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Beyond Early Infant Diagnosis: Changing the Approach to HIV-Exposed Infants

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Abstract

Despite dramatic global progress with implementing prevention of mother-to-child HIV transmission (PMTCT) programs, there were 160,000 new pediatric HIV infections in 2016. More than 50% of infant HIV infections now occur in the postpartum period, reflecting the relatively high coverage of interventions in the antenatal period and the need for greater attention to the breastfeeding mother and her HIV-exposed infant (HEI). Early diagnosis and treatment are critical to prevent morbidity and mortality in HIV-infected children; however, early infant HIV testing rates remain low in most high HIV-burden countries. Furthermore, systematic retention and follow-up of HEI in the postpartum period and ascertainment of final HIV status remain major program gaps. Despite multiple calls to action to improve infant HIV testing rates, progress has been marginal due to a lack of focus on the critical health care needs of HEI coupled with health system barriers that result in fragmented services for HIV-infected mothers and their families. In this paper, we describe the available evidence on the health outcomes of HEI, define a comprehensive care package for HEI that extends beyond early HIV testing, and describe successful examples of integrated services for HEI.

Keywords

HIV-exposed infants; early infant diagnosis; mother-infant pairs; prevention of mother-to-child HIV transmission; ACT Initiative

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OVERVIEW OF PROGRESS WITH PREVENTION OF MOTHER-TO-CHILD HIV TRANSMISSION AND HIV-EXPOSED INFANT SERVICES

Globally, there are an estimated 1.4 million pregnant women living with HIV each year, and their infants are exposed to and at risk of HIV acquisition while in utero, during labor and delivery and during breastfeeding.[1] The success of prevention of mother-to-child HIV transmission (PMTCT) programs has resulted in a dramatic decline in new pediatric HIV infections from 490,000 (430,000–560,000) in 2000 to 160,000 (100,000–220,000) in 2016.[1,2] The ambitious 5 year "Global Plan Towards the Elimination of New HIV Infections Among Children and Keeping Their Mothers Alive" (referred to as the "Global Plan") was convened by UNAIDS and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and mobilized stakeholders worldwide to reduce new pediatric HIV infections by 90% and AIDS-related maternal deaths by 50% in 21 high burden countries.[3] Global scale-up of antiretroviral therapy (ART) has been the primary contributor to decreased mother-to-child HIV transmission and more than 90% of HIV-infected pregnant women in Botswana, Namibia, South Africa, Swaziland, Uganda and Zimbabwe received antiretroviral medications to prevent vertical transmission in 2016.[2,4]

Despite these successes, multiple programmatic barriers to elimination of mother-to-child HIV transmission in sub-Saharan Africa (SSA) remain, including gaps in lifelong ART adherence, prevention and early identification of incident HIV infection during pregnancy and breastfeeding, and loss to follow-up of mothers and infants in the postpartum period.[5,6] When the Global Plan ended in 2015, only 7 of the 21 priority countries in SSA had reduced new pediatric HIV infections by more than 70% since 2009.[4] In West and Central Africa, progress with PMTCT services has been particularly limited, with Cameroon, Chad, Cote d'Ivoire, the Democratic Republic of the Congo and Nigeria having a 30% or less decline in new pediatric HIV infections by 2015.[4] Additionally, although the World Health Organization (WHO) has recommended for more than 10 years that all HIV-exposed infants (HEI) have access to HIV virologic testing by age 4–6 weeks of life [referred to as early infant diagnosis (EID)],[6,7] access to EID has been stagnant; only 51% of the estimated 1.2 million HEI in the 21 Global Plan priority countries received HIV testing within 8 weeks of birth in 2015, a slight increase from 49% in 2013.[4] Without ART, both perinatally- and postnatally-infected infants face very high mortality rates (52% and 26%, respectively) by 1 year of age.[8] Access to early HIV testing must be coupled with immediate ART initiation as a medical emergency for this vulnerable population.[9] Additionally, since more than half of infant HIV infections occur perinatally,[1] systematic care and testing throughout the breastfeeding period, which can extend for 2 or more years in many countries, is critical to ensure optimal outcomes for HEI and HIV-infected infants.

Recognizing the ongoing challenges in reducing new pediatric HIV infections and AIDS-related deaths for HIV-infected children, the 2-year Accelerating Children's Treatment Initiative was developed near the end of the Global Plan and launched at the Africa Leadership Summit in August 2014 to close gaps in access to services for HIV-exposed and HIV-infected infants and children.[10] Ambitious target-driven initiatives such as the Global Plan and the Accelerating Children's Treatment Initiative have proven invaluable in drawing

attention, resources, and action towards preventing HIV in children and addressing the service gaps for HIV-infected children, most of whom acquire HIV through vertical transmission. This recognition prompted the 2016 launch of "Start Free, Stay Free, AIDS Free," a global framework led by PEPFAR and the Joint United Nations Programme on HIV and AIDS (UNAIDS) which aims to reduce the number of newly infected children to <40,000 by 2018 and 20,000 by 2020, and to provide 1.4 million children with HIV treatment by 2020. Central to this effort will be optimization of the identification, care, and retention of HEI throughout the risk period.[11] In this paper, we describe the unmet needs of HEI, including innovations to further the prevention gains made over the last decade and to improve long-term outcomes of HIV-exposed uninfected (HEU) infants.

BARRIERS TO TESTING AND CARE FOR HEI

Laboratory, service-delivery, and systems issues that have limited EID service scale up, including late or non-return of mother–infant pairs for infant HIV testing, laboratory reagent stock-outs, and long result turn-around times, have been well-documented.[12] While the importance of early HIV testing cannot be overemphasized, the other needs of HEI, especially later in the breastfeeding period, receive much less attention, resulting in high loss to follow-up during the breastfeeding period.[13,14] Although guidance on select components of HEI testing and care is available, public health and clinical guidance on the optimal service package for HEI and their mothers throughout the breastfeeding period is disjointed.[6,15–18] Additionally, the complexity of the recommendations often leads to limited operational feasibility in resource-constrained settings, prompting many national programs to define their own approaches.[19] Finally, recommendations for the care of HIV-infected mothers and their infants are often developed and published separately, such that there is no clearly defined and integrated package of services for mother–infant pairs on which to base facility and community programs and processes. Management of HEI and their breastfeeding mothers is a rapidly changing and complex endeavor at both patient and program levels; impractical or unclear recommendations may lead to provider non-adherence to guidelines, fragmented services, and subsequent poor quality of care that contributes to high loss-to-follow-up rates.

Another major barrier to successful HEI testing and care is absent or ineffective systems for referral, linkage, and monitoring of mother–infant pairs between multiple service delivery points. Fragmented health systems in which women and their infants must attend multiple clinics to receive maternal viral load monitoring, infant growth and development monitoring, immunizations, and infant virological testing contribute to client and provider burden and disengagement from care for both mother and child. Despite the need for strong linkages and collaborations between the multi-dimensional aspects of care, most programs have struggled to maintain linkage and cross-referral systems.[20,21]

SERVICE DELIVERY MODELS

As access to ART has rapidly increased, greater attention has been paid to differentiated models of HIV service delivery to improve patient satisfaction and health outcomes.[6,15] Although differentiated care discussions often focus on identifying populations that require

less intensive services, this concept can also be used to tailor and enhance patient services, particularly those such as the HIV-infected mother and HEI, that may be at risk of or experiencing poor clinical outcomes. Within the differentiated service delivery consultations, however, HEI have not been defined as a separate population, nor has the mother–infant pair been grouped.

A comprehensive approach to the mother–infant pair's health needs during the breastfeeding period is promising for this population. Guillaine et al[22] describe the success of a "Combined Clinic" in Rwanda, which provided maternal and infant care, including regular home visits and nutritional supplementation, until the child was 18 months of age; in this program no mothers were lost to follow-up during breastfeeding and 95% of HEI received HIV testing. Successful "mother–infant pair" clinics have incorporated innovative approaches, such as text message reminders, and have relied on a comprehensive approach to encourage retention and linkage.[23] Linkage to existing community-based programs is essential, as access to social support systems has been shown to improve uptake of services and retention.[24] For example, in Nigeria, leveraging the faith community successfully increased uptake of services for HEI (including infant virological testing and antiretroviral prophylaxis) and promoted male involvement in HIV-related family care.[25]

Integrated service delivery models may also hold promise in addressing the health system challenges faced by many countries with a high HIV burden. Most maternal and child health services are provided by non-physicians through task sharing practices.[26] Community health workers often provide HIV counseling, ART adherence support, and home visits to support retention in care.[27] There are promising examples of mother–infant pair models of care leveraging Community health workers from Malawi and Uganda, demonstrating the potential for lay health workers to promote comprehensive care for HEI and their mothers.[28,29] However, non-physician healthcare workers, particularly lay health workers, may not be formally recognized within the health care system. Increased attention to health care worker professional development, including formalizing the role of lay health workers, is critical to ensuring access to HIV-related and comprehensive health care for mother–infant pairs.[26]

ADDRESSING THE SPECIAL NEEDS OF HEI

Patient-centered care is essential to caring for HEI, especially considering their need for close follow-up during the breastfeeding period. Research has shown that even HEU children may have disparities across a range of growth, developmental and immunological parameters compared to their HIV-unexposed counterparts.[30] The number of HEU infants is large; in the last 10 years, over 8.5 million infants were exposed to HIV in utero, and 5.5 million were exposed to antiretroviral medications while in utero without acquiring the infection.[31] The health and nutritional consequences of HIV exposure are still under investigation; however, evidence shows that HEU infants have worse nutritional status than HIV-unexposed infants, even when their mothers are receiving lifelong ART.[32] A meta-analysis by Brennan found that HEU children had a >70% increased risk of mortality compared to HIV-unexposed infants; this risk was present across all age bands studied and did not improve significantly with PMTCT services.[33] A study from Botswana, where ART

for pregnant women is widely available, found that 46% of under 2-year mortality occurred among HEU although they only account for 25% of the under 2 year population.[34] The reasons for this excess mortality are likely multifactorial, including immunologic impairment in both mother and infant, increased exposure to opportunistic infections from living in HIV-affected households, and the socioeconomic milieu into which infants are born. In-utero exposure to HIV and to antiretroviral medications, especially protease inhibitor-based regimens, have also been linked to increased preterm birth and low birth weight, which are universal risk factors for increased morbidity and mortality.[35–38]

Given the potential health disparities for HEI, counseling for HIV-infected mothers about infant health needs should start during the antenatal period to emphasize both the importance of HEI care and the importance of ART adherence, retention and viral load monitoring for the mother's own health and for reducing ongoing risk of HIV transmission during the breastfeeding period. Meaningful engagement with women receiving PMTCT services through effective counseling and peer/mentor mothers is important for minimizing loss to follow-up of mother–infant pairs.[39,40] Additionally, improving male partner engagement in antenatal and infant care, along with support to the mother for HIV status disclosure, are critical to reducing fear and stigma-related reasons for disengagement from HIV care.[41,42]

DEFINING A COMPREHENSIVE PACKAGE OF CARE FOR HEI

Providing a high-quality, comprehensive and integrated HEI care package has the potential to improve health outcomes for HEI and their families. We propose that the components of this care package include the standard medical interventions for HEI as well as routine infant care, family care, and linkage to support services (Table 1). This package recognizes that infants have needs specific to their HIV-exposure in addition to routine health care needs, and that the health of an HEI is further dependent on the health and well-being of the family. As described below, each component of this proposed care package is high-impact, safe, feasible, and effective in reducing infant morbidity and mortality. When developing and implementing country-specific HEI service delivery models, ensuring access to all of the services in this package should be a priority.

Identification of HEI and Infant HIV Testing

The success of the infant HIV testing program is highly dependent on early identification and enrollment of HEI and their mothers in PMTCT services with systematic follow-up until final HIV status determination at the end of the breastfeeding period. As described earlier, although early HIV diagnosis is necessary to reduce HIV-related infant mortality, the coverage of EID is much lower than 6-week immunization coverage and maternal postnatal PMTCT retention, indicating multiple missed opportunities to identify HEI in inpatient wards or other facility entry points, such as immunization visits and/or maternal postnatal care and ART follow-up.[43] Approaches to improving EID coverage include scheduling 6-week postpartum mother–infant pair appointments prior to or at birth, active tracking for missed appointments, maternal HIV testing and screening for infant HIV exposure at immunization clinics (see Case Study), and demand creation for antenatal care, facility delivery, and postnatal care. For infants who present to the health facility for EID,

optimizing the system and logistics of conventional laboratory-based infant virological testing or introducing point-of-care testing may reduce the time it takes to receive results and improve linkage to ART for infants who are identified as HIV-infected.[44] Birth testing is also being introduced in several high HIV-burden countries as part of the strategy for earlier diagnosis; however, implementing birth HIV testing can be operationally complex and does not replace the need for additional testing near 6 weeks of age as well as during and at the end of breastfeeding.[6,45–47] In addition to improving early HIV testing efforts, active follow-up and retention in care of HEI during the breastfeeding period are essential to identify incident infant HIV infections and link HIV-infected infants to ART, especially since the majority of infant HIV infections now occur during the postpartum period.[1] Additionally, given the high HIV incidence among pregnant and breastfeeding women in sub-Saharan Africa,[48] improving implementation of repeat maternal HIV testing is critical to identify incident maternal HIV infections and ensure that all HEI receive necessary follow-up and testing.[49]

Preventive Care

Cotrimoxazole and infant antiretroviral prophylaxis have long been shown to prevent opportunistic infections and reduce the risk of HIV acquisition, respectively.[50,51] The WHO 2016 guidelines included the option of enhanced postnatal prophylaxis for infants at high risk of HIV acquisition. These high-risk infants (defined primarily by recent maternal HIV diagnosis and/ or ART initiation or high maternal HIV viral load) are now eligible for up to 12 weeks of prophylaxis with a combination regimen of zidovudine and nevirapine.[6] This approach has the potential to reduce HIV acquisition among high-risk infants, yet implementation challenges include complex antiretroviral dosing requirements, limited coverage of routine maternal viral load monitoring during pregnancy, and operational difficulty identifying high-risk infants at the time of delivery. National implementation plans for enhanced postnatal prophylaxis, including revisions to national guidelines and healthcare worker training, support and job aids/standard operating procedures, would underpin effective scale-up of this new recommendation. Evaluation of enhanced postnatal prophylaxis scale-up in early-adopting countries will provide useful lessons for other national programs.

In addition to their risk for HIV acquisition, HEI are at higher risk of tuberculosis (TB) exposure than HIV-unexposed infants. TB in pregnancy is associated with both adverse maternal and infant outcomes.[52] Thus, TB screening for pregnant and breastfeeding women, contact screening of all adults with active TB disease, and initiation of eligible HEI on TB preventive treatment are key interventions to reduce TB-related morbidity and mortality among HEI.

Routine Infant Care

Routine infant care, including immunizations, growth and developmental milestone monitoring, infant feeding counseling and support, and childhood illness management, should be included in a comprehensive HEI care package.[53] Integrated service delivery points where infants can receive both HIV-specific and general infant services on the same day are optimal, especially when care can be coordinated with HIV-related services for the

mother. Given the potential negative effects of HIV exposure on nutritional status,[32] growth monitoring is critical both to identify those HEI who need nutritional support, and to identify malnutrition as a potential sign of HIV infection and indication for HIV testing and clinical evaluation. Additionally, given reports of higher rates of low birth weight and preterm delivery among HEI, enhanced early neonatal care may be needed.[54]

Family Care

Improving outcomes for HEI is largely dependent on ensuring the health of the mother and the family unit, from both clinical risk and social well-being perspectives.[55–60] Ensuring viral suppression during pregnancy and breastfeeding is the most critical intervention to reduce the risk of HIV transmission to the infant,[61] making ongoing assessments of maternal ART adherence and routine viral load monitoring at recommended intervals essential during the breastfeeding period. Delivering HIV-related services through a family-based care model provides an important opportunity beyond the antenatal clinic to ensure that HIV testing is offered to male partners and to HIV-exposed siblings. Involving fathers of HEI has been shown to promote HIV status disclosure within families and further protect against loss to follow-up of the mother and infant.[62] The postpartum period also presents an important opportunity for family planning service provision to promote child spacing, which has also been shown to improve perinatal outcomes.[63]

Community Linkages and Referrals

HEI are members of families that are at higher risk for social, financial and physical vulnerabilities. In addition to meeting clinical needs of HIV-affected families, it is essential to ensure that linkages to a social support system [eg, orphans and vulnerable children programs and community-based comprehensive care services] exist for HEI and HIV-infected children.[59,64] Orphans and vulnerable children programs can provide wraparound services to support HIV-affected households, thereby playing a critical role in the achievement of 90–90-90 goals for HIV-infected children and long-term support for HEI.[65] Monitoring bidirectional linkage between HIV testing, treatment and clinical care with community- or facility-based social services are important to ensure effective referrals.

Case study: integrated postnatal maternal HIV retesting and HIV-exposed infant screening within the immunization program to improve identification and uptake of PMTCT services in Kenya

Kenya adopted a national policy recommending life-long ART for pregnant and breastfeeding women in 2014.[66] Mother-to-child HIV transmission rates have dropped 3-fold from 26% in 2009 to 8.3% in 2016 with the highest drop between 2014 and 2016 as ART coverage expanded.[67,68] However, the mother-to-child HIV transmission rate remains over 8% at the end of the breastfeeding period, with over 6000 new infants infected in 2016.[2] Late antenatal clinic attendance, incident maternal HIV infections during late pregnancy or the postpartum period, loss to follow-up from ART, and persistent viremia among HIV-infected women are among reasons for ongoing new pediatric HIV infections.[48,69–73]

The 2015–2019 Kenya AIDS Strategic Framework identified the integration of HEI screening in immunization programs as an opportunity to improve child survival through early HIV identification, treatment and follow up. Kenya has a strong immunization program, with over 80% coverage for 6-week vaccinations, including the pentavalent and oral polio virus-1 (OPV1) vaccines.[74,75] Immunization visit timing aligns with the recommended time for postnatal maternal HIV retesting and infant virological testing, thus offering an opportunity to address mothers and infants who were missed or lost from the PMTCT program. In 2016, through PEPFAR implementing partners in western Kenya, the Centers for Disease Control and Prevention-Kenya piloted and rolled out an integrated maternal HIV retesting and HEI screening program at the 6-week OPV1 visit in 556 facilities.

As part of the pilot, PMTCT peer support staff were trained to review Maternal Child Health booklets to identify and re-test all women who were HIV-negative or of unknown HIV status in accordance with national PMTCT guidelines.[76,77] Figure 1 provides an overview of this approach. Infants were categorized as “new HEI” when their mothers were newly identified as HIV-positive, “known HEI” when mothers were already documented as HIV-infected, or as “non-HEI” when mothers were identified as HIV-negative. Newly-identified HIV-infected mothers and “new HEI” were linked to maternal ART, infant antiretroviral prophylaxis and infant virological testing per national guidelines.[78] Data fields were added to the immunization register to capture the outcomes of HIV screening. Program data from October 2016 to September 2017 revealed that, of the 96,037 infants who received OPV1, 98% (93,867) were screened for HIV exposure through maternal HIV status assessment; of these, 1% (1,025) were “new HEI.” Twelve percent of all infants receiving OPV1 (11,214) were HEI (“known HEI” and “new HEI” combined), with 99.5% (11,167) confirmed as linked with ongoing PMTCT services, including infant HIV testing, from the immunization program.[79] Additional data review and analysis are being planned to collect final HEI outcomes, including positivity rates and linkage to ART for HIV-infected infants.

Due to the impact of this pilot program, Kenya’s National AIDS and STI Control Programme adopted this strategy as part of the national standard of care and incorporated the HEI screening indicators into the Ministry of Health’s monthly HIV reporting tool; discussions about incorporating variables in the immunization register are ongoing. Kenyan guidelines also recommend repeat HIV testing for mothers at 6 months and 18 months after delivery, which aligns with later infant immunization visits. These changes will facilitate improved identification of early and late HIV exposure.[78] These results affirm that integration of HIV services within Maternal Child Health clinics, including national immunization programs, provides a critical opportunity to eliminate mother-to-child HIV transmission.

DISCUSSION

As ambitious global efforts to eliminate mother-to-child transmission of HIV and control the HIV epidemic advance, it will be critical to ensure that the complex needs of the millions of HEI receive focused attention. The public health community is still coming to understand the long-term health consequences of exposure to HIV, including for those who remain

uninfected. Streamlined, comprehensive, clear, and feasible service delivery guidance would help ensure that providers are adequately trained to provide comprehensive care for HEI. Raising the quality of care, meaningfully engaging women during pregnancy through counseling and mentorship from peer mothers, closing the gaps in early identification of HIV-infection among mothers, and optimizing services to meet the needs of the mother–infant pair are critical for maintaining retention after delivery and providing care for HEI. Finally, as described in this paper, a well-defined, holistic and comprehensive approach that recognizes the need to provide integrated services for the mother–infant pair and their family unit will be important strategies to optimize health outcomes.

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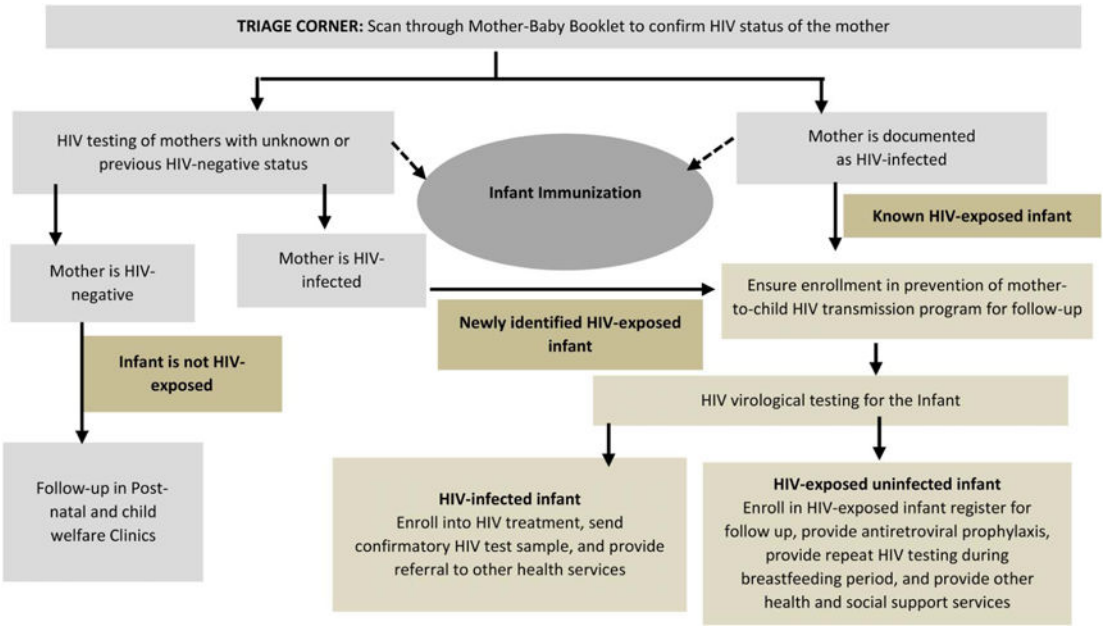

FIGURE 1.
Overview of HIV screening in immunization settings, western Kenya.

TABLE 1.

Components of a Comprehensive Care Package for HEI

I. Identification of HEI and infant HIV testing
a. Early identification of HIV-exposed infants through early and repeat HIV testing of women at their first antenatal care visit, in the third trimester (or at labor and delivery) and in the postpartum period, along with systematic follow-up of mother–infant pairs
b. Early infant diagnosis according to national guidelines (4–6 weeks of age, or birth testing AND early infant test)
c. Testing during the breastfeeding period to identify incident HIV infections. Final HIV test 3 months after cessation of breastfeeding
d. Post-test counseling and immediate linkage of HIV-infected infants to lifelong antiretroviral therapy
II. Preventive care
a. Antiretroviral prophylaxis from birth to 6–12 weeks of age, including enhanced postnatal prophylaxis for high-risk infants
b. Cotrimoxazole prophylaxis from 4–6 weeks of age until final HIV test result is negative
c. Tuberculosis (TB) screening and TB preventive therapy for infants in contact with active TB cases
III. Routine infant care
a. Immunizations
b. Growth monitoring and nutritional support
c. Developmental screening
d. Infant feeding counseling to promote exclusive breastfeeding for 6 mo
IV. Family care and support
a. Ensure maternal antiretroviral treatment adherence and maternal viral suppression at routine intervals during pregnancy and breastfeeding
b. Caregiver counseling and education on postnatal care and HIV-exposed infant services
c. Family HIV testing: Sexual partners and other biological children
d. Male partner engagement in health care services
e. Family planning
V. Community linkages and referrals
a. Tracking of mother–infant pair for missed appointments and loss to follow-up
b. Linkage with community-based support systems and support groups
c. Referral to social welfare programs (eg, orphans and vulnerable children services)