastfeeding continues to be overlooked [52, 53].

Alternate entry points are needed outside of traditional facility-based services for PMTCT. In a randomized study of home- versus facility-based HIV testing, couples allocated to the home visit arm were more likely to test for HIV together (85% vs. 36%, $p<0.001$); in addition, more HIV-seropositive men (12% vs. 8%, $p=0.25$) and more HIV-discordant couples (15% vs. 5%, $p=0.003$) were identified through the home-based strategy [54*]. Similarly, the cluster-randomized "Goodstart" study showed positive outcomes with structured community-based support during pregnancy and breastfeeding. At 12 weeks of age, women in the intervention arm reported higher rates of exclusive breastfeeding and increased infant weight and length for age z-scores, but HIV-free survival (a primary outcome) did not differ significantly between groups [55]. Entry into PMTCT from novel venues such as church congregations are encouraging and currently under study [56].

Task-shifting strategies hold promise, particularly where human resources are limited, but their overall public health benefit may depend on the extent to which they can be implemented. In one study in Malawi, trained traditional birth attendants referred nearly all HIV-infected patients to health centers; however, the patient transportation to the health center and provider tracking of referrals were persistent challenges [57]. Similar work in rural Mozambique demonstrated increases in referral to health facilities when traditional healers underwent a structured educational intervention; however, the overall rates remained low [58]. In South Africa's Free State, a 32-facility cluster-randomized studied the impact of lay health worker support at the facility level, which included health promotion sessions, one-one-meetings to promote HIV testing and linkages to care, and targeted HIV education. The intervention was not associated with improved PMTCT uptake across most indicators, except for antenatal HIV retesting at 32 weeks gestation, where a modest but significant increase was observed (adjusted OR: 1.34, 95%CI: 1.01–1.77) [59].

While efforts have been made to understand the population impact of PMTCT services [60–62], their translation into practical interventions for frontline providers has been more limited. Gimbel and colleagues designed a simple, Excel-based spreadsheet to reconstruct the PMTCT cascade at the facility level, using commonly collected program indicators [63]. Integration of this tool into ongoing monitoring and evaluation activities could result in tailored, context-specific responses to local challenges. Similarly, formal quality improvement approaches could provide a structured framework for targeted interventions. Several pilot studies have been conducted in PMTCT to date [64, 65]; a larger cluster-randomized trial in Kenya, Mozambique, and Cote d'Ivoire is currently studying this very question [66].

Linking HIV-infected women to long-term care

By simplifying the criteria for ART eligibility, the Option B+ approach reduces bottlenecks for treatment initiation. While the absolute numbers of women initiating ART have increased, there remain considerable challenges for short- and long-term retention in care. Nearly one-fifth (17%) of women initiating Option B+ in Malawi had become lost to follow-up (LTFU) by 6 months on treatment, with significant heterogeneity between sites. When compared to women who started ART because of low CD4 counts and/or advanced clinical staging, those who started therapy during pregnancy were five times more likely to never return following their initial visit (OR: 5.0, 95%CI: 4.2–6.1) [67]. In a retrospective cohort from Cape Town, South Africa, approximately one-third of women who initiated ART during pregnancy had disengaged from care in the 6 months following delivery, with higher rates observed in the postpartum period than in pregnancy (6.2 vs. 2.4 per 100 woman-months, $p<0.0001$) [68]. In separate qualitative studies, commonly reported reasons for stopping ART included travel, cost of transportation, conflicts with work commitments, negative treatment from health providers, and stigma [46, 69].

Poor long-term adherence and retention can threaten the expected maternal health benefits of Option B+. Women who prematurely interrupt lifelong treatment risk viral rebound and disease progression; poor adherence may select for drug resistant HIV variants, which can later comprise treatment when ART is re-initiated. In addition, a purported benefit of Option B+ is the decreased risk for mother-to-child transmission in future pregnancies, since the initiation of ART prior to conception should lead to prolonged viral suppression. In a cross-sectional study of pregnant South African women, however, nearly one-quarter who reported initiated ART prior to conception had detectable viremia at first antenatal visit [70].

Several have sought to better understand the impact of health delivery on patient retention in care. In one novel study, von Lettow and colleagues compared four distinct models of Option B+ delivery in the South East Zone of Malawi, to determine which was associated with the best retention outcomes. These “models of care” were categorized as follows: facilities where newly identified HIV-positive women initiate and continue ART within antenatal care until delivery (Model A, n=75), facilities where newly identified HIV-positive women receive their first does of ART at the antenatal clinic but are then referred to the adult ART services for long-term care (Model B, n=38), facilities where newly identified HIV-positive women are referred from ART clinic for initiation and follow-up of ART (Model C, n=18), and facilities serving as referral sites, without antenatal services (Model D, n=9). Compared to Model B, facilities based on Model C was more than five times more likely to have retention rates of >92% (adjusted OR: 5.4, 95%CI: 1.2–28.0). Model A (adjusted OR: 3.0, 95%CI: 0.7–12) and Model D (adjusted OR: 9.1, 95%CI: 0.9–84) also appeared promising, though comparisons did not reach statistical significance [71**]. Although the authors note important limitations with this analysis – including geographic focus on a single region of Malawi, a relatively small number of facilities for the extensive multivariable analysis, and the potential selection bias for Models C and D because of a lack of linkage data – this nevertheless provides important insights into how service delivery models may influence PMTCT program performance.

The specific interventions proposed for improving retention in Option B+ largely mirror those described for the general HIV treatment. A systematic review conducted by Govindasamy and colleagues demonstrated encouraging early findings for a number of promising interventions; however, the majority of published studies relied on data from observational cohorts and the overall evidence base was judged to be low [72]. Results from numerous ongoing trials – to be completed in the coming years – is expected to improve our understanding of these strategies applied to the context of Option B+ [73, 74].

Linking HIV-infected infants to long-term care

Initiation of ART in HIV-infected children within the first 12 weeks of life reduces mortality and HIV progression by 75% [75]. Universal HIV treatment is now recommended for HIV-infected children under five years of age [2], but less than one-quarter of HIV-infected children ever start [4]. A major barrier has been the timely HIV screening through early infant diagnosis (EID) programs and, for those who are diagnosed with HIV, linkages to long-term pediatric care.

Despite increased investments in health infrastructure, EID testing among HIV-exposed infants remains low in sub-Saharan Africa. The technology needed to accurately diagnose newborns (i.e., HIV DNA PCR) is technically complex and limited mostly to reference laboratories. Where it does exist, the time from sample collection to results reporting can be lengthy [76]. A recent chart review in rural Zambia showed that the median time from specimen collection to results reporting was 92 days (IQR: 84, 145) [77]. In Uganda, length of turnaround time, HIV testing point, and child age at sample collection further influenced receipt of infant HIV result [78]. Several approaches have been undertaken to increase EID testing and improve results reporting. Expanding services to different venue types has helped to increase access to HIV-exposed infants of differing demographic and clinical characteristics [79]. In Malawi, for example, EID testing at immunization points provided access to younger HIV-exposed children, higher uptake of HIV testing, and better linkages to subsequent care when compared to traditional “under-5” clinics [80]. Seidenberg and colleagues used a mobile phone-based system to transmit EID test results from a central laboratory to health facilities. Over a 19-month observation window, the intervention reduced the time of results reporting from 44 days to 27 days [81]. Point-of-care technologies hold great promise in this arena [82, 83], but trials of their effective field implementation are still ongoing.

Infant HIV testing provides an important entry point for pediatric HIV care. In order to avert the clinical complications of HIV infection, however, timely linkage to and retention in clinical services are paramount. A number of studies have characterized the magnitude of this problem. A meta-analysis performed by Sibanda, et al. found that one-third of newborn infants was LTFU by 3 months following delivery. In a subset of five eligible studies, 46% of children were lost following infant HIV testing [84]. In South Africa's Western Cape, a retrospective analysis of laboratory data showed a steady increase in successful linkages to care from 2005 to 2010; however, the peak of 71% (reported in 2010) remains modest and demonstrates significant room for improvement [85]. At present, there have been few

intervention studies targeting these critical steps along the continuum of care; as such, the evidence base for effective program implementation remains relatively sparse.

New directions in PMTCT implementation research

We provide a survey of new research conducted within the field of PMTCT. Although each prong faces unique challenges, we observed numerous cross-cutting clinical and public health themes, each representing an opportunity for future work. Health service delivery must be optimized in ways that improve access to populations in need and increase retention once they are engaged in care. Commonly evaluated approaches have incorporated human resource (e.g., lay workers) and technology-based (e.g., mobile phone reminders) components; while these have shown to be effective in a number of settings, their incorporation into broader structural approaches appear highly promising. Active linkage strategies between health services – including integration where possible – are urgently needed. Appropriate dissemination and engagement among stakeholders can help to ensure that lessons learned from addressing one prong of PMTCT can be appropriately considered, adapted, and implemented for others.

To provide ongoing safety and effectiveness data, there is need for ongoing clinical surveillance within newly implemented health services. For example, recent work by Scarsi and colleagues suggested higher rates of contraceptive failure with efavirenz-based regimens, possibly due to pharmacokinetic interactions [86]. Early results from the multi-center IMPAACT PROMISE study demonstrated higher rates of preterm birth and low birthweight infants among women using three-drug combination regimens during pregnancy, compared to those on short-course zidovudine and intrapartum nevirapine [87]. In both cases, population-level data would greatly enhance our understanding about the “real world” impact of such interventions, while providing the framework to evaluate new interventions developed to address them.

The design of new implementation strategies must consider not only the target populations, but also the context in which they reside. The case of female-initiated pre-exposure prophylaxis for HIV prevention is illustrative. These interventions – either administered orally or applied vaginally – were developed to engage women in settings where social and cultural norms may limit individual medical decision-making. After a series of negative randomized trials [88–90], however, it appears that aspects of study context (e.g., acceptability, patient preferences) were inadequately addressed [91*]. This may have led to poor adherence and a possible confounding of the intervention's biological effect. Similarly, several studies have reported significant proportions of women who refuse PMTCT services outright, or silently default from care, when not fully prepared to initiate lifelong ART during pregnancy. Resource-appropriate tools could be used to assess ART readiness and appropriately triage women to different intensities of provider and peer support in the critical window immediately following treatment initiation. Finally, when context is well characterized and understood, even simple interventions can result in significant impact. In a randomized trial in Malawi, for example, Nyondo and colleagues showed that a basic invitation card directed at partners increased levels of male involvement at later antenatal and PMTCT visits [92].

We also advocate for better integration of implementation science principles into ongoing PMTCT research. While the evaluation of program strategies has been common in PMTCT clinical and epidemiologic studies, it is only recently that HIV researchers have engaged implementation scientists to better understand the discipline. This is reflected in the diversity of projects included in this review. Although most of our referenced studies would be loosely termed “implementation research” within the HIV scientific community, central tenets of implementation research were often poorly articulated or missing altogether. For example, context (i.e., components of the social, cultural, economic, political, legal, and physical environment in which implementation took place) features prominently in the early design of implementation strategies, since interventions must be adapted to the setting in which they are carried out. Description of key contextual features is important to understanding why interventions may or may not work in a given setting; if shown to be effective, these characteristics may also help others looking to adapt the intervention to their individual setting [93]. Fidelity – the extent to which program implementation meets the original expectation of its designers [94] – should also be routinely measured in implementation studies. Without this information, it may be difficult to differentiate between ineffective interventions and otherwise promising strategies that have not been fully implemented (also known as a “Type III” error [95]). Structured reporting of implementation strategies, similar to CONSORT statement for clinical research, is needed [96]. Such standardization, could greatly improve the quality of implementation research literature while ensuring that complex strategies are adaptable and scalable in other global settings.

Conclusion

Significant investments in PMTCT implementation research have led to new and important advancements in the field. Nevertheless, there remain many unanswered questions in the realm of implementation that must be urgently addressed. Those conducting such studies should incorporate implementation research principles and frameworks to inform the development of context-relevant PMTCT strategies [97]. Finally, it is not enough to have the goal of effective implementation without addressing the sustainability of evidence-based PMTCT interventions in real world settings [98]. By considering these factors holistically, we will move more rapidly towards our ultimate goal of eliminating pediatric HIV and improving the lives of mothers and infants through the implementation of effective, well-designed public health programs.

Acknowledgments

This work was funded in part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01 HD075131). Trainee support was provided by the Doris Duke Charitable Foundation Clinical Research Mentorship Program.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance •• Of major importance

1. Chi BH, Stringer JS, Moodley D. Antiretroviral Drug Regimens to Prevent Mother-To-Child Transmission of HIV: A Review of Scientific, Program, and Policy Advances for Sub-Saharan Africa. Curr HIV/AIDS Rep. 2013
2. World Health Organization. [Accessed March 8, 2015] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. http://www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html
3. Chi BH, Adler MR, Bolu O, Mbori-Ngacha D, Ekouevi DK, Gieselman A, et al. Progress, challenges, and new opportunities for the prevention of mother-to-child transmission of HIV under the US President's Emergency Plan for AIDS Relief. J Acquir Immune Defic Syndr. 2012; 60(Suppl 3):S78–87. [PubMed: 22797744]
4. Joint United Nations Programme on HIV/AIDS. [Accessed March 7, 2015] Progress Report on the Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive. 2014. http://www.unaids.org/sites/default/files/media_asset/JC2385_ProgressReportGlobalPlan_en_0.pdf
5. Woolf SH, Johnson RE. Inattention to the fidelity of health care delivery is costing lives. Am J Public Health. 2007; 97:1732–1733. author reply 1733. [PubMed: 17761559]
6. Leroy JL, Habicht JP, Pelto G, Bertozzi SM. Current priorities in health research funding and lack of impact on the number of child deaths per year. Am J Public Health. 2007; 97:219–223. [PubMed: 17194855]
7. Schackman BR. Implementation science for the prevention and treatment of HIV/AIDS. J Acquir Immune Defic Syndr. 2010; 55(Suppl 1):S27–31. [PubMed: 21045596]
8. Glasgow RE, Eckstein ET, Elzarrad MK. Implementation science perspectives and opportunities for HIV/AIDS research: integrating science, practice, and policy. J Acquir Immune Defic Syndr. 2013; 63(Suppl 1):S26–31. [PubMed: 23673882]
9. Padian NS, Holmes CB, McCoy SI, Lyerla R, Bouey PD, Goosby EP. Implementation science for the US President's Emergency Plan for AIDS Relief (PEPFAR). J Acquir Immune Defic Syndr. 2011; 56:199–203. [PubMed: 21239991]
10. Rabin BA, Brownson RC, Haire-Joshu D, Kreuter MW, Weaver NL. A glossary for dissemination and implementation research in health. J Public Health Manag Pract. 2008; 14:117–123. [PubMed: 18287916]
11. Glasgow RE, Vinson C, Chambers D, Khoury MJ, Kaplan RM, Hunter C. National Institutes of Health approaches to dissemination and implementation science: current and future directions. Am J Public Health. 2012; 102:1274–1281. [PubMed: 22594758] ** This paper outlines a conceptual framework for dissemination and implementation science, reviews the terminology used within the discipline, and descrbes core values that should underpin future work in the field.
12. Peters, DH.; Tran, NT.; Adam, T. Implementation research in health: a practical guide. WHO Press; Geneva: 2013.
13. Vermund SH, Hayes RJ. Combination prevention: new hope for stopping the epidemic. Curr HIV/AIDS Rep. 2013; 10:169–186. [PubMed: 23456730]
14. Brown JL, Sales JM, DiClemente RJ. Combination HIV prevention interventions: the potential of integrated behavioral and biomedical approaches. Curr HIV/AIDS Rep. 2014; 11:363–375. [PubMed: 25216985]
15. Roxby AC, Unger JA, Slyker JA, Kinuthia J, Lewis A, John-Stewart G, et al. A lifecycle approach to HIV prevention in African women and children. Curr HIV/AIDS Rep. 2014; 11:119–127. [PubMed: 24659344]
16. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med. 2014; 11:e1001608. [PubMed: 24586123] * This paper reviews the emerging literature about HIV acquisition during pregnancy and breastfeeding and, through a meta-analysis, provides pooled estimates for HIV incidence over these at-risk periods.
17. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. JAMA. 2014; 312:362–371. [PubMed: 25038355]

18. Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies. Lancet Infect Dis. 2015
19. Morrison CS, Chen PL, Kwok C, Baeten JM, Brown J, Crook AM, et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. PLoS Med. 2015; 12:e1001778. [PubMed: 25612136]
20. Colvin CJ, Harrison A. Broadening the debate over HIV and hormonal contraception. Lancet Infect Dis. 2015
21. McCoy SI, Ralph LJ, Padian NS, Minnis AM. Are hormonal contraceptive users more likely to misreport unprotected sex? Evidence from a biomarker validation study in Zimbabwe. AIDS Behav. 2014; 18:2259–2264. [PubMed: 24619603]
22. Rees H, The Echo Consortium. DMPA and HIV: why we need a trial. Contraception. 2014; 90:354–356. [PubMed: 25183263]
23. Ramirez-Avila L, Nixon K, Noubary F, Giddy J, Losina E, Walensky RP, et al. Routine HIV testing in adolescents and young adults presenting to an outpatient clinic in Durban, South Africa. PLoS One. 2012; 7:e45507. [PubMed: 23029060]
24. Nkala B, Khunwane M, Dietrich J, Otwombe K, Sekoane I, Sonqishe B, et al. Kganya Motsha Adolescent Centre: a model for adolescent friendly HIV management and reproductive health for adolescents in Soweto, South Africa. AIDS Care. 2015:1–6.
25. Stanton B, Wang B, Deveaux L, Lunn S, Rolle G, Li X, et al. Assessing the Effects of a Complementary Parent Intervention and Prior Exposure to a Preadolescent Program of HIV Risk Reduction for Mid-Adolescents. Am J Public Health. 2015; 105:575–583. [PubMed: 25602877]
26. Pettifor A, Nguyen NL, Celum C, Cowan FM, Go V, Hightow-Weidman L. Tailored combination prevention packages and PrEP for young key populations. J Int AIDS Soc. 2015; 18:19434. [PubMed: 25724507]
27. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. J Int AIDS Soc. 2015; 18:19408. [PubMed: 25724504]
28. Santelli JS, Edelstein ZR, Wei Y, Mathur S, Song X, Schuyler A, et al. Trends in HIV acquisition, risk factors and prevention policies among youth in Uganda, 1999–2011. AIDS. 2015; 29:211–219. [PubMed: 25535753]
29. Dunbar MS, Kang Dufour MS, Lambdin B, Mudekunye-Mahaka I, Nhamo D, Padian NS. The SHAZ! project: results from a pilot randomized trial of a structural intervention to prevent HIV among adolescent women in Zimbabwe. PLoS One. 2014; 9:e113621. [PubMed: 25415455]
30. Sarnquist CC, Rahangdale L, Maldonado Y. Reproductive health and family planning needs among HIV-infected women in Sub-Saharan Africa. Curr HIV Res. 2013; 11:160–168. [PubMed: 23432491]
31. Khu NH, Vwalika B, Karita E, Kilembe W, Bayingana RA, Sitrin D, et al. Fertility goal-based counseling increases contraceptive implant and IUD use in HIV-discordant couples in Rwanda and Zambia. Contraception. 2013; 88:74–82. [PubMed: 23153896]
32. Wall KM, Vwalika B, Haddad L, Khu NH, Vwalika C, Kilembe W, et al. Impact of long-term contraceptive promotion on incident pregnancy: a randomized controlled trial among HIV-positive couples in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2013; 63:86–95. [PubMed: 23202814]
33. Imbuki K, Todd CS, Stibich MA, Shaffer DN, Sinei SK. Factors influencing contraceptive choice and discontinuation among HIV-positive women in Kericho, Kenya. Afr J Reprod Health. 2010; 14:98–109. [PubMed: 21812203]
34. Laryea DO, Amoako YA, Spangenberg K, Frimpong E, Kyei-Ansong J. Contraceptive use and unmet need for family planning among HIV positive women on antiretroviral therapy in Kumasi, Ghana. BMC Womens Health. 2014; 14:126. [PubMed: 25306546]
35. Haddad L, Wall KM, Vwalika B, Khu NH, Brill I, Kilembe W, et al. Contraceptive discontinuation and switching among couples receiving integrated HIV and family planning services in Lusaka, Zambia. AIDS. 2013; 27(Suppl 1):S93–103. [PubMed: 24088689]
36. Patel R, Baum S, Grossman D, Steinfeld R, Onono M, Cohen C, et al. HIV-positive men's experiences with integrated family planning and HIV services in western Kenya: integration fosters male involvement. AIDS Patient Care STDS. 2014; 28:418–424. [PubMed: 24927494]

37. Raifman J, Chetty T, Tanser F, Mutevedzi T, Matthews P, Herbst K, et al. Preventing unintended pregnancy and HIV transmission: effects of the HIV treatment cascade on contraceptive use and choice in rural KwaZulu-Natal. J Acquir Immune Defic Syndr. 2014; 67(Suppl 4):S218–227. [PubMed: 25436821]

38. Grossman D, Onono M, Newmann SJ, Blat C, Bukusi EA, Shade SB, et al. Integration of family planning services into HIV care and treatment in Kenya: a cluster-randomized trial. AIDS. 2013; 27(Suppl 1):S77–85. [PubMed: 24088687] * This cluster-randomized trial compared a strategy of integrated family planning and HIV services to the standard of care (i.e., non-integrated services) to determine whether this approach increased uptake of contraception among HIV-infected women.

39. Malarcher S, Meirik O, Lebetkin E, Shah I, Spieler J, Stanback J. Provision of DMPA by community health workers: what the evidence shows. Contraception. 2011; 83:495–503. [PubMed: 21570545]

40. Malangu N. The future of community pharmacy practice in South Africa in the light of the proposed new qualification for pharmacists: implications and challenges. Glob J Health Sci. 2014; 6:226–233. [PubMed: 25363125]

41. Schouten EJ, Jahn A, Midiani D, Makombe SD, Mnthambala A, Chirwa Z, et al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. Lancet. 2011; 378:282–284. [PubMed: 21763940]

42. Kieffer MP, Mattingly M, Giphart A, van de Ven R, Chouraya C, Walakira M, et al. Lessons learned from early implementation of option B+: the Elizabeth Glaser Pediatric AIDS Foundation experience in 11 African countries. J Acquir Immune Defic Syndr. 2014; 67(Suppl 4):S188–194. [PubMed: 25436817]

43. Ahmed S, Kim MH, Abrams EJ. Risks and benefits of lifelong antiretroviral treatment for pregnant and breastfeeding women: a review of the evidence for the Option B+ approach. Curr Opin HIV AIDS. 2013; 8:473–488.

44. Ngarina M, Tarimo EA, Naburi H, Kilewo C, Mwanyika-Sando M, Chalamilla G, et al. Women's preferences regarding infant or maternal antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV during breastfeeding and their views on Option B+ in Dar es Salaam, Tanzania. PLoS One. 2014; 9:e85310. [PubMed: 24465532]

45. Kim, MH.; Ahmed, S.; Kazembe, PN.; Hosseinipour, M.; Giordano, TP.; Chiao, EY., et al. Impact of Option B+ on uptake, retention, and transmission: a pre/post study in Lilongwe, Malawi [Abstract 883]. 2014 Conference on Retroviruses and Opportunistic Infections; Boston, MA. 2014.

46. Tweya H, Gugsa S, Hosseinipour M, Speight C, Ng'ambi W, Bokosi M, et al. Understanding factors, outcomes and reasons for loss to follow-up among women in Option B+ PMTCT programme in Lilongwe, Malawi. Trop Med Int Health. 2014

47. Dryden-Peterson S, Lockman S, Zash R, Lei Q, Chen JY, Souda S, et al. Initial Programmatic Implementation of WHO Option B in Botswana Associated With Increased Projected MTCT. J Acquir Immune Defic Syndr. 2015; 68:245–249. [PubMed: 25501611]

48. Gourlay A, Birdthistle I, Mburu G, Iorpenda K, Wringe A. Barriers and facilitating factors to the uptake of antiretroviral drugs for prevention of mother-to-child transmission of HIV in sub-Saharan Africa: a systematic review. J Int AIDS Soc. 2013; 16:18588. [PubMed: 23870277] ** This systematic review synthesizes the existing medial literature around uptake, initiation, and adherence to PMTCT services in African settings.

49. Kohler PK, Ondenge K, Mills LA, Okanda J, Kinuthia J, Olilo G, et al. Shame, guilt, and stress: Community perceptions of barriers to engaging in prevention of mother to child transmission (PMTCT) programs in western Kenya. AIDS Patient Care STDS. 2014; 28:643–651. [PubMed: 25361205]

50. Gourlay A, Wringe A, Birdthistle I, Mshana G, Michael D, Urassa M. “It is like that, we didn't understand each other”: exploring the influence of patient-provider interactions on prevention of mother-to-child transmission of HIV service use in rural Tanzania. PLoS One. 2014; 9:e106325. [PubMed: 25180575]

51. Stringer EM, Chi BH, Chintu N, Creek TL, Ekouevi DK, Coetzee D, et al. Monitoring effectiveness of programmes to prevent mother-to-child HIV transmission in lower-income countries. Bull World Health Organ. 2008; 86:57–62. [PubMed: 18235891]

52. Heemelaar S, Habets N, Makukula Z, van Roosmalen J, van den Akker T. Repeat HIV testing during pregnancy and delivery: missed opportunities in a rural district hospital in Zambia. Trop Med Int Health. 2015; 20:277–283. [PubMed: 25418130]

53. Technau KG, Kalk E, Coovadia A, Black V, Pickerill S, Mellins CA, et al. Timing of maternal HIV testing and uptake of prevention of mother-to-child transmission interventions among women and their infected infants in Johannesburg, South Africa. J Acquir Immune Defic Syndr. 2014; 65:e170–178. [PubMed: 24759066]

54. Osoti AO, John-Stewart G, Kiarie J, Richardson B, Kinuthia J, Krakowiak D, et al. Home visits during pregnancy enhance male partner HIV counselling and testing in Kenya: a randomized clinical trial. AIDS. 2014; 28:95–103. [PubMed: 23942059] * This randomized study evaluated a home-based strategy for HIV counseling and testing as a means to increase male partner engagement and mutual disclosure of HIV status

55. Tomlinson M, Doherty T, Ijumba P, Jackson D, Lawn J, Persson LA, et al. Goodstart: a cluster randomised effectiveness trial of an integrated, community-based package for maternal and newborn care, with prevention of mother-to-child transmission of HIV in a South African township. Trop Med Int Health. 2014; 19:256–266. [PubMed: 24433230]

56. Ezeanolue EE, Obiefune MC, Yang W, Obaro SK, Ezeanolue CO, Ogedegbe GG. Comparative effectiveness of congregation- versus clinic-based approach to prevention of mother-to-child HIV transmission: study protocol for a cluster randomized controlled trial. Implement Sci. 2013; 8:62. [PubMed: 23758933]

57. Hamela G, Kabondo C, Tembo T, Zimba C, Kamanga E, Mofolo I, et al. Evaluating the benefits of incorporating traditional birth attendants in HIV prevention of mother to child transmission service delivery in Lilongwe, Malawi. Afr J Reprod Health. 2014; 18:27–34. [PubMed: 24796166]

58. Audet CM, Salato J, Blevins M, Amsalem D, Vermund SH, Gaspar F. Educational intervention increased referrals to allopathic care by traditional healers in three high HIV-prevalence rural districts in Mozambique. PLoS One. 2013; 8:e70326. [PubMed: 23936407]

59. Stinson, K.; van Zyl, D.; Mdebuka, H.; Zeelie, JP.; Boateng, M.; Colvin, CJ., et al. Lay health worker support to strengthen PMTCT: a randomised controlled trial in South Africa [Abstract 886]. 2014 Conference on Retroviruses and Opportunistic Infections; Boston, MA. 2014.

60. Stringer EM, Ekouevi DK, Coetzee D, Tih PM, Creek TL, Stinson K, et al. Coverage of nevirapine-based services to prevent mother-to-child HIV transmission in 4 African countries. JAMA. 2010; 304:293–302. [PubMed: 20639563]

61. Stringer JS, Stinson K, Tih PM, Giganti MJ, Ekouevi DK, Creek TL, et al. Measuring Coverage in MNCH: Population HIV-Free Survival among Children under Two Years of Age in Four African Countries. PLoS Med. 2013; 10:e1001424. [PubMed: 23667341]

62. Goga AE, Dinh TH, Jackson DJ, Lombard C, Delaney KP, Puren A, et al. First population-level effectiveness evaluation of a national programme to prevent HIV transmission from mother to child, South Africa. J Epidemiol Community Health. 2015; 69:240–248. [PubMed: 25371480]

63. Gimbel S, Voss J, Mercer MA, Zierler B, Gloyd S, Coutinho Mde J, et al. The prevention of mother-to-child transmission of HIV cascade analysis tool: supporting health managers to improve facility-level service delivery. BMC Res Notes. 2014; 7:743. [PubMed: 25335783]

64. Bhardwaj S, Barron P, Pillay Y, Treger-Slavin L, Robinson P, Goga A, et al. Elimination of mother-to-child transmission of HIV in South Africa: rapid scale-up using quality improvement. S Afr Med J. 2014; 104:239–243. [PubMed: 24893500]

65. Mate KS, Ngubane G, Barker PM. A quality improvement model for the rapid scale-up of a program to prevent mother-to-child HIV transmission in South Africa. Int J Qual Health Care. 2013; 25:373–380. [PubMed: 23710069]

66. Sherr K, Gimbel S, Rustagi A, Nduati R, Cuembelo F, Farquhar C, et al. Systems analysis and improvement to optimize pMTCT (SAIA): a cluster randomized trial. Implement Sci. 2014; 9:55. [PubMed: 24885976]

67. Tenthani L, Haas AD, Tweya H, Jahn A, van Oosterhout JJ, Chimbwandira F, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('Option B+') in Malawi. AIDS. 2014; 28:589–598. [PubMed: 24468999]

68. Phillips T, Thebus E, Bekker LG, McIntyre J, Abrams EJ, Myer L. Disengagement of HIV-positive pregnant and postpartum women from antiretroviral therapy services: a cohort study. J Int AIDS Soc. 2014; 17:19242. [PubMed: 25301494]
69. Clouse K, Schwartz S, Van Rie A, Bassett J, Yende N, Pettifor A. "What they wanted was to give birth; nothing else": barriers to retention in option B+ HIV care among postpartum women in South Africa. J Acquir Immune Defic Syndr. 2014; 67:e12–18. [PubMed: 24977376]
70. Myer, L.; Phillips, T.; Zerbe, A.; Hsiao, M.; McIntyre, J.; Abrams, E. Detectable viremia among pregnant women on antiretroviral therapy initiating antenatal care [Abstract 874]. 2014 Conference on Retroviruses and Opportunistic Infections; Boston, MA. 2014.
71. van Lettow M, Bedell R, Mayuni I, Mateyu G, Landes M, Chan AK, et al. Towards elimination of mother-to-child transmission of HIV: performance of different models of care for initiating lifelong antiretroviral therapy for pregnant women in Malawi (Option B+). J Int AIDS Soc. 2014; 17:18994. [PubMed: 25079437] ** This novel study compared different models of service delivery across key indicators of PMTCT site performance
72. Govindasamy D, Meghij J, Kebede Negussi E, Clare Baggaley R, Ford N, Kranzer K. Interventions to improve or facilitate linkage to or retention in pre-ART (HIV) care and initiation of ART in low- and middle-income settings--a systematic review. J Int AIDS Soc. 2014; 17:19032. [PubMed: 25095831]
73. Rollins N, Chanza H, Chimbwandira F, Eliya M, Nyasulu I, Thom E, et al. Prioritizing the PMTCT implementation research agenda in 3 African countries: INtegrating and Scaling up PMTCT through Implementation REsearch (INSPIRE). J Acquir Immune Defic Syndr. 2014; 67(Suppl 2):S108–113. [PubMed: 25310115]
74. Sturke R, Harmston C, Simonds RJ, Mofenson LM, Siberry GK, Watts DH, et al. A Multi-Disciplinary Approach to Implementation Science: The NIH-PEPFAR PMTCT Implementation Science Alliance. J Acquir Immune Defic Syndr. 2014; 67(Suppl 2):S163–167. [PubMed: 25310124]
75. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008; 359:2233–2244. [PubMed: 19020325]
76. Ciaranello AL, Park JE, Ramirez-Avila L, Freedberg KA, Walensky RP, Leroy V. Early infant HIV-1 diagnosis programs in resource-limited settings: opportunities for improved outcomes and more cost-effective interventions. BMC Med. 2011; 9:59. [PubMed: 21599888]
77. Sutcliffe CG, van Dijk JH, Hamangaba F, Mayani F, Moss WJ. Turnaround time for early infant HIV diagnosis in rural Zambia: a chart review. PLoS One. 2014; 9:e87028. [PubMed: 24475214]
78. Mugambi ML, Deo S, Kekitiinwa A, Kiyaga C, Singer ME. Do diagnosis delays impact receipt of test results? Evidence from the HIV early infant diagnosis program in Uganda. PLoS One. 2013; 8:e78891. [PubMed: 24282502]
79. Preidis GA, McCollum ED, Kamiyango W, Garbino A, Hosseinipour MC, Kazembe PN, et al. Routine inpatient provider-initiated HIV testing in Malawi, compared with client-initiated community-based testing, identifies younger children at higher risk of early mortality. J Acquir Immune Defic Syndr. 2013; 63:e16–22. [PubMed: 23364511]
80. McCollum ED, Johnson DC, Chasela CS, Siwande LD, Kazembe PN, Olson D, et al. Superior uptake and outcomes of early infant diagnosis of HIV services at an immunization clinic versus an "under-five" general pediatric clinic in Malawi. J Acquir Immune Defic Syndr. 2012; 60:e107–110. [PubMed: 22614897]
81. Seidenberg P, Nicholson S, Schaefer M, Semrau K, Bweupe M, Masese N, et al. Early infant diagnosis of HIV infection in Zambia through mobile phone texting of blood test results. Bull World Health Organ. 2012; 90:348–356. [PubMed: 22589568]
82. Jani IV, Meggi B, Mabunda N, Vubil A, Sitoe NE, Tobaiwa O, et al. Accurate early infant HIV diagnosis in primary health clinics using a point-of-care nucleic acid test. J Acquir Immune Defic Syndr. 2014; 67:e1–4. [PubMed: 24933096]
83. Reid SD, Fidler SJ, Cooke GS. Tracking the progress of HIV: the impact of point-of-care tests on antiretroviral therapy. Clin Epidemiol. 2013; 5:387–396. [PubMed: 24124392]

84. Sibanda EL, Weller IV, Hakim JG, Cowan FM. The magnitude of loss to follow-up of HIV-exposed infants along the prevention of mother-to-child HIV transmission continuum of care: a systematic review and meta-analysis. AIDS. 2013; 27:2787–2797. [PubMed: 24056068]

85. Hsiao NY, Stinson K, Myer L. Linkage of HIV-infected infants from diagnosis to antiretroviral therapy services across the Western Cape, South Africa. PLoS One. 2013; 8:e55308. [PubMed: 23405133]

86. Scarsi, KK.; Darin, KM.; Nakalema, S.; Back, D.; Byakika-Kibwika, P.; Else, L., et al. Levonorgestrel implact + EFV-based ART: unintended pregannncies and associated PK data [Abstract 85LB]. 2015 Conference on Retroviruses and Opportunistic Infections; Seattle, WA. 2015.

87. Fowler, MG.; Qin, M.; Fiscus, SA.; Currier, JS.; Makanani, B.; Martinson, F., et al. PROMISE: efficacy and safety of 2 strategies to prevent perinatal HIV transmission [Abstract 31LB]. 2015 Conference on Retroviruses and Opportunistic Infections; Seattle, WA. 2015.

88. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012; 367:411–422. [PubMed: 22784040]

89. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015; 372:509–518. [PubMed: 25651245]

90. Rees, H.; Delany-Moretlwe, SA.; Lombard, C.; Baron, D.; Panchia, R.; Myer, L., et al. FACTS 001 Phase III trial of pericoital tenofovir 1% gel for HIV prevention in women [Abstract 26LB]. 2015 Conference on Retroviruses and Opportunistic Infections; Seattle, WA. 2015.

91. van der Straten A, Stadler J, Montgomery E, Hartmann M, Magazi B, Mathebula F, et al. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. PLoS One. 2014; 9:e89118. [PubMed: 24586534] * This ancillary study to the VOICE trial provides key insights about women's experience with pre-exposure prophylaxis (both oral and vaginal) along a socio-ecological framework

92. Nyondo AL, Choko AT, Chimwaza AF, Muula AS. Invitation Cards during Pregnancy Enhance Male Partner Involvement in Prevention of Mother to Child Transmission (PMTCT) of Human Immunodeficiency Virus (HIV) in Blantyre, Malawi: A Randomized Controlled Open Label Trial. PLoS One. 2015; 10:e0119273. [PubMed: 25734485]

93. Edwards N, Barker PM. The importance of context in implementation research. J Acquir Immune Defic Syndr. 2014; 67(Suppl 2):S157–162. [PubMed: 25310123]

94. Woolf SH, Johnson RE. The break-even point: when medical advances are less important than improving the fidelity with which they are delivered. Ann Fam Med. 2005; 3:545–552. [PubMed: 16338919]

95. Basch CE, Sliepcevich EM, Gold RS, Duncan DF, Kolbe LJ. Avoiding type III errors in health education program evaluations: a case study. Health Educ Q. 1985; 12:315–331. [PubMed: 4077544]

96. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implement Sci. 2013; 8:139. [PubMed: 24289295]

97. Powell BJ, McMillen JC, Proctor EK, Carpenter CR, Griffey RT, Bunger AC, et al. A compilation of strategies for implementing clinical innovations in health and mental health. Med Care Res Rev. 2012; 69:123–157. [PubMed: 22203646]

98. Wiltsey Stirman S, Kimberly J, Cook N, Calloway A, Castro F, Charns M. The sustainability of new programs and innovations: a review of the empirical literature and recommendations for future research. Implement Sci. 2012; 7:17. [PubMed: 22417162]