TECHNICAL BRIEF: Measurement of mother-to-child transmission of HIV in countries with high HIV prevalence in women of reproductive age

Acknowledgements

Contents

Abbreviations and Acronyms

ANC   antenatal care

ART   antiretroviral therapy

ARV   antiretroviral

CDC   U.S. Centers for Disease Control and Prevention

DBS   dried blood spot

EA   enumeration area

EID   early infant diagnosis

EMTCT   elimination of mother-to-child transmission

GAM   UNAIDS Global AIDS Monitoring

Global Fund Global Fund to Fight AIDS, Tuberculosis and Malaria

GVAC   Global Validation Advisory Committee

HDSS   health and demographic surveillance system

HEI   HIV-exposed infant

HIV   human immunodeficiency virus

M&E   monitoring and evaluation

MCH   maternal and child health

MTCT   mother-to-child transmission

PEPFAR   United States President's Emergency Plan for AIDS Relief

PMTCT   prevention of mother-to-child transmission

UNAIDS   Joint United Nations Programme on HIV/AIDS

UNICEF   United Nations Children's Fund

USAID   United States Agency for International Development

WHO   World Health Organization

© UNICEF/UNI22174747/Gonzalez Farran

Executive summary

Programs aimed at eliminating mother-to-child transmission (MTCT) of HIV in countries with a high HIV burden have substantially reduced the number of new paediatric HIV infections through routine HIV testing of pregnant women and provision of lifelong antiretroviral therapy (ART) to HIV-infected mothers. Although corresponding data systems for the collection and analysis of key MTCT indicators have improved, timely and reliable measurement of program impact remains a key challenge. Rates of both MTCT and HIV-free survival should be calculated to determine effectiveness of

prevention of MTCT (PMTCT) programs, and estimates must account for the entire period of potential transmission (i.e., until after cessation of breastfeeding). This necessitates a long duration of follow-up and high coverage of key interventions throughout the postnatal period.

Due to gaps in program coverage, data availability and data quality, most countries with a high HIV prevalence rely on mathematical models such as the AIDS Impact Model (AIM) in Spectrum for national population-based MTCT estimates. The Spectrum model uses a variety of sources

to incorporate all possible transmission scenarios; although country-submitted program data is integral, evidence-based assumptions are also used to cover program data gaps and account for transmission outside of PMTCT programs. In addition to filling in data that is unavailable or cannot be measured through program data (e.g., incident infection in pregnant and breastfeeding women, infant mortality), models can also help clarify the impact of different interventions and generate comparable estimates of MTCT between countries.

Programs aimed at eliminating MTCT of HIV in countries with a high HIV burden have substantially reduced the number of new paediatric HIV infections through routine HIV testing of pregnant women and provision of ART to HIV-infected mothers.

Although MTCT rate should be measured at the population level, facility-based MTCT rates derived from routine program data can provide valuable information for program monitoring and improvement and data triangulation, and optimization of PMTCT program data should be a high priority. Due to significant issues with retention and data quality in the postpartum period, efforts should prioritize follow-up of HEIs at infant service delivery points and documentation of infant final status outcomes. Use of a cohort monitoring approach may be beneficial, as longitudinal data enables improved monitoring and reporting and also enhances facility-level awareness and management of issues vital

for clinical follow-up (e.g., patient tracking, test result return, ART linkage). As part of program data strengthening, countries should also critically assess current PMTCT data collection and reporting requirements to ensure a streamlined and sustainable approach that focuses on essential measures and outcomes.

Several countries have conducted large nationally representative studies to generate population-level estimates of PMTCT program impact. Although these studies can provide useful information, accumulating experience has highlighted significant issues related to conducting these types of surveys. These include high

financial and human resource costs, long protocol development and approval times due to complex study designs and consent requirements, time-intensive and complex data management procedures with lengthy data analysis periods, and delayed release of results that limits utility for program management. Because of these issues, surveys or special studies should be reserved for validation of program data and modeled estimates and/ or collection of key supplemental information. When needed, a community-based survey approach is recommended to provide a population-based MTCT and HIV-free survival estimate that does not require prolonged study follow-up.

Introduction

Background

Programs aimed at eliminating mother-to-child transmission (MTCT) of HIV in countries with a high HIV burden have substantially reduced the number of new paediatric HIV infections through routine HIV testing of pregnant women and provision of lifelong antiretroviral therapy (ART) to HIV-infected mothers. In 2019, 95% [71 – 100%] of HIV-infected mothers in East and Southern Africa received ART, up from 50% [37-60%] in 2010.[1] However, 74,000 [50,000 – 120,000] new paediatric HIV infections occurred in the region in 2019, highlighting that significant efforts are still needed to achieve the Start Free Stay Free AIDS Free goals for an AIDS free generation.[2]

Prevention of mother-to-child transmission (PMTCT) programs have undergone dramatic changes as interventions have evolved from provision of single-dose nevirapine to lifelong triple-drug ART ('Option B+'). These programmatic shifts have necessitated corresponding new approaches to program monitoring, and countries have made substantial progress in developing systems for the collection and analysis of key PMTCT indicators, especially in the antenatal period.

Measurement of PMTCT program impact has proven to be challenging, however.

PMTCT program effectiveness as determined by the MTCT rate (proportion of children born to HIV-infected mothers who acquire HIV infection through vertical transmission) and the HIV-free survival rate (proportion of HIV-exposed children who are alive and HIV-uninfected at cessation of breastfeeding) requires the incorporation of multiple factors from pregnancy to the end of breastfeeding. Follow-up of mother-infant pairs and collection of quality data throughout this period is hampered by the complexity and variation of PMTCT programs, especially in the postpartum period (Box 1).

National programs and donors require reliable estimates of MTCT and HIV-free survival for program planning and management as well as for documentation of population-level MTCT rates as outlined in the World Health Organization (WHO) Global Validation of Path to Elimination criteria. Because of challenges in PMTCT program monitoring, most countries with a high HIV prevalence in women of reproductive age rely on mathematical models for national MTCT estimates. In addition, several countries have conducted nationally representative studies to determine PMTCT program impact. Both models and special studies are useful and can provide key supplemental information on PMTCT program effectiveness. However, there has been increasing recognition that reliance on models and studies is suboptimal and that efforts should focus on developing a more sustainable, timely, and program-centered approach for MTCT measurement in high burden settings that aligns with and supports efforts to strengthen the collection and use of routine PMTCT program data.

Purpose of this document

This document outlines the fundamentals of PMTCT impact determination and provides considerations for development of pragmatic, streamlined and resource-efficient systems for MTCT estimate generation in high burden settings. The guidance attempts to acknowledge the current reality of PMTCT program data and the need for reliable MTCT rates while also encouraging a forward-looking approach towards sustainable PMTCT program data improvements. The specific objectives are to:

- Delineate the key principles and components for MTCT rate calculation

- Describe how models are used to estimate population-based MTCT rates

- Highlight the utility of facility-based MTCT estimates derived from routine program data

- Outline key considerations for strengthening PMTCT data for MTCT calculation

- Describe the role of special studies for MTCT rate determination

- Provide an example study protocol for population-level estimates of MTCT and HIV-free survival when needed.

Please note that this document is intended for countries in sub-Saharan Africa with a high prevalence of HIV among women of reproductive age. Although many of the underlying principles are relevant to settings with a lower burden of HIV, the guidance is not targeted for those programs.

BOX 1	Unique program characteristics that impact PMTCT program monitoring and evaluation

- HIV-infected mothers often transition between ART programs and PMTCT programs with each pregnancy.

- Programs involve multiple service delivery points, cadres of staff, and data collection points (e.g., antenatal clinics, maternity centers, mother-baby clinics).

- Continuity of care after delivery is required for both the HIV-infected mother and HIV-exposed infant.

- Because women may breastfeed for up to 3 years in many countries, prolonged mother-child follow-up is required to ensure accurate determination of the infant's final status (i.e., after cessation of breastfeeding).

- There are no standardized postpartum service delivery models for HIV-negative women that can be adapted for the repeat testing of HIV-negative breastfeeding women required to detect maternal incident infection.

Key principles for measuring PMTCT program impact

MTCT measurements should account for the entire exposure period. HIV transmission from mother-to-child can occur in utero, during delivery, or during breastfeeding. Virologic suppression in the mother through provision of ART can nearly eliminate the risk of transmission; however, even small and transient increases in maternal viral load can be associated with transmission, so early and sustained virologic suppression is required.[3] In many high HIV burden countries more than half of women breastfeed at least 2 years,[4] thus the potential exposure period is at least 3 years. Calculation of a final MTCT rate requires incorporation of multiple programmatic and patient-level factors that contribute to virologic non-suppression during the entire exposure period.

MTCT rate should be measured at the population level, but facility-based MTCT rates can provide valuable information for program monitoring and improvement and data triangulation. Figure 1 illustrates the multiple potential scenarios in which MTCT can occur and highlights the significant role of infections that occur outside of routine programs due to undetected incident infection and dropout from ART programs. This underscores the need for a population-based national MTCT calculation given the proportionally larger risk of transmission among mothers who do not access the health system at all or access services late. However, facility-based MTCT rate calculations (i.e., MTCT among women and infants

enrolled in the PMTCT program) can be useful in identifying health system and program gaps and targeting improvements.

Measurement of MTCT of HIV should include calculation of both the MTCT rate and HIV-free survival. Using both measures allows the most accurate determination of the population-level effectiveness of the national PMTCT program.

• **MTCT rate** is the proportion of children born to HIV-infected mothers who acquire HIV infection through vertical transmission. This calculation focuses on the coverage and impact of HIV-specific components of care provided by the PMTCT program (e.g., HIV testing, ART provision,

Figure 1. Contribution of patient/program factors leading to new paediatric HIV infections in 2 African regions (Source: UNAIDS 2020 estimates)

Legend:
- Started ART late in pregnancy; child infected during breastfeeding
- Started ART during pregnancy; child infected during breastfeeding
- Started ART before pregnancy; child infected during breastfeeding
- Mother infected during breastfeeding
- Dropped off ART; child infected during breastfeeding
- Did not receive ART during breastfeeding
- Started ART late in the pregnancy; child infected during pregnancy
- Started ART during the pregnancy; child infected during pregnancy
- Started ART before the pregnancy; child infected during pregnancy
- Mother infected during pregnancy
- Dropped off ART during pregnancy; child infected during pregnancy
- Did not receive ART during pregnancy

viral suppression, infant infection status at end of breastfeeding).

- **HIV-free survival** is defined as the proportion of children born to HIV-infected mothers who are alive and HIV-uninfected at a defined timepoint, usually following cessation of breastfeeding. This measure incorporates factors external to the HIV PMTCT program (e.g., non-HIV-related causes of mortality such as malaria and cholera), and thus provides an important complementary and holistic view of outcomes of the children of HIV-infected mothers. This metric is especially important given that HIV-exposed uninfected (HEU) children have increased risk of morbidity and

mortality compared to children without HIV exposure.[5]

Infant HIV infection status after cessation of breastfeeding (i.e., 'final outcome status') is the gold standard indicator of MTCT, but calculation of MTCT at other timepoints may be informative. To account for transmission risks in utero, at delivery, and during breastfeeding, WHO recommends HIV-exposed infants be tested at 6 weeks of age, 9 months of age, 3 months after cessation of breastfeeding, and any time there are signs or symptoms suggestive of HIV infection. Testing of HIV-exposed infants at birth for earlier detection of in-utero infection may also be considered in some countries.[6]

MTCT calculations earlier than the final outcome can better establish the timing of new paediatric infections and help target programmatic interventions, and many programs align earlier MTCT calculations with the recommended testing time points for infant virologic testing. When calculating MTCT rates across the various time points, it is critical to align the denominators as much as possible to allow valid comparisons.

- **Early transmission:** Determination of the MTCT rate at 6-8 weeks can estimate transmission in-utero or during delivery. In countries with a long duration of breastfeeding, the early MTCT rate alone is not an adequate measure of PMTCT program effectiveness because it does not account for the entire breastfeeding period.

- **'Late' and/or 'final outcome' transmission:** These estimates account for transmission of HIV during breastfeeding. A true 'final outcome' calculation is done at least 12 weeks after cessation of breastfeeding. However, even within the same country there may be a wide range of breastfeeding duration, so usually a late transmission time point (e.g., 12, 18, or 24 months) is defined that best fits the breastfeeding cultural context of the country. Later time points will reflect more final outcomes and include additional mortality.

Population-based MTCT measurements

MTCT models

The Global AIDS Monitoring (GAM) guidance defines the national MTCT rate as the estimated proportion of children newly infected with HIV from MTCT among women living with HIV delivering in the past 12 months.

- Numerator: Estimated number of children newly infected with HIV in the previous 12 months from MTCT

- Denominator: Estimated number of births to women living with HIV in the previous 12 months

Ideally, it would be possible to use program data for measurement of the GAM indicator. However, as noted above, accurate national MTCT rates must account for all major transmission scenarios and thus require robust program data throughout the entire transmission period, including information on women and children who do not access PMTCT services and women who seroconvert after HIV testing at ANC. In high burden countries, this is often unavailable, so mathematical models such as the AIDS Impact Model (AIM) in Spectrum are used to generate annual population-based MTCT estimates for both 6-week and final (after cessation of breastfeeding) transmission. In addition to filling in gaps for data

that is unavailable or cannot be measured through program data, models can also help clarify the impact of different interventions[7] and allow comparable measure of MTCT between countries.

Elements of the Spectrum MTCT Rate Calculation

The Spectrum MTCT rate estimate is embedded within the full Spectrum Child Model (Figure 2). The MTCT calculation begins with the number of births to HIV-infected women, which is estimated using demographic, surveillance, survey, and HIV epidemic parameters. Program data on women receiving treatment and duration of breastfeeding are applied to those births to calculate the annual number of new paediatric HIV infections.

Key model elements and inputs for the MTCT rate calculation are summarized in Table 1.[8] As shown, the model uses a variety of sources; although country-submitted program data is integral, evidence-based assumptions are also used to fill in program data gaps and account for transmission outside of PMTCT programs.

Figure 2. Spectrum Child Model

1 Demographic Data

Total fertility rate

Age distribution of fertility

Number of women aged 15-49 years (by five-year age group)

2 Surveillance and survey data

3 Epidemic patterns

Female/male ratio of incidence

Age distribution of incidence

Mortality

4 Fertility Adjustment

Reduced fertility among HIV+ women

Matched prevalence to ANC

MTCT Rate Calculation

5 Number of births to HIV+ women

6 Number of women receiving ARV prophylaxis or treatment Including retention during pregnancy

7 Number of children born HIV+

8 Breastfeeding Patterns + incidence during BF

9 Number of new child HIV infections

15 AIDS-related deaths among children

11 Disease progression among children not receiving ART

14 Survival among children receiving ART

13 Number of children receiving ART and CTX by age

12 Distribution of age of ART initiation

10 Children living with HIV

■ Assumptions ■ Country team input ■ Calculation

Table 1. Key Elements of the Spectrum MTCT Rate Calculation

Element	Data Type	Source
Number of HIV+ pregnant women	Calculation and country input	Fertility from World Population Prospects 2019; ANC HIV prevalence from routine testing (If unavailable, fertility reduced based on CD4 count and maternal age)
Transmission during the peripartum period (Includes pregnancy and delivery, plus 4-6 weeks after delivery in breastfeeding populations)		
Number of women receiving ART during pregnancy by timing of ART start (before pregnancy, early in pregnancy, <4 weeks before delivery)	Country input	Programme data
Peripartum probability of transmission (%)	Assumption	• ART started before pregnancy: 0.26 • ART started during pregnancy (>4 weeks duration): 1.4 • ART started <4 weeks before delivery: 8.2 • No ART during pregnancy: 19.7
Retention on ART during pregnancy	Country input	If programme data unavailable, evidence-based assumption used: • 80% of women retained in care at delivery • 7.5% transmission among women who drop out
Incident infection during pregnancy - **Maternal incidence rate** - **Transmission probability for incident infection**	Calculation (incidence); Assumption (transmission)	• Incidence rate with age adjustment for fertility • 18% transmission for incident infection during pregnancy
Transmission during the postpartum period (Calculated as monthly probabilities multiplied by duration of breastfeeding)		
Duration of breastfeeding (by 2-month intervals)	Country-specific assumptions	Based on survey data by HIV serostatus and smoothed using regional data
Number of women receiving ARVs during breastfeeding	Country input	Based on women receiving ARVs during pregnancy, excluding drop-outs
Breastfeeding probability of transmission (% per month)	Assumption	• ART start before pregnancy: 0.023 • ART start during pregnancy: 0.11 • No ART: 0.89
Monthly drop out during breastfeeding	Country input if available; otherwise assumption	Default assumptions if no programme data available: <12 months: 1.2% probability of LTFU per month >12 months: 0.7% probability of LTFU per month
Incident infection during breastfeeding - **Maternal incidence** - **Probability of transmission**	Calculation (incidence); Assumption (transmission)	• Uses duration of breastfeeding as above multiplied by age specific incidence from Spectrum calculations • 27% chance of transmission for incident infection during breastfeeding

Considerations for select MTCT rate components

Several key components of the MTCT rate deserve special mention due to specific data challenges and recent programmatic developments that may impact measurement.

Incident infection during pregnancy and breastfeeding

As seen in Figure 1, a significant number of new paediatric HIV infections are due to incident maternal infection in pregnancy and breastfeeding. A woman's risk of HIV acquisition is more than doubled during pregnancy and the postpartum period, and women who acquire HIV infection during pregnancy or breastfeeding are at particularly high risk of transmitting the virus to the fetus or breastfeeding infant due to high HIV viral loads.[9,10] As PMTCT programs more effectively identify HIV-infected women early in pregnancy and initiate effective ART, women who seroconvert late in pregnancy or during breastfeeding will become an even larger contributor to overall rates of MTCT.

Repeat testing to detect maternal incident infection

To detect incident infection during pregnancy, WHO recommends repeat HIV testing in the third trimester (or as soon as possible afterward) for pregnant women in high prevalence settings who are HIV-negative at the first ANC visit.[11] However, these recommendations are not widely implemented, monitoring indicators have not been developed, and incident maternal

infections are generally not disaggregated in national program data.[12] Detection of postpartum incident HIV infections is particularly problematic, as follow-up of HIV-negative mothers throughout breastfeeding is not the standard of care. Although some countries have piloted HIV testing of breastfeeding mothers at infant immunization clinics, implementation has not been scaled-up widely due to implementation challenges.[13] Furthermore, despite their disproportionate contribution to national MTCT rates, the absolute number of women with incident HIV infection during pregnancy and breastfeeding is relatively small, even in high HIV burden countries, thus high levels of testing coverage in HIV-negative breastfeeding women may be required to significantly reduce infant HIV infections. Given these issues, detection of incident maternal infection in breastfeeding will likely remain a gap in the short-term.

Innovations for improving prevention, detection, and quantification of maternal infections

Several key programmatic and surveillance interventions may enhance efforts to decrease and measure maternal incidence. Widespread use of PrEP in pregnant and breastfeeding women at substantial risk of incident HIV infection as recommended by WHO could play a significant role in decreasing the number of maternal seroconversions and thus lowering the risk of MTCT.[14] In addition, the routine HIV testing required for PrEP use

may also help create sustainable service delivery models for repeat testing of HIV-negative women.

Recency assays allow determination of whether an HIV infection was acquired within the past six months; use of these tests in newly diagnosed PLHIV is being scaled-up in several countries as a tool for real-time surveillance and public health response.[15] Although the role of recency assays for quantifying maternal seroconversion is currently not well-defined, they could potentially aid in quantifying maternal incidence for use in MTCT rate calculations.[16]
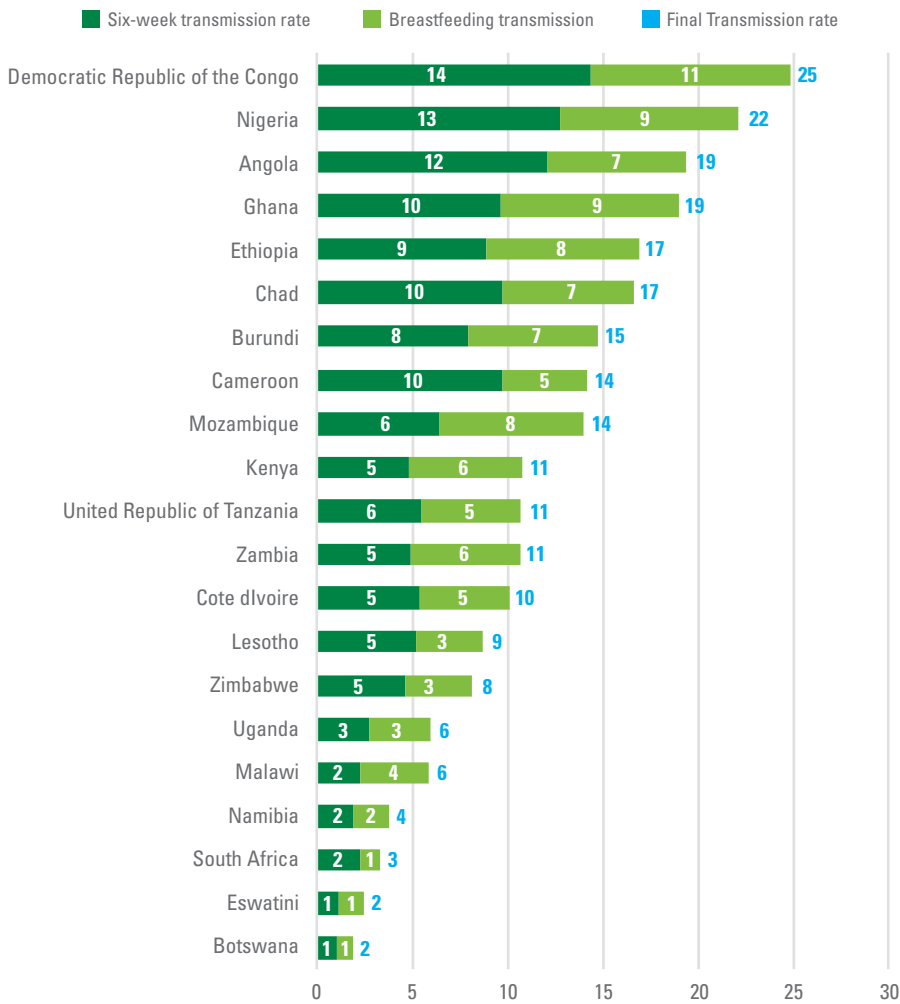
Breastfeeding duration

In many high burden settings, almost half of MTCT occurs during breastfeeding (Figure 3). Duration of breastfeeding is a critical data point for national programs because it determines 1) how long an infant is exposed to HIV and 2) duration of MTCT risk related to incident infection in a breastfeeding woman. Despite the importance of this data for both MTCT rate determination and program planning, there are few studies on duration of breastfeeding in women living with HIV. Updated country-specific data is required, as breastfeeding duration can change over time in response to economic stability, changing messages to women, and other factors.[17]

Retention during pregnancy and breastfeeding

Follow-up of mother-infant pairs until cessation of breastfeeding is critical for both programmatic

Figure 3. MTCT rates at 6 weeks and at end of breastfeeding in select countries, 2019. (Source: UNAIDS 2020 estimates)

Legend: ■ Six-week transmission rate ■ Breastfeeding transmission ■ Final Transmission rate

Country	Six-week transmission rate	Breastfeeding transmission	Final Transmission rate
Democratic Republic of the Congo	14	11	25
Nigeria	13	9	22
Angola	12	7	19
Ghana	10	9	19
Ethiopia	9	8	17
Chad	10	7	17
Burundi	8	7	15
Cameroon	10	5	14
Mozambique	6	8	14
Kenya	5	6	11
United Republic of Tanzania	6	5	11
Zambia	5	6	11
Cote dIvoire	5	5	10
Lesotho	5	3	9
Zimbabwe	5	3	8
Uganda	3	3	6
Malawi	2	4	6
Namibia	2	2	4
South Africa	2	1	3
Eswatini	1	1	2
Botswana	1	1	2

quality and MTCT calculation. Mothers who do not receive ANC or PMTCT services or are not retained in care have a higher likelihood of transmission, and the HIV-exposed infant does not receive recommended infant testing, antiretroviral prophylaxis, and routine services. PMTCT program data show substantial rates of attrition throughout the PMTCT cascade, with large discrepancies between the number of HIV-positive pregnant women and the number of HIV-exposed infants undergoing infant testing.[18] Postpartum adherence to ART and retention in care is particularly problematic.[19]

Mortality in HIV-exposed infants

Ascertainment and reporting of infant deaths in high HIV prevalence settings is often incomplete, and the precise cause of death is rarely known. Even for women enrolled in PMTCT services, infant deaths that occur between delivery and the first post-birth facility visit may go undetected, as mothers are unlikely to visit immunization or other MCH clinics and report the child's survival status. This has led to concerns about inaccuracy of rates of MTCT and HIV-free survival in areas with high infant mortality.

CHAMPS (Child Health and Mortality Prevention Surveillance)) is a long-term program in multiple sites in sub-Saharan Africa and South Asia that aims to identify and address causes of stillbirth and death in children <5 years of age through a multi-pronged approach that includes the use of minimally invasive tissue sampling, verbal autopsy, and expert panel review of each death. Although still early in implementation, preliminary CHAMPS data from 3 sites in areas with high HIV prevalence (Mozambique, South Africa, and Western Kenya) found that among the first 1321 cases evaluated, 5.8% of deaths were attributable to HIV (1.0% in neonates <4 weeks of age and 14.9% in children 1-59 months of age). In addition, 27.1% of cases were found to be HIV-exposed but uninfected (32.6% in neonates; 23.4% in 1-59 months) (www.champshealth.org). These findings suggest that incomplete information on deaths in HEIs prior to the first post-birth facility visit is unlikely to be causing significant underestimation of the MTCT rate; however, these results highlight the marked impact of HIV exposure on HIV-free survival and underscore the importance of this metric. It will be important to follow these findings for CHAMPS sites in high-burden HIV areas to confirm early results and further refine how infant mortality is factored into MTCT and HIV-free survival rate calculations.

Facility-based MTCT measurements using routine program data

The goal for all PMTCT programs is high uptake of services for mother-infant pairs throughout the period of risk of transmission along with a robust and sustainable monitoring system. This combination of program coverage and quality data would enable timely and reliable population-level estimates of program impact using routinely collected indicators. Significant progress towards this goal has been made, but high prevalence or high burden

HIV settings continue to have challenges in both programmatic implementation and monitoring.

Gaps in coverage of key interventions are a substantial barrier to use of program data for calculation of population-level MTCT rates because even high-quality PMTCT program data excludes the following critical groups:

- Infants who are known to be HIV-exposed but are not enrolled in services or

are lost to follow-up before determination of final outcome

- Infants who are not known to be HIV-exposed due to undetected maternal HIV infection (i.e., mothers are never tested for HIV or mothers develop incident infection after HIV testing earlier in the exposure period)

Despite these limitations, optimizing PMTCT program data quality should remain a high priority because robust data:

The goal for all PMTCT programs is high uptake of services for mother-infant pairs throughout the transmission period along with a robust and sustainable monitoring system.

- Enhances the ability to detect program gaps and design targeted quality improvement measures that improve patient and program outcomes

- Helps quantify coverage and effectiveness of program interventions

- Provides data that is timelier and more actionable than models or special studies

- Best reflects current implementation practices and thus can better inform strategic planning and program management

- Improves population-level model estimates by increasing the accuracy of program-based model inputs

- Enables facility-based MTCT estimates (i.e., those derived from routinely collected program data) that can supplement and validate rates derived from population-based models or special studies

Considerations for strengthening routine PMTCT program data for MTCT measurement

Elimination of MTCT is not a one-time milestone, but a continuous long-term effort that requires sustained program and data quality. Key considerations for developing high-quality, streamlined, and pragmatic PMTCT data systems for MTCT

measurement are outlined below.

Programs should focus on closing key programmatic and data gaps in the postnatal period, with a specific emphasis on follow-up of HEIs at infant service delivery points.

- Most countries in Southern and East Africa have achieved high coverage of first antenatal (ANC1) visits, HIV testing at ANC1, and rapid provision of ART to pregnant women. However, postnatal follow-up of mother-infant pairs remains a significant weakness and severely hampers efforts to reduce and measure MTCT.

- Determination of HEI final outcome status is the linchpin of MTCT program impact, so

enrollment of mother-infant pairs and retention until cessation of breastfeeding should be the overarching goal of service delivery and monitoring efforts.

- Given the implementation challenges and high levels of coverage required for impact, scale-up of programs to detect incident infection in HIV-negative breastfeeding women should not be a short-term priority unless a program has already been successful in addressing HEI follow-up and testing. Country efforts to promote maternal retesting should focus on the late ANC period as the most cost-effective strategy for prevention of infant HIV infections.[20]

Countries should strongly consider using birth cohort monitoring to allow longitudinal follow-up of HEIs and documentation of outcomes.

- As noted in the 2015 IATT Option B+ M&E framework[21], determination of HEI final outcome status is best achieved through use of a cohort monitoring approach. Longitudinal data enables improved monitoring and reporting and also enhances facility-level awareness and management of issues vital for clinical follow-up (e.g., LTFU, patient tracking, test result return tracking, ART linkage).

- Birth cohorts are often simpler to implement than mother-infant pair or maternal registers because the antenatal and postnatal service delivery points are different in many countries.

- Birth cohort monitoring can help quantify HEI program coverage (i.e., the proportion of all HEIs enrolled in services), a key issue in preventing MTCT and in interpreting differences between facility-based MTCT estimates and population-based MTCT estimates. Accurate determination of the total number of expected HEIs can be a challenge. The number of HIV-infected pregnant women is often used as a proxy measure, but this does not account for pregnancy losses, which may be up to 15% in some settings.[22] Ideally, data on live births is collected at the point of infant delivery; however, data quality will depend on the prevalence of facility deliveries and vital registration coverage so countries should determine the best approach based on their context.

- HEIs who present to care should be enrolled in the cohort based on month of birth (vs. month of registration). This approach makes it simpler for staff to determine appropriate interventions based on age (e.g., testing at 9 months) and facilitates interpretation of data for each milestone at the facility and program levels.

Countries should critically assess current PMTCT data collection and reporting requirements to ensure a parsimonious and streamlined approach that is focused on essential measures and outcomes.

Because most programs have suboptimal data on HEI final status outcomes, other program indicators are collected for use as proxy measures and/or for inputs into models. High coverage and quality of the HEI final status outcomes would preclude the need for reporting on many 'upstream' indicators and thus final status outcomes should be the primary focus of improvement efforts.

Facility-level documentation and data review

At the facility-level, collection and documentation of key clinical and program indicators (e.g., in patient charts and registers) is critically important for individual patient care, quality improvement initiatives, and strategic planning. However, program and facility leadership should carefully review the amount of documentation required by facility-level staff and make every attempt to eliminate documentation that is duplicative or extraneous.

Only a minimum set of essential indicators should be included in PMTCT registers. Reasons for a streamlined approach include the following:

- Inclusion of numerous indicators produces large and unwieldy registers that are difficult to produce, store, and manage. This can lead to register availability delays, space constraints, and inefficient clinic workflows.

- Extensive documentation in the registers is burdensome to facility staff and diverts time from clinical care responsibilities. It also contributes to suboptimal data quality, necessitates more time for training, and complicates data quality assessments.

- If data on additional indicators is required for quality improvement initiatives or other purposes, a targeted review of individual patient charts and/or a short-term data collection exercise can be conducted to provide the necessary information.

- Emphasis on only a select set of essential indicators promotes improved data quality and enhances facility staff understanding and awareness of the most priority outcomes (e.g., retention, infant status outcomes).

PMTCT program managers should emphasize the necessity of regular facility-level review of data and ensure that real-time data use for program improvement is a routine part of clinic procedures. Facility staff should follow standard operating procedures for data review, data validation, and data triangulation and should receive regular supportive supervision in addition to refresher trainings. PMTCT program data should also be included in existing and planned electronic medical record systems to facilitate clinical care and data review.

Reporting of PMTCT program indicators

Compilation and review of facility summary reports at higher levels (i.e., subnational and national) should be tightly focused on priority indicators that are essential for determination of program impact and strategic planning. In many countries, facilities must submit aggregate data for a large number of longitudinal and cross-sectional indicators on a monthly basis. Completing lengthy facility summary reports is time-consuming for facility staff (especially given the additional reporting requirements for other program areas) and is often associated with suboptimal data quality. In addition, in many settings this data is not being reviewed and used in a way that justifies the frequency at which it is being requested.

To promote a more focused, sustainable, and efficient approach, PMTCT leaders at the national and subnational levels should carefully review the facility reporting requirements and consider the following:

- Mandatory reporting should focus on essential indicators required for measurement of program impact and PMTCT cascade analysis. Requiring only targeted information on facility summary forms reduces the reporting burden and promotes data completeness and accuracy by allowing staff to develop proficiency in reporting only the key indicators. Core indicators for consideration are shown in Box 2.

  - In the postnatal period, data quality for the infant status outcomes should be a particular priority, as the disaggregations can highlight programmatic gaps that require closer investigation. For example, many infants LTFU would re-focus efforts on patient tracking, while a high proportion of infants reported without a test result would prompt review of infant virologic testing and result return.

  - Reporting to higher levels on provision of services (e.g., cotrimoxazole, receipt of antiretroviral prophylaxis) should be de-emphasized.

- Requirements for monthly PMTCT reporting should be re-evaluated.

  - Quarterly reporting is likely the most frequent interval necessary for PMTCT program monitoring; some indicators may require even less frequent reporting (e.g., semi-annual, annual).

  - Programs should emphasize that less frequent reporting will be associated with higher expectations and standards for completeness and accuracy of the submitted data.

Future potential: case-based surveillance for measurement of PMTCT impact

The goal of case-based surveillance is to inform public health response by providing continuous epidemiological data on all persons living with HIV. Most case-based surveillance systems focus on identifying newly diagnosed PLHIV and following 'sentinel events' (e.g., viral load measurements, opportunistic infections, etc.) in each individual until death. Only a few countries in sub-Saharan Africa have implemented case-based surveillance, but many countries have initiated planning processes.[23]

| BOX 2 | Core Indicators for Measurement of PMTCT Program Impact |

Antenatal

- Number of pregnant women attending ANC1
- Maternal Box HIV status
- Maternal ART status in pregnancy

Postnatal

- Number of HEIs enrolled
- Maternal ART status during breastfeeding
- Early MTCT: Infant status at 6 weeks of age*
  - Tested positive
  - Tested negative
  - Alive and in care but no test result available
  - LTFU
  - Transferred out
  - Died
- Late MTCT: Infant status at 18-months of age**
  - Tested positive
  - Tested negative
  - Alive and in care but no test result available
  - LTFU
  - Transferred out
  - Died

*For reporting: 6 weeks = by 2 months of age.
**For reporting: 18 months = by 24 months. If possible, final outcome status (after cessation of BF) is optimal.

Case-based surveillance has the potential to provide near real-time information on PMTCT outcomes and impact. For example, an electronic case-based surveillance system that included all HIV-infected pregnant women and collected data on key PMTCT-related services and outcomes (e.g., infant birth, infant virologic testing, final outcome, infant death) as sentinel events would substantially streamline efforts to determine PMTCT program impact.

Integration of MCH data into a national case-based surveillance system requires long-term vision and effort, so it is critical that MCH perspectives and needs are considered from the earliest phases of planning and design. To facilitate this, national PMTCT leaders should ensure PMTCT and paediatric program representation in case-based surveillance technical working groups and/or planning committees. These representatives can promote PMTCT/MCH integration into the case-based surveillance system by advocating for the following:

- Inclusion of MCH-specific facilities and service delivery points (e.g., ANC, maternity, paediatric sites) and enrollment of pregnant/ breastfeeding women and their HEIs

- Collection of essential MCH data elements (e.g., ART, maternal viral load, ART prophylaxis, final outcome) and designation of these as sentinel events

- Linkage to EID and PMTCT data and triangulation with other sources that include MCH data (e.g., PHIA, other surveys)

- Disaggregation by age, sex, and pregnancy status in case-based surveillance dashboards

Measurement of MTCT with special studies

Published MTCT impact evaluations

In 2012, WHO published the "A Short Guide on Methods: Measuring the Impact of National PMTCT Programmes': towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive" which summarized different approaches to the measurement of PMTCT program impact, including modeling, surveys and surveillance, and use of program data.[24] Because of the limitations in routine program data discussed above, several countries have conducted large nationally representative special studies to generate population-level estimate of PMTCT program impact (Table 2). The studies used either a facility-based or community-based approach to measure MTCT rate and/or HIV-free survival, and most included multiple secondary objectives, including coverage of key PMTCT interventions, retention in PMTCT programs, and association between transmission and maternal characteristics (e.g., HIV drug resistance, viral load).

The facility-based surveys were primarily conducted in immunization clinics with enrollment of infants during the first DPT1 visit (usually near six weeks of age). Some also included prospective cohort designs with follow-up of HEIs up to 18 to 24 months and/or follow-up of HIV-negative postpartum women to allow measurement of incident infection during breastfeeding. The community-based studies were primarily cross-sectional household surveys, and many were designed using existing health and demographic surveillance

Table 2. Selected PMTCT impact evaluations in Africa

Country, Year Published	Data Type	Data Type	Source
eSwatini, 2018[25]	Study Type	Main Outcomes	Sample size
Malawi, 2018[26]	National cross-sectional survey with facility-based enrollment at health facilities that provided PMTCT services	MTCT at 4-26 weeks	33,744 mother-infant pairs
Zambia, 2018[27]	Sub-national prospective cohort of HIV-infected woman and their newborns recruited from facilities and community-based networks	12-month HIV-free survival of HIV-exposed infants	827 mother-infant pairs
Zimbabwe, 2018[28]	National prospective cohort study with facility-based enrollment from immunization clinics.	Cumulative MTCT at 6 weeks, 6 months, and 18 months	6051 caregiver-infant pairs for baseline interview
Rwanda, 2017[29]	Longitudinal observational study with facility-based enrollment. Women followed for 24 months	HIV-free survival at 24 months	608 HIV-infected pregnant women
Zimbabwe, 2016[30]	Two serial sub-national cross-sectional surveys with community enrollment (2012 and 2014)	1. HIV-free infant survival and MTCT rate at 9-18 months 2. Number of HIV infections averted	2012: 7683 mother-infant pairs 2014: 9283 mother-infant pairs
South Africa, 2015[31]	National cross-sectional study with facility-based enrollment from immunization clinics - nested study to assess impact of maternal seroconversion	MTCT at 4-8 weeks, stratified by timing of maternal infection	10475 caregiver-infant pairs enrolled; 9802 included in this analysis
South Africa, 2015[32]	National cross-sectional study with facility-based enrollment from immunization clinics	MTCT at 4-8 weeks	10,178 caregiver-infant pairs
Kenya, 2014[33]	National population-based cross-sectional household survey	Cumulative MTCT at 5 years	2862 women tested/63 HIV-exposed children tested
Malawi, 2014[34]	Sub-national cross-sectional study with enrollment from immunization clinics	Population and district level MTCT rates by 12 weeks	5634 caregiver-infant pairs
Cameroon Cote d'Ivoire South Africa Zambia, 2013[35]	Community-based household survey nested in the PMTCT Effectiveness in Africa: Research and Linkages to Care Study (PEARL Study)[36]	HIV-free survival at 24 months	7985 mother-infant pairs
Rwanda, 2012[37]	Nationally representative household survey with enrollees identified from facility ANC/PMTCT registers	HIV-free survival at 9-24 months	2982 mother-infant pairs (1434 HIV-infected mothers)
Kenya, 2011[38]	Sub-national cross-sectional study with facility-based enrollment from immunization clinics	Assessment of PMTCT service uptake MTCT at 6-week immunization visit	2700 mothers

systems. Several also used facility data to supplement information on HIV-infected participants.

In general, Spectrum estimates for both early and late transmission are higher than those in published survey findings (both facility- and community-based), though some comparative estimates are quite close. There are several potential reasons for the differing estimates. Spectrum estimates may be higher because the model includes all infections through the end of breastfeeding, including transmission to children who have died; in contrast, most studies are unable to capture full or final transmission because follow-up is shorter than the duration of breastfeeding due to resource and time constraints. The lower values in the studies may also reflect the difficulty of capturing all incident maternal infections due to high LTFU in prospective studies and bias from study effects. Lastly, discrepancies between study and Spectrum estimates can stem from inaccurate program data provided to Spectrum as model inputs (e.g., due to double counting women receiving ART or insufficient data about retention on treatment).

Role of special MTCT surveys

Although special nationally representative surveys to measure MTCT rate such as those outlined above can provide valuable information, accumulating experience has highlighted significant issues related to conducting these types of surveys (Box 3).

BOX 3 **Implementation barriers for MTCT rate studies**

Funding requirements
- Costs of a high-quality nationally representative study range from USD $1 –6 million.

Consent
- Multiple levels of written informed consent often required (e.g., maternal consent for interview or HIV testing, maternal consent for infant testing, guardian consent for underage mothers in some countries). Consent at the household level is also required for community-based surveys.

Human resources
- Large study coordination teams are needed for coordination and oversight of field processes, data collection/management, training, lab testing, etc.
- Dedicated study staff are usually required due to the limited capacity of facility staff or community health workers to take on additional study responsibilities. Studies who rely on existing clinic staff must often provide monetary incentives for enrollment and completion of study forms.

Data collection and management
- Data management is time-intensive and complex even with successful use of electronic data capture.
- Quality of existing data (registers, medical records)

often hampers attempts to verify patient reports or collect additional clinical information.
- Data cleaning and analysis often require months to years.

Duration of study implementation and result release
- Protocol development and ethical clearance are often prolonged due to complex study designs and multiple components (e.g., laboratory testing, caregiver interviews, record review, etc.)
- Because of the long study duration (or retrospective period in community surveys) and time required for analysis and report writing, findings usually reflect program structure and implementation years earlier, making it difficult to interpret and apply findings to current programs.

Statistical considerations
- Most published studies enrolled very large sample sizes to achieve a precise national MTCT rate. However, high precision may be less important (depending on the objective and nature/frequency of the studies) and lower precision can decrease sample sizes considerably.
- MTCT studies are often designed with an overly complex level of stratification for the research question.

These include high financial and human resource costs, long protocol development and approval times due to complex study designs and consent requirements, time-intensive and complex data management procedures with lengthy data analysis periods, and delayed release of results that limits utility for program management. Concerns have also been raised that these studies divert resources from efforts to strengthen routine program data quality.

Because of these issues, there is increasing awareness that a more pragmatic and sustainable approach to measurement of HIV MTCT in high burden national programs is needed. It is unlikely that countries will have access to the funding and human resources necessary to conduct surveys of a similar scale and complexity on a routine basis and efforts should focus on optimization of routine PMTCT program data as noted in the previous section.

For these reasons, surveys or special studies should be reserved for validation of program data and modeled estimates and/or collection of key supplemental information. Potential reasons to conduct a streamlined and focused survey include:

- Validation of program data

- Inadequate and/or unreliable program data (e.g., data quality assessment reveals significant discrepancies)

- Need for key program data that is not routinely available (e.g., HIV seroconversion during pregnancy and breastfeeding, HIV rates in migrant or other special populations)

- Submission for validation for Path to Elimination

- Need for data that can improve calculation of MTCT within the Spectrum model (e.g., infant mortality, maternal viral load suppression, incidence, breastfeeding duration, LTFU)

- Determination of the impact of major policy and/or program changes that cannot be evaluated through routine data

To mitigate the resource requirements and implementation challenges and to improve the timeliness of results, surveys should use a robust but parsimonious approach that is tightly focused on key objectives and core outcomes. In addition, the survey's design should not strive for statistical rigor beyond what is required to answer the specific study question.

Recommended methodology for supplemental measurement of MTCT

For programs that feel a supplemental study is needed to determine MTCT rates, a community-based household survey is recommended due to the following advantages:

- Provides population-level data because all mother-infant pairs are included irrespective of whether they access health services, thus avoiding the biases of facility-based designs

- Captures key components of the MTCT rate (e.g., incident infection during pregnancy and breastfeeding, infant deaths) without the need for long-term follow-up of prospective cohorts

- Can be incorporated into existing health demographic surveys and HIV program systems

- Can incorporate nested cohort components if needed

A sample protocol with details on the recommended methodology can be found in Appendix 1.

Conclusion

A rigorous yet streamlined and pragmatic approach is integral to development of a PMTCT program data system that allows reliable determination of MTCT rates and HIV-free survival in high burden settings. Coverage of key interventions, especially in the postnatal period, will be fundamental to achievement of these goals and enrollment and retention of mother-infant pairs is critical. Although models play a valuable role in providing population-level estimates and special studies may be required for supplemental information, efforts should focus on developing a more sustainable, timely, and program-centered approach for MTCT measurement that aligns with and supports efforts to strengthen the collection and use of routine PMTCT program data.

Appendix 1.

Protocol template: a community-based survey for measurement of mother-to-child transmission of HIV and HIV-free survival in HIV-exposed children aged 18-24 months

Purpose of this document: The following protocol and associated study forms (see Appendix 2) can be used to support development of a country-specific protocol. These are provided for illustrative purposes only; countries should carefully consider their specific needs and context when adapting this methodology for their own use. Notes on adaptation are included in italics. Special appreciation is extended to Frances Cowan and the Centre for Sexual Health and HIV/AIDS Research Zimbabwe (CeSHHAR Zimbabwe)/University of California, Berkeley (UCB) Collaborative Evaluation Programme who developed the original protocol and study forms on which these were based.

Considerations for COVID-19: All planning and implementation of household-based surveys should be reviewed in the context of the COVID-19 global pandemic. Country-specific SOPs should be adapted or created to ensure that survey procedures minimize risk of exposing survey participants and staff to COVID-19, appropriately respond to and limit transmission if survey staff develop COVID-19 illness, optimize use of personal protective equipment (PPE), and reduce the potential for additional community transmission resulting from survey activities. Development of these procedures and guidelines should consider the COVID-19 epidemiological context within each country and should be aligned with the country's policies and requirements as set forth by the MOH and other regulatory authorities.

Rationale

A population-based, cross-sectional, household survey will be conducted to measure the impact of the prevention of mother-to-child transmission (PMTCT) program on vertical HIV transmission from HIV-infected mothers to their children at 18-24 months, as well as HIV-free survival among 18-24 month old HIV-exposed infants. This population-based approach offers a significant advantage over studies that use facility-based cohorts, as it includes all infants irrespective of whether the mother accessed antenatal care and other PMTCT services.

[Note: The 18-24 month age period was selected based on typical durations of breastfeeding; this range can be adjusted if the typical length of breastfeeding within the study population is shorter or longer.]

Goals and Objectives

Goal: To measure the population-level impact of the national PMTCT program on MTCT of HIV at 18-24 months and HIV-free survival in HIV-exposed children aged 18-24 months.

[Note: This methodology can be used to generate national or subnational (e.g., province) estimates.]

Primary outcome measures

1. Proportion of infants born to HIV-infected mothers who were alive and HIV-uninfected at 18-24 months of age (HIV-free survival)

2. Proportion of infants born to HIV-infected mothers who were HIV-infected at 18-24 months of age (i.e., mother-to-child transmission of HIV, or MTCT)

Secondary outcome measures

1. Duration of breastfeeding at the population level in HIV-negative and HIV-infected mothers

2. Estimated mortality among HIV-exposed children and HIV-infected mothers

3. Uptake of PMTCT interventions (antenatally and postpartum)

4. Incident HIV infections among pregnant and breastfeeding women

Study population

Eligible to participate: Mothers or caregivers (at least 15 years of age) of children born between 18 and 24 months prior to the survey and their 18 to 24-month-old infants (including infants who have died)

Inclusion criteria

- Mother or caregiver is 15 years of age or older

- Delivered or provides care for an infant (alive or deceased) who is, or who would have been, 18-24 months of age at the time of the survey

- Able and willing to provide written informed consent

- Willing to receive her HIV test result and HIV test result of her 18-24-month old child

Sample Size and Sampling

[Note: The steps outlined below are intended to provide only general guidance on the suggested methodology. Involvement of a statistical expert is critical for final sample size calculations and sampling processes.]

Sample size calculation

The primary goal of performing sample size calculations is to ensure the study will be able to produce national (or subnational) estimates of MTCT and HIV-free survival in infants aged 18-24 months—as outlined in the survey objectives—with the desired level of precision (i.e., desired confidence interval width). This calculation is intended to generate the target enrollment number of mothers or caregivers of children born between 18-24 months prior to the survey and their corresponding 18-24-month-old infants. Because this is a complex sample survey, sample size calculations will need to account for clustering through the use of a design effect. They will also need to account for non-participation and HIV prevalence among pregnant women.

Questions to consider that impact sampling:

- It is essential to carefully determine the level of statistical precision and rigor that is required to impact the management and design of your country's PMTCT program. Choosing a statistical rigor that provides only the core level of information needed for program evaluation can minimize the sample size, and thus dramatically reduce the resources (financial and human) required for survey implementation.

- Key considerations include the following:
  - o Are national and/or subnational estimates required?
  - o Is an accepted current MTCT rate estimate available?
  - o What is the intended use of the survey results?
  - o What financial and human resources are available for the survey?

- For example, if the current MTCT rate is estimated to be 6% and the aim is to submit survey results for global validation (i.e., demonstrate a rate of <5%), then tighter confidence bounds may be needed. Conversely, if the current estimated MTCT rate is 18% and the survey aims to assess PMTCT program progress and/or performance, then less precision may be required.

Sampling

Because the goal is to estimate population parameters, the community surveys will aim to comprise a representative sample of mother-infant pairs.

- A multistage sample selection procedure may be used as outlined below.
- The administrative terms (e.g., region, district, enumeration area, etc.) are used for illustrative purposes but will vary in each country context.
- Collaboration with the Central Statistical Office is recommended; in addition, efficiencies may be gained by eliciting input from other projects with relevant experience (e.g., demographic and health surveillance systems (DHSS), Population-Based HIV Impact Assessments (PHIA), etc.).

Key steps in the sampling process

1. Determine which areas of the country (e.g., region/province) will be included in the survey.
   - Due to finite resources, areas should be selected to balance generalizability and internal validity. Factors to consider include geographic size, urban vs. rural, areas with high and low HIV prevalence, representation of major ethnic groups, implementing partner presence, and PMTCT program coverage and performance.

2. Create a sampling frame of enumeration areas (EAs).
   - If the survey aims to generate estimates for specific subnational units, the EAs should be stratified by the subnational units of interest.

3. Select EAs using a probability proportional to size (PPS) sampling.
   - The number of EAs selected will depend on the sample size calculations.

4. Construct the household sampling frame within each selected EA by generating a list of all eligible households (i.e., those with infants born in the last 18-24 months)
   - Identifying all eligible mother-infant pairs (regardless of whether the child is currently alive) can be done using community health workers and other methods (e.g., immunization registers, respondent-driven sampling).

5. Using the list of eligible households within each selected EA (per step 4), randomly select those households which will be approached for survey participation.
   - The number selected will be based on sample size calculations.
   - Study staff will visit all eligible households in each selected EA to confirm whether an eligible birth has occurred and, if so, will invite them to participate.

Enrollment and study procedures

Overview of procedure for household surveys

An overview of the household survey procedures is summarized here; further details are outlined below. The household surveys and blood sample collection will be conducted in one visit in the participants' home; participants will only be interviewed/visited once with no follow-up activities except for return of results for infants with new HIV diagnoses. The household questionnaire will be administered in approximately 30-60 minutes (on average) and all survey activities should be completed within one hour. Completion of the questionnaires will include review of patient-held mother and infant health cards.

Depending on whether the infant and/or the mother are alive at the time of the survey, the following information/sample will be collected from each participating mother-infant pair.

If both the infant and the mother are alive:

- Questionnaire from the mother
- HIV rapid testing in the home for all mothers without a known positive HIV status (as confirmed by documentation in the patient-held card)
- Dried blood spot sample (DBS) from HIV-infected mothers
- DBS sample from infants whose mothers are HIV-infected or are unavailable

If the infant is alive and the mother is deceased:

- Questionnaire from the caregiver
- Verbal autopsy of the mother
- DBS sample from the infant

If the infant is deceased and the mother is alive:

- Questionnaire from the mother
- Verbal autopsy of the infant
- HIV rapid testing in the home for all mothers without a known HIV positive status (as confirmed by documentation in the patient-held card)
- DBS sample from HIV-infected mothers

Survey Questionnaires

All field staff will be trained on obtaining informed consent from participants, completion of the standardized survey instruments, HIV rapid testing and counseling, and the collection of DBS.

1. Trained study staff will seek informed consent from the mother/caregiver to complete the questionnaire and to collect blood samples from herself and her eligible infant (between 18-24 months of age). The mothers of infants 18-24 months of age can consent to participate in both, neither, or either part of the questionnaire and blood sample collection components.

2. After written consent has been obtained, trained field staff will interview the mothers/caregivers in the local language using a structured questionnaire that is uploaded to a portable electronic device. The survey will last 30-60 minutes and will capture the mother's demographic characteristics, clinical history, and her experience with PMTCT services and HIV testing for the eligible child. Information on antenatal care use, HIV status, and PMTCT regimens

obtained verbally will be verified using data on the mothers' and children's patient-held cards (when available).

3. Through verbal autopsies, the questionnaire will also capture information on 1) infants who would have been eligible had they still been alive and/or 2) the deceased mothers of eligible infants.

Blood sample collection and HIV testing

DBS samples will be collected from consenting mothers and from infants whose mothers have consented to the collection of blood spots from their child. Collection of DBS will occur in the participant's home or another place selected by the participant. The procedure is minimally invasive and widely accepted throughout Africa and requires that a trained member of the survey team collect small spots of blood onto a piece of filter paper by gently pricking an adult's finger or an infant's heel with a lancet.

For each DBS collection, the surveyor will follow standard infection control precautions and will collect the DBS sample following standards of practice for DBS collection in adults and infants. The samples will be air dried onto filter paper and stored at room temperature pending transport to a laboratory for HIV testing. The filter papers will be labeled with unique barcodes that are also entered into the tablets for the corresponding questionnaires to ensure that survey data can be linked to laboratory results.

Maternal HIV testing

- For mothers with an HIV unknown or negative status, HIV rapid testing will be conducted at the home per the national algorithm with approved rapid HIV test kits.
  - o If the results of the rapid test algorithm show the mother is HIV negative, no further blood samples will be collected.
  - o If the results of the rapid test algorithm show the mother is HIV positive (i.e., a new diagnosis of HIV infection), a DBS sample will be collected for confirmatory serologic testing at a central laboratory.
  - o If the results of the rapid test algorithm are inconclusive, a DBS sample will be collected for confirmatory serologic testing at a central laboratory.
- Mothers with known HIV infection will not undergo HIV rapid testing, but will have a DBS collected for confirmatory serologic testing (e.g., ELISA, Geenius, or equivalent)
- No blood samples or testing will be conducted for non-biological mothers/caregivers.

Infant blood sample collection and HIV testing

- A DBS sample will be collected on all 18 to 24-month-old children whose mothers have known and confirmed HIV infection or whose mothers are found to be HIV seropositive or inconclusive as a result of home-based HIV rapid testing.
- A DBS sample will also be collected on all children whose mothers are not present in the household.

HIV DNA PCR tests

HIV DNA testing will be performed at a central laboratory on all DBS collected from participating infants in accordance with the national infant testing algorithm.

[Note: Programs with access to point-of-care HIV DNA PCR testing may consider its use instead of central laboratory testing.]

Test result return and referrals to care

Willingness to receive maternal and infant test results is a requirement for participation in the testing component of the survey; if a mother refuses to receive her test results or a mother/caregiver indicates they do not want to receive the child's test results, then the testing portion of the survey will be concluded.

Maternal test result return

For mothers who undergo rapid HIV testing at the household, results will be returned at the time of the interview. Those with a new diagnosis of HIV will be referred for care and treatment services per procedures outlined below. Mothers with positive or inconclusive results on HIV rapid testing per the national HIV testing guidelines will have a DBS collected for confirmatory testing and will be able to receive those test results at the local facility of their choice. Mothers with known positive HIV status (prior to the survey) who have a DBS collected for confirmatory testing will not receive the confirmatory test results unless the testing does not confirm HIV positive status; in this situation, study staff will return to the household to provide the test results and arrange necessary follow-up testing per national guidelines.

Infant test result return

All mothers/caregivers participating in the study will be able to obtain their infants' HIV DNA PCR test results at their local clinic within 4 weeks from the survey date. However, if an infant with previously unknown/negative HIV status is found to have HIV infection on PCR testing (i.e., the infant has newly diagnosed HIV infection), study staff will return to the household within 2 weeks of sample collection to deliver the result and expedite referrals to care and treatment for the child.

In order to receive the results of their infants' test (and, if applicable, maternal HIV test results) participants who have DBS samples collected will be requested to provide identifying information (e.g., name, national ID number, date of birth, address), which will be linked with their blood samples using a numerical barcode label.

Participants will be able to collect their infant's HIV test results (and, if applicable, maternal HIV test results) at the local health facility with their national ID card (or another means of identification) to allow identity verification. HIV test results will be sent to the clinics in sealed envelopes. Clinic healthcare providers will provide pre- and post-test counseling and HIV test results to the mother/caregiver-infant pairs at the health facilities. Ministry of Health HIV counseling procedures will be followed when returning the test results to participants.

Referrals for HIV services and other health care
Maternal referrals

- Women newly diagnosed with HIV by survey staff or women with known HIV infection but who are not on ART will be referred to the local clinic of their choice for ART and support services. They will also be offered facilitated linkage to a clinic through a community health worker.

   o If they accept facilitated linkage, they will be asked to provide consent for their information to be shared with a community health worker to facilitate active linkage using a 'Linkage to Care Facility Form' completed by survey staff. The Linkage to Care Facility Form will be delivered to the appropriate facility and will provide community health workers affiliated with that facility the contact information of consenting participants for the purposes of active linkage.

- Women with known HIV positive status will be encouraged to remain in, or return to, care and to continue recommended visits for their HIV-exposed infants.

- All women with HIV infection (newly diagnosed or known positive) will be encouraged to have sexual partners and all biological children tested for HIV (if not already conducted) and will be given information and referrals to a local clinic that has the appropriate testing services.

Child referrals

As mentioned above, expedited result return and referral to care will be initiated for all infants with newly diagnosed HIV infection.

- The laboratory will notify study staff within 48 hours of all infant samples with a positive virologic HIV test. Study staff will review each case and determine if the infant is a new HIV diagnosis (i.e., the infant was previously HIV negative or had unknown status).

- For infants newly diagnosed with HIV, survey staff will return to the household within 7 days of receipt of the result from the lab; during the visit, they will inform the mother/caregiver of the test result, counsel on the importance of urgent ART initiation and offer facilitated linkage to care.

  o If the mother/caregiver accepts facilitated linkage for the child, they will be asked to provide consent for their information to be shared with a CHW to facilitate active linkage to care, and survey staff will complete a 'Linkage to Care Facility Form'. The Linkage to Care Facility Form will be delivered to the appropriate facility and will provide CHWs affiliated with that facility the contact information of the mother/infant pair for the purposes of active linkage.

- All community health workers, field staff, and facility staff participating in linkage to care will adhere to local guidelines and protocols for active linkage, including follow-up procedures and documentation of enrollment in care. If standard protocols and procedures for active linkage are not already available, a SOP will be developed to provide detailed guidance on active linkage processes.

Consent and Confidentiality

Consent

Once an eligible mother or caregiver is identified, the survey staff will introduce themselves, explain the data collection process and all the benefits and risks of participating in the study, and ensure that the participants are aware of the voluntary nature of their participation. Written informed consent will be requested of all participants, and no data collection will take place prior to obtaining informed consent. Participants will sign or mark consent on both an electronic tablet form and a written copy of the form, which they will retain. All consent materials will be available in the local language(s).

After the questionnaire portion of the survey, mothers/caregivers will be asked to provide separate consent for HIV testing and/or collection of blood samples from herself and her 18-24-month-old infant(s) (if applicable). The mothers of infants 18-24 months of age can consent to participate in both, neither, or either part of the questionnaire and blood sample collection components. However, receipt of both maternal and infant HIV test results will be a requirement for collection of the mother and/or infant HIV test. If the mother/caregiver refuses receipt of her test results or those of her infant, this will be considered a refusal for the testing component of the survey.

[Optional] All study participants will receive a small token (e.g., bar of soap or other small household item) to compensate them for donating their time to the study. The value of the items will be small enough not to unduly influence participants. Participants will receive the same compensation irrespective of whether they complete the survey or withdraw before completing the study.

Confidentiality

To minimize any possible discomfort and promote a greater sense of privacy, the following will be part of study procedures:

- The interviewer will ask to conduct the survey in a location away from other members of the household.
- Female interviewers will be utilized wherever possible and survey assistants will be trained in asking sensitive questions.

The survey procedures (questionnaire, maternal blood sample, infant blood sample) will be linked using anonymous unique barcode labels to allow analyses using these types of data; however, no identifying information will be necessary for this purpose. Identifying information will be collected on 1) consent forms, 2) blood sample return sheets (if applicable), and 3) linkage to care forms (if applicable). The consent forms (obtained for all participants) will be unlinked with the survey materials, as the unique barcode label will not be placed on consent forms. To allow mothers/caregivers to receive their HIV confirmatory test results and those of their infants (if applicable), we will collect identifying information (e.g., name, national ID number, date of birth, address) which will be linked with the blood samples to allow participants to collect their results at their local clinics.

Risks and Discomforts

The physical risks of participating in the household survey are very small. HIV rapid testing and the collection of DBS from mothers and infants may cause brief discomfort at the site of the finger/heel stick, but infections at the site of the finger/heel stick are rare, and are not associated with any serious complications. The primary risk of the household survey is the potential distress related to the questionnaire. The questionnaire includes questions regarding the mother's HIV status and speaking about HIV infection and healthcare seeking behaviors can be uncomfortable for individuals. Additionally, questions regarding pregnancy and infant feeding practices in connection to any deceased children born in the eligibility time period may be distressing for participants.

Participants will provide identifying information (e.g., name, national ID number, date of birth, address), to allow identity verification at the local clinic where they will collect the HIV test results. Hence, there is a minimal chance of breach of confidentiality due to collection of identifying information, which could result in unwanted disclosure of HIV status and associated potential distress. Participants who receive their HIV test results and/or their infants' test results may find out for the first time that they are HIV-infected, which would result in emotional distress.

To minimize the distress associated with receiving the news of an HIV-positive test during the household rapid testing, results will be provided by a trained survey staff member according to standard HIV testing and counselling guidelines.

Data entry, management, and analysis

Data collection will be done using real-time data collection and web-based data management to increase cost-effectiveness, efficiency, and data quality. Management of the entire data collection process will be done by [organization], who will be responsible for coordination, training the data collection teams, ensuring quality control, and providing basic project oversight of the data collection process.

Authorized study staff members will have access to the forms used in data collection. Only the data manager, project coordinator and the project director will have access to the questionnaire databases and the HIV test results; only the data manager will have access to the dataset containing identifying information. At no time will study staff have access to any identifying bio-behavioral data.

Every effort will be taken to protect the confidentiality of the participants in this study. The local survey firm will ensure the proper storage of the consent forms upon transfer from the field to their office. All forms used in data collection will be securely stored in a locked cabinet, to which only designated survey staff members will have access. Each tablet used in the field will be password-protected and encrypted. The questionnaires, as well as the dataset containing identifying information, which are collected on tablets will be password-protected and encrypted; these password-protected and encrypted files will be backed-up daily on password-protected cloud storage and then on a password-protected computer at the main office. All study materials, paper and electronic, will be stored in a locked office, and only limited staff will have access to the documents and the databases. Computers containing study databases will be placed in secure locations to prevent theft and will have a built-in password protection scheme to prevent unauthorized access to data in the case of theft. Nonetheless, the dataset containing identifying information saved on computers at the main office will be password-protected and encrypted. The databases will be regularly backed-up onto a password-protected encrypted external hard drive.

Survey data will be retained on a secure password-protected computer for ten years to complete data analysis. The HIV test results of infants will be kept for 25 years (i.e., 7 years after they reach maturity). Data will only be transferred to individual password-protected computer hard drives when active data analysis is underway. All study documents and data will be available only to study investigators and key study personnel. Dried blood samples will be securely stored under proper conditions with the laboratory until all samples have been processed, checked, and the results submitted to the database. The laboratory will destroy the samples according to standard biohazard procedures after the completion of HIV testing and quality assurance activities (expected within maximum one year of survey completion).

All analyses will control for the complex design of the survey (e.g., clustering, stratification, and weighting). Appropriate software and survey procedures will be used to estimate population proportions and confidence intervals (e.g., SAS, Stata, SUDAAN, R, etc.). Domain analysis will be performed on subpopulations.

For deceased mothers and infants, verbal autopsy data will be analyzed by two separate trained investigators to determine cause of death and determine the potential for HIV-related etiologies.

Appendix 2.

Supporting documents for protocol development

The following documents are examples of forms and standard operating procedures used in similar surveys that are available in an online resource library. These are intended only as selected samples that may be useful in study planning and implementation; modifications will be required, and additional documents may be necessary, to align with the specific country protocol.

- Household screening for eligible infants (Community health worker)
- Household screening form to confirm eligible infants (Survey staff)
- Form for documenting ineligible mothers
- Form for documenting deceased infants and deceased mother
- Data return form
- Generic recruitment script
- Study consent form
- Consent for specimen storage
- Survey Registration Form
- Instructions for completing survey registration form
- Mother/caregiver questionnaire
- Active Linkage Form
- Survey data collection SOP
- Blood specimen handling SOP

References

1. UNAIDS 2019 Data Report. (Accessed Jan 29, 2020): https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf

2. Start Free Stay Free AIDS Free 2019 Report (accessed Jan 30, 2020); https://www.unaids.org/sites/default/files/media_asset/20190722_UNAIDS_SFSFAF_2019_en.pdf

3. Landes M, van Lettow M, Nkhoma E, et al. Low detectable postpartum viral load is associated with HIV transmission in Malawi's prevention of mother to child transmission programme. J Int AIDS Soc. 2019;22(6).

4. UNICEF, 2018. Breastfeeding: A Mother's gift for every child. https://www.unicef.org/publications/files/UNICEF_Breastfeeding_A_Mothers_Gift_for_Every_Child.pdf

5. Brennan AT, Bonawitz R, Gill CJ, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS. 2016;30(15):2351-2360.

6. World Health Organization, December 2018. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. https://www.who.int/hiv/pub/guidelines/ARV2018update/en/.

7. Mahy M, Stover J, Kiragu K, et al. What will it take to achieve virtual elimination of mother-to-child transmission of HIV? An assessment of current progress and future needs. Sex Transm Infect. 2010;86 Suppl 2:ii48-55.

8. Stover J, Glaubius R, Mofenson L, et al. Updates to the Spectrum/AIM model for estimating key HIV indicators at national and subnational levels. AIDS. 2019;33 Suppl 3:S227-S234.

9. Thomson KA, Hughes J, Baeten JM, John-Stewart G, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. J Infect Dis 2018;218(1):16-25.

10. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med 2014;11:e1001608.

11. WHO, November 2019. Consolidated Guidelines for on HIV Testing Services for a Changing Epidemic. Accessed March 12, 2020. https://www.who.int/hiv/topics/vct/en/.

12. de Beer S, Kalk E, Kroon M, Boulle A, et al. A longitudinal analysis of the completeness of maternal HIV testing, including repeat testing in Cape Town, South Africa. J Int AIDS Soc. 2020 Jan;23(1):e25441.

13. McCollum ED, Johnson DC, Chasela CS, et al. Superior Uptake and Outcomes of Early Infant Diagnosis of HIV Services at an Immunization Clinic Versus an "Under-Five" General Pediatric Clinic in Malawi. J Acquir Immune Defic Syndr. 2012;60(4):e107-e110.

14. WHO. Preventing HIV during pregnancy and breastfeeding in the context of PrEP. 2017 Jul. Available from: https://www.who.int/hiv/pub/toolkits/prep-preventing-hiv-during-pregnancy/en/

15. Kim AA, Behel S, Northbrook S, Parekh BS. Tracking with recency assays to control the epidemic: real-time HIV surveillance and public health response. AIDS. 2019;33(9):1527-1529.

16. Meeting Report: WHO Working Group on HIV Incidence Measurement and Data Use. March 2018, Boston, MA, USA. Accessed October 16, 2020. https://www.who.int/diagnostics_laboratory/links/180622_boston_meeting_report.pdf?ua=1

17. Jackson D, Swanevelder S, Doherty T, Lombard C, et al. Changes in rates of early exclusive breast feeding in South Africa from 2010 to 2013: data from three national surveys before and during implementation of a change in national breastfeeding policy. BMJ Open. 2019 Nov 18;9(11):e028095.

18. Hosseinipour M, Nelson JA, Trapence C, et al. Viral suppression and HIV drug resistance at 6 months among women in Malawi's Option B+ program: Results from the PURE Malawi Study. J Acquir Immune Defic Syndr. 2017;75(Suppl 2):S149-S155.

19. Myer L, Dunning L, Lesosky M, et al. Frequency of Viremic Episodes in HIV-Infected Women Initiating Antiretroviral Therapy During Pregnancy: A Cohort Study. Clin Infect Dis. 2017;64(4):422-427. doi:10.1093/cid/ciw792

20. Meisner J, Roberts DA, Rodriguez P, et al. Optimizing HIV retesting during pregnancy and postpartum in four countries: a cost effectiveness analysis. J Int AIDS Soc. 2021;24(4):e25686.

21. IATT, WHO, UNICEF, CDC. March 2015. Monitoring and Evaluation Framework for Antiretroviral Treatment for Pregnant and Breastfeeding Women Living with HIV and their Infant. https://www.childrenandaids.org/sites/default/files/2017-05/IATT-Framework-Monitoring-Evaluation-Framework-for-ART-Treat.pdf Accessed October 21, 2020.

22. Dellicour S, Aol G, Ouma P, et al. Weekly miscarriage rates in a community-based prospective cohort study in rural western Kenya. BMJ Open. 2016;6(4). doi:10.1136/bmjopen-2016-011088

23. Holmes JR, Dinh T-H, Farach N, et al. Status of HIV

Case-Based Surveillance Implementation — 39 U.S. PEPFAR-Supported Countries, May–July 2019. MMWR Morb Mortal Wkly Rep. 2019;68(47):1089-1095. doi:10.15585/mmwr.mm6847a2

24. WHO. July 2012. A Short Guide on Methods: Measuring the Impact of National PMTCT Programmes: towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. https://www.who.int/hiv/pub/mtct/national_pmtct_guide/en/ . Accessed October 28, 2020.

25. Chouraya C, Machekano R, Mthethwa S, Lindan K, et al. Mother-to-Child Transmission of HIV and HIV-Free Survival in Swaziland: A Community-Based Household Survey.AIDS Behav. 2018 Jul;22(Suppl 1):105-113. doi: 10.1007/s10461-018-2121-6. PMID: 29696404

26. van Lettow M, Landes M, van Oosterhout JJ, et al. Prevention of mother-to-child transmission of HIV: a cross-sectional study in Malawi. Bull World Health Organ. 2018;96(4):256-265.

27. Chi BH, Mutale W, Winston J, et al. Infant Human Immunodeficiency Virus-free Survival in the Era of Universal Antiretroviral Therapy for Pregnant and Breastfeeding Women: A Community-based Cohort Study From Rural Zambia. Pediatr Infect Dis J. 2018;37(11):1137-1141.

28. Dinh T-H, Mushavi A, Shiraishi RW, et al. Impact of Timing of Antiretroviral Treatment and Birth Weight on Mother-to-Child Human Immunodeficiency Virus Transmission: Findings From an 18-Month Prospective Cohort of a Nationally Representative Sample of Mother-Infant Pairs During the Transition From Option A to Option B+ in Zimbabwe. Clin Infect Dis. 2018;66(4):576-585.

29. Gill MM, Hoffman HJ, Ndatimana D, Mugwaneza P, et al. 24-month HIV-free survival among infants born to HIV-positive women enrolled in Option B+ program in Kigali, Rwanda: The Kabeho Study. Medicine (Baltimore). 2017 Dec;96(51):e9445.

30. Buzdugan R, Kang Dufour M-S, McCoy SI, et al. Option A improved HIV-free infant survival and mother to child HIV transmission at 9-18 months in Zimbabwe. AIDS. 2016;30(10):1655-1662.

31. Dinh TH, Delaney KP, Goga A, Jackson D, 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 May 5;10(5):e0125525.

32. Goga AE, Dinh TH, Jackson DJ, Lombard C, et al.First population-level effectiveness evaluation of a national programme to prevent HIV transmission from mother to child, South Africa. J Epidemiol Community Health. 2015 Mar;69(3):240-8.

33. Muthoni L, Kellogg TA, Kim AA, Katana A, et al. Mother-to-child transmission of HIV in Kenya: results from a nationally representative study. Sirengo M,. J Acquir Immune Defic Syndr. 2014 May 1;66 Suppl 1:S66-74.

34. Sinunu MA, Schouten EJ, Wadonda-Kabondo N, et al. Evaluating the impact of prevention of mother-to-child transmission of HIV in Malawi through immunization clinic-based surveillance. PLoS ONE. 2014;9(6):e100741.

35. Stringer JSA, Stinson K, Tih PM, et al. Measuring coverage in MNCH: population HIV-free survival among children under two years of age in four African countries. PLoS Med. 2013;10(5):e1001424.

36. Ekouevi DK, Stringer E, Coetzee D, et al. Health Facility Characteristics and Their Relationship to Coverage of PMTCT of HIV Services across Four African Countries: The PEARL Study. PLoS One. 2012;7(1).

37. Ruton H, Mugwaneza P, Shema N, et al. HIV-free survival among nine- to 24-month-old children born to HIV-positive mothers in the Rwandan national PMTCT programme: a community-based household survey. J Int AIDS Soc. 2012;15:4.

38. Kinuthia J, Kiarie JN, Farquhar C, Richardson BA, et al. Uptake of prevention of mother to child transmission interventions in Kenya: health systems are more influential than stigma. J Int AIDS Soc. 2011 Dec 28;14:61.

unicef ⬤
for every child