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Defining gaps in PrEP delivery for pregnant and breastfeeding women in high burden settings using an implementation science framework

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Summary

Pregnancy is a period of high HIV acquisition risk for African women, and pregnant women who become acutely infected with HIV account for up to one-third of vertical HIV transmissions. To protect women and eliminate vertical transmission, the World Health Organization recommends offering oral tenofovir-based pre-exposure prophylaxis (PrEP) to HIV-negative pregnant and postpartum women with substantial HIV acquisition risk. PrEP implementation for pregnant and postpartum women lags behind other high-risk populations. Unique considerations for PrEP implementation arise during pregnancy and postpartum, including integration of provider training, clinical delivery, and monitoring PrEP exposure and outcomes within existing maternal health systems, yet few implementation data are available to generate evidence in this context. In this Viewpoint, we examine current PrEP delivery among pregnant and postpartum African women, identify gaps in evidence according to the RE-AIM framework, and offer recommendations to guide the implementation science research agenda to optimize PrEP for these populations.

Keywords

pre-exposure prophylaxis; PrEP; pregnancy; breastfeeding; PMTCT; prevention of mother to child transmission; HIV

Background

For young women in East and southern Africa, high background risks of HIV acquisition are elevated more than two-fold during pregnancy and the postpartum period.[1] Pregnancy-related biological changes may increase HIV susceptibility[2,3] and sexual behavioral changes during this period in women or their male partners that may alter risk of HIV exposure.[4] Pregnant women who become acutely infected with HIV account for up to 30% of all vertical HIV transmissions in high HIV burden settings.[5–7] To protect women and eliminate vertical HIV transmission, the World Health Organization (WHO) recommends offering oral tenofovir-based pre-exposure prophylaxis (PrEP) to HIV-negative pregnant and breastfeeding women at substantial risk of HIV acquisition (incidence >3%) as part of a comprehensive HIV prevention strategy that includes screening and treatment for sexually transmitted infections, appropriate risk reduction counselling, HIV testing and counselling for male partners, and provision of male and female condoms.[8] Despite PrEP implementation progressing globally, only a small minority of PrEP users worldwide are women of reproductive age, national PrEP guidelines often do not include discussion of PrEP use during pregnancy or breastfeeding, and PrEP implementation for pregnant and postpartum women lags behind other populations.

It is crucial to move from establishing “if” PrEP delivery is appropriate for pregnant and postpartum women at risk for HIV infection to considering “how” to optimize PrEP implementation in these populations. This shift will require generating new data unique to pregnant and postpartum women.[9] We identify opportunities in the research agenda related to PrEP delivery for pregnant and postpartum women guided by the RE-AIM, an implementation science framework used to identify gaps and facilitate research for evidence-based health interventions.[10] The RE-AIM domains, updated in 2019[11], include reach, effectiveness, and maintenance–which are operationalized at the individual level (i.e., those who are intended to benefit)—and adoption, implementation, and maintenance, which focus on provider, facility, and program levels.

Applying RE-AIM to PrEP delivery for pregnant and postpartum women

In this paper, we synthesize how current studies approach PrEP implementation science evidence generation at each level for HIV-uninfected women during pregnancy and the postpartum period. Implementation science frameworks facilitate understanding of how and why interventions are or are not implemented successfully.[10] For PrEP use among pregnant and postpartum women, the RE-AIM framework aligns well with addressing PrEP cascade steps.[10] Specifically, RE-AIM was developed to enhance the impact of health promotion interventions by evaluating dimensions most relevant to implementation outside of the context of clinical trials[12] and can guide planning and evaluation of evidence-based interventions.[13,14] Each RE-AIM domain[10] requires application and adaptation across levels (individual, provider, facility, and program) to reflect considerations unique to PrEP delivery for pregnant and breastfeeding women at risk of HIV. We operationalize definitions for each RE-AIM element across levels in Table 1.

Reach

Determinants of reach

Understanding reach and its determinants among programs offering PrEP to pregnant and postpartum women could help define priorities for scale-up and monitoring coverage progress. Clearinghouses currently monitoring PrEP implementation globally and regionally could consider tracking or disaggregating PrEP use among pregnant and postpartum women for evaluating and comparing reach across settings. Several current studies evaluate determinants of PrEP uptake among pregnant and postpartum women offered PrEP which could help inform the potential reach of PrEP programs (Table 2). Although most studies are ongoing[16–19], anticipated evidence from multiple countries (Kenya, Malawi, South Africa, Uganda, Zambia, and Zimbabwe) will include whether women with higher HIV risk accept PrEP when offered during pregnancy and postpartum, reasons for accepting or declining PrEP in this group, and demographic and behavioral characteristics of PrEP acceptors. In the recently completed PrEP Implementation for Young Women and Adolescents (PrIYA) Program, a significant proportion of pregnant and postpartum women with behavioral risk factors for HIV did not initiate PrEP, including 63% of women with partners of unknown HIV status, and low perception of HIV risk was a common (30%) reason for declining PrEP in this group.[20] Previous studies have shown an imbalanced relationship between perceived versus actual HIV risk among pregnant women, based on self-reported sexual behaviors.[21,22] Other studies from Kenya and South Africa found changes in sexual behavior and risk perception from early pregnancy into later pregnancy (e.g., sexual activity declines and consequently HIV risk perception decreases) and into the postpartum period which may be a determinant of PrEP uptake.[23–26]

PrOM[27] and PrEPARE[28] are currently the only studies evaluating determinants of reach for PrEP programs among pregnant and postpartum women beyond the individual level. Both studies will evaluate characteristics of antenatal care (ANC)/postnatal care (PNC) clinics and internal/external factors that influence a facility's PrEP screening activities (e.g. availability of trained staff and PrEP drugs in the facility, etc.). Gaps remain regarding whether additional specialized training is required for PrEP prescribers (typically physicians or clinical officers) to effectively deliver PrEP during pregnancy or if other cadres (e.g. nurses or pharmacists) could support PrEP provision or independently prescribe in clinical settings frequented by pregnant and postpartum women to expand reach. Additionally, understanding if and how pregnant women with partners who are living with HIV (or with partners of unknown HIV status) are systematically identified and subsequently offered PrEP could guide scale-up efforts in high HIV prevalence settings.

Strategies to enhance reach

Integration within routine ANC/PNC clinics is an attractive strategy for improving PrEP implementation reach within HIV high-burden settings[9] because ANC attendance is high (87–97%)[29] and achieves near-universal HIV testing among pregnant women.[30] PMTCT services, including a supply chain for antiretrovirals, are already integrated into ANC/PNC[31], and PrEP delivery could leverage this infrastructure for efficiency.[32] In the PrIYA Program, nurse-led teams worked with ANC/PNC staff at 16 facilities in Kisumu, Kenya, to

determine optimal clinic flow for PrEP integration into ANC and PNC clinics.[33] Clinics developed successful approaches for integrating PrEP delivery within ANC/PNC. However, PrEP-specific activities took 20 minutes per client [33] which could translate to several additional hours of work per week, potentially limiting reach. Encouraging early ANC attendance is an important maternal health promotion strategy and could increase opportunities for incorporating PrEP messaging at multiple visits.

More research is needed to improve reach by optimizing PrEP integration within ANC/PNC, including innovative provider training strategies or task-shifting approaches to increase the number of ANC/PNC attendees who receive PrEP services. Initiatives to identify HIV-serodiscordance in pregnancy and postpartum through male partner self-testing and couples testing may increase PrEP demand or influence PrEP use patterns.[34] Ongoing research evaluates diverse implementation strategies to enhance the number of women reached with PrEP counseling during pregnancy and to increase PrEP uptake. The PrOM study[27] will test a package of three pre-determined strategies, including video-based PrEP counseling in waiting areas, facility-based HIV self-testing to streamline confirmation of HIV-negative status, and expedited PrEP prescribing to increase the number of clients who can access PrEP services in busy ANC clinics. The PrEPARE study[28] will test three implementation strategies informed by factors identified in qualitative work in prior studies.[34,35] Two studies are incorporating same-day sexually transmitted infection (STI) testing (as an objective marker for HIV risk) prior to PrEP counselling within routine ANC in Kenya and South Africa to strengthen cues to action and increase PrEP demand and uptake among pregnant women.[16,36]

Effectiveness

Determinants of effectiveness

Ongoing studies evaluate PrEP effectiveness by assessing reductions in HIV incidence and potential adverse pregnancy and infant outcomes in Kenya, Malawi, South Africa, Uganda, and Zimbabwe using research data systems built for each project.[37] However, routine surveillance systems are few and underutilized to measure HIV incidence, PrEP exposure, and adverse events among pregnant and postpartum women. Therefore, there is no robust comparison between pregnant and postpartum women enrolled in PrEP demonstration projects and general populations of pregnant and postpartum women. Gaps also include questions of when best to initiate (or re-initiate) PrEP and counseling approaches for restarting PrEP, whether PrEP should be taken when not sexually active and how to ensure appropriate monitoring using available health information systems. Pharmacokinetic studies show lower PrEP exposure during pregnancy, which could affect both efficacy and effectiveness.[38,39] Under conditions of near perfect adherence in directly observed therapy studies among African women, PrEP levels measured in dried blood spots were 31–37% lower in pregnancy than postpartum.[39] These findings suggest that strict adherence is needed during pregnancy for PrEP effectiveness.

Strategies for enhancing effectiveness

Effectiveness of strategies that support PrEP delivery and use move beyond PrEP efficacy. More studies are needed to test whether risk-based PrEP counseling improves effectiveness or if existing data systems could be leveraged to identify women who could benefit from PrEP without an additional screening activity. PrEP effectiveness at the population-level during pregnancy and postpartum is dependent on the proportion of pregnant and postpartum women who take PrEP, their risk of HIV acquisition, and prevention-effective adherence. Strengthening established surveillance systems with attention to improving data quality and completeness could facilitate utilizing routine program data to measure maternal HIV incidence, PrEP exposure, or adverse outcomes. A recent mathematical model in South Africa demonstrated that maternal PrEP use could reduce infant HIV acquisition by 13%, and reduce overall HIV acquisition by 2.3% if one-third of high-risk pregnant women took PrEP.[40] Additional mathematical modeling work suggests that systematic risk-based screening approaches for identifying women who may benefit from PrEP could maximize HIV prevention impact.[32] WHO recommends that HIV risk should be assessed periodically as a woman's risks may change over time either making PrEP no longer necessary or recognizing new risks and need for PrEP,[8] underscoring the importance of open discussion about HIV prevention to empower women to seek PrEP in periods of increased HIV vulnerability.[23]

The ongoing PrEP Implementation for Mothers in ANC Care (PrIMA) study is a cluster randomized trial that aims to determine an efficient and effective model for PrEP among pregnant women attending public sector ANC clinics in Western Kenya.[17] In PrIMA, 20 clinics are randomized to either universal PrEP offer following standardized counselling or risk screening using a validated HIV risk score developed specifically for pregnant Kenyan women.[41] PrIMA will compare by randomization arm maternal HIV incidence, PrEP uptake, PrEP adherence, and "appropriate" PrEP use with objective evidence of potential risk.[17] Outcomes of PrIMA reflect the balance between HIV preventive effectiveness and avoiding unnecessary PrEP exposure to women at low risk, while also considering cost-effectiveness and efficiencies of PrEP delivery approaches. By contrast, the PrEP in pregnancy and postpartum (PrEP-PP) study in South Africa is being conducted in a high HIV incidence community and is therefore not applying an added behavioral-based risk stratification.[16] PrIYA used an HIV risk assessment tool adapted from one developed by the Kenya Ministry of Health to identify pregnant and postpartum women with high HIV risk and guide PrEP counseling[42], although all women (regardless of self-reported HIV risk behaviors) were informed that PrEP was available if they perceived they were at risk for HIV.[43,44]

Adoption

Determinants of adoption

The establishment of national guidelines in HIV high-burden settings is an important first step for expanding PrEP adoption. Current guidelines differ in including and/or recommending PrEP use during pregnancy and postpartum.[45] Kenyan guidelines were the first to recommend PrEP use for pregnant and postpartum women in its national PrEP

policies, and programmatic delivery is ongoing.[33,46] Guidelines in Eswatini, Uganda[47], and Zimbabwe[48] are permissive of PrEP use during pregnancy.[45] Botswana has policies that allow PrEP for serodiscordant couples trying to conceive but do not explicitly recommend PrEP for pregnant and breastfeeding women.[45] The desire for additional safety data on maternal PrEP use has hindered inclusion of pregnant women in PrEP guidelines in Malawi, Zambia, and other HIV high-burden settings.[45] South Africa recently added high-risk pregnant and breastfeeding women to their PrEP guidelines[49], though PrEP policies initially labeled PrEP as "contraindicated" during pregnancy and breastfeeding which stymied implementation. Programmatic adoption of PrEP for pregnant and postpartum women will require that national PrEP policies include considerations for all women at substantial HIV risk, regardless of pregnant and breastfeeding status, and promote roll-out of PrEP in these populations. Additionally, there is a need for guidelines to clarify how PrEP should be implemented among pregnant and lactating women, including in existing PMTCT services.

Strategies to enhance adoption

Gaps remains about how programs can increase the number of facilities or providers within facilities that provide PrEP to pregnant and postpartum women. Task shifting risk assessments and data collection and conducting community education to improve client awareness of PrEP and reduce counseling session duration were identified as potential implementation strategies to enhance PrEP delivery within ANC in Kenya by providers.[35] In settings where creatinine or hepatitis B virus testing is required by national PrEP guidelines[47], laboratory testing adds significant time and cost within already constrained health systems which can hinder whether facilities can provide PrEP services. Given the rarity of medical PrEP ineligibility[53], low rates of sustained PrEP use, and safety of short-term PrEP[54,55], data suggest that not mandating creatinine testing at PrEP initiation will generally be a safe decision. De-medicalizing PrEP initiation and reducing barriers to programmatic adoption such as resource-intensive laboratory testing could be one strategy to enhance adoption. Additionally, PrEP drug availability at the national level could influence the number of facilities that adopt and sustain PrEP delivery, particularly if national PrEP availability is subject to donor funding and shifting priorities.

Implementation

Determinants of implementation

Programmatic PrEP delivery within routine ANC is not yet scaled-up in most settings. As countries that are considering or planning PrEP delivery within ANC move to implementation, programs should systematically identify structural factors to target PrEP delivery improvements beyond the individual level. PrEP stock-outs or absence of other essential resources, such as registers or job aids specific to PrEP counseling within ANC, were cited by providers as strong determinants of unsuccessful implementation during the PrIYA program.[35] While standardized tools for assessing the availability and utilization of resources within health systems exist for some services[56]—including ANC, family planning, and HIV care—adaptation of these tools are needed to include PrEP service availability and utilization assessments. The ongoing PrOM study utilizes an adapted readiness assessment

tool to quantify available PrEP services and will determine whether these are modified by implementation strategies.[27]

Current qualitative studies also evaluate determinants of provider and facility level PrEP implementation. A recent landscaping study in Malawi and Zambia found low PrEP awareness among pregnant women and providers, and feasibility of integration into ANC was a concern.[50] In contrast, Kenyan providers were enthusiastic about the feasibility, acceptability, and anticipated sustainability of integrating PrEP services into ANC clinics.[35] Both studies noted common barriers to implementation, including time and space constraints, stock outs of PrEP, and gaps in client awareness and provider training.[50,51] Providers reported confidence engaging in challenging discussions related to sexuality with clients, providing accurate information related to PrEP safety, and supporting women to make client-centered decisions regarding PrEP.[35] In-depth interviews with providers working with pregnant women in Cape Town, South Africa, highlighted that limited knowledge about PrEP led to confusion over the effectiveness and safety of PrEP in pregnancy *(Davey, in press*). Effectively communicating the evidence on PrEP safety during pregnancy could influence implementation and help providers feel confident in addressing safety concerns and counseling pregnant women on PrEP.[51,52]

Strategies to enhance implementation

Further studies are warranted that test implementation strategies aiming to improve provider-delivered PrEP services, including patient-facing strategies to enhance counseling such as mobile decision tool applications. Provider training using standardized patient actors is currently being tested to improve provider implementation of PrEP counseling and delivery within MCH clinics in Kenya.[57] This trial involves standardized patient actors role-playing during provider training (implementation strategy) and evaluates its impact through a ‘mystery shopper’ evaluation in MCH clinics. No other studies were identified that test implementation strategies at the provider and/or facility level, despite recognition of the important role of provider training and confidence for delivering PrEP to pregnant women (*Davey, in press*)[58]. Ensuring fidelity of PrEP implementation through evaluation of whether job aids or other provider tools exist, the quality of PrEP counseling and services, and whether delivery aligns with national guidelines could also improve PrEP implementation for pregnant and postpartum women. Mentorship models or performance-based incentive approaches that integrate PrEP in pregnancy/postpartum targets within overall PMTCT targets could potentially motivate PrEP implementation at the provider and facility level. Studies that test implementation strategies should examine the mechanisms of action to understand why strategies succeed or fail to improve implementation outcomes.

Maintenance

Determinants of maintenance

PrEP maintenance for pregnant and postpartum women includes considerations at the individual (i.e., long-term PrEP use or PrEP persistence) and clinic/program-level (i.e., sustainable delivery).[11] Understanding PrEP persistence patterns and determinants among pregnant and postpartum women could inform initiatives to improve maintenance in this

population. For example, persisting with PrEP use requires health systems that support repeat follow-up visits and sustain PrEP delivery. Several ongoing studies will evaluate maintenance of PrEP use[16–19], although, limited data are currently available. In PrIYA, >50% of pregnant women discontinued PrEP within 30 days of initiation.[44] Although some factors contributing to PrEP continuation may be universal, unique considerations arise or may change during pregnancy and the postpartum period. In qualitative studies, women's reported motivation for PrEP in pregnancy was driven by the desire to have an HIV-free infant.[58,59] PrEP continuation may be reduced postpartum if perception of the infant's risk of HIV is reduced, similar to patterns of ART use in the postpartum period [60–62], and remembering to take PrEP pills may be difficult with additional demands of motherhood.[63] Alterations in sexual behavior within relationships during and after pregnancy may also influence women's HIV risk perception and PrEP use.[25] Common symptoms of pregnancy overlap with PrEP-related side effects, which negatively impact PrEP continuance among pregnant women.[58,59] In PrIYA, side effects were the most frequently (25%) reported reason for discontinuing PrEP[64] and pregnant women who experienced side effects were twice as likely to discontinue. These data suggest that pregnant women and new mothers may require additional support for PrEP maintenance, and evidence from ongoing studies will elucidate determinants of continuing PrEP, particularly in the postnatal period where in-built follow-up diminishes.

We did not identify any studies that evaluate provider- or facility-level factors associated with PrEP continuation. Sustainable delivery is a major challenge in countries with high HIV burden[65] and currently is it not adequately addressed in PrEP projects. Ascertaining maintenance or sustainability of PrEP delivery at the provider and facility level will require longer-term evaluation in which research procedures do not artificially enhance this metric. Future evaluations should incorporate evaluation of sustaining PrEP delivery after a study team is replaced by existing programmatic staff, including cost implications. To date, it is unclear whether and how systems work to incorporate PrEP delivery for pregnant and postpartum women and continue offering PrEP after demonstration projects and studies finish. Additionally, approaches for decreasing burden on health facilities and PrEP users by simplifying PrEP follow-up (e.g., peer or community delivery models, pharmacy pick-up, etc.) are currently being evaluated in other populations.[66] Pregnant and postpartum women frequently attend facilities for ANC/PNC, infant immunizations, and growth monitoring and contraception services, though attendance location may vary based on timing (e.g., residing with relatives during late pregnancy and early postpartum). Innovative approaches for streamlining PrEP follow-up, decreasing follow-up burden within ANC/PNC, and supporting continued PrEP use among mobile populations are needed but have not been tested to date.

Strategies to enhance maintenance

Though some ongoing studies will evaluate determinants of maternal PrEP continuation, only one study to date tested an implementation strategy to improve PrEP persistence in this population. A non-randomized pilot evaluation of a 2-way short message service (SMS) communication platform within a programmatic PrEP delivery setting in Kenya found very high acceptance (98%), an almost 2-fold greater early PrEP continuation, and higher self-

reported adherence among pregnant and postpartum women enrolled in the SMS program.[67] More robust studies are needed that test implementation strategies to promote protection-effective PrEP adherence. Very few ongoing studies evaluate implementation strategies for providers or programs. Evidence from other HIV programs, such as utilization of quality assurance/quality improvement systems for PMTCT and antiretroviral therapy (ART), could guide feasible, operational sustainability of PrEP in high HIV burden settings.[65] Additionally, in settings where ANC and PNC may be delivered separately or by different providers, strategies to improve maintenance of PrEP programs integrated within both ANC and PNC are required to ensure continuity of PrEP services.

Cost

Current foci of RE-AIM include an emphasis on cost[11], as it is an important driver of successful implementation. PrIYA quantified the cost per client month of PrEP in MCH clinics and provided strategies for reducing programmatic costs.[68] Ongoing health economic studies embedded within PrIMA assess the cost-effectiveness and cost-utility of risk-guided versus universal offer of PrEP for pregnant women, reflecting differences in PrEP reach, adoption, implementation, and maintenance observed during the trial.[34] Assessing the budget impact of different strategies for PrEP delivery in pregnancy will be critical to reflect the size of the population of pregnant women, the duration of PrEP use, and the expected number of PrEP users under different scenarios. Existing studies that model the number of potential pregnant PrEP users under different roll out scenarios[32,40] may be enhanced by the addition of costing information to assess affordability. Planned budget impact analysis studies within the PrEPARE study[28] will assess the changes in cost associated with each tested implementation strategy and investigate Kenyan policymakers' understanding and perceived usefulness of such analyses.

Recommendations for future implementation science research

We applied the RE-AIM framework to guide the implementation science agenda for PrEP in pregnancy and the postpartum period. Our work complements previous syntheses of how to integrate determinants of HIV incidence along the prevention cascade within program design[69] by utilizing a framework developed to enhance the impact of interventions through improved implementation. Several key opportunities for implementation science emerged to fill gaps that will remain even after evidence from ongoing studies is accrued (Figure 1), including:

- Increasing geographic representation of PrEP delivery studies reaching pregnant and postpartum women
- Improving surveillance of safety and effectiveness during scale-up
- Focusing beyond individual level determinants and strategies in order to facilitate program-level implementation
- Increasing the number of studies that test strategies for improving PrEP implementation and maintenance at all levels during pregnancy through the postpartum period

Reaching population impact of PrEP for pregnant and postpartum women will require understanding context-specific determinants of successful PrEP delivery and testing strategies that improve PrEP implementation outcomes at multiple levels. Seven of the 10 studies we identified that evaluate implementation determinants, outcomes, or strategies for delivering PrEP to pregnant and/or postpartum women are based in three counties of Western Kenya. Kenya created an enabling environment with early national policies on PrEP in pregnancy.[33,46] Thus, it is not surprising that the preponderance of data are from Kenya at this point.

These studies will contribute to the evidence base across multiple RE-AIM domains and levels, and assess heterogeneity in RE-AIM domains between facilities and providers, yet additional studies from outside Kenya are needed to determine how PrEP delivery could be translated to other African settings with high HIV burden. Only one study (IMPAACT 2009) includes multiple countries (Malawi, South Africa, Uganda, and Zimbabwe) and will be able to assess how implementation determinants and outcomes differ across diverse settings. Barriers to and solutions for effective PrEP delivery for pregnant and postpartum women are likely to vary by setting, arguing for context-specific evidence. Monitoring PrEP maintenance and effectiveness within programmatic delivery settings is challenging given the time-varying nature of behavioral risks and lack of linkage between PrEP, HIV testing, and MCH information systems in many settings; thus, robust surveillance systems are needed.

Qualitative studies, among both pregnant women and providers, consistently cite the importance of training and supporting providers to ensure PrEP availability and identify and counsel pregnant women for successful PrEP delivery.[35,58] Yet, few current studies evaluate provider, facility, or program level determinants and outcomes for PrEP implementation among pregnant and postpartum women. In scaling up other interventions, such as PMTCT, understanding the environment and processes of implementation was crucial for addressing major bottlenecks that impeded programmatic delivery.[70] Focusing implementation science studies on the challenges of effective and sustainable PrEP delivery is critical for primary prevention of maternal HIV and elimination of vertical HIV transmission. Future studies should test provider training strategies, specifically on communicating PrEP safety information, and evaluate health systems reorganization to improve PrEP delivery.

Currently, individual-level determinants of PrEP use during pregnancy and postpartum are more well-researched than other areas of PrEP implementation. Available data suggest PrEP adherence may be suboptimal among pregnant women for reasons unique to pregnancy and waning may occur during the postpartum period[20,63,71], similar to studies among women receiving ART. Data accruing from ongoing studies will help further elucidate patterns of uptake and objective adherence among pregnant and postpartum women, though few test strategies to improve outcomes. Studies are needed testing implementation strategies to enhance individual-level PrEP outcomes, ideally with large, representative samples.

In conclusion, we strongly recommend a research agenda that moves from the “if” to the “how” of implementing PrEP during pregnancy and postpartum in different contexts, with special focus on increasing geographic representation, improving surveillance of safety and

effectiveness during scale-up, focusing beyond individual level determinants and strategies for PrEP implementation, and delivering PrEP with an emphasis on personal choice, involving feedback from pregnant and postpartum women in program design, and in the context of comprehensive HIV prevention. Increasing studies that test strategies for improving provider delivered PrEP services, including patient-facing strategies, and enhancing PrEP reach, adoption, implementation, and maintenance during pregnancy through the postpartum period will be critical for sustainable PrEP delivery in pregnancy and postpartum among women at risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Thomson KA, Hughes J, Baeten JM, et al. Increased Risk of Female HIV-1 Acquisition Throughout Pregnancy and Postpartum: A Prospective Per-coital Act Analysis Among Women with HIV-1 Infected Partners. J Infect Dis 2018.
2. Silasi M, Cardenas I, Kwon JY, Racicot K, Aldo P, Mor G. Viral infections during pregnancy. Am J Reprod Immunol 2015; 73(3): 199–213. [PubMed: 25582523]
3. Racicot K, Kwon JY, Aldo P, Silasi M, Mor G. Understanding the complexity of the immune system during pregnancy. Am J Reprod Immunol 2014; 72(2): 107–16. [PubMed: 24995526]
4. Crawford-Williams F, Fielder A, Mikocka-Walus A, Esterman A. A critical review of public health interventions aimed at reducing alcohol consumption and/or increasing knowledge among pregnant women. Drug Alcohol Rev 2015; 34(2): 154–61. [PubMed: 24840708]
5. Johnson LF, Stinson K, Newell ML, et al. The contribution of maternal HIV seroconversion during late pregnancy and breastfeeding to mother-to-child transmission of HIV. Journal of acquired immune deficiency syndromes (1999) 2012; 59(4): 417–25. [PubMed: 22193774]
6. Dinh TH, Delaney KP, Goga A, et al. Impact of Maternal HIV Seroconversion during Pregnancy on Early Mother to Child Transmission of HIV (MTCT) Measured at 4–8 Weeks Postpartum in South Africa 2011–2012: A National Population-Based Evaluation. PLoS One 2015; 10(5): e0125525.
7. UNAIDS. Start Free Stay Free AIDS Free - 2019 report, 2019.
8. WHO Technical brief. Preventing HIV during pregnancy and breastfeeding in the context of pre-exposure prophylaxis (PrEP). Geneva: World Health Organization 2017.
9. Joseph Davey DL, Bekker LG, Gorbach PM, Coates TJ, Myer L. Delivering preexposure prophylaxis to pregnant and breastfeeding women in Sub-Saharan Africa: the implementation science frontier. AIDS 2017; 31(16): 2193–7. [PubMed: 28723709]
10. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999; 89(9): 1322–7. [PubMed: 10474547]
11. Glasgow RE, Harden SM, Gaglio B, et al. RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. Front Public Health 2019; 7: 64. [PubMed: 30984733]

12. Green LW, Glasgow RE. Evaluating the relevance, generalization, and applicability of research: issues in external validation and translation methodology. Eval Health Prof 2006; 29(1): 126–53. [PubMed: 16510882]

13. Glasgow RE, Green LW, Klesges LM, et al. External validity: we need to do more. Ann Behav Med 2006; 31(2): 105–8. [PubMed: 16542124]

14. Klesges LM, Estabrooks PA, Dzewaltowski DA, Bull SS, Glasgow RE. Beginning with the application in mind: designing and planning health behavior change interventions to enhance dissemination. Ann Behav Med 2005; 29 Suppl: 66–75. [PubMed: 15921491]

15. AVAC. Global PrEP Tracker. 2019 https://www.prepwatch.org/resource/global-prep-tracker/ (accessed December 28 2019).

16. NIH Research Portfolio Online Reporting Tools (RePORT). Evaluation of Pre-Exposure Prophylaxis (PrEP) in Pregnant and Breastfeeding Women (PrEP-PP) (NCT03902418). 2019 https://clinicaltrials.gov/ct2/show/NCT03902418?term=Coates&draw=2&rank=10 (accessed October 26, 2019.

17. Dettinger JC, Kinuthia J, Pintye J, et al. PrEP Implementation for Mothers in Antenatal Care (PrIMA): study protocol of a cluster randomised trial. BMJ Open 2019; 9(3): e025122.

18. Clinicaltrials.gov. Evaluating the Pharmacokinetics, Feasibility, Acceptability, and Safety of Oral Pre-Exposure Prophylaxis for HIV Prevention During Pregnancy and Postpartum (IMPAACT 2009) (NCT03386578). 2019 https://clinicaltrials.gov/ct2/show/NCT03386578 (accessed October 26, 2019.

19. Matthews LT, Jaggernath M, Kriel Y, et al. Protocol for a longitudinal study to evaluate the use of tenofovir-based PrEP for safer conception and pregnancy among women in South Africa. BMJ Open 2019; 9(7): e027227.

20. Kinuthia J, Pintye J, Abuna F, Mugwanya K, Lagat H, Onyango D, Bengel E, Dettinger J, Baeten J, John-Stewart G. Pre-exposure prophylaxis uptake and early continuation among pregnant and postpartum women within maternal child health clinics in Kenya: results from an implementation programme. The lancet HIV 2019; In Press.

21. Dearborn JL, Lewis J, Mino GP. Preventing mother-to-child transmission in Guayaquil, Ecuador: HIV knowledge and risk perception. Glob Public Health 2010; 5(6): 649–62. [PubMed: 19960396]

22. Darak S, Gadgil M, Balestre E, et al. HIV risk perception among pregnant women in western India: need for reducing vulnerabilities rather than improving knowledge! AIDS Care 2014; 26(6): 709–15. [PubMed: 24215183]

23. Joseph Davey D, Farley E, Gomba Y, Coates T, Myer L. Sexual risk during pregnancy and postpartum periods among HIV-infected and -uninfected South African women: Implications for primary and secondary HIV prevention interventions. PloS one 2018; 13(3): e0192982. [PubMed: 29509759]

24. Joseph Davey D, Farley E, Towriss C, et al. Risk perception and sex behaviour in pregnancy and breastfeeding in high HIV prevalence settings: Programmatic implications for PrEP delivery. PloS one 2018; 13(5): e0197143. [PubMed: 29758064]

25. Kinuthia J, Richardson BA, Drake AL, et al. Sexual Behavior and Vaginal Practices During Pregnancy and Postpartum: Implications for HIV Prevention Strategies. J Acquir Immune Defic Syndr 2017; 74(2): 142–9. [PubMed: 27828872]

26. Kinuthia J, Drake AL, Matemo D, et al. HIV acquisition during pregnancy and postpartum is associated with genital infections and partnership characteristics. AIDS (London, England) 2015; 29(15): 2025–33.

27. NIH Research Portfolio Online Reporting Tools (RePORT). PREP OPTIMIZED FOR MOTHERS (PROM): EFFICIENT PREP INTEGRATION IN MCH CLINICS. 2019 https://projectreporter.nih.gov/project_info_description.cfm?aid=9873846&icde=47173495.

28. NIH Research Portfolio Online Reporting Tools (RePORT). TESTING IMPLEMENTATION STRATEGIES TO IMPROVE DELIVERY OF PREP FOR PREGNANT AND POSTPARTUM WOMEN IN KENYA. 2019 https://projectreporter.nih.gov/project_info_description.cfm?aid=9844671&icde=47174595.

29. UNICEF. Antenatal care coverage data warehouse. 2019 https://data.unicef.org/topic/maternal-health/antenatal-care/ (accessed November 11 2019).

30. Hensen B, Baggaley R, Wong VJ, et al. Universal voluntary HIV testing in antenatal care settings: a review of the contribution of provider-initiated testing & counselling. Trop Med Int Health 2012; 17(1): 59–70. [PubMed: 22032300]

31. Suthar AB, Hoos D, Beqiri A, Lorenz-Dehne K, McClure C, Duncombe C. Integrating antiretroviral therapy into antenatal care and maternal and child health settings: a systematic review and meta-analysis. Bull World Health Organ 2013; 91(1): 46–56. [PubMed: 23397350]

32. Pintye J, Singa B, Wanyonyi K, et al. Pre-exposure prophylaxis (PrEP) for HIV prevention among HIV-uninfected pregnant women: estimated coverage using risk-based versus regional prevalence approaches. Sex Transm Dis 2018.

33. Pintye J, Kinuthia J, Roberts DA, et al. Integration of PrEP Services Into Routine Antenatal and Postnatal care: Experiences from an Implementation Program in Western Kenya. J Acquir Immune Defic Syndr 2018.

34. Dettinger JC, Kinuthia J, Pintye J, et al. PrEP Implementation for Mothers in Antenatal Care (PrIMA): study protocol of a cluster randomised trial. BMJ Open 2019; 9(3): e025122.

35. Beima-Sofie K, Wagner A, Pintye J, et al. Implementation challenges and strategies in integration of PrEP into maternal and child health and family planning services: Experiences of frontline healthcare workers in Kenya. 10th International AIDS Society (IAS) Conference on HIV Science Mexico City, Mexico; 2019 7.

36. NIH Research Portfolio Online Reporting Tools (RePORT). Enhancing integrated delivery of PrEP within antenatal care with STI testing and expedited partner treatment. 2019 https://projectreporter.nih.gov/project_info_description.cfm?aid=9679456&icde=47174673 (accessed October 26, 2019.

37. Joseph Davey DL, Pintye J, Baeten JM, et al. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? J Int AIDS Soc 2020; 23(1): e25426.

38. Pyra M, Anderson PL, Hendrix CW, et al. Tenofovir and tenofovir-diphosphate concentrations during pregnancy among HIV-uninfected women using oral preexposure prophylaxis. AIDS 2018; 32(13): 1891–8. [PubMed: 29894385]

39. Anderson PL, Stranix-Chibanda L, Huang S, et al. TFV-DP in DBS for pregnant/postpartum adolescent and young women on PrEP in Africa (Abstract No. 980). Conference on Retroviruses and Opportunistic Infections (CROI) Boston, Massachusetts, USA; 2020.

40. Joseph Davey DL, Bekker LG, Gomba Y, Coates T, Myer L, Johnson LF. Modelling the potential impact of providing preexposure prophylaxis in pregnant and breastfeeding women in South Africa. AIDS (London, England) 2019; 33(8): 1391–5.

41. Pintye J, Drake AL, Kinuthia J, et al. A risk assessment tool for identifying pregnant and postpartum women who may benefit from pre-exposure prophylaxis (PrEP). Clin Infect Dis 2016.

42. Kinuthia J, Pintye J, Abuna F, et al. Pre-exposure prophylaxis uptake and early continuation among pregnant and post-partum women within maternal and child health clinics in Kenya: results from an implementation programme. Lancet HIV 2020; 7(1): e38–e48.

43. Ministry of Health NASCP, . Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya 2016. Nairobi, Kenya: NASCOP, 7 2016 Print. 2016.

44. Kinuthia J, Pintye J, Mugwanya K, et al. High PrEP uptake among Kenyan pregnant women offered PrEP during routine antenatal care (Abstract #1366). Conference on Retroviruses and Opportunistic Infections (CROI) Boston, MA, USA; 2018.

45. Davies N, Heffron R. Global and national guidance for the use of pre-exposure prophylaxis during peri-conception, pregnancy and breastfeeding. Sex Health 2018; 15(6): 501–12. [PubMed: 30447703]

46. Ministry of Health NASCP. Guidelines on use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya 2016. Nairobi, Kenya, 7 2016.

47. Government of Uganda Ministry of Health. Consolidated Guidelines for Prevention and Treatment of HIV in Uganda, 2018.

48. Ministry of Health and Child Care Z. Implementation Plan for HIV Pre-Exposure Prophylaxis in Zimbabwe 2018–2020. 2018 (accessed June 3 2019).

49. Health SANDo. GUIDELINES FOR THE PROVISION OF PRE-EXPOSURE PROPHYLAXIS (PrEP) TO PERSONS AT SUBSTANTIAL RISK OF HIV INFECTION. Pretoria, South Africa, 2019.
50. Zimba C, Maman S, Rosenberg NE, et al. The landscape for HIV pre-exposure prophylaxis during pregnancy and breastfeeding in Malawi and Zambia: A qualitative study. PloS one 2019; 14(10): e0223487.
51. Beima-Sofie KM, Trinidad SB, Ngure K, et al. Lessons from PrEP: A Qualitative Study Investigating How Clinical and Policy Experts Weigh Ethics and Evidence When Evaluating Preventive Medications for Use in Pregnant and Breastfeeding Women. AIDS and behavior 2018.
52. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. AIDS 2017; 31(2): 213–32. [PubMed: 27831952]
53. Abuna F, Kinuthia J, Lagat H, et al. A Field Evaluation of Point-of-Care Creatinine Testing Within a Large PrEP Implementation Program in Western Kenya. J Acquir Immune Defic Syndr 2019; 82(1): e8–e10. [PubMed: 31219932]
54. Marcus JL, Hurley LB, Hare CB, et al. Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation. J Acquir Immune Defic Syndr 2016; 73(5): 540–6. [PubMed: 27851714]
55. Wang X, Nwokolo N, Korologou-Linden R, et al. InterPrEP: internet-based pre-exposure prophylaxis with generic tenofovir disoproxil fumarate/emtrictabine in London - analysis of pharmacokinetics, safety and outcomes. HIV Med 2018; 19(1): 1–6. [PubMed: 28657199]
56. World Health Organization. Service availability and readiness assessment (SARA). 7 2015 https://www.who.int/healthinfo/systems/sara_introduction/en/ (accessed October 26, 2019.
57. Clinicaltrials.gov. Standardized Patient Encounters to Improve PrEP Counseling for Adolescent Girls and Young Women in Kenya (PrIYA-SP). 2019 https://clinicaltrials.gov/ct2/show/NCT03875950 (accessed October 26, 2019.
58. Pintye J, Beima-Sofie KM, Kimemia G, et al. "I Did Not Want to Give Birth to a Child Who has HIV": Experiences Using PrEP During Pregnancy Among HIV-Uninfected Kenyan Women in HIV-Serodiscordant Couples. J Acquir Immune Defic Syndr 2017; 76(3): 259–65. [PubMed: 28777265]
59. Heffron R, Thomson K, Celum C, et al. Fertility Intentions, Pregnancy, and Use of PrEP and ART for Safer Conception Among East African HIV Serodiscordant Couples. AIDS Behav 2017.
60. Fayorsey RN, Chege D, Wang C, et al. Mother Infant Retention for Health (MIR4Health): Study Design, Adaptations, and Challenges With PMTCT Implementation Science Research. J Acquir Immune Defic Syndr 2016; 72 Suppl 2: S137–44. [PubMed: 27355501]
61. Schnack A, Rempis E, Decker S, et al. Prevention of Mother-to-Child Transmission of HIV in Option B+ Era: Uptake and Adherence During Pregnancy in Western Uganda. AIDS Patient Care STDS 2016; 30(3): 110–8. [PubMed: 27308804]
62. Elwell K. Facilitators and barriers to treatment adherence within PMTCT programs in Malawi. AIDS Care 2016; 28(8): 971–5. [PubMed: 26984065]
63. Pintye J, Escudero J, Kinuthia J, et al. Motivations for early PrEP discontinuation among Kenyan adolescent girls and young women: A qualitative analysis from a PrEP implementation program (WEPED822). International AIDS Society (IAS) Conference on HIV Science Mexico City, Mexico; 2019.
64. Pintye J, Kinuthia J, Baeten J, et al. PrEP Side-effects and Discontinuation in Pregnant and Non-Pregnant Women (Abstract #PD08.04). HIV Research for Prevention (HIVR4P) Madrid, Spain; 2018.
65. Torpey K, Mwenda L, Thompson C, Wamuwi E, van Damme W. From project aid to sustainable HIV services: a case study from Zambia. J Int AIDS Soc 2010; 13: 19. [PubMed: 20529255]
66. O'Malley G, Barnabee G, Mugwanya K. Scaling-up PrEP Delivery in Sub-Saharan Africa: What Can We Learn from the Scale-up of ART? Curr HIV/AIDS Rep 2019; 16(2): 141–50. [PubMed: 30796608]

67. Pintye J, Rogers Z, Kinuthia J, et al. Two-Way Short Message Service (SMS) Communication May Increase Pre-Exposure Prophylaxis Continuation and Adherence Among Pregnant and Postpartum Women in Kenya. Glob Health Sci Pract 2020.
68. Roberts DA, Barnabas RV, Abuna F, et al. The role of costing in the introduction and scale-up of HIV pre-exposure prophylaxis: evidence from integrating PrEP into routine maternal and child health and family planning clinics in western Kenya. Journal of the International AIDS Society 2019; 22 Suppl 4: e25296.
69. Hargreaves JR, Delany-Moretlwe S, Hallett TB, et al. The HIV prevention cascade: integrating theories of epidemiological, behavioural, and social science into programme design and monitoring. Lancet HIV 2016; 3(7): e318–22. [PubMed: 27365206]
70. Sturke R, Harmston C, Simonds RJ, et al. A multi-disciplinary approach to implementation science: the NIH-PEPFAR PMTCT implementation science alliance. Journal of acquired immune deficiency syndromes (1999) 2014; 67 Suppl 2: S163–7. [PubMed: 25310124]
71. Pintye J, Kinuthia J, Abuna F, et al. Frequent detection of tenofovir-diphosphate among young Kenyan women in a real-world PrEP implementation program (Abstract # TUAC0305LB). International AIDS Society (IAS) Conference on HIV Science Mexico City, Mexico; 2019.
72. Mugwanya KK, Pintye J, Kinuthia J, et al. Integrating preexposure prophylaxis delivery in routine family planning clinics: A feasibility programmatic evaluation in Kenya. PLoS Med 2019; 16(9): e1002885.
73. NIH Research Portfolio Online Reporting Tools (RePORT). PREP ADHERENCE AMONG AGYW: A MULTIDIMENSIONAL EVALUATION. 2019 https://projectreporter.nih.gov/project_info_description.cfm?aid=9732598&icde=47173430.
74. Matthews L, Jaggernath M, Kriel Y, et al. High uptake and adherence to periconception PrEP among women in South Africa (Abstract #TUPDC01). International AIDS Society Conference on HIV Science Mexico City, Mexico; July 2019.
75. NIH Research Portfolio Online Reporting Tools (RePORT). A DYAD APPROACH TO COMBINATION HIV PREVENTION IN PREGNANCY FOR ZAMBIA AND MALAWI (R01AI131060). 2019 https://projectreporter.nih.gov/project_info_description.cfm?aid=9830007&icde=48087739&ddparam=&ddvalue=&ddsub=&cr=9&csb=default&cs=ASC&pball=.

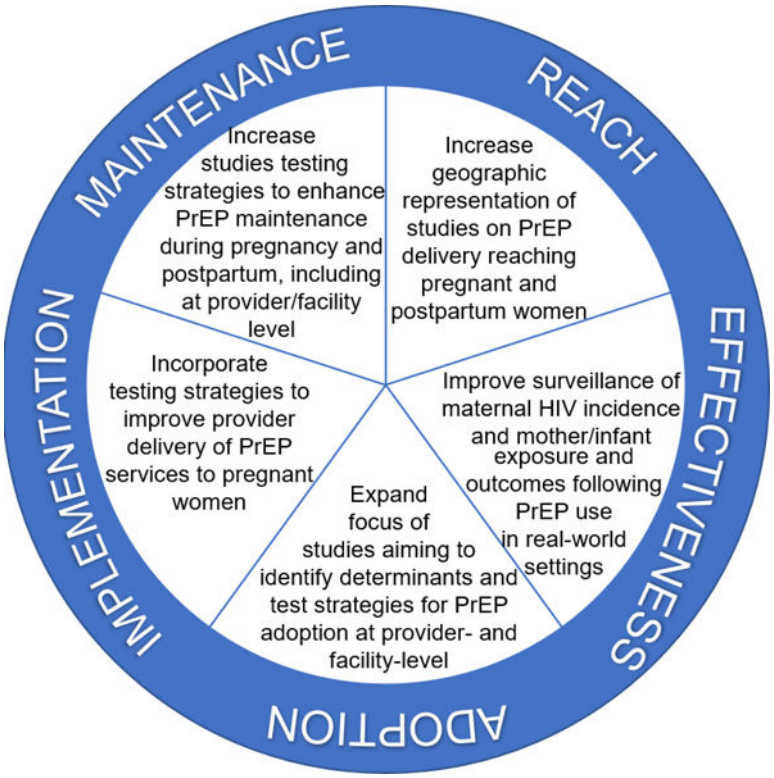

Figure 1. Key implementation science research opportunities to address evidence gaps of PrEP delivery for pregnant and postpartum women organized by the RE-AIM framework

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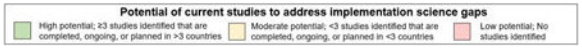
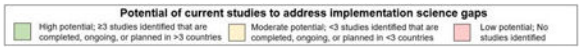
Table 1.

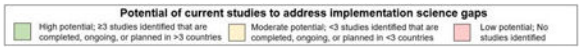
Application of the RE-AIM framework to PrEP delivery for pregnant and postpartum women in HIV high-burden settings, and potential for completed, ongoing, and planned studies to address implementation science gaps



RE-AIM definition	Domain applied to PrEP delivery for pregnant/postpartum women	Implementation science gaps	
		Determinants of successful delivery	**Strategies to enhance delivery**
Reach is the absolute number, proportion, and representativeness of individuals who are willing to participate in a given initiative	Individual: women who are **offered** any PrEP information/ screening	• Are pregnant women with risk factors for HIV more or less likely than women without risk factors for HIV to be offered PrEP in setting where HIV risk behaviors are stigmatized? • Are pregnant women with risk factors for HIV (e.g., women who are HIV-negative in serodiscordant couples) identified in antenatal care and provided with PrEP?	• Does task shifting PrEP information delivery (e.g., from nurses to HIV counselors or videos) increase the number of women receiving PrEP information within MCH settings? • Does self-administration of HIV behavioral risk screening in MCH clinics increase the number of pregnant and postpartum women who receive PrEP counseling? • Is risk screening effective at identifying women who are at-risk for HIV?
	Individual: women who **initiate** PrEP	• Will women with substantial risk for HIV accept daily oral PrEP when offered during pregnancy and breastfeeding? • What are the demographic and behavioral characteristics of women who initiate or decline PrEP during pregnancy and breastfeeding? • Why do pregnant and breastfeeding women with substantial HIV risk decline PrEP? Are these reasons specific to periods of pregnancy and breastfeeding? • What are barriers and facilitators to PrEP initiation during pregnancy and postpartum?	• Which demand creation strategies, including community-based activities, work to support PrEP initiation among pregnant and postpartum women who may benefit from PrEP? • Do effective demand creation strategies differ between pregnant and postpartum women? • Does integrating STI testing improve accurate risk perception and subsequent adoption of PrEP to improve effectiveness?
	Providers: health care providers **trained** on PrEP delivery	• What additional training is required for PrEP providers to deliver high-quality PrEP services to pregnant and breastfeeding women? • What cadre of providers has the appropriate training to provide PrEP services, including prescribing PrEP?	• What are the best provider training strategies for improving PrEP delivery to pregnant and breastfeeding women? • Can training with standardized patients improve coverage of PrEP counseling within MCH settings?
	Program/Facility: facilities that have been **exposed** to PrEP	• What are the characteristics of MCH clinics that successfully screen all pregnant and postpartum women for PrEP?	• Does integrating PrEP delivery into other services accessed by pregnant and postpartum women increase reach?



RE-AIM definition	Domain applied to PrEP delivery for pregnant/postpartum women	Implementation science gaps	
		Determinants of successful delivery	**Strategies to enhance delivery**
		• What internal and external factors influence PrEP screening for pregnant and postpartum women within the facility setting?	• Can community-based activities increase reach of PrEP programs for at-risk pregnant women?
Effectiveness is the impact of an intervention on outcomes, including potential negative effects, quality of life, and economic outcomes.	Individual: incident HIV infections averted among PrEP initiators	• Do incident HIV infections occur among pregnant and postpartum PrEP users? • Is the frequency of adverse clinical event related to PrEP use modified by periods of pregnancy and postpartum?	• Does integrating behavioral risk assessment with empiric HIV risk scores improve efficiency of identifying pregnant and postpartum women likely to benefit from PrEP?
Adoption is the absolute number, proportion, and representativeness of settings and intervention agents who are willing to initiate a program	Provider: health care providers who **deliver** PrEP	• Does workload and client volume impact the likelihood that providers will be willing to deliver PrEP to pregnant and postpartum women? • Do providers' attitudes and beliefs about PrEP use during pregnancy and breastfeeding influence whether they are willing to deliver PrEP for pregnant and postpartum women?	• Which strategies can increase the number of providers who deliver PrEP services to pregnant and postpartum women?
	Program/Facility: programs/facilities that **provide** PrEP	• Do national guidelines that allow for or recommend PrEP for pregnant and breastfeeding women with substantial risk for HIV increase the number of facilities that provide PrEP?	• Can mentorship models between facilities increase the number of facilities that provide PrEP?
Implementation is the intervention agents' fidelity to the various elements of an intervention's protocol	Facility: facilities that **provide** the necessary elements for PrEP delivery (e.g. PrEP stock, reporting registers)	• How does annual seasonality affect availability of PrEP stock and ability to delivery PrEP at MCH clinics? • Do rural MCH clinics face greater PrEP procurement challenges than urban facilities?	• Do quality improvement collaboratives between clinics reduce stock outs and delivery interruptions at clinics?
	Provider: health care providers who deliver all elements of PrEP counseling and dispensation **accurately**	• Is PrEP screening, counseling, and dispensing consistently delivered across staff who deliver PrEP to pregnant and postpartum women? • What is the quality of PrEP counseling and services for pregnant and postpartum women?	• Do job aids, checklists, or virtual fidelity monitoring improve provider fidelity to PrEP delivery? • Do strategies to improve quality of PrEP delivery and counseling for pregnant and postpartum women improve PrEP implementation?
Maintenance is the extent to which a program or policy becomes	Individual: women who **persist** with PrEP use	• Will women who initiate PrEP during pregnancy persist with PrEP use through the postpartum period?	• Which strategies can increase PrEP continuation for postpartum women (e.g., visits



RE-AIM definition	Domain applied to PrEP delivery for pregnant/postpartum women	Implementation science gaps	
		Determinants of successful delivery	**Strategies to enhance delivery**
institutionalized or part of the routine organizational practice		• What demographic characteristics are associated with disengagement from PrEP services? • Is PrEP adherence altered during pregnancy or the postpartum period? • What sociodemographic characteristics are associated with poor adherence during pregnancy or the postpartum period?	by community health extension workers during the neonatal period)? • What strategies can successfully support appropriate PrEP adherence for pregnant and postpartum women with high HIV acquisition risk? • Do reminder-based mobile message systems work to maintain adherence to PrEP for pregnant and postpartum women?
	Provider: health care providers who **continue to deliver** PrEP after time	• Following demonstration projects and studies, how many clinical staff trained on delivering PrEP to pregnant and breastfeeding women continue to deliver PrEP?	• Does integrating PrEP counseling into antenatal care clinical encounters increase the number of providers who continue to deliver PrEP? • Do individual provider champions promoting PrEP delivery influence provider continuation?
	Program/Facility: programs/facilities that **continue to provide** PrEP after time	• Is PrEP delivery for pregnant and breastfeeding women part of national PrEP programs?	• Does clinic-level performance-based financing increase the number of clinics continuing to offer PrEP services over time?

Table 2.

Completed, ongoing, and planned studies related to PrEP delivery during pregnancy and postpartum that evaluate implementation parameters

Current status of evidence generation: Completed; final results published | Ongoing; preliminary results disseminated | Planned; no results disseminated

Project name and citation(s)	Population	Geographic Setting	Study design[1]	Implementation parameters		
				Determinants measured	Outcomes measured	Strategies tested or developed
PrEP Implementation for Young Women and Adolescents (PrIYA) Program[20,33,72]	Clients at maternal child health (n=9376) and family planning (n=1271) clinics	Kenya	Observational cohort; 16 clinics	Quantitative determinants of individual level reach (uptake)	Quantitative measurement of individual reach and maintenance	Employing task shifting, flow reorganization, provider training
Evaluating PrEP cascade in pregnant and postpartum women (PrEP-PP)[16] (NCT03902481 & (NCT03826199 formative study)	Clients at antenatal clinics (n=1200 anticipated)	South Africa	Hybrid Effectiveness-Implementation; Observational cohort study	Mixed methods determinants of individual level reach (uptake), implementation and maintenance	Mixed method measurement of individual reach and effectiveness	Evaluating one model of PrEP counseling, SMS and phone call follow up
PrEP Adherence among AGYW: A Multi-Dimensional Evaluation (PrIYA-Qual)[35,63,73]	Clients (n=140) and providers (n=50) at maternal child health and family planning clinics	Kenya	Qualitative evaluation; 8 sites	Qualitative determinants of individual- and provider-level acceptability, feasibility, adoption, and sustainability	Qualitative assessment of PrEP persistence, discontinuation, non-adherence, and stop/re-starting	Development of adaptations to delivery
PrEP Implementation for Mother in Antenatal Care (PrIMA) Study[17] (NCT03070600)	Clients at antenatal clinics (n=4500, anticipated)	Kenya	Hybrid Effectiveness-Implementation; cluster RCT; 20 clinics	Quantitative determinants of individual level reach (uptake)	Quantitative measurement of individual reach, effectiveness, and maintenance	Quantitative testing risk-guided counseling to enhance appropriate individual adoption and effectiveness
Periconception PrEP for HIV-exposed Ugandan Women[74] (NCT03832530)	Women expecting to get pregnant (n=150)	Uganda	Observational cohort study	Quantitative determinants of individual level reach (uptake), implementation and maintenance	Quantitative measurement of individual reach (uptake) and maintenance	Safer conception counseling inclusive of periconception PrEP
Enhancing Integrated Delivery of PrEP within Antenatal Care with STI Testing and Expedited Partner Treatment[36]	Clients at antenatal clinics (n=600, anticipated)	Kenya	Hybrid Effectiveness-Implementation; Interrupted time series; 2 sites	Quantitative determinants of individual level reach (uptake)	Quantitative measurement of individual reach and effectiveness	Evaluating integration of STI testing with ANC-PrEP as an implementation strategy to improve PrEP uptake
Evaluating the Pharmacokinetics, Feasibility, Acceptability, and Safety of Oral Pre-Exposure Prophylaxis for HIV Prevention During Pregnancy and Postpartum (IMPAACT 2009)[18] (NCT03386578)	Clients at antenatal and postnatal clinics (n=390, anticipated)	Zimbabwe, Uganda, South Africa and Malawi	Hybrid Effectiveness-Implementation; Interrupted time series; Parallel observational cohort study	Quantitative determinants of individual level reach (uptake)	Quantitative measurement of individual reach, effectiveness, maintenance, and safety	Enhanced adherence support, including SMS messaging and feedback of drug levels with tailored counseling

Project name and citation(s)	Population	Geographic Setting	Study design[1]	Implementation parameters		
				Determinants measured	Outcomes measured	Strategies tested or developed
PrEP Optimized for Mothers (PrOM): Efficient PrEP integration in MCH clinics[27]	Clients and providers at antenatal and family planning clinics (anticipated sample size not reported)	Kenya	Hybrid Effectiveness-Implementation; Interrupted time series; 8 clinics	Qualitative determinants of reach (penetration and uptake) in setting of integration; quantitative determinants of facility-level implementation	Quantitative measurement of implementation outcomes: reach (penetration and uptake), adoption, implementation, maintenance (continuation); service outcomes: timeliness and efficiency; patient outcomes: patient and HCW satisfaction	Testing of one package of strategies (video counseling, HIV self-testing, and expedited prescribing)
Safer Conception for Women: PrEP Uptake/Adherence to Reduce Peri-conception HIV Risk for South African Women (ZINK study)[19] (NCT03194308)	Women expecting to get pregnant (n=350), anticipated)	South Africa	Hybrid Effectiveness-Implementation; Observational cohort study	Quantitative determinants of individual level reach (uptake), implementation and maintenance	Quantitative and qualitative measurement of individual reach (uptake) and maintenance	Evaluating safer conception counseling and messaging for HIV-negative women seeking to conceive and with pregnancy
Standardized Patient Encounters to Improve PrEP Counseling for Adolescent Girls and Young Women in Kenya (PrIYA-SP)[57] (NCT03875950)	Providers at maternal child health and family planning clinics (n=240, anticipated)	Kenya	Hybrid Effectiveness-Implementation; RCT; 24 clinics	Quantitative facility-level determinants of PrEP delivery (e.g., stock-outs, no. of staff trained on PrEP counseling)	Quantitative measurement of provider fidelity and implementation	Testing standardized patient actor training strategy to enhance provider reach and implementation
Testing Implementation Strategies to Improve Delivery of PrEP for Pregnant and Postpartum Women in Kenya (PrEPARE)[28]	Clients and providers at antenatal clinics (anticipated sample size not reported)	Kenya	Hybrid Effectiveness-Implementation; Interrupted time series; 16 clinics	Mixed methods identification and prioritization of determinants of reach (penetration) and implementation (fidelity)	Quantitative measurement of implementation outcomes: reach (penetration), implementation (fidelity), cost; service outcomes: timeliness, efficiency; patient outcomes: satisfaction	Mixed methods development and testing of 3 strategies TBD based on determinants
An integrated strategy to support antiretroviral therapy and pre-exposure prophylaxis adherence for HIV prevention in pregnant and breastfeeding women: a pilot study (Tonse Pamodzi 2) [75]	Clients at antenatal clinics, including 200 HIV-negative women	Malawi, Zambia	Parallel pilot randomized trials to support ART and PrEP adherence	Mixed methods identification of determinants of individual-level adherence (maintenance)	Quantitative measurement of individual-level adherence. Quantitative and qualitative measurement of fidelity, feasibility, and acceptability of intervention	Combination behavioral intervention, including patient-centered counseling and adherence support

[1]All studies with effectiveness-implementation designs denoted in Table 1 utilize a hybrid type I design (i.e., testing effects of a clinical intervention on relevant outcomes while observing and gathering information on implementation) except the PrEP Optimized for Mothers (PrOM) Study[27] and the Testing Implementation Strategies to Improve Delivery of PrEP for Pregnant and Postpartum Women in Kenya (PrEPARE) Study[28] which utilizes a hybrid type III design.