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Implementation of Repeat HIV Testing during Pregnancy in Kenya

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IMPLEMENTATION OF REPEAT HIV TESTING DURING PREGNANCY IN KENYA

by

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A DISSERTATION

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ABSTRACT

It is estimated that a third of all mother-to-child transmission (MTCT) of HIV occurs in women with incident HIV infection during pregnancy, potentially contributing to over 37,000 pediatric HIV infections globally and 4,300 infections in Kenya on an annual basis. Since most pregnant women with acute HIV infection test negative for HIV during routine early-pregnancy antenatal testing, they may not receive access to life-saving antiretroviral therapy (ART) for their own sake, as well as to prevent perinatal HIV transmission. A comprehensive strategy to eliminate MTCT will require identifying and addressing incident HIV infection. International recommendations suggest that pregnant women in generalized epidemic settings be offered retesting three months after an initial negative HIV test early in pregnancy. The Kenyan Ministry of Health has officially adopted these guidelines, but little is known about the implementation successes and challenges.

This dissertation is comprised of three manuscripts examining the implementation of repeat HIV testing during pregnancy in Kenya using primary and secondary data collected from October 2014 to May 2015. The aims of this dissertation are to use qualitative and quantitative research approaches to (A) determine the current rate of antenatal retesting at a large district hospital in southwestern Kenya, as well as identify factors associated with retesting and estimate the incidence of HIV during pregnancy, through retrospective analysis of antenatal clinic records; (B) explore the barriers and

enablers to retesting at four socioecological levels (client, provider, facility, and health system) using the Ferlie and Shortell Framework for Change through in-depth interviews with health care providers and managers; and (C) model the cost, health impact, and cost-effectiveness of expanded repeat HIV testing during pregnancy in the Kenyan setting, compared to initial HIV testing alone.

Findings suggest that HIV incidence during pregnancy among women in southwestern Kenya remains high. While retesting rates have increased since guideline dissemination, implementation efforts appear to have lagged in some sub-groups, in particular leaving high-risk young, unmarried women less likely to get retested. Although some barriers to repeat HIV testing of pregnant women exist, health care providers and program managers generally see implementation as important, feasible, and acceptable. Implementation of repeat HIV testing in high HIV-prevalence areas of Kenya is cost-effective and likely to avert substantial new pediatric infections, but will require a multi-sector commitment to capitalize on community strengths.

Keywords: mother-to-child transmission of HIV, pregnancy, HIV testing, implementation, Kenya, cost-effectiveness analyses

DEDICATION

To the One who gives me breath and in whom is hidden all the treasures of wisdom and knowledge, may my work always honor you. *Soli Deo gloria.* To mothers living with HIV in Kenya and around the globe, I share in your hope for a world where every child is born HIV-free. I hope this dissertation contributes to making that goal a reality.

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INTRODUCTION

Background

Despite the fact that mother-to-child transmission of HIV is highly preventable through effective testing and treatment programs, over 110,000 children worldwide acquired HIV infection through vertical transmission in 2015.[1] In an era of widespread antiretroviral drug availability, virtual elimination of MTCT is achievable – as indicated by transmission rates as low as 1.2% in both high and middle income countries[2,3]– through a comprehensive approach that depends not only on treatment initiation and adherence, but also on the identification, linking, and retaining of HIV-infected mothers in HIV care.[4,5] Testing for HIV is the first critical step to identifying women who have been infected with HIV.

Globally, the integration of HIV care services into antenatal settings rapidly improved the uptake of an initial HIV test from 8% in 2005 to 44% in 2013 among all low and middle-income countries; and 74% in sub-Saharan African countries.[6] However, persistently high MTCT has prompted governments, international organizations and experts to call for repeat HIV testing, defined as retesting 3 months after the initial antenatal clinic test, during pregnancy in areas of high HIV incidence as a key strategy to eliminate MTCT.[6-8] Pregnant women who test HIV-negative at first antenatal care (ANC) visit continue to be at risk of HIV acquisition and thus MTCT throughout pregnancy, delivery, and breastfeeding. A recent meta-analysis found that in sub-Saharan African

countries, the cumulative incidence of HIV during pregnancy ranged from 0.2% to 13.8%, with a pooled incidence of 3.6% (95% CI: 1.9, 5.3).[7]

As women with prevalent infection have been increasingly identified at first ANC visit, a modeling study from South Africa estimated that a third of all MTCT now occurs among women with incident infection during pregnancy.[9] Due to elevated viral loads, incident HIV infection during the pregnant and postpartum periods has a high risk of vertical HIV transmission to infants and horizontal transmission to HIV-negative sexual partners.[10,11] Evidence that pregnancy may be a time of elevated risk for acquisition of HIV due to biological and behavioral factors[12-14] further justifies the need to identify and treat women during this time, especially as they may be more likely than usual to be accessing health care services.[15]

Most recent estimates suggest that Kenya, which is among 22 priority countries that together account for over 90% of MTCT, still has over 15% of HIV-positive women experiencing MTCT by the time of weaning, resulting in roughly 13,000 pediatric HIV infections annually.[16,17] This vertical transmission rate remains unacceptably high, exceeding national[18] and international[5] targets despite the fact that 95% of women received antenatal care and 93% were tested for HIV at least once.[17] One Kenyan study found the cumulative incidence of HIV infection in pregnancy to be 2.6% nationally and 5.3% in the Nyanza region,[19] the area of highest HIV prevalence at 15.1%.[20] Although the Kenya HIV testing services has officially adopted international guidelines on repeat HIV testing, implementation is low and many missed opportunities for repeat HIV testing exist.[8] Research has found the acceptability of repeat HIV testing in Kenya to be high,[19] but adoption of the repeat testing policy to be challenged by realities of the

implementation environment.[21] Thus, there is an urgent need to understand the challenges to completely implementing repeat HIV testing policy at scale in Kenya and other high HIV burden settings.

Overview of the Dissertation

This dissertation utilizes qualitative and quantitative research approaches to examine the implementation of repeat HIV testing during pregnancy in a high HIV prevalence region of Kenya. In particular, it incorporates quantitative analysis of medical records (aim 1), qualitative analysis of data from in-depth interviews (aim 2), and an economic evaluation (aim 3) to provide a deeper understanding of the processes and contexts influencing adoption of HIV retesting during pregnancy, as well as to help decision and policy makers direct limited resources to programs with the highest potential impact and sustainability.[22] Data for the first two aims were gathered in Migori County, Kenya, by the dissertation author from primary and secondary data sources between October 2014 and May 2015. Approval to conduct this study was granted by the University of Alabama at Birmingham Institutional Review Board (Appendix A) and the Kenya Medical Research Scientific and Ethical Review Unit (Appendix B).

This dissertation is a response to the need for an implementation science approach to investigate and address the major bottlenecks that impede effective adoption, integration, and scale-up of repeat HIV testing. Implementation science, the study of strategies to adopt and integrate evidence-based health interventions and change practice patterns within specific care settings,[23] is crucial for bridging the gap between research and evidence-based practice. Many interventions and policies that are effective and

evidence-based get backlogged in the research 'pipeline'[24] or stagnate soon after implementation[25] due to insufficient prior consideration of the contextual circumstances.

Study Aims

The first study aim was to determine the current rate of antenatal retesting at a large district hospital in southwestern Kenya, identify factors associated with retesting, and estimate the proportion of retested women who seroconvert during pregnancy through retrospective analysis of antenatal clinic records. Research from the Kenyan setting has demonstrated that interventions designed to increase repeat HIV testing have been successful,[19] but little is known about implementation in the absence of a specific intervention. Although the generalizability of the retesting rate determined in the current study may be limited by the use of data from a single site, knowing factors associated with retesting will allow us to determine how to address the deficits. Estimating the seroconversion rate will allow us to compare incidence in our region with reports of high HIV incidence during pregnancy in nearby regions.

The second study aim was to explore the barriers and enablers to repeat HIV testing at four socioecological levels (client, provider, facility, and health system) using the Ferlie and Shortell Framework for Change[26] through in-depth interviews with 20 health care providers and clinic managers. Much research has been done on the barriers to initial HIV testing, including stigma, lack of information, perceptions of privacy and confidentiality, poor waiting time, poor relationship with health staff and fear of being diagnosed HIV-positive.[27-32] However, the barriers to repeat HIV testing are less clear.[33] In addition, while barriers from the patient's perspective are relatively well researched,

little research is done on limitations experienced by providers of HIV testing and counseling services. The objective of this aim was to understand how local stakeholders perceive the importance of retesting, the barriers to implementation, and their assessment of the best ways to achieve retesting targets.

The third study aim was to model the cost, health impact, and cost-effectiveness of expanded repeat HIV testing during pregnancy in the Kenyan setting, compared to initial HIV testing alone. In order to appropriately implement repeat HIV testing, it is crucial to determine the appropriate timing of HIV retesting efforts to minimize use of limited resources, maximize benefit from treatment, and achieve a high likelihood of intervention sustainability from a fiscal perspective.[34,35]

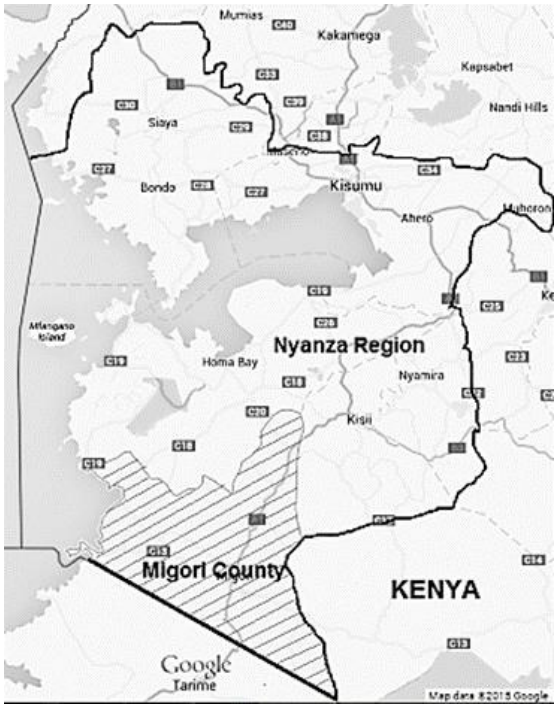
Study Setting

The Nyanza region of western Kenya, on the shores of Lake Victoria, has the highest prevalence of HIV in the country, with 15.1% of adults 15-49 years of age testing HIV-positive.[20] Women of reproductive age in Nyanza, and particularly in the southwestern county of Migori (Figure 1), have a significantly higher prevalence of HIV at 18.5% than women in other regions of the country, and have a higher prevalence of HIV compared to men in their age groups, with 10% of women aged 15-24 years infected and 22.9% of women aged 25-34 years infected.[17,20] The most recent population-wide Kenya AIDS Indicator Survey found that 49.7% of people living with HIV in Nyanza were unaware of their HIV-positive status.[36] With MTCT rates estimated at 15.1%, and 41.1% of women expressing a desire to have more children in the future, this represents a

substantial number of fetuses and infants who will be exposed to HIV through their mothers.[17,37]

Health care facilities in Migori County provided data for this dissertation. The facilities are supported by Family AIDS Care and Education Services (FACES), a Centers for Disease Control and Prevention (CDC) President's Emergency Plan for AIDS Relief (PEPFAR)-funded program for HIV research, care, prevention, and treatment.[38] FACES is administered through the Kenya Ministry of Health and Kenya Medical Research Institute (KEMRI) in conjunction with the University of California, San Francisco.

Figure 1. Study setting in Migori County, southwestern Kenya



Recent studies in the southwestern Kenyan region have found HIV incidence rates among pregnant women to be 3.1 per 100 person-years among women who newly tested

positive during antenatal care,[39] and 2.35 per 100 person-years among women who were documented HIV-negative 3 months prior at an initial antenatal care HIV test.[40] In the latter study by Drake et al., 88% of women who were newly diagnosed with incident HIV infection during pregnancy had detectable viral loads in their breastmilk and 2 of 25 infants (8%) had perinatally acquired HIV.[40] While official 2013 estimates of the national cumulative 5-year MTCT rate are 15%,[17] one large study of HIV-exposed infants enrolled in 62 facilities found the MTCT in 2013 to be 5.2% at 18 months, a 2.2 percentage point drop from two years prior. The apparent incongruence in these MTCT rates may stem from the fact that only following known HIV-exposed infants may underestimate the true MTCT rate because it fails to include cases of perinatal transmission that may have occurred among women who acquired HIV during the pregnancy and postpartum periods, and whose children may not have been designated HIV-exposed and followed for HIV testing and treatment. Thus, taken together, these studies suggest that incident HIV infection during pregnancy may contribute significantly to the perinatal HIV transmission burden in Kenya.

Study Significance

Pregnant Women are at a High Risk of Incident HIV Infection

Pregnant women who are HIV-seronegative at their first antenatal visit continue to be at risk of incident HIV infection during the remainder of the pregnancy and postpartum breastfeeding periods. As such, young children do not cease to be at risk of acquiring HIV from their mothers until they have been weaned. Research suggests that risk of HIV acquisition may be higher during pregnancy when compared to other time intervals in a woman's life.[12] Several potential mechanisms for increased susceptibility

have been suggested. These include biological factors such increased HIV-1 co-receptor expression in the genital tract mucosa or altered antibody- and cell-mediated immune responses due to elevated estrogen and progesterone.[41-43] Behavioral factors influencing increased susceptibility during and prior to pregnancy include higher frequency of unprotected sexual activity – in order to conceive or because they are already pregnant and thus not concerned about conception as an unintended consequence – and decreased sexual activity reported by pregnant or lactating women, potentially leading to riskier behavior among male spouses such as extramarital sexual contacts.[10,13,14,44-46] A recent meta-analysis found that in sub-Saharan African countries, the cumulative incidence of HIV during pregnancy ranged from 0.2% to 13.8%, with a pooled incidence of 3.6% (95% CI: 1.9, 5.3), a rate similar to "high risk" cohorts.[7] One Kenyan study found that the mean cumulative incidence of HIV acquisition during pregnancy was 2.6% nationally, and 5.3% in Nyanza province.[19]

Acute HIV Infection is associated with Elevated Risk of Horizontal and Vertical Transmission

HIV infectiousness is partially determined by the blood viral load, which follows a U-shaped curve, being the highest following acute infection, lower during latency, and increasing with advancing disease.[47-49] The likelihood of horizontal transmission of HIV between serodiscordant couples per coital act depends on the infectiousness of the HIV-infected index case and the susceptibility of the uninfected partner.[50,51] One study with couples demonstrated that the risk of horizontal transmission within the first three months of infection was 12-fold higher than the risk one year after infection, a result consistent

with other research.[52,53] Infectiousness may be further exacerbated in pregnancy due to a hormonally-induced increase in HIV-1 RNA shedding in cervical and vaginal secretions.[54-56] Mugo et al. found HIV incidence in male partners of infected women to be 3.46 versus 1.58 per 100 person-years (hazard ratio 2.31, 95% CI: 1.22, 4.39) when their partners were pregnant versus not pregnant, even after adjusting for sexual behavior and other confounders.[10]

The likelihood of vertical transmission from mother to child is also increased with acute infection. Women who have plasma HIV-1 RNA levels exceeding 100,000 copies per milliliter have a 63.3% transmission rate to their infants compared with a 0% and 16% transmission rate among women with less than 1000 copies/mL and 1000-10,000 copies/mL, respectively.[11] Additionally, women with acute HIV infection may have a maternal immune response that is insufficiently mature to allow for significant transfer of protective immunity to the child via placental or breast milk transfer of antibodies.[57,58]

Efforts to prevent HIV transmission during acute HIV infection (AHI), defined as the time from HIV acquisition until seroconversion[59] (when measurable antibodies develop in the blood[60]), are hampered by challenges with diagnosing AHI in resource-limited settings. Nucleic acid amplification testing, necessary to detect AHI in its earliest stages of ramp-up viremia, is cost-prohibitive even in high-income settings.[61] Fourth generation rapid HIV test kits, which are capable of detecting both HIV antigens as well as antibodies, have yet to be adopted as part of official Kenyan testing algorithms.[62] Current recommendations, which constitute screening test KHB Colloidal Gold, confirmatory test First Response, and tie-breaker Uni-Gold, rely on third generation rapid

HIV tests that detect antibodies, resulting in a diagnosis delay known as the "window period" that may range from 14 days to 3 months.[63]

Knowledge of HIV Status May Empower Women to Adopt Beneficial Health Behaviors

Knowledge of HIV status is associated with a greater likelihood of modifying behavior; such as by adopting safer sexual practices, uptake of ART, linkage to HIV care, delivery in a health care facility, and safer infant feeding.[46,64-66] Although challenges surrounding linkage to HIV care services and ART adherence persist, women who are aware of their HIV status are able to proactively protect their children and sexual partners. A meta-analysis found that 75% of women have adequate ART adherence during pregnancy, compared to 53% during the postpartum period, a finding that may be attributable to maternal concerns of transmitting HIV to her fetus in utero, which may diminish after the birth.[67-69] HIV care and treatment are also important to decrease the risk of pregnancy-related complications such as stillbirth, pre-term deliveries, and low birthweight infants.[70]

Delivery in a health care facility with skilled providers is a key strategy for reducing risk of MTCT and reducing maternal morbidity and mortality.[71] While ever being tested for HIV during pregnancy is associated with an increased likelihood that women will deliver in a facility, in Kenya, only 43% of women deliver in a health care facility with a skilled provider.[71,72] Repeat testing for HIV in late pregnancy may give providers time to encourage women to deliver with a skilled birth attendant who can administer ART treatment or prophylaxis if the woman is seropositive, take precautions

to minimize transmission during a vaginal delivery, or perform a caesarean section to greatly reduce transmission risk.

Knowledge of HIV Status Allows for ART Uptake to Protect Maternal Health

The World Health Organization (WHO) has set the goal of providing ART coverage to 90% of pregnant women with HIV by 2015.[73] Identifying all pregnant women who are living with HIV is the first step to achieving this target. Antenatal care clinics may be the only source of contact that healthy reproductive-aged females have with the health care system, thus a lack of testing and linkage to care during ANC visits may represent a missed opportunity. New guidance from the WHO and CDC-PEPFAR supports a prevention of mother-to-child transmission (PMTCT) of HIV strategy that recommends all HIV-positive pregnant women, regardless of CD4 count, receive triple ART for life.[74] This strategy, called Option B+, has streamlined an earlier recommendation that used a CD4 count cutoff of 350 cells/mm^3 to determine whether pregnant woman were placed on full ART treatment or temporary prophylaxis to prevent MTCT. Option B+ is in line with the overall shift adopted by the international community to move from a focus on PMTCT for the sake of the child to improving long-term health outcomes for both children and their mothers. The Kenya National AIDS and STI Control Programme (NASCOP) is rolling out Option B+ as the standard of care in their PMTCT programs, in line with national goals to reduce vertical transmission to below 5% by 2015 and to keep mothers alive.[75] These goals align with the objective of reducing the number of orphaned and vulnerable children born into a family with members living with HIV.[76]

Incident HIV Infection May Contribute Significantly to MTCT

With close follow-up of HIV-positive mothers, monitored adherence to ART regimens, elective cesarean delivery, and in some circumstances avoidance of breastfeeding, high- and middle- income countries have achieved MTCT rates of 1-2%, thus "virtually eliminating" transmission risk.[2,75] In countries where women may have less access to antenatal care services, HIV testing and treatment, delivery in a health care facility, and where extended breastfeeding is common, MTCT rates can range from 15% in non-breastfeeding populations to up to 45% after 24 months of breastfeeding.[77-79] As ART during pregnancy, delivery, and breastfeeding successfully decreases the number of infants born to women identified as HIV positive early in pregnancy, a greater proportion of HIV-positive infants will be born to mothers who had incident HIV infections in later pregnancy. A recent modeling study by Johnson et al.[9] predicted that as of 2014, 34% of all MTCT has been among children whose mothers seroconverted during pregnancy. The study also found that repeat HIV testing in late pregnancy would reduce the number of new HIV infections in children by 11.2%, even though the incremental benefit per 1000 HIV tests would be 7.2 averted infections, compared to 62.5 averted infections for the initial antenatal test. Thus, in high prevalence settings, retesting may be a crucial means of achieving MTCT rates below 5%.[7]

IMPLEMENTATION OF REPEAT HIV TESTING DURING PREGNANCY IN SOUTHWESTERN KENYA: SUCCESSES AND MISSED OPPORTUNITIES

by

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ABSTRACT

BACKGROUND: It is estimated that a third of all mother-to-child transmission (MTCT) of HIV occurs among women with incident HIV infection during pregnancy, making repeat HIV testing during the late antenatal period a crucial time to identify and initiate treatment for newly infected women. International recommendations, adopted in 2011 as part of the Kenya Ministry of Health guidelines, suggest that pregnant women in generalized epidemic settings be offered retesting three months after an initial negative HIV test early in pregnancy.

METHODS: Retrospective analysis of longitudinal data was conducted for a cohort of 2145 women attending antenatal care (ANC) at a large district hospital in southwestern Kenya. Data were abstracted from registers for all women who attended ANC from the years 2011 to 2014.

RESULTS: Although 90.4% of women first came to ANC prior to their third trimester and 27.5% had at least 4 ANC visits, 59.7% of all women went to delivery without a repeat HIV test despite having last tested HIV-negative more than 3 months prior. Missed opportunities for retesting stemmed from failure to achieve process measures, including early enough gestation at first ANC visit (≤ 28 weeks) to later be eligible for retesting, returning to ANC at all, and returning to ANC when eligible (accounting for 9.6%, 14.2%, and 26.8% of ANC attendees respectively), as well as outcome measures, including failure to be retested even when eligible at one or more visits (accounting for 73.2% of eligible returnees). Being unmarried and aged 20 or younger was associated

with an increase in mean gestational age of first visit by 2.52 weeks (95% CI: 1.56, 3.48) and a 2.59 odds (95% CI: 1.90, 3.54) of failing to return to clinic, compared to those who were married and over 20 years of age. On retest, two women tested HIV-positive, suggesting a cumulative incidence of 1.5% from early to late pregnancy and an incidence rate of 4.4 per 100 person-years. After adjusting for potential confounders, only later year of pregnancy (2013 vs. 2012 and 2011) was associated with receipt of a retest among eligible returnees, suggesting that guideline implementation successfully increased retesting rates.

CONCLUSIONS: Missed opportunities for repeat HIV testing among pregnant women may contribute to continuing high rates of MTCT in Kenya and similar settings in sub-Saharan Africa, particularly in light of current recommendations that all pregnant women who test HIV-positive be started immediately on lifelong antiretroviral therapy. Contributors to missed opportunities include patient factors, such as not returning to ANC after testing negative for HIV early in pregnancy, and health system factors, such as a failing to retest eligible women.

BACKGROUND

As pregnant women with chronic HIV infection are increasingly identified as being seropositive at their first visit to antenatal care clinics, pregnant women who experience HIV seroconversion during the perinatal period will contribute to a growing proportion of mother-to-child transmission (MTCT) events.[1] This is particularly true because acute HIV infection is associated with elevated viral loads that increase risk of transmission during pregnancy, delivery, and through breastfeeding.[2,3]

Repeat HIV testing during pregnancy allows women who have seroconverted since first antenatal test to be aware of their HIV status and take up lifelong ART for their own sake, as well as to prevent MTCT.[4] Infants born to mothers of known HIV-positive status are often more closely followed as HIV-exposed infants: they are given HIV prophylaxis at delivery and for a period of time after birth, tested through early infant diagnosis programs, and immediately initiated on antiretroviral therapy (ART) if found to be infected with HIV.[5,6]

In Kenya, there are roughly 1.5 million pregnancies and 87,000 HIV-positive pregnant women per annum.[7] The MTCT rate is estimated to be 15%, accounting for 13,000 new childhood infections in Kenya every year.[8,9] In mid-2011, the Kenya Ministry of Health adopted international guidelines recommending that repeat HIV testing be offered three months after an initial negative HIV test result in early pregnacy.[10] While one study in Kenya found the acceptability of provider-initiated retesting in late pregnancy to be 93.5%,[11] only one known study from Zambia has

reported the retesting rate in a non-intervention setting to be 24.5% among eligible pregnant women.[12] Additionally, little is known about gaps in implementation of repeat HIV testing and the factors associated with a lack of retesting, thus making it challenging to address the deficits.

The purpose of this paper is to determine the current rate of antenatal repeat HIV testing, identify missed opportunities and factors associated with retesting, and estimate the incidence of HIV during pregnancy at a large hospital in southwestern Kenya.

METHODS

Setting and Context

This study was conducted at a large government hospital in rural southwestern Kenya, an area of the country with the highest HIV prevalence at 15.1%.[13] The facility is one of three district hospitals in the county and has a large patient volume comprising of primarily low-income clients. The Kenya AIDS Indicator Survey 2012 found that for Kenya overall, 95.4% of reproductive-aged women attended antenatal care (ANC) clinic during pregnancy, 93.1% of whom were tested for HIV at ANC during their last pregnancy.[14] In the study setting, Kenya Ministry of Health facilities are supported by Family AIDS Care and Education Services, a PEPFAR-funded program that provides integrated HIV and ANC care.[15] Kenya adopted provision of lifelong ART for pregnant women regardless of CD4 count (Option B+) in June 2014. On-site rapid HIV testing in ANC clinics is provider-initiated and protocol comprises the use of HIV screening test kits, with a confirmatory test conducted for all HIV-positive test results as per the national algorithm.[16]

Study Design

Longitudinal antenatal record data for the full pregnancy were abstracted from paper antenatal care registers for all women attending the antenatal clinic in the years 2011 to 2014. Data for pregnant women were included in the study if they had a last menstrual period (LMP) in the years 2011, 2012, or 2013. Women were excluded if they had their first antenatal visit at a different clinic, since it would constitute missing information on whether they had an HIV test and the gestation at which they had their first visit. Ethical approval was given by the Kenya Medical Research Institute Scientific and Ethical Review Unit (SERU) and the University of Alabama at Birmingham Institutional Review Board. As the data were gathered as a part of routine medical care and de-identified after linkage, individual patient consent was not solicited as a part of this study.

Variable Definitions

Women had an initial HIV test if their records noted that they tested HIV-negative or HIV-positive on their first ANC clinic visit, or they were a known HIV-positive individual when they initially presented for ANC. Women were eligible for a repeat HIV test if their records noted that they visited the ANC clinic again at least 12 weeks after an initial visit with an HIV-negative test result. Women were coded as having been retested if records indicated an HIV-negative or HIV-positive test on re-visit. Women were ineligible for a repeat HIV test if they had previously tested positive for HIV or if their first clinic visit occurred after 28 weeks gestation, making it too late for them to have another HIV test during the current pregnancy.

A missed opportunity was noted if women were not retested even though eligible at one or more clinic visits. Seroconversion during pregnancy was defined as having an HIV-negative result at the initial HIV test, and an HIV-positive result on retest. Village distance from the hospital was estimated by utilizing the expertise of local facility transport staff, who deliver supplies such as medicines and biological specimens between government health facilities, to determine the distance between women's village locations as listed in the ANC register and the hospital. Pregnancy cohorts were defined by the year of their LMP.

Data Analysis

Data that had been entered into an electronic database were cleaned and analyzed in SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). Bivariate analyses were conducted with chi-squared and t-test statistics to assess the statistical association of patient demographic variables with process indicators, including early enough gestation at first visit and returning to antenatal clinic, and outcome measures such as getting a repeat HIV test.[17] Specifically, to understand the characteristics of women who received repeat HIV testing as compared to those who did not, we ran a series of analyses with the dependent variables (A) gestational age at first visit, which impacts whether or not a woman will become eligible for repeat HIV testing, (B) whether or not the woman returned to clinic, which impacts being offered a repeat HIV test, and (C) whether or not the woman received a retest.

Although we considered p-values below 0.05 to indicate statistical significance, all analyses were assessed in the context of their substantive significance. Both bivariate

and multivariate models were presented since the unadjusted models provide information on the target population for implementation of strategies, while the adjusted models account for confounding to better describe what factors drive the trends.

RESULTS

Characteristics of the Study Population

A total of 2160 women who had an LMP in the years 2011, 2012, and 2013 attended antenatal clinic at the study facility. We excluded 15 women from the dataset for having their first antenatal visit at a different clinic, leaving us with a sample of 2145 (Table 1). Ninety-six women had two pregnancies fall within the time span of data collected; only the first pregnancy was included in analyses. Of the 2145 women remaining in the sample, the average age was 23.5 years (interquartile range [IQR], 19-27) with an average estimated village distance from clinic of less than 5 kilometers (IQR 1-5). Just over a quarter (27.5%) of the women had at least the 4 recommended ANC visits at the clinic, with approximately a quarter having only one ANC visit (23.4%). Fifteen percent of the women were either single or no longer in a marital relationship and 28.4% of all women had four or more children. Most women came for their first ANC visit during the second trimester (68.8%), with a mean gestational age of 21.6 weeks (IQR 18-26).

Nineteen percent of the sample already knew of their HIV-positive status at first ANC visit, while another 6.8% were diagnosed as being HIV-positive for the first time at the time of their first ANC visit for this pregnancy. At delivery, 13.9% were considered to be known HIV-negative, having had their most recent HIV test within the last three

months, and 59.7% of all women went to delivery without a repeat HIV test despite having last tested HIV-negative more than 3 months prior. Overall acceptance of the HIV test during pregnancy was very high at 97.8%.

Table 1. Descriptive statistics for the study sample (N = 2145)

Variable	Mean (sd)	n (%)
Age (years)	23.5 (5.48)	
Estimated village distance from hospital (km)	4.7 (6.45)	
Gestational at first ANC visit (weeks)	21.6 (6.3)	
Year of pregnancy		
2011		519 (24.1)
2012		738 (34.4)
2013		888 (41.4)
Number of ANC visits		
1		501 (23.4)
2		509 (23.7)
3		545 (25.4)
≥ 4		590 (27.5)
Marital status		
Married		1785 (83.3)
Single		225 (10.4)
Widowed/ Divorced/ Separated		99 (4.6)
Missing		36 (1.7)
Gravida		
Primigravid		602 (28.0)
2		530 (24.7)
3		401 (18.9)
4		289 (13.5)
5		182 (8.5)
≥6		141 (6.4)
Gestation at first ANC visit		
≤ 12 weeks		221 (10.4)
13-20 weeks		731 (33.9)
21-28 weeks		986 (45.9)
29-36 weeks		203 (9.5)
≥ 37 weeks		4 (0.3)
HIV Status at delivery		
Known HIV positive at first visit		413 (19.3)
Newly diagnosed HIV-positive in ANC		143 (6.7)
Negative		300 (14.0)
Previously negative*		1245 (58.0)
Not done/ Missing		44 (2.0)

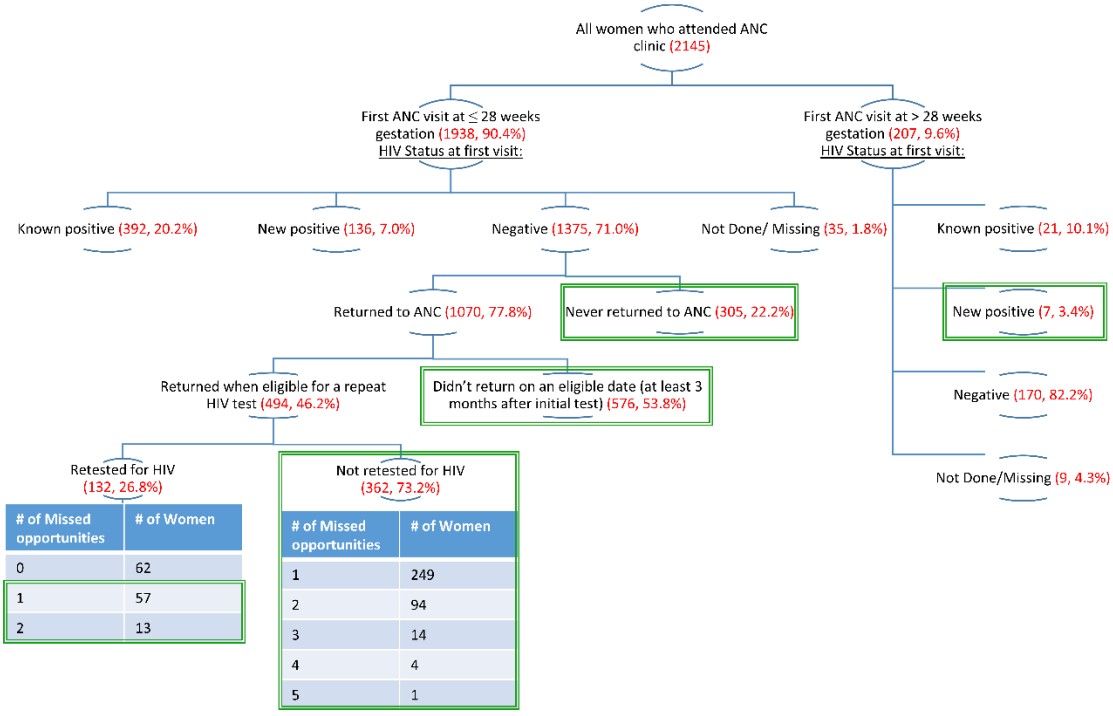
* Defined as having had more than three months pass since the last HIV-negative test result.
ANC = antenatal care

Characterizing Missed Opportunities

Of all women in our sample, 210/2164 (9.8%) presented after 28 weeks gestation for their first antenatal visit of this pregnancy, making them ineligible for repeat HIV testing later in pregnancy or at delivery (Figure 1). Among these women, 8/210 (3.8%) tested HIV-positive for the first time, possibly constituting a missed opportunity for early ART initiation to suppress viral load and prevent MTCT.

The majority of women (1938/2164, 90.4%) initially presented at ANC by 28 weeks gestation. Of those, 392/1938 (20.2%) were known HIV-positive and 136/1938 (7.0 %) were newly HIV-positive, leaving 1387/1938 (71.0%) who tested HIV-negative, who would eventually become eligible for a retest later in pregnancy. Of these eligible women, 310/1375 (22.2%) never returned to the ANC clinic and 494/1375 (46.2%) eventually returned to clinic on a date at which they were eligible for retesting. Of those who became eligible, 132/494 (26.8%) were eventually retested, while 362/494 (73.2%) were not retested, even though eligible at multiple visits. Of the total of 1375 women who should have had a repeat HIV test later in pregnancy, only 132 (9.6%) were re-tested.

Figure 1. Missed opportunities for repeat HIV testing and early ART initiation



†Percentages are a subset of the level right above.
Green boxes indicate missed opportunities for repeat HIV testing and/or early intervention of MTCT through initiating ART

Thus, missed opportunities to retest all 1375 potentially eligible women included (A) women who did not return to clinic at all, (B) women who did have visits spaced out in such a way that they were eligible when they did return, and (C) women who were not retested, even though eligible at multiple ANC visits.

Characterizing Factors associated with Process and Outcome Measures

Factors associated with Early Gestational Visit

Known HIV-positive status at first visit was significantly associated with earlier gestation at first visit when compared with being HIV-negative or newly diagnosed as HIV-positive in bivariate analyses (Table 2). Being married was also associated with

earlier gestational age at first visit when compared to previously married (widowed, divorced, or separated) or unmarried status. Later year of pregnancy, higher parity, and older age were similarly associated with earlier gestation at first visit— a trend that held true for parity and age even when we dichotomized the gestational age to being less than or greater than 28 weeks at first ANC visit.

Women who lived at a greater distance from the clinic came, on average, earlier than women who lived closer to the clinic. We independently assessed factors associated with the continuous variable of living further away from the clinic using non-parametric methods to account for the non-normal distribution of distances. We found that there was no difference by marital status or age, but that being of known HIV-positive status, older age, and higher parity did correlate with living further away (results not shown). Since two of these characteristics contributed to earlier gestation of first visit, we ran a multivariate model and found that after adjusting for both age and HIV status, greater village distance from clinic was no longer associated with earlier gestation at first visit.

However, because the small population of women who lived far from the clinic (operationalized as the 5% of the population who lived in a village ≥15 km away) appeared to have different characteristics than other clients, we ran sensitivity analysis excluding them from all our models. Doing so did not qualitatively change the reported results.

Factors associated with Returning to Clinic

Having a first antenatal care visit by 28 weeks gestation was associated with 3.8 times the odds (95% CI: 2.85, 5.14) of returning to clinic over having a first antenatal care visit after 28 weeks. Known HIV-positive status at first visit was associated with 2.3 times the odds (95% CI: 1.69, 3.14) of returning to clinic compared with being HIV-negative in bivariate analyses. Women who were older, had higher parity, were married, and had a later year of pregnancy were also significantly more likely to return to clinic.

Being unmarried and aged 20 or younger was associated with an increase in mean gestational age of first visit by 2.52 weeks (95% CI: 1.56, 3.48) and a 2.59 odds (95% CI: 1.90, 3.54) of failing to return to clinic, compared to those who were married and over 20 years of age. Being diagnosed with HIV during pregnancy was also a risk factor for failing to return to antenatal clinic, as newly positive women had a 0.62 odds (95% CI: 0.42, 0.92) of returning to clinic compared to those who tested negative in pregnancy even after adjusting for potential confounders. This is in contrast to women who knew their HIV-positive status during pregnancy and who had a significantly increased odds of returning to antenatal care.

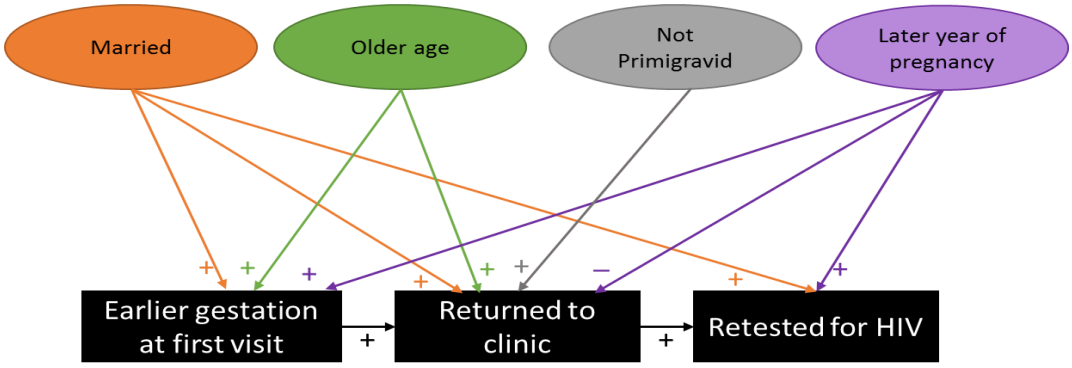
Table 2. Factors affecting gestation at first visit and return to clinic

		Gestation at first visit (weeks)						Returned to clinic at least once					
		Bivariate analyses			Multivariable analyses			Bivariate analyses			Multivariable analyses		
Factor	**N**	**Mean**	**(sd)**	**p-value**	**β**	**(se)**	**p-value**	**OR**	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
HIV status at first visit													
Negative	1545	22.4	(6.0)	<0.0001	Ref.		<0.0001	Ref.		<0.0001	Ref.		<0.001
Newly positive	143	21.4	(5.7)		-0.91	(0.55)		0.74	(0.51, 1.07)		0.62	(0.42, 0.92)	
Known positive	413	18.6	(6.5)		-4.1	(0.36)		2.38	(1.69, 3.14)		1.85	(1.32, 2.58)	
Marital status													
Married	1785	21.3	(6.4)	<0.0001	Ref.		<0.05	Ref.		<0.0001	Ref.		<0.001
Prev. married	99	22.7	(5.3)		1.62	(0.66)		0.55	(0.35, 0.85)		0.56	(0.35, 0.90)	
Single	225	23.8	(5.5)		3.33	(0.47)		0.38	(0.28, 0.51)		0.49	(0.35, 0.69)	
LMP year													
2011	519	22.3	(5.9)	<0.01	Ref.		<0.05	Ref.		0.48	Ref.		<0.05
2012	738	21.7	(6.3)		-0.86	(0.35)		0.92	(0.79, 1.22)		0.92	(0.68, 1.23)	
2013	888	21.2	(6.4)		-1.22	(0.36)		0.74	(0.57, 0.96)		0.77	(0.58, 1.02)	
Age of patient													
≤15 years	124	23.4	(6.0)	<0.0001	Ref.		0.745	Ref.		<0.0001	Ref.		<0.001
16 - 20 years	649	22.4	(5.9)		-0.32	(0.63)		1.18	(0.78, 1.78)		1.06	(0.68, 1.65)	
21 - 30 years	1147	21.2	(6.4)		-1.24	(0.63)		1.89	(0.78, 1.78)		1.33	(0.84, 2.10)	
≥31 years	225	20.8	(6.8)		-1.89	(0.75)		2.97	(1.75, 5.05)		1.87	(1.04, 3.39)	
Village dist. from clinic													
≤5 km	1598	21.7	(6.3)	<0.0001	Ref		0.1	Ref.		<0.001	Ref.		0.72
6 - 15 km	334	21.9	(6.1)		0.49	(0.37)		1.4	(1.07, 1.84)		1.07	(0.79, 1.44)	
16 - 30 km	93	18.8	(6.3)		-1.55	(0.66)		1.59	(1.18, 2.15)		0.78	(0.46, 1.34)	
≥31 km	21	18.1	(5.4)		-2.50	(1.32)		1.74	(1.33, 2.28)		0.74	(0.26, 2.12)	
Parity*													
Primigravid	602	21.5	(6.0)	0.33	N/A	N/A	N/A	Ref.		0.93	N/A	N/A	N/A
2	530	21.7	(6.4)		N/A	N/A		1.09	(0.82, 1.45)		N/A	N/A	
3	401	21.2	(6.5)		N/A	N/A		0.99	(0.60, 1.61)		N/A	N/A	
4	608	21.9	(6.2)		N/A	N/A		0.98	(0.35, 2.69)		N/A	N/A	

*Parity was excluded from multivariate analyses because of its collinearity with age.
CI = Confidence interval; sd = Standard deviation; se = Standard error; LMP = last menstrual period; Prev. = previously; N/A = not applicable; OR = odds ratio; aOR = adjusted odds ratio

The results of univariate analyses from Table 2 are summarized in Figure 2. The presence of a line indicates a statistically significant association, the direction of correlation of which is indicated next to the arrow.

Figure 2. Factors associated with earlier gestation at first visit, returning to clinic, and getting retested for HIV (bivariate analyses)



Factors associated with Getting Retested for HIV

In order to determine factors associated with getting retested in our target population – all the women who came early enough to be eligible for retesting – we assessed the relationship between patient characteristics and retesting among all women who had tested HIV-negative by 28 weeks gestation. In bivariate analyses, we found that only marital status and year of pregnancy were significantly associated with getting retested (Table 3). In the multivariate model, after adjusting for returning to clinic, marital status was no longer associated with retesting (aOR = 0.63, 95% CI: 0.33, 1.18), suggesting that individual-level factors were not influential in whether or not a woman got retested.

When only considering women who did return to clinic and became eligible for retesting (n=494), we found that only year of pregnancy, which correlated with the

dissemination of Kenyan national guidelines on repeat HIV testing in mid- to late-2011, was associated with getting retested. Using a multivariate Poisson regression model to examine the factors associated with having multiple missed opportunities for retesting yielded a similar result.

Examining the 494 patients who did return to clinic and were eligible for retesting by year of pregnancy, we found that in 2011, only 1 of 105 eligible patients was retested (0.95%); in 2012, 31 of 162 eligible patients were retested (19.14%); and in 2013, 100 of 227 (44.05%) eligible patients were retested.

Table 3. Factors associated with getting retested for HIV (bivariate analyses)

	Retested for HIV among target population (N=1375)				Retested for HIV among eligible women who returned to clinic (N = 494)			
Factor	**N**	**Odds Ratio**	**(95% CI)**	**P-value**	**N**	**Odds Ratio**	**(95% CI)**	**P-value**
Marital status								
Married	1113	Ref.		0.038	425	Ref.		0.73
Not married	237	0.54	(0.30, 0.96)		56	0.89	(0.47, 1.7)	
LMP year								
2011	316	Ref.		<0.0001	105	Ref.		<0.0001
2012	466	22.2	(3.01, 163)		162	24.3	(3.27, 181)	
2013	593	63.4	(8.80, 456)		227	81.0	(11.1, 591)	
Age of patient								
≤15 years	89	Ref.		0.17	21	Ref.		0.52
16 - 20 years	479	2.21	(0.77, 6.33)		157	0.99	(0.23, 3.84)	
21 - 30 years	711	2.58	(0.92, 7.24)		283	1.72	(0.54, 5.40)	
≥31 years	96	1.41	(0.38, 5.19)		33	1.58	(0.51, 4.87)	
Parity								
Primigravid	479	Ref.		0.77	21	Ref.		0.91
2	346	1.09	(0.69, 1.73)		157	0.97	(0.58, 1.60)	
3	247	0.93	(0.55, 1.58)		283	0.97	(9.54, 1.75)	
4	301	0.83	(0.50, 1.38)		33	0.82	(0.46, 1.44)	
Village distance from clinic								
≤15 km	1264	Ref.		0.17	457	Ref.		0.11
>15 km	50	0.37	(0.09, 1.5)		19	0.30	(0.70, 1.35)	

Outcomes of Repeat HIV Testing

The 132 women who were retested contributed a mean of 125 days (range: 83 to 196 days) between initial HIV test and retest, for a total of 45.4 person-years. Two women seroconverted from being HIV-negative at initial test to being HIV-positive on retest, corresponding to a (2/132) 1.5% cumulative incidence and an incidence rate of (100/45.4*2) 4.4 per 100 person-years. Extrapolating the incidence rates to our target population would suggest that had we retested all potentially eligible women (N = 1375), we may have identified an additional 18 women who had seroconverted by delivery.

DISCUSSION

Repeat HIV testing and early ART initiation are important components of antenatal care in settings of high HIV incidence. Utilizing routinely collected antenatal record data from a large hospital in southwestern Kenya, our study found that the dissemination and implementation of guidelines for repeat HIV testing were successful in making a considerable impact on rates of repeat HIV testing through encouraging provider-initiated rather than patient-initiated requests for retest. Specifically, guideline dissemination was associated with an increase in retesting from less than 1% in 2011 to nearly 45% in 2013. However, missed opportunities continue to exist for both repeat HIV testing as well as early ART initiation, leading to potential MTCT of HIV that may have otherwise been intervened upon.

Key missed opportunities included later gestation at first antenatal care visit, leading to potentially delayed initial identification of HIV-seropositivity and linkage to HIV care, failing to return to antenatal clinic after an initial visit, and failing to get

retested even though eligible. Conversely, earlier gestation was associated with returning to clinic, which was in turn associated with getting retested for HIV. Factors contributing to earlier gestation at first visit included known HIV-positive status at first visit, being married, and being of older age. Similar factors contributed to likelihood of returning to clinic, with the addition of higher parity. Thus, all these demographic characteristics may have influenced likelihood of getting retested for HIV.

We found that initial HIV testing rates (97.8%) in our study were higher than the national average (93.1%), potentially given the higher HIV prevalence in the region.[8] In a recent meta-analysis, Drake et al. report the pooled cumulative incidence of HIV during pregnancy to be 1.5% (95% CI 1.2%-1.8%), although African countries had a higher rate when compared to non-African countries (3.6% versus 0.3%, respectively, $p<0.001$).[18] They also reported a pooled incidence rate of 4.7 (95% CI 3.3-6.1) per 100 person-years.[18] Kinuthia et al. reported data from the Nairobi and Nyanza regions of Kenya supporting a cumulative incidence 2.6% and an incidence rate of 6.8 per 100 person-years.[11] The cumulative incidence rate of 1.5% and incidence rate of 4.4 per 100 person-years reported in this study thus correspond closely to the rates reported in the literature. We also found that known HIV-positive status at first visit was significantly associated with earlier gestation at first visit and returning to clinic, possibly because this group is already engaged in health care at the facility, is used to accessing care, or have been encouraged by HIV providers to access ANC early to prevent MTCT.

Several themes relevant to improving the implementation of repeat HIV testing guidelines emerged from the data. At the patient level, various types of stigmas may have influenced ANC choices. For women who were young and/or unmarried, as well as

women who were previously married, stigma may have influenced a later average gestation at first presentation to clinic, as well as a lower likelihood of returning to clinic and thus lower retesting rates. These data are corroborated by both the qualitative[19] and quantitative[20] literature. We also found that women newly diagnosed as being HIV-positive in ANC were significantly less likely to return to clinic – a crucial group to focus on for the prevention of MTCT and linkage to care for their own health. Women who were HIV-positive were more likely to live further away from the clinic, suggesting that stigma may have led them to seek antenatal care away from their home, just as the literature indicates that HIV stigma may lead individuals to seek general HIV care far from home.[21]

At the clinic level, factors unrelated to patient choices may have been more influential in determining who received retesting once they returned to clinic at a time when they were eligible, as seen by the fact that receipt of retesting was uncorrelated with demographic characteristics. This also suggests that providers did not seem to target certain profiles of women for retesting. In contrast, year of last menstrual period was highly predictive of getting retested, given women returned to clinic at a time when they were eligible, indicating that the dissemination of retesting guidelines may have driven an increase in provider-initiated testing. However, the fact that nearly 60% of women still failed to get retested more than a year after guideline dissemination and that women continued to fall through the cracks even though eligible at multiple visits is concerning. Our prior data found that ability of providers to remember when three months have elapsed since last test, clinic workload on day of patient visit, and availability of adequate HIV test kits may impact whether providers offer retesting.[19]

The current study has several strengths including the prospectively-collected, longitudinal nature of the data with both demographic factors and process/outcome measures. It also spanned the pregnancy duration as well as the time prior to and after the dissemination of national repeat HIV testing guidelines. We were limited by our inability to determine if women were retested at some point during their pregnancy at other antenatal care facilities, although we limited the likelihood of this occurrence by restricting the dataset to women who had their first antenatal care at our site and thus likely treated it as their primary care location. Similarly, we were unable to determine if miscarriage was a reason for non-return to ANC and were limited in our sociodemographic variables to those which are routinely collected data. This was also a single, semi-rural study site that was supported by FACES and thus may not be representative of ANC in other areas.

In conclusion, repeat HIV testing rates seem to have increased in the post-guideline era, but improving late-pregnancy detection of incident HIV infection may require community mobilization and messaging surrounding earlier and more consistent ANC visits – strategies that will also likely improve general antenatal care – and the importance of HIV retesting. Further research should assess whether these findings are also applicable to other settings, determine the driving factors for multiple missed opportunities for eligible women such as potential refusal of HIV retesting relative to initial HIV testing, and assess clinic-level factors such time of day or day of week that may impact provider-initiated testing. In addition, other studies should attempt to link antenatal care testing with delivery and postnatal testing to assess retesting and ART initiation and retention for women that acquired HIV in the perinatal period.

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IMPLEMENTATION OF REPEAT HIV TESTING DURING PREGNANCY IN KENYA: A QUALITATIVE STUDY

by

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ABSTRACT

BACKGROUND: Repeat HIV testing in late pregnancy has the potential to decrease rates of mother-to-child transmission of HIV by identifying mothers who seroconvert after having tested negative for HIV in early pregnancy. Despite being national policy in Kenya, the available data suggest that implementation rates are low.

METHODS: We conducted 20 in-depth semi-structured interviews with healthcare providers and managers to explore barriers and enablers to implementation of repeat HIV testing guidelines for pregnant women. Participants were from the Nyanza region of Kenya and were purposively selected to provide variation in socio-demographics and job characteristics. Interview transcripts were coded and analyzed in Dedoose software using a thematic analysis approach. Four themes were identified a priori using Ferlie and Shortell's Framework for Change and additional themes were allowed to emerge from the data.

RESULTS: Participants identified barriers and enablers at the client, provider, facility, and health system levels. Key barriers at the client level from the perspective of providers included late initial presentation to antenatal care and low proportions of women completing the recommended four antenatal visits. Barriers to offering repeat HIV testing for providers included heavy workloads, time limitations, and failing to remember to check for retest eligibility. At the facility level, inconsistent volume of clients and lack of space required for confidential HIV retesting were cited as barriers. Finally, at the health

system level, there were challenges relating to the HIV test kit supply chain and the design of nationally standardized antenatal patient registers. Enablers to improving the implementation of repeat HIV testing included client dissemination of the benefits of antenatal care through word-of-mouth, provider cooperation and task shifting, and it was suggested that use of an electronic health record system could provide automatic reminders for retest eligibility.

CONCLUSIONS: This study highlights some important barriers to improving HIV retesting rates among pregnant women who attend antenatal clinics in the Nyanza region of Kenya at the client, provider, facility, and health system levels. To successfully implement Kenya's national repeat HIV testing guidelines during pregnancy, it is essential that these barriers be addressed and enablers capitalized on through a multi-faceted intervention program.

Keywords: PMTCT, pregnancy, HIV counseling and testing, Kenya, Guideline implementation

BACKGROUND

The integration of HIV testing into antenatal care settings has been a key contributor to the decline in mother-to-child transmission (MTCT) of HIV. Of the 22 priority countries identified by the Joint United National Programme on HIV/AIDS (UNAIDS) that account for over 90% of all MTCT, as of 2012 seven had achieved testing rates of over 90% of pregnant women and 14 had achieved at least 50%.[1] While this is encouraging, a recent meta-analysis found the pooled cumulative incidence of new HIV infections during pregnancy and the postpartum period in African countries is 3.6% (95% CI: 1.9%-5.3%), suggesting that a single antenatal test may fail to capture an important subset of women who acquire HIV during this period and whose infants are at high risk of HIV acquisition due to elevated viral loads associated with acute HIV infections.[2] Additionally, as women with prevalent infection are increasingly identified at the first antenatal visit, it is estimated that 34% of all MTCT in the future will be among women with incident infection after the first antenatal care (ANC) clinic visit.[3]

Experts have called for HIV re-testing in late pregnancy, a recommendation that has been adopted by the international elimination of MTCT agenda.[2,4] In Kenya, repeat HIV testing in the ANC setting, defined as retesting three months after initial presentation at antenatal clinic, is national policy.[5] Although more than 90% of pregnant women in Kenya receive an initial HIV test and research suggests that retesting acceptability is high,[6] current rates of retesting among pregnant women in Kenya are unknown. There is a lack of data on the implementation of repeat testing in sub-Saharan Africa; only one

known observational study, conducted in Zambia, reports the rate of repeat HIV testing during pregnancy to be 24.5% at a district hospital.[7]

Much research has been done on the barriers to initial HIV testing in sub-Saharan Africa among the general population, identifying factors such as stigma, lack of information, perceptions of lack of privacy and confidentiality, poor relationships with health staff, and fear of being HIV-positive.[8,9] However, the barriers and enablers to repeat HIV testing among pregnant women who have already accepted HIV testing once are less clear.[10]

In order to address these gaps in the literature, we carried out 20 qualitative semi-structured in-depth interviews with administrators and providers of healthcare to explore the barriers and enablers to retesting pregnant women for HIV in rural Kenyan health facilities. It is anticipated that this research will help inform the design of a multi-faceted intervention to improve implementation of the HIV repeat testing policy for pregnant women in Kenya and other similar settings globally.

METHODS

Setting and Context

Data were gathered in the Nyanza region of Kenya, which has the highest prevalence of HIV in the country at 15.1%.[11] Although much of the population lives in rural areas, 96% of pregnant women attended at least one antenatal care appointment in 2012 and 93.1% received at least one HIV test, making antenatal care clinics an important site for HIV testing and linkage to HIV treatment.[12] Of the three study sites, all of which were located in rural areas, one site was in a mining community, another in a

farming community, and the last in a community that engages in a range of income-generating activities.

Study Design

Ethics approval was given by the Kenya Medical Research Institute Ethical Review Committee and the University of Alabama at Birmingham Institutional Review Board. A qualitative in-depth interview guide was developed based on a review of the literature assessing the common barriers and enablers to HIV testing in all populations. Participants were identified from three ANC clinics affiliated with Family AIDS Care Education and Services (FACES),[13] a CDC-PEPFAR funded initiative that supports government health facilities in providing comprehensive HIV prevention, care, and treatment services. Twenty healthcare providers and managers were chosen from a sampling frame of all potential participants at the study-approved sites, purposively selecting them for variation in socio-demographics and job characteristics. A sample size of 20 was chosen in order to include the perspectives of different types of providers and managers working at the study sites. Data saturation was achieved in 20 interviews, indicating that the sample size was sufficient for this qualitative study. Types of participants interviewed included nurses, community health workers, health educators, HIV testing counselors, laboratory technicians, facility coordinators, FACES program technical advisors, trained lay healthcare workers, and administrative staff involved in finances and procurement.

Participant demographic and job characteristics were collected using a standard questionnaire. A single interviewer (AJR) conducted in-depth interviews using the semi-

structured interview guide, which had been pilot tested for question clarity with two volunteers. All interviews lasted approximately one hour and were conducted in English, a national language of Kenya in which most healthcare providers are fluent. Following signed informed consent, participants were interviewed in a private setting and reimbursed 400 Kenyan Shillings (roughly equivalent to US $5) as compensation for their time. Interviews were digitally recorded and transcribed verbatim by experienced transcriptionists without identifying information.

Data Coding and Analysis

Interview transcripts were coded and analyzed by a single researcher (AJR) using the Dedoose qualitative software program (SocioCultural Research Consultants, LLC; Los Angeles, California). The coding and analysis were conducted using a thematic analysis approach.[14] Four initial major themes were identified using Ferlie and Shortell's Framework for Change, which posits that change can be focused at the individual level, the group or team level, the organizational level, and the larger system or environmental level, and adapted to the Kenyan setting.[15,16] Additional sub-themes were allowed to emerge from the data, and categorized into being either 'enablers' or 'barriers' to retesting.

RESULTS

Participant Characteristics

All 20 of the healthcare providers and managers approached agreed to participate. Sixty-five percent self-identified as healthcare providers with the majority of their time spent engaging with patients; the remainder primarily fulfilled managerial or administrative roles. The average age was 34 years, the average time in current job was 4.7 years, and 35% were female. In terms of the highest level of education, 15% (3 participants) had completed high school or less, 45% had a certificate or diploma, 25% had a bachelor's degree, and 15% had a master's degree or higher (Table 1).

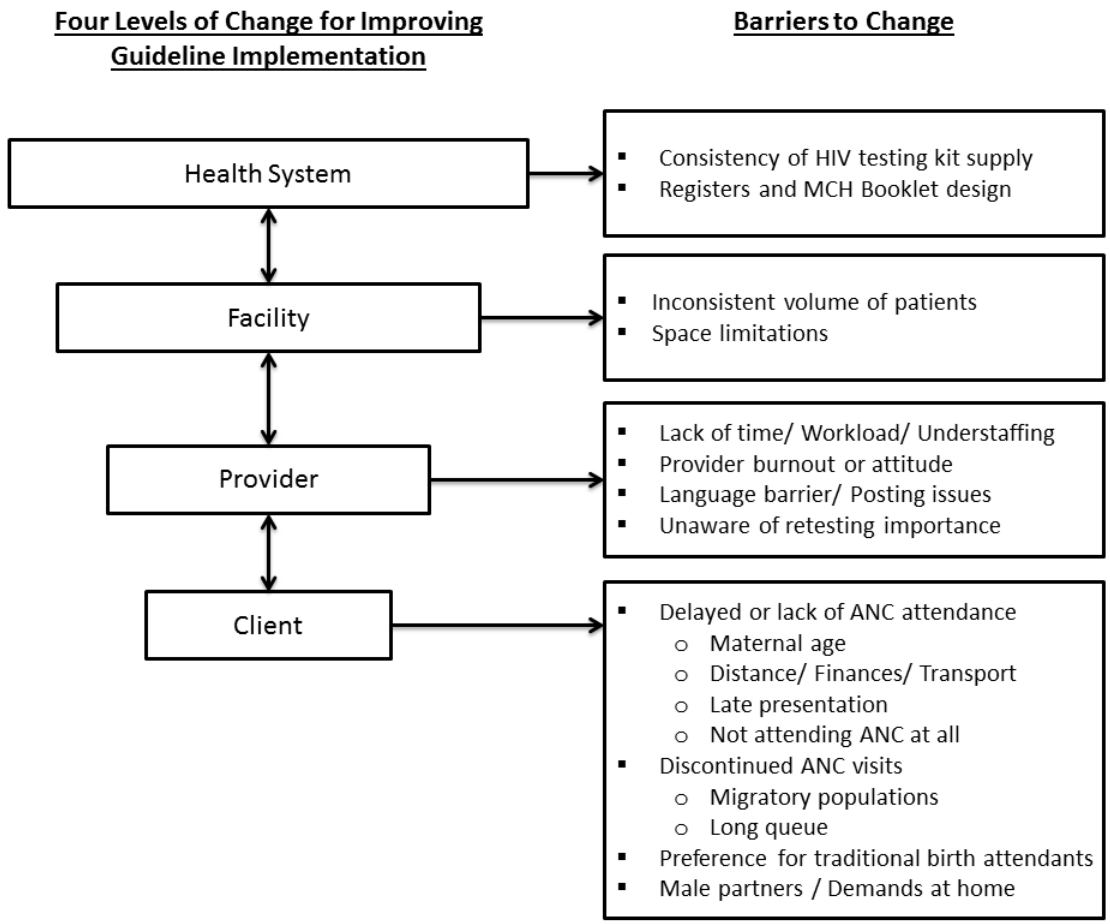
Table 1: Interview Participant Characteristics

Participant Characteristics (n = 20)	Proportion or Average
Job Type	
Healthcare provider	65%
Managerial or administrative	35%
Gender – Female	35%
Age (average, in years)	34
Time in Current Job (average, in years)	4.7
Highest Level of Education	
Form 4 Completion or less	15%
Certificate or Diploma	45%
Bachelor's Degree	25%
Master's Degree or higher	15%

Barriers

Participants identified barriers to improving guideline implementation at four levels of change: the client, provider, facility, and health system levels (Figure 1).

Figure 1: Barriers to Improving Guideline Implementation at Four Levels of Change



Adapted from Shortell[15] and Proctor et al.[17] Used with permission.

Barriers at the Client Level

Providers generally acknowledged that repeat HIV testing rates were low among women attending their clinics, with their estimations of the proportion getting tested at their clinic varying from 30% to 100%. Client-level barriers to a higher retesting rate discussed by the providers fell into four main categories: (A) factors influencing a late initial presentation for ANC or the decision to not come to clinic at all (B) factors influencing discontinued antenatal clinic visits after their initial visit, (C) preference for community-based services from traditional birth attendants, and (D) male partner factors.

Factors influencing delayed initial presentation or antenatal clinic non-attendance

Maternal age. While pregnant women of all ages attended the clinics, some providers sensed that different issues might hinder younger and older women from attending clinic. According to one nurse, lack of knowledge and anticipated stigma resulted in late initial ANC presentation, especially for young women.

> "Especially the young girls, they tend to really hide… and most of them are actually forced to come to the clinic… They are reluctant to come because [for] one thing they are not aware they are supposed to start antenatal clinic; they are young mothers so they don't even know. They are pregnant but their main worry is not how the baby will be [but] it is just what people will say, … and then maybe they fear that probably they will be expelled from school because that is what happens most of the time... probably they come as late as 8 months (#4, female, nurse)."

Conversely, older women may have different reasons for avoiding the clinic, including feeling like "if her daughter comes to the clinic here and then she also comes to the clinic… it wouldn't be a good picture [because] she is still giving birth and the daughter is also giving birth (#1, female, trained lay healthcare worker)." Alternatively, older women of higher parity may feel "knowledgeable enough (#14, female, health educator)" to skip antenatal appointments.

Distance/ Financial strain/ Lack of transportation. Distance to the clinic – and by extension the lack of transportation or finances to pay for transportation – influenced when women began antenatal clinic or whether they came for more than one appointment. Some participants felt that financial barriers were a definite hindrance; one provider commented that some women could barely afford to pay for food, much less transportation. In addition, time spent at the clinic is lost income. Said a community health worker, "They feel that 'If I went to dig for somebody the garden I would get 200 shillings but if I go to the clinic I will not get a single cent.' (#11, male, community health worker)." Other participants disagreed that financial barriers could hinder attendance, particularly with the introduction of free antenatal and delivery services at government health facilities, and because women had come to value their appointments.

Late presentation. One of the most raised challenges to antenatal care in general, and to the recommended frequency of HIV testing in pregnancy in particular, was the late stage of pregnancy at which many women present for their first visit, which is commonly after the first trimester. If tested after 28 weeks, they will not be eligible for a retest

during antenatal care or delivery and may be subsequently lost to follow up in the postpartum period. Participants posited that several factors may contribute to this phenomenon. Some women may not realize that they are pregnant. They may not track their menstrual periods and may fail to notice or associate a missed period with pregnancy, particularly if they are without access to a pregnancy test. There may also be cultural issues associated with openly acknowledging pregnancy:

> "Pregnancy is a private thing. There are people who when they are pregnant, they are stigmatized… They even don't share with the husband for quite some time, even after the pregnancy is four, five months… There are people who would wait for the pregnancy to be visible before they come. That is when now they believe that they are really pregnant (#3, male, community health worker)."

Not attending antenatal clinic at all. A subset of women may have unique reasons for avoiding clinic altogether. They include women who had an uneventful first pregnancy and assume that all subsequent pregnancies will be similarly smooth, women who do not consider pregnancy to be a "sickness" requiring a trip to a hospital, and women who belong to religions forbidding visits to health facilities. One provider commented, "There are people because of their religion they are not allowed to go to the health facility. Like we have the 'Legio Mariae,' a church that with their belief people [in this area of Kenya] don't go to the facility (#1, female, trained lay healthcare worker)."

Factors influencing discontinued ANC visits

Migratory populations. Participants in two of the facilities described that one major challenge to a higher retesting rate was the migratory nature of employment in the surrounding areas. One manager noted that this complicated antenatal care in general, and HIV repeat testing in particular, because "chances are you are seeing this woman today and you'll never see her again (#18, male, nurse, FACES program technical advisor)." One provider noted the influx of women associated with new companies moving into the locale, while another reflected on the population in his service area:

> "[I have seen] some new faces even of women… who are not married or are sex commercial workers, they go where there is money, they float around (#7, female, trained lay healthcare worker)."
>
> "[Some women] come for mining purposes, stay there for almost two months or three, you know, the mining also has its season. There are seasons that it's booming; [but a rainy] season like now, it's now low. Some clients now migrate towards the lake for fishing and even some go home for farming … depending on how [they are] generating the income (#12, male, health educator)."

Long queue. As is the case in many clinics, patients are not given appointment times but rather come in the morning and wait to be seen. Women, particularly those with young children in tow, may struggle with the long wait associated with some clinic days. Several participants raised this issue and one health educator in particular commented:

> "The clients… will wait until they become tired… due to lack of the staffs they may stay there for long before they are seen. So they will be waiting, their

children get crying, so these mothers will start complaining… That may bring a challenge to those mothers because if you come to the clinic at eight, then you will leave the clinic even at twelve (#14, female, health educator)."

If women have had a frustrating waiting experience, this may negatively influence their desire to return. One participant expressed the sentiment that some women may experience:

"[When] they come, they find that there are already twenty people in the queue and you have to wait to be attended to so those are some of the things that make them really feel that they should not come to the clinic." (#11, male, community health worker)

Preference for Traditional birth attendants. Several participants explained that in many rural areas, traditional birth attendants (TBAs) are respected members of the community who provide labor and delivery services. In addition to potentially spending more time with laboring mothers than do clinic-based providers and using traditional medicine, which may be more in line with an expectant mother's belief system, one manager summarized the myriad of other reasons succinctly:

"Personalized care, comfort, the home environment, rumors about the hospital… The traditional birth attendant gives extra things like… tea and porridge once they deliver. The traditional birth attendants can be paid in kind. They can be given chicken… instead of money. She's someone you know from the village and you trust her and you want to have your baby with someone you trust, someone you know. (#18, male, nurse, FACES program technical advisor)."

TBAs seldom provide antenatal care services, so women may initially attend clinic and get tested for HIV, but ultimately decide to have a home-based birth with a TBA. Labor is an important time to emergently intervene on HIV transmission, and given that 28% of women rely on TBAs for delivery services,[18] the lack of repeat HIV retesting services by many TBAs may limit their ability to prevent mother-to-child transmission.

Male partners/ Demands at home. Expectant mothers may have limitations placed on them by their male partners or their responsibilities at home. One provider commented that male partners may even forbid their wives from attending clinic. Other providers commented that women may be afraid to test for HIV without their partner's consent or presence. On the other hand, some male partners are supportive of women attending clinic, partially because they know that HIV testing is routine during antenatal care. At least three participants agreed with a provider who said,

> "I know the male partner; they will be happy once they get to know [the pregnant woman's HIV] status. …They take it as once the partner is negative they already know their status that they are negative (#2, male, laboratory technician)."

One provider even commented that men "sneak look at the mother-baby booklet [a maternal and child health record], see the [HIV] result and interpret that to be their own result (#4, female, nurse)."

Pregnant women also have competing demands at home. They may fear that if they spend half a day traveling to, waiting at, and returning from the clinic, they will neglect their tasks and raise the ire of their husbands.

Barriers at the Provider Level

Lack of time/ High workload coupled with understaffing

The most frequently cited provider-level hindrance to retesting for HIV was the problem of a high patient volume, coupled with insufficient time to dedicate to each patient. Two main coping mechanisms were discussed – a nurse described postponing testing and an HIV testing counselor discussed pressure to cut counseling sessions short:

> "At times it is so hectic. You are one person and you have to test clients, probably they are several [waiting to be] tested at the initial test and others who come for retest. So probably you will just postpone the one for the retest because you have too much work load (#4, female, nurse)."
>
> "You need to have time with somebody and provide an environment where somebody can freely speak of the true issues that are challenging to him or her… [but] there is a queue out there with angry clients who are feeling that you are taking a lot of time (#5, female, HIV testing counselor)."

Thus, several providers commented that a high workload may be associated with a decrease in the quality of HIV-testing services that are offered. However, participants expressed that HIV retesting does take less time than the initial test since the counseling portion is less comprehensive. Some providers felt like ANC clinics were understaffed and that staff was expected to provide too many services (ANC, delivery services, postnatal care, and child welfare clinic), particularly in smaller facilities.

Burnout/ Attitude

Related to the issue of workload and pressure is the problem of provider burnout. As one participant described, counseling is different for each client and can be mentally draining:

> "There is burnout. The staff who is offering the service is already tired probably she has done HIV counseling and testing for 30 people. They've talked, they are very tired. You can imagine if one tests HIV negative it's different from when one tests positive because when one tests HIV positive there is that psychosocial support that comes with the counseling and therefore the counseling is prolonged (#3, male, community health worker)."

In spite of the integration of HIV services into regular clinic flow and the fact that most providers are trained in HIV testing and counseling, some providers still felt that HIV testing was the purview of dedicated HIV counselors. Leaving the responsibility of HIV testing to those individuals may result in women going untested when client volume is heavy.

Language barrier/ Posting

One unanticipated barrier to providers offering HIV retesting services stems from the nature of job postings in rural areas. On occasion, these areas may not have local staff that are trained at the level of nurses or clinical officers, so these providers have to be hired from a different region of the country. This poses issues including language barriers, long commutes for providers who choose to stay in the nearest city center, and sometimes, "many are not ready to work in this region… they come and see the terrains

and they just go back (#11, male, community health worker).” The impact of this challenge extends far beyond the issue of HIV repeat testing.

Unaware of retesting importance

While all the participants interviewed for this study demonstrated a clear understanding of the importance of retesting and stressed its necessity, they cautioned that not all providers may appreciate it in the same way. Some providers stated that they had personal experience with women seroconverting later in pregnancy, but that not all nurses or counselors would have had that experience. One participant described the thinking of some providers: “The retest may also be assumed as a waste of resources: ‘this woman has already tested, she knows her HIV status, why do we test again?’ (#11, male, community health worker)”

Barriers at the Facility Level

Inconsistent volume of patients

Unlike in facilities or departments where patients are booked for appointments, clients show up at rural antenatal clinics on days that suit them best, especially if it is their initial visit. Participants frequently mentioned that some days – in particular market days on which clients are already traveling to town for selling or buying purposes – had a much heavier clinic volume. Additionally, most women tended to start lining up early in the morning, with few or no women coming in the afternoon. One provider said that this had to do with local beliefs:

> "Something set in the mind in the community that for antenatal care you have to go in the morning… there is a myth in [the local language] Dholuo that when you go after eating ugali [the staple food] at noon… the nurse wouldn't hear the baby but would hear the ugali in the stomach (#1, female, trained lay healthcare worker)."

Space limitations

Due to the confidential nature of HIV testing and counseling, a private space is essential. Participants commented on the fact that some clients decline testing if they have confidentiality concerns. Lack of space can also hamper a team-based approach to care, where overworked providers can call in back-up HIV testing counselors to concurrently attend to patients who are waiting. Makeshift rooms – such as tents or storage areas – are sometimes used in these facilities for HIV testing purposes. As one community health worker commented:

> "Lack of space is a major, major, major issue. You'll find a whole MCH [maternal and child client group] with a very congested room. This is the place where you do palpation [of the uterus for fundal height and] you want to do testing. It compromises confidentiality a lot. So space is an issue. Or even counseling session will be done in public or you do it in a group which is not very sufficient (#11, male, community health worker)."

Barriers at the Health System Level

Consistency of HIV testing kit supply

Nearly all providers mentioned HIV testing kit shortages as a major challenge to consistently providing repeat HIV testing for pregnant women. As one community health worker commented:

> "There were times when you can go around three weeks without the test kits. So it was a major challenge because the mothers will come back but with no test kits you cannot test them. You will again rebook them [for a new appointment]. There was a time when it went throughout the month without testing (#13, male, trained lay healthcare worker)."

When asked which clients would be prioritized in the event that it was necessary to ration remaining test kits, providers almost unanimously stated that pregnant women were a priority over patients in the outpatient or inpatient wards. As one manager commented, "We prioritize… the baby who is not born because we want to eliminate transmission of [HIV from] mother to child (#6, male, facility manager)." However, when faced with an expectant mother needing an initial test or a retest, providers reported that they would choose to forgo the retest.

Due to the complex system of reporting, approval, and distribution, delays in delivery of test kits can range from a few days to a month or more. Participants had difficulty pinpointing a single source of delay. One manager acknowledging potential fault on the facility side, but also mentioned that the number of kits ordered frequently do not match up with the number delivered: "One [reason for test kit shortages] is reporting. If the flow of reports is not good, back to the national system, then there could be delays.

[Additionally] you order 100 and you're given 50, it would be an issue (#17, male, FACES program manager)."

Registers and MCH Booklet Design

Since HIV testing is not a service that is offered at every antenatal care visit – unlike palpating the expectant mother's abdomen to determine fundal height – determining eligibility for HIV retest is something that the provider must remember to initiate. However, this process is not easy given the nature of the medical records. These registers, designed by the National AIDS and STI Control Programme (NASCOP), record each patient visit sequentially in one book organized by visit date, rather than longitudinally for each individual patient. While this design may be optimal to allow for uniform service delivery and outcome reporting, it requires provider effort to flip back and forth through the register to find prior patient visit data. One FACES program technical advisor commented:

> "From the register it's difficult to answer the question 'Who should be retested?' because of the way the register is limited and its design… Maybe in the future if electronic registers can be designed in such a way that we can be able to determine eligibility for retesting then people would be sensitized and they know [it is time to retest]. And we can even give feedback and tell them this month we had 50 people eligible for retesting and we only tested 5; what could have gone wrong? But right now the way things are we can't do that easily. It will take you a lot of time (#18, male, nurse, FACES program technical advisor)."

Additionally, while the Maternal and Child Health (MCH) booklet kept in possession of the woman is a useful clinical tool for longitudinally tracking the health of the woman and her child, it does not have dedicated space for multiple HIV test results.

Enablers

Enablers at the Client Level

Motivations for attending antenatal clinic

Providers suggested that it was important to understand the motivations that their clients had for attending antenatal clinic, in order to encourage early and continued visits. The reasons they gave for why pregnant women may attend ANC included concern for the health of their infants, encouragement from other women in their peer group, successful facility marketing of free antenatal care and delivery services, or because they had benefited from attending antenatal care for previous pregnancies. Others felt like being able to receive preventative testing and medications (such as for syphilis or malaria); or gifts like t-shirts, insecticide-treated nets, and lessos (traditional cloth wraps) were the main incentives.

Beliefs about PMTCT possibility

Participants also emphasized many expectant mothers are beginning to see the fruits of successful prevention of mother-to-child transmission (PMTCT) efforts among their HIV-positive acquaintances. One manager shared the power of positive testimony:

> "They used to know that once you are HIV-positive automatically the child will come out HIV-positive… they were seeing it as something that is obvious [and] expected. But of late once they have started to hear and have seen others who have gone through PMTCT [who] have come out with babies who are HIV-negative. Now the mothers [who are] HIV-positive want to know how she is going to get an HIV-negative child (#9, male, facility manager)."

Thus, word of mouth was described as a powerful enabler of HIV retesting programs.

Enablers at the Provider and Facility Levels

Participants felt that that cooperation and task redesign may help implement change at the provider team and facility levels. They recommended that all healthcare providers working in maternal and child health should be trained on HIV testing and counseling and work together as a team when the patient volume is heavy. For example, one provider said, "…Let them all be trained on testing so that we don't miss an opportunity because one of the healthcare providers doesn't know how to test (#5, female, HIV testing counselor)." A change in the organizational culture may be required, such that providers no longer see some duties as "a responsibility of such and such a person (#11, male, community health worker)." Additionally, one participant commented that strategically placing motivated staff was important: "We've identified dedicated staffs to be champions… so other staffs see the way they work and now they feel motivated and say 'Eh kumbe hata sisi we' – [meaning] even us we are able to do it (#20, male, administrator)."

Enablers at the Health System Level

Numerous enablers to retesting were identified at the health system level, particularly pertaining to a steady supply of HIV test kits. One administrator involved in procurement (#19) commented that timely funding disbursement, tight collaboration between donor agencies and various branches of the government, and accurately projected budgets were crucial for consistent supplies. Another administrator involved in finances and procurement (#16) applauded the move from a paper-based to electronic format of ordering supplies, as this not only improved speed of orders reaching supply warehouses, but also accuracy of reporting.

DISCUSSION

Previous literature has documented the barriers to an initial antenatal HIV test among pregnant women, as well as barriers to HIV retesting in other populations who have been tested at least once.[8-10] This study focused on the barriers to repeat HIV testing among pregnant women in sub-Saharan Africa, a strategy that experts have called for to address incident HIV during pregnancy and the associated high risks of HIV-related maternal mortality and MTCT to infants.[2] The main finding of our study is that implementing a higher retesting rate will require a multi-faceted approach and a successful strategy will likely address barriers that exist on four levels, as represented in Ferlie and Shortell's Framework for Change: the client, provider, facility, and health system levels. The issue of low repeat antenatal testing rates is not isolated from other clinic performance indicators. Therefore, if some of the barriers and associated enablers identified in this study are addressed, there are likely to be positive implications not only

for antenatal retesting rates, but also for prenatal care overall and the quality of HIV-related care services provided to all patients.

We found that various client-level barriers contribute to late initial presentation and not returning to antenatal clinic, or not attending clinic at all. The contributing factors identified in this study corroborate results found in the literature, implicating age that is significantly younger or older than the average reproductive ages (15-49),[19,20] lack of formal education or knowledge about importance of attending ANC early in the gestational period,[21,22] delays by clients in recognizing their pregnancy,[21] and not considering pregnancy a health condition that should be treated at a health facility.[23] Addressing late presentation and not returning to antenatal clinic may have benefits for other maternal and child health services in addition to PMTCT, including early folic acid and iron supplementation,[24] better malaria prevention,[25,26] ability to complete syphilis treatment before delivery,[27] and lower risk of delivery complications for HIV-positive women.[28]

While addressing client-level barriers may be important, Ferlie and Shortell suggest that strategies focusing on individuals alone are seldom effective in an attempt to improve policy implementation.[16] At the provider and facility levels, we found that heavy and inconsistent client volume put an emotional strain on providers contributing ultimately to burnout. Our results indicate that an individualized solution to each clinic is required; some clinics may need additional dedicated HIV testing and counseling personnel while others may need to have their clinicians performing HIV testing alongside their regular duties, thus providing integrated care.

Finally, at the health system level, occasional stock-outs of HIV test kits was identified as the most important barrier to consistently offering repeat HIV testing services. Challenges with supply chain issues are common in countries with a developing infrastructure. Studies show that in addition to impacting HIV testing and counseling programs,[29] supply chain issues also affect effective integration of HIV and antenatal services,[30] entry and engagement into the HIV continuum of care,[31] avoidance of antiretroviral therapy interruptions,[32] and provider compliance with HIV care guidelines.[33] Correlates of these supply chain issues include lack of a national stock buffering capacity and long delays from facilities submitting orders to receipt of requested supplies,[34,35] although our data suggest that the move to electronic ordering in Kenya has reduced delays. Additionally, to address the challenges associated with identifying when patients are eligible to receive retesting, while electronic medical records may be ideal, a more realistic goal may be to modify existing registers and booklets to allow for easier longitudinal follow-up.

While several of the barriers and enablers identified in this study are relevant to other clinic services provided, such as offering the initial HIV test at ANC, we felt that several factors uniquely impact repeat HIV testing. In order for retesting to take place, clients need to return to ANC. Therefore barriers influencing discontinued ANC visits, such as being disappointed with long clinic wait times or engaging in seasonal/migratory work, directly put clients at risk of slipping through the holes in HIV care net. One enabler that we identified which may combat this barrier could be the positive testimony of prior clients. This concept has been powerfully employed in the form of "mentor mothers," HIV-positive women who have been through PMTCT services and serve as

peer counselors in antenatal care settings.[36,37] Another barrier that seemed to be more problematic for repeat testing than initial testing was the lack of HIV test kits, since providers preferentially used limited supplies for initial testing.

The current study has several strengths including the range of perspectives that the participants represented, from direct full-time clinical providers to mid-level program technical advisors and upper-level management. While it is not possible to capture the full scope of possible healthcare provider populations using a sample of three healthcare facilities, the providers at these clinics are likely to reflect those working at rural government health facilities in Nyanza province in general.

Despite these strengths, the study has several limitations. Given that our sample did not include clients or health system administrators, caution should be taken when interpreting barriers and enablers presented at these socioecological levels. Our results may also have limited applicability to urban settings, where the patient population may have easier access to antenatal clinics and greater educational attainment or understanding of the value of early and continued prenatal visits. Additionally, urban facilities may have an appointment system to regulate patient visit dates and times and thus provider workload. The health infrastructure in urban areas may also allow for easier to access to backup HIV test kits and be more conducive to implementation of an electronic medical record system. Finally, the government clinics chosen are all supported by Family AIDS Care Education and Services, a program that provides a level of mentoring and support for PMTCT that other neighboring facilities may not have. While the providers and managers were able to comment on barriers at the provider and facility levels respectively, more research may need to be conducted to better understand

the client perspectives on the barriers they experience to repeat testing. Similarly, investigating perspectives from Ministry of Health and other government-level officials may be valuable for further understanding health system implementation challenges.

CONCLUSIONS

While providers and managers of antenatal care clinics expressed the importance of repeat HIV testing in the key population of pregnant women – both for the sake of the mother and the child, they also shared concerns about barriers at the client, provider, facility, and health system levels that prevented them retesting all pregnant women. In order to meet international and national goals of eliminating mother to child transmission of HIV, a multi-faceted intervention that addresses the barriers and capitalizes on the enablers identified may be required improve antenatal retesting rates. Further research into the implementation challenges of such an intervention will be valuable for facility coordinators, health system administrators, and policy makers.

DECLARATIONS

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Availability of Data and Materials

The dataset supporting the conclusions of this article is held by the authors and may be made available if a special request is made.

Authors' Contributions

Conceptualized and designed the study: AJR CRC JMT. Acquired the data: AJR EW. Analyzed the data: AJR. Wrote the paper: AJR JMT. Reviewed and edited the manuscript: AJR EW ZK EAB PO CRC JMT. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethics approval was given by the Kenya Medical Research Institute Ethical Review Committee (FWA00002066; SSC 2797) and the University of Alabama at Birmingham Institutional Review Board (FWA00005960; X140304009). All participants gave signed informed consent prior to participating.

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REPEAT HIV TESTING DURING PREGNANCY IN KENYA: AN ECONOMIC EVALUATION

by

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ABSTRACT

BACKGROUND: Repeat HIV testing during late pregnancy may identify women who have seroconverted since the initial HIV test early in pregnancy, allowing them to adopt lifelong antiretroviral therapy (ART) for the sake of their own health as well as to prevent mother-to-child transmission of HIV. We evaluated the cost-effectiveness of repeat HIV testing during late pregnancy in Kenya, compared to an initial antenatal test in early pregnancy alone.

METHODS: We used TreeAge software to model a decision tree with the initial decision node comparing the alternative strategies and the successive branches representing decisions made during pregnancy. At delivery of the infant, each branch culminated in a state-transition model following the mother-infant pair in one-month cycles for a ten-year horizon. All inputs were drawn from the literature and varied across their range or distribution in univariate and probabilistic sensitivity analyses.

RESULTS: In the base case, the retesting strategy was very cost-effective for the Kenyan setting at $1,098 per quality-adjusted life year (QALY) saved, with fewer infant HIV infections (757), infant deaths (30), and maternal deaths (178) per 100,000 women. Results were sensitive to low cumulative incidence of HIV during pregnancy and monthly cost of maternal ART (thresholds of 1% and $45, respectively). Probabilistic sensitivity analyses confirmed the base-case analysis.

CONCLUSIONS: This modeling study indicates that repeat HIV testing is likely to be cost-effective and result in fewer infant HIV infections. In an era of lifelong ART for

mothers, retesting for HIV may not only be life-saving for mothers, but it may also contribute to the elimination of perinatal HIV transmission in Kenya.

BACKGROUND

Despite the fact that mother-to-child transmission (MTCT) of HIV is highly preventable through effective testing and treatment programs, an estimated 13,000 new HIV infections occur annually among Kenyan children, accounting for 4% of all pediatric infections globally.[1,2] Kenya, which is among 22 priority countries that account for over 90% of global MTCT, has over 15% of HIV-positive women still experiencing MTCT by the time of weaning, even though 95.4% of women report attending antenatal care (ANC) during their last pregnancy, at which 93.1% of them got tested for HIV at least once.[2] Although Kenya and other sub-Saharan African countries have officially adopted World Health Organization guidelines on repeat HIV testing during late pregnancy, which can identify incident HIV infections, implementation of repeat HIV testing is low and many missed opportunities for repeat HIV testing exist.[3,4]

Studies have suggested that as efforts to prevent perinatal HIV transmission are increasingly successful among women who test HIV-positive early in pregnancy, a growing proportion of MTCT is among women with incident HIV infection during pregnancy and the postpartum period.[5,6] One modeling study from South Africa found that as of 2014, 34% of all MTCT is among women who have newly seroconverted after their first antenatal visit, and a study from Botswana reported that this rate may be even higher at 43% for their setting.[6,7]

A recent meta-analysis of 47 studies found that in sub-Saharan African countries, the cumulative incidence of HIV during pregnancy ranged from 0.2% to 13.8%, with a

pooled incidence of 3.6% (95% CI: 1.9, 5.3).[8] The risk of MTCT is significantly higher among women with acute versus chronic infection, a result that is likely due to the much higher HIV RNA load that is generally seen during acute HIV infection.[9,10] Plasma viral loads have been directly correlated with risk of transmission both during pregnancy[11] and breastfeeding.[12]

It is important to determine the appropriate timing of HIV retesting efforts to minimize use of limited resources, maximize benefit from treatment, and achieve a high likelihood of sustainability of retesting from a fiscal perspective.[13,14] Studies have found that retesting may be cost-effective during pregnancy, at the onset of labor, or after birth under certain assumed parameters.[15-18] However, some of these studies[15,16] are limited by the fact that initiating treatment at or after delivery may represent a missed opportunity to avert vertical transmission during late pregnancy. In addition, the proportion of women who deliver in health facilities is less than 50% in many resource-poor settings,[15,19] so a strategy that relies heavily on retesting at labor may miss women who choose to deliver without a skilled birth attendant. Other studies[15,17,18] are based on older guidelines for prevention of MTCT that stipulate antiretroviral therapy (ART) use during pregnancy but not lifelong treatment, and as such may have over-estimated the cost-effectiveness of retesting by failing to account for the costs of maternal postnatal ART use. Additionally, none of the studies explicitly tracked both maternal and child outcomes postnatally, instead projecting based on characteristics available at delivery.

This study presents a timely analysis in light of newer guidelines for immediate, lifelong ART use among women diagnosed with HIV during pregnancy, a policy referred to as "Option B+".[20] Using a unique state-transition model that allows for postpartum

tracking of both maternal and infant health outcomes, the objective of this study is to estimate the 10-year incremental cost-effectiveness of repeat HIV testing during pregnancy in Kenya, compared to an initial antenatal HIV test in early pregnancy alone.

METHODS

Analytic Overview

We developed an individual-based stochastic model utilizing TreeAge Pro software (TreeAge Software Inc, Williamstown, MA) according to guidelines established by the ISPOR-SMDM Modeling Good Research Practices Task Force.[21] Our model of 100,000 women evaluated two antenatal HIV testing strategies from the perspective of the Kenyan national health system: (a) a single HIV test early in pregnancy at the first antenatal visit (Strategy 1) and (b) Strategy 1 plus a repeat HIV test three months after the initial HIV test (Strategy 2). Model outcomes for both mothers and infants included costs, quality-adjusted life years (QALYs), HIV infections, and deaths. We calculated the incremental cost-effectiveness ratio (ICER) to express the comparative value of the strategies.

Guided by World Health Organization (WHO) recommendations,[22] we determined the cost-effectiveness of the strategy by whether the ICER was less than the Kenya annual *per capita* GDP in 2015 (<$1,376; "very cost-effective"), between one and three times the *per capita* GDP ($1,376 to $4,128; "cost-effective"), or greater than three times the *per capita* GDP (>$4,128, "not cost-effective").[23] These thresholds represent the potential societal willingness to pay for health benefits gained from the health interventions in question. We simulated a cohort of 100,000 women who would be

eligible for a repeat HIV test during pregnancy because they had previously tested HIV-negative at a former antenatal care appointment that was prior to 28 weeks gestation during the current pregnancy. We report all costs in 2016 US$ and parameterized our individual-based model with biological, behavioral, and treatment uptake data from the literature.

Input Parameters

Baseline Cohort Characteristics

All women entering the model (Table 1) were assigned a CD4 count based on a population-based distribution,[24] as well as a viral load, based on the number of days that have passed since their HIV exposure event.[25,26] Throughout the model, we tracked CD4 count as a function of HIV status, treatment status, time since initiation of ART, and viral load suppression status, which may be indicative of treatment adherence and/or resistance. We also tracked the viral load of HIV-positive women during pregnancy as a function of treatment status and time since initiation of ART. If they were not known to be HIV-positive, women were assigned a time to stop breastfeeding from a distribution;[27] otherwise, they stopped breastfeeding at 12 months as per WHO guidance.[28]

HIV Transmission

Antenatal HIV transmission is directly correlated with maternal viral load.[9,11] All HIV transmission that occurred during delivery is implicitly modeled in the HIV transmission rate during pregnancy. Postpartum HIV transmission, conditional on the

mother still breastfeeding, is a function of maternal treatment and child prophylaxis status.[29,30]

HIV Testing and Treatment

All women in the retesting arm were retested for HIV three months (12 weeks) after their initial antenatal HIV test using 4th generation rapid HIV test kits. All infants of women who tested positive for HIV on retest were tested for HIV at 6 weeks postpartum, as per WHO guidance.[31] Women and children who tested positive were offered antiretroviral therapy regimens tenofovir /emtricitabine/ efavirenz (TDF/FTC/EFV) or abacavir/lamivudine/ Lopinavir/Ritonavir (ABC/3TC + LPV/r), respectively, and could either accept or refuse treatment. To avoid overstating the benefit of retesting while also accurately reflecting the positive health outcomes that may accrue as a result of being aware of their HIV status for additional time, we allowed women who did not test positive during the current pregnancy to get retested during the next pregnancy, with their birth spacing interval drawn from a distribution.[32]

Mortality at Delivery

Women who have tested positive for HIV are generally encouraged to deliver in a health facility and may do so at higher rates than women who have not tested positive for HIV.[33] In our model, maternal mortality (Table 2) was a function of delivery location but not disease status, since newly HIV-infected women have a similar immunological status to HIV-negative women and thus do not have an increased mortality risk related to HIV.

Infants had a higher risk of being born stillborn if maternal viral loads were in excess of 50,000 copies/ml and if they were born at home.[34]

Postnatal Morality

Postpartum maternal mortality was a function of time since delivery, HIV infection status, and CD4 count.[35-37] Infants had a baseline risk of mortality that depended on their HIV exposure status and infection status, as well as their age in months.[38,39] Children whose mothers had died during childbirth had an increased risk of mortality in the first 4 years, and particularly in the first month of life.[40] Their risk of death from HIV was reduced if they were on antiretroviral therapy.[41]

Utility Inputs

Mothers and children without HIV were assigned a utility of 1 QALY per year (Table 3); children with HIV were assigned a monthly utility from within a distribution; and HIV-positive mothers were assigned a utility per month based on their CD4 count in that month, with increasing CD4 counts yielding a higher quality of life.

Cost Inputs

In order to promote generalizability of the ICERs beyond the Kenyan setting, we used published costs in our model. We included costs of HIV testing, treatment, and the excess cost of facility deliveries over non-facility deliveries. We chose to compare the relative costs of the two strategies from the perspective of the Kenyan national health system. Thus, we excluded indirect costs borne by patients such as time and travel costs

to antenatal clinic, as well as the costs of HIV infection from the perspective of patients. For direct costs, we assume that the testing strategies do not affect the number or timing of antenatal visits because retesting is attached to a visit that would otherwise occur.

Time and Discounting

We selected a time horizon of ten years beyond the time of delivery, allowing us to capture the impact of HIV infection on mortality while limiting the ability of infants in the model to attain age of sexual maturity and thus transmit HIV to potential future sexual partners. Future costs and DALYs are discounted at 3% annually in the base case.[42,43]

Table 1: Disease, treatment, and transmission probability estimates

Input	Base Case	95% CI (or Range)	Ref.	Distribution (parameters) or Table
Disease status and testing				
CD4 count during pregnancy, initial distribution	825	350-1200	[24]	Table
CD4 count postpartum among HIV-positive mothers, by viral status if on treatment	-	350-1200	[25,44]	Table
Viral load during pregnancy among HIV-positive mothers, by days since infection and treatment initiation, if applicable				
Among mothers not on treatment	-	1 - 1x10^6	[25,26]	Table
Among mothers on treatment	-	1 - 1x10^6	[45]	Table
Viral load postpartum, by viral suppression status	-	1 - 1x10^6	[25,26]	Gamma (3, 0.001)
Probability of being continually virally suppressed to ≤400 copies/ml	0.623	0.42, 0.82	[44]†	-
Rapid HIV test sensitivity	0.995	-	[17]	-
Rapid HIV test specificity	0.998	-	[17]	-
Treatment and skilled delivery				
Probability of Option B+ HAART initiation				
Among mothers diagnosed during pregnancy	0.85	0.65, 0.95	[46]†	Beta (119, 21)
Among mothers diagnosed postpartum	0.35	0.25, 0.45	[47]†	Beta (31, 58)
Among infants	0.80	0.70, 0.90	[48]†	Beta (2, 5)
Probability of facility delivery with a skilled attendant				
Among mothers known HIV-positive	0.486	0.446, 0.506	[33]†	Beta (290, 330)
Among mothers not tested HIV-positive	0.399	0.359, 0.439	[33]†	Beta (238, 359)
HIV Acquisition and Transmission				
During pregnancy				
Cumulative probability of maternal HIV acquisition	0.025	0.0075 - 0.053	[8,49]†	Beta (17, 462)
Cumulative probability of transmission, by VL	-	0 - 0.406	[9]	Table
At delivery and postpartum				
Probability of maternal HIV acquisition, per person-month	0.0024	0.0015, 0.0033	[8]	Beta (27, 11460)
Postpartum breastfeeding length, in months				
Among mothers known HIV-positive	6	-		Table
Among mothers not tested HIV-positive	-	6 - 30	[27]	Table
Postnatal transmission probability, per person-month				
Among mothers not on treatment	-	0.001 - 0.0094		Table
Among mothers on HAART and infant on nevirapine		0.001 - 0.0023	[29,30]	Table

†An assumption was made concerning the 95% CI (Confidence Interval) or Range.
Ref. = reference; Prob. = probability; VL = viral load;

Table 2: Mortality probability estimates

Input	Base Case	95% CI (or Range)	Ref.	Distribution (parameters) or Table
Child				
Stillbirth, per live birth	0.023	0.0018, 0.0031	[50]	Beta (19, 805)
Excess odds of stillbirth if maternal plasma viral load >50,000 copies/ml	2.05	-	[34]	-
Postpartum mortality rate (Month 1; 2-12; 13-48), per person-month				
HIV unexposed	0.017; 0.001; 0.0005	-	[38,39]	-
HIV exposed, uninfected	0.019; 0.001; 0.0005	-	[38,39]	-
HIV exposed, infected	0.019; 0.008; 0.002	-	[38,39]	-
Excess odds of postpartum mortality if mother died in childbirth (Month 1; 2-48)	7.0; 4.66	-	[40]	-
Reduced odds of postpartum mortality if on ART	0.342	0.327, 0.356	[41]	Beta (1202, 2312)
Mother				
Maternal mortality at delivery	0.00385	0.002, 0.0045	[51]	Beta (37, 9600)
Reduced odds of maternal mortality with skilled delivery	0.245	0.16,0.33	[52]	Beta (24,76)
Postpartum mortality rate during first 24 months, per person-month				
Among HIV-positive mothers, by CD4	-	0.0004-0.012	[35]	Table
Among HIV-uninfected mothers	0.000158	0.00005, 0.00025	[35]	Gamma (10, 63200)
Postpartum mortality rate after 24 months, per person-month				
Among HIV-positive mothers, by CD4	-	0.0006 to 0.048	[36]	Table
Among HIV-uninfected mothers	0.00016	0.00006, 0.00026	[37]	Gamma (10, 63200)

CI = Confidence Interval; Ref. = reference

Table 3: Utility and cost inputs

Input	Base Case	95% CI or Range	Reference	Distribution or Formula
Utility (QALYs)				
HIV-positive child	0.82	0.72, 0.92	[32]†	Beta (47, 10)
HIV-positive mother, as function of CD4 count	0.85	0.749 - 0.95	[53]†	Formula
Healthy mother or child	1	-		-
Cost ($)				
Children on ABC/3TC/EFV, per month	22.80	13, 33	[54]†	Gamma (22, 1)
Mothers on TDF/FTC/EFV, per month	8.50	4, 12	[55]†	Gamma (18, 2)
4th generation rapid HIV test, per kit	3.33	2, 5	[18]†	Gamma (19, 6)
Excess cost of a facility over a home delivery	68.70	58.70, 78.70	[56]	Gamma (188, 3)

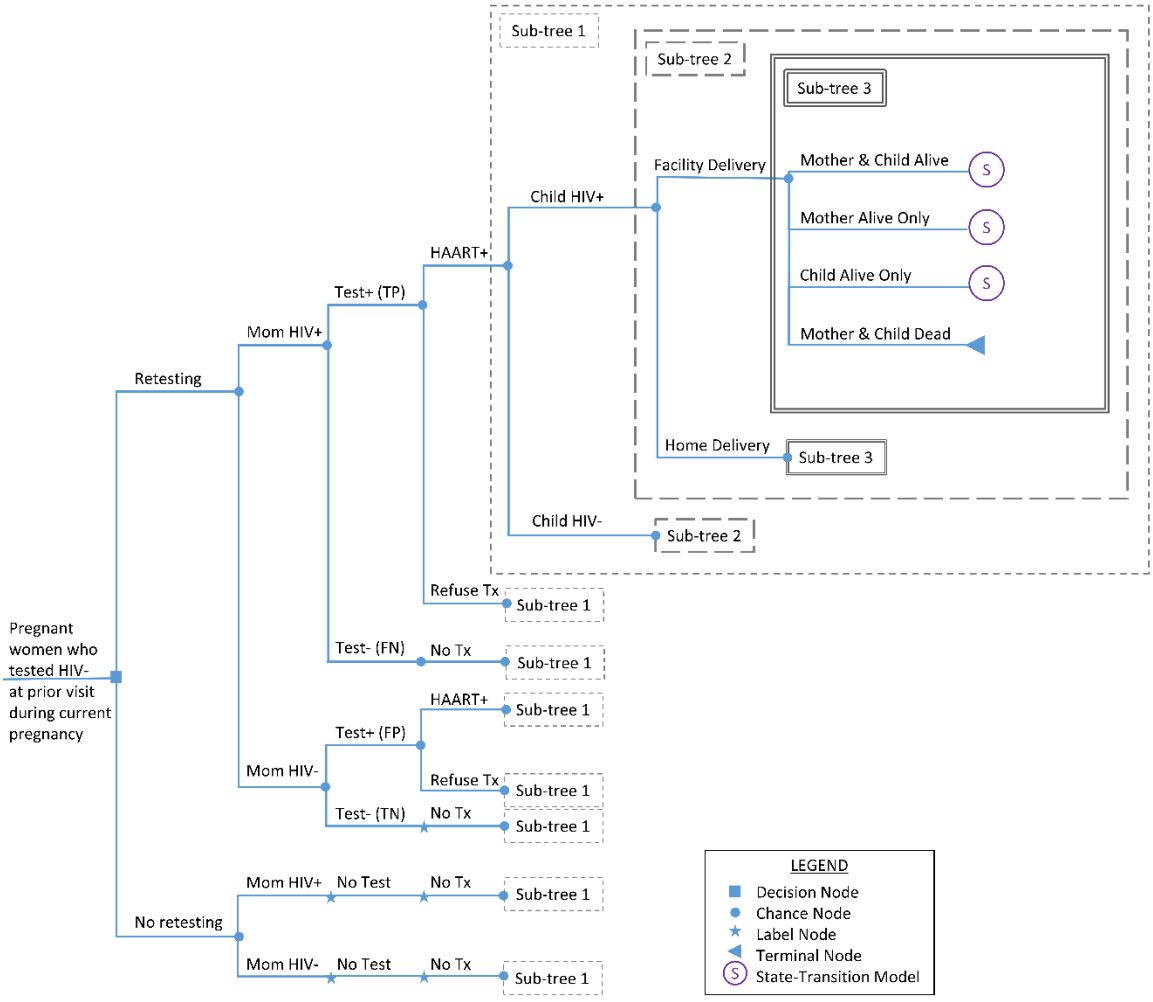
†An assumption was made concerning the 95% CI (Confidence Interval) or Range.
QALYs = quality-adjusted life years

Model

Decision Tree

We constructed a decision tree (Figure 1) with an initial decision node from which the possible strategies originated. Short-term events with probabilities contingent on the identification of HIV infection, including being offered highly active antiretroviral therapy (HAART) and delivery in a facility, were modeled in the decision tree, with each branch culminating in a state-transition model (STM), allowing us to simulate various health states for the mother-infant pair.

Figure 1: Decision tree



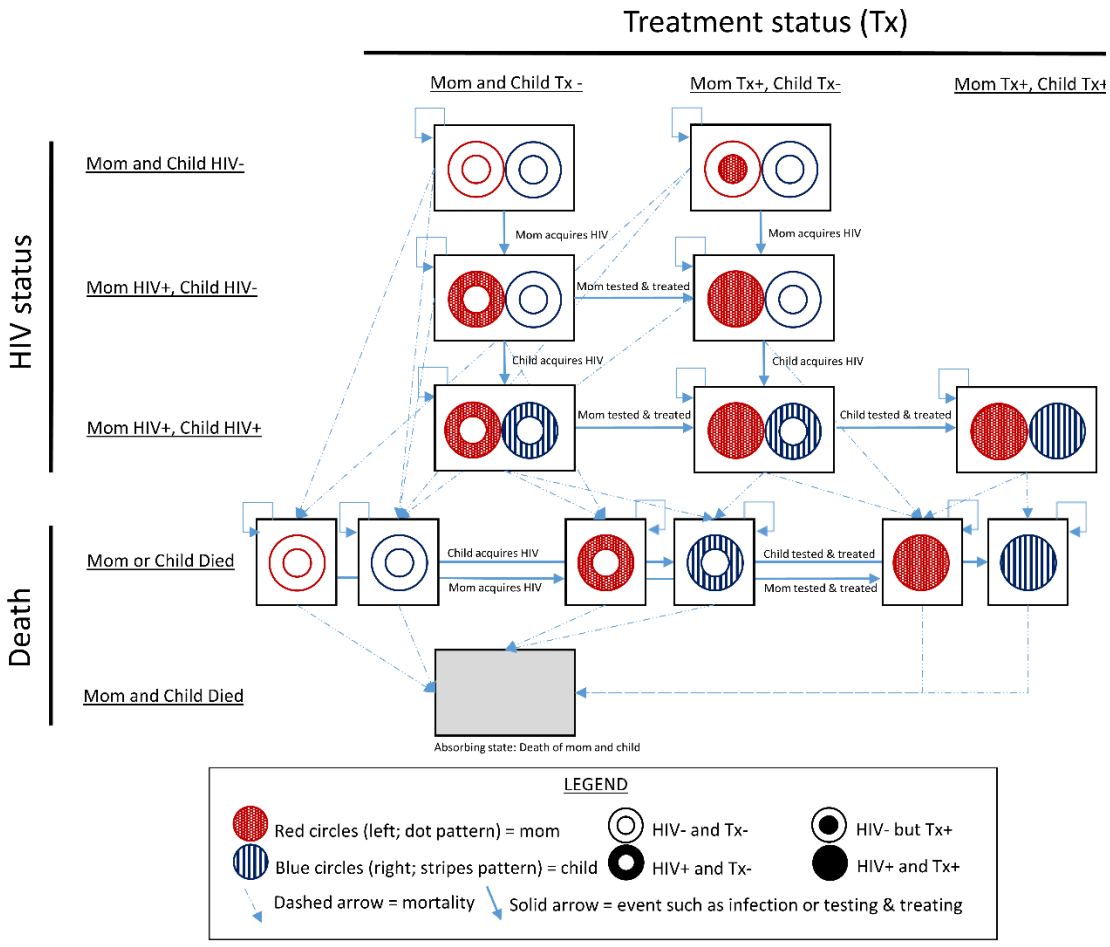
Our decision tree allowed pregnant women who tested negative for HIV at a prior visit during the current pregnancy to undergo either no retesting (Strategy 1) or retesting (Strategy 2). In each scenario, women could acquire HIV over the course of their pregnancy or remain uninfected. For women who received a retest, they may either test positive (Test+) or negative (Test-), and based on test sensitivity and specificity these results may be true positives (TP), true negatives (TN), false positives (FP), or false negatives (FN). Women who tested positive were all offered treatment (Tx) and had the

option of accepting HAART or refusing treatment (Refused). Regardless of their treatment status, they may transmit HIV to their child (cHIV+) or not transmit HIV (cHIV-). Women then chose whether to deliver in a facility with a skilled birth attendant or at home with a traditional birth attendant. If both mother and child died at delivery, the simulation for that mother-infant pair ended in a terminal node. Otherwise, if at least one member of the mother-infant pair survived, the simulation continued into the state-transition model (STM) in the health state that reflected the HIV, treatment, and living statuses of both member of the pair.

State-Transition Model

An STM (Figure 2) allows for the description of the HIV and treatment statuses of the mother-infant pair (or individual, if one member of the pair has already died), in terms of the conditions that the individuals can be in ("states," represented by the boxes), how they can move among such states ("transitions," represented by the arrows), and how likely such moves are ("transition probabilities").[21] The transitions are due to events including acquisition of HIV, getting tested and treated, and dying. The STM progresses in cycles of one month and incorporates half-cycle correction. All women and children in the model were subject to a background mortality rate regardless of their HIV status.

Figure 2: State-transition model



Sensitivity Analyses

Univariate sensitivity analyses were conducted by varying individual parameters within plausible ranges to evaluate the impact on the relative cost-effectiveness of the strategies. Key parameters included the cost and utility discount rates, costs of screening and treating HIV, utility of HIV for mother and child, cumulative probability acquiring HIV during pregnancy, and probability of uptake of treatment by both mother and child.

Probabilistic sensitivity analyses (PSA) were conducted to address sampling uncertainty and capture potential variability around our base case estimates.[57] Our input

parameters have distributions representing the uncertainty around the base-case estimate. PSA employs second-order Monte Carlo simulation to sample from these distributions, allowing the joint effect of parameter uncertainty to be assessed.

Assumptions and Ethics

Several assumptions were made to simplify the model: We assumed that (a) mothers were truly negative at first HIV test and thus were all new seroconversions if they tested positive in the model, (b) women accepting HAART remained on treatment throughout the model, regardless of the level of their adherence, which is reflected in the parameter on viral suppression, (c) regardless of viral suppression status, women remained on first-line ART throughout the duration of the model, (d) being on antiretroviral treatment if falsely identified as HIV-positive did not affect quality of life, and (e) future pregnancies were only important insofar as they offered another opportunity for an HIV test. Since it is unlikely that future pregnancies differentially impacted health outcomes and costs in either strategy arm, we did not explicitly model them in the state-transition model.

Ethical approval for the overall study related to repeat HIV testing during pregnancy was given by the Kenya Medical Research Institute Scientific and Ethical Review Unit (SERU) and the University of Alabama at Birmingham Institutional Review Board. Our simulation model had no effect on the clinical treatment of any real persons and all input parameters were drawn from the literature.

RESULTS

Base Case

The addition of repeat HIV testing during pregnancy to an initial HIV test produces a base case incremental cost-effectiveness ratio of $1,098 (Table 4; ($14,421,207– $12,753,297)/(1,629,076 – 1,627,557 QALYs)). This strategy is very cost-effective for the Kenyan setting using a threshold of $1,367. The retesting strategy also resulted in fewer cases of infant HIV transmission antenatally (504) and postnatally through breastfeeding (253) in our hypothetical cohort of 100,000 women, suggesting a 93.1% excess (95% CI: 77.5%, 110.2%) of perinatal HIV transmissions in the no-retesting strategy compared to the retesting strategy. It also resulted in fewer deaths among both mothers (178) and children (30) over a 10 year time frame. The total excess cost of adding repeat HIV testing would be $16 per woman when accounting for both testing and long-term treatment costs. The cost per infant HIV infection averted is $2,203 and the cost per mother or infant death averted is $8,018.

Repeat HIV testing was associated with an additional 280 facility deliveries among HIV-positive women, based on the assumption that HIV-positive women are more likely to deliver in a health facility, which along with the benefit of treatment may have contributed to fewer maternal deaths. However, retesting also resulted in an additional 192 women who were falsely identified as HIV-positive (false positives) and 8 women who were falsely identified as HIV-negative (false negatives).

Table 4: Model outcomes from base-case analyses

Outcome	Strategy 1 (No Retesting)	Strategy 2 (Retesting)	Excess in Strategy 2
Costs, $	12,753,297	14,421,207	1,667,909
Quality-adjusted Life Years (QALYs)	1,627,557	1,629,076	1,518
Child HIV infections during pregnancy	609	105	-504
Child HIV infections during breastfeeding	1583	826	-253
Maternal deaths	3,996	3,818	-178
Child deaths	8,496	8,466	-30

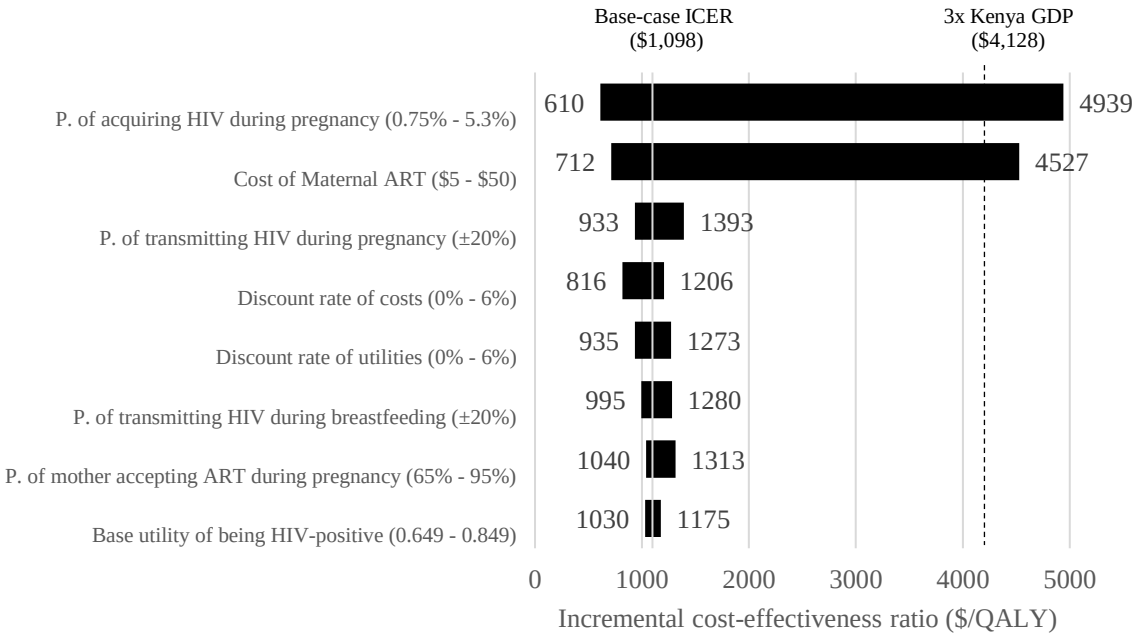
All costs and effects are per 100,000 women and 100,000 infants modeled; deaths may be due to background mortality or HIV-related causes.

Sensitivity Analyses

Univariate Analyses

These results were robust to changes in all but a few key variables as determined by univariate analyses. Probability of maternal HIV acquisition during pregnancy was a key determinant of cost-effectiveness, with increasing cost-effectiveness at higher incidence rates. Retesting was no longer cost-effective for cumulative incidence rates during pregnancy below 1%, as demonstrated in Figure 3 by the extension of the black bar beyond the threshold signifying 3x the GDP *per capita* in Kenya. The model was also sensitive to the cost of antiretroviral therapy for the mother; when the monthly cost exceeded $45 retesting was no longer cost-effective. Although the model was not sensitive to the maternal ART acceptance rate during pregnancy throughout the range specified in our model, we found the threshold below which resting was no longer cost-effective to be 35%. The model was robust to variations in HIV transmission rates during pregnancy and breastfeeding, utility of HIV-infection for both mother and child, and discount rates for both utilities and costs.

Figure 3. Tornado diagram



P. = probability

Probabilistic Sensitivity Analyses

Our results were cost-effective 73.4% of the time, as represented by all ICERs plotted to the right of the cost-effectiveness threshold in the ICER plane of Figure 4(A), representing 500 draws through second-order Monte Carlo simulation. In 22.6% of the scenarios, repeat HIV testing was both more costly and less effective (ICERs in the NW quadrant) and thus dominated. This was likely due to stochastic variations in background mortality.

In 100% of the scenarios, retesting averted infant HIV infections, with 23.6% of the scenarios estimating over 1,000 averted infections, as shown in Figure 4(B). On

average, the models found that retesting was associated with 784 fewer infections per 100,000 women, which came at an average cost of $1,778,677.

Since societal willingness to pay (WTP) for a QALY may vary across settings and GDP *per capita*, we have included a cost-effectiveness acceptability curve (Figure 5) to provide non-Kenyan policy makers with additional information about the cost-effectiveness of repeat HIV testing for their setting. At a societal WTP below $500/QALY, repeat HIV testing is cost-effective 38.6% of the time and thus may not be the preferred option. However, as the WTP exceeds $673/QALY, repeat HIV testing is more likely to be the option that provides the best health outcomes at a premium that is societally acceptable.

Figure 4: Cost-effectiveness planes

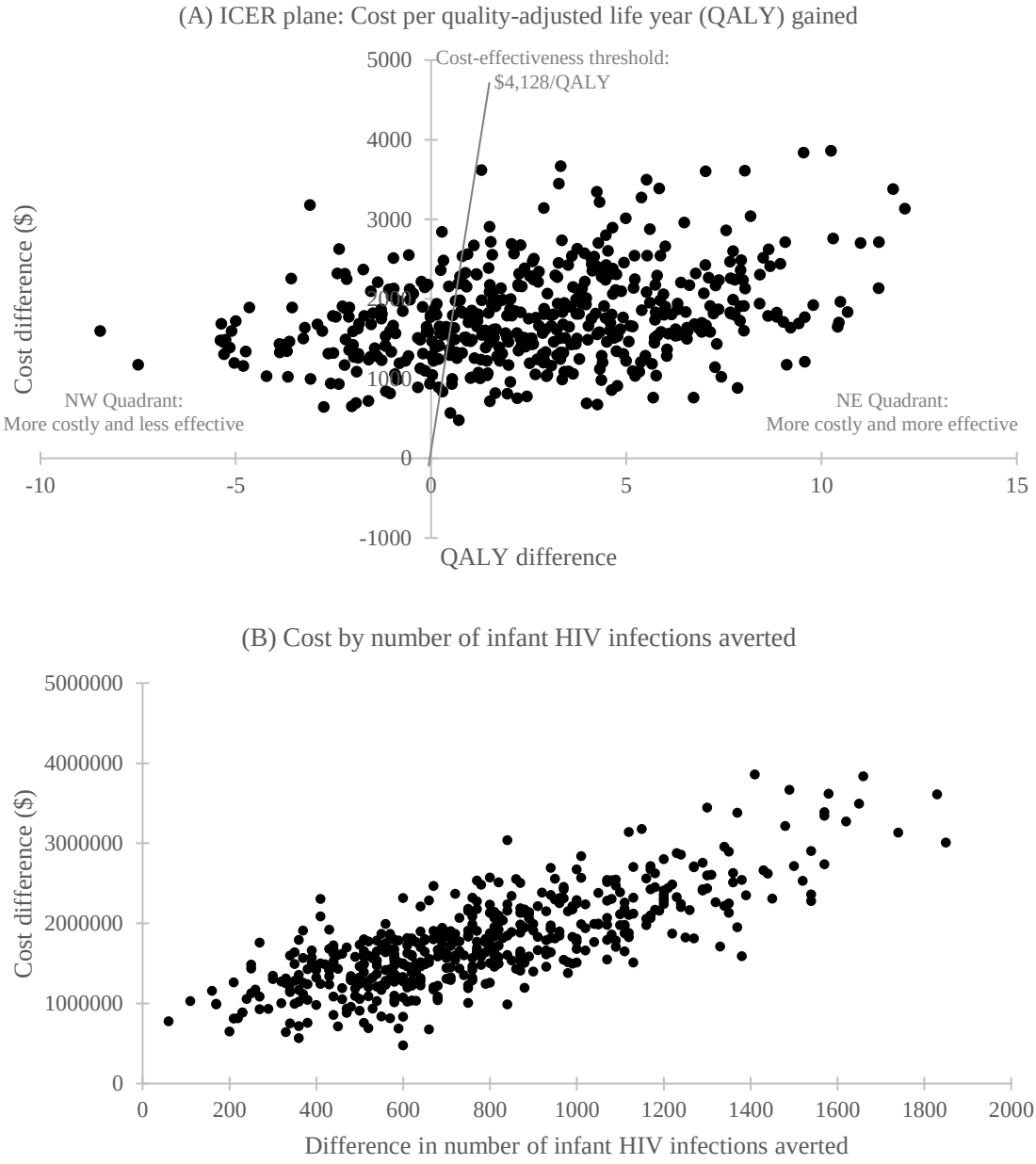
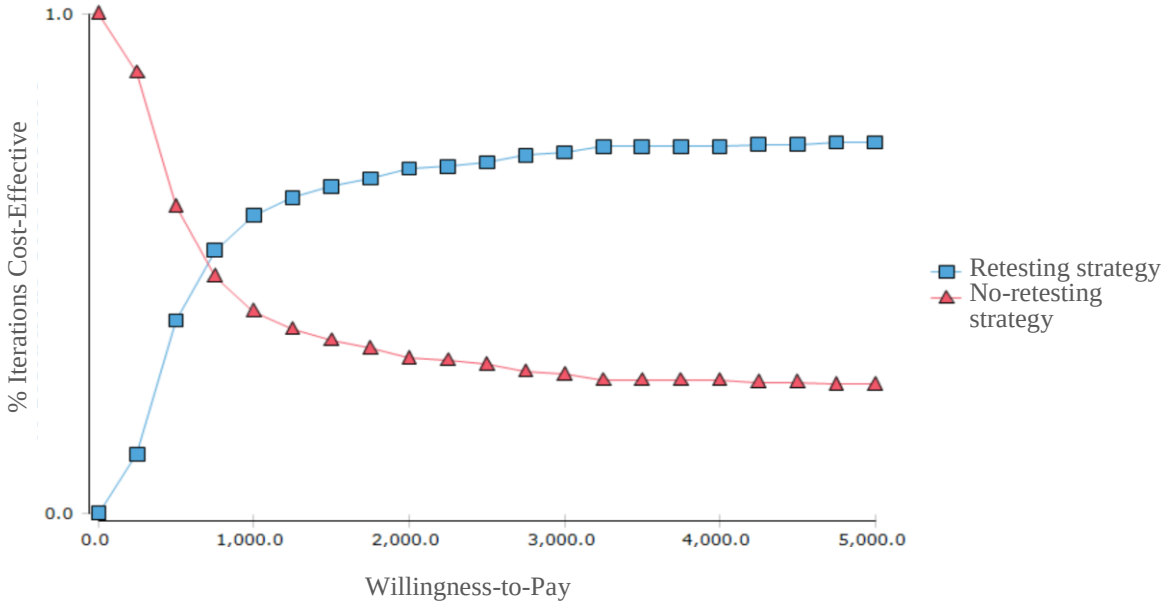


Figure 5: Cost-effectiveness acceptability curve



DISCUSSION

Under the base-case assumptions, for 100,000 women who had previously tested HIV-negative at an early pregnancy antenatal care appointment, late pregnancy repeat HIV testing with a 4th generation HIV test was cost-effective for the Kenyan setting at $1,098/QALY when considering the benefits of 757 averted perinatal HIV transmissions and 208 reduced deaths of both mother and child. Importantly, infant HIV infections were averted in 100% of the scenarios, suggesting that retesting may contribute to efforts to eliminate MTCT and achieve the goal of an AIDS-free generation.

The present analysis revealed that although the retesting strategy was cost-effective under the base-case assumptions, it was sensitive to several variables that may plausibly tip the scale in favor of not focusing on HIV retesting during pregnancy in

some settings. In particular, in settings where HIV incidence is low during pregnancy or the cost of maternal ART regimens is prohibitively high, policy makers should be aware that the long-term costs of retesting may exceed the level that society is willing to pay. Of note, it is possible that retesting may be more expensive without providing additional benefit, particularly if background mortality happens to be higher in the retesting group.

As a property of imperfect sensitivity and specificity values for rapid HIV tests, misdiagnosis may occur. Since false-negatives have a chance to potentially get retested during a future pregnancy or at a regular clinic visit, retesting will cause no detriment to them above and beyond what the no-retesting strategy would have. However, the false-positives may have initiated treatment unnecessarily and be subject to the side- and potential adverse-effects of antiretroviral therapy. While confirmatory testing may reduce the number of individuals in both categories, conditions in which tests are conducted are often far from ideal and may include the use of expired tests or the possibility of user errors such as when reading and interpreting weak lines.[58] Thus, our misdiagnosis estimates likely represent the worst case scenario.

This analysis improves on prior studies that assessed the cost-effectiveness of retesting during the perinatal period for settings including the US Virgin Islands,[15] Uganda,[16] South Africa,[17] and India[18] in several ways. In particular, the use of a stochastic model allows us to explore the implications of joint parameter uncertainty on our cost-effectiveness estimates. Deterministic studies are likely to underestimate uncertainty since in reality, parameters do not vary in isolation.[57] This study also incorporates a unique state-transition model that allows for the joint tracking of both maternal and infant health outcomes in the postpartum phase, a model that has not been

previously reported on in the perinatal HIV transmission cost-effectiveness literature. In addition, prior studies considered long-term costs of antiretroviral therapy for the child but not the mother, an important consideration in the current Option B+ era.

Our study has several limitations. We did not model transmission of HIV from the women to their HIV-negative sexual partners or from HIV-positive children to their future sexual partners. Thus, we did not account for potential benefits accrued from initiating ART or infections averted to prevent horizontal transmission. We also ignored the impact of preterm birth, which could increase morbidity attributable to HIV, although 10-year mortality was probably accurately captured due to our use of estimates from population-based cohorts from the literature. Finally, we did not explicitly model the possibility of MTCT during delivery, the use of nevirapine during labor, and the potential for cesarean deliveries to reduce transmission, which likely would have further lowered the transmission rate among women who retested HIV-positive. It is likely that these omissions rendered our estimates conservative.

Finally, our analysis could have been improved by designing a starting cohort with demographic characteristics that may affect transition probabilities, which would have facilitated examination of heterogeneity in the cost-effectiveness estimates; thus allowing us to determine if we should target certain sub-groups of pregnant women with retesting efforts. This may be particularly relevant in settings where the ICER is close to the limit of societal willingness to pay. Future studies should expand the current analysis to determine cost-effectiveness in other scenarios and settings. They should also consider assessing the appropriate timing of retesting efforts postpartum, as well as jointly consider the timing of maternal retesting relative to early infant diagnosis testing. Finally,

they may want to further assess the impact of additional potential misdiagnoses due to expanded testing.

In conclusion, this analysis provides evidence that repeat HIV testing is cost-effective in the Kenyan setting and may substantially reduce the number of infant HIV infections. By increasing the number of women on ART and identifying children of newly HIV-infected mothers as being HIV-exposed infants in need of closer follow-up, it may also decrease maternal and child mortality. Studies have already found repeat HIV testing in the Kenyan setting to be acceptable and feasible.[4,49] Given the high risk of vertical transmission among pregnant women with incident HIV infection, repeat HIV testing during late pregnancy may be an important strategy for the elimination of mother-to-child transmission of HIV in Kenya.

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CONCLUSIONS AND FUTURE DIRECTIONS

All children deserve an HIV-free start to life. Since 2009, over 1.2 million women living with HIV have given birth to and weaned HIV-free children.[1] While we have much to celebrate, efforts to ensure an AIDS-free generation must continue until we can eliminate perinatal HIV transmission in every country carrying the burden of HIV. This feat has already been achieved by Cuba, Thailand, Belarus, and Armenia, giving nations around the world hope.[80] Introducing a repeat antenatal HIV test may seem like a small step to take in the grand scheme of HIV testing, care, and treatment programs. However, research suggests that it may be a key component of a successful strategy to eliminate perinatal HIV transmission.[8]

Taken together, the three manuscripts comprising this dissertation have used qualitative and quantitative approaches to understanding the successes and challenges of implementing repeat HIV testing during pregnancy in Kenya. The first aim was completed using retrospective analysis of longitudinal antenatal clinic data for a cohort women (N = 2164) attending antenatal care at a large district hospital in southwestern Kenya. The second aim used qualitative data from in-depth interviews with health care providers and clinic managers (N = 20) to explore the barriers and enablers to retesting at four socioecological levels using the Ferlie and Shortell Framework for Change. The third aim used an individual-based stochastic model to compare a no-retesting strategy (only one HIV test during pregnancy) to a retesting strategy in terms of incremental cost-

effectiveness, number of infant HIV infections averted, and reduction in maternal and child deaths.

Overall, study findings suggest that the Kenyan Ministry of Health's adoption of international HIV retesting guidelines for pregnant women in mid-2011 has positively influenced retesting rates at one district hospital in southwestern Kenya, as demonstrated by an increase in the proportion of pregnant women retested from less than 1% in 2011 to nearly 45% in 2013. Interviews with local stakeholders suggest that an increase in retesting is not limited to a few clinics but has been adopted at many sites, albeit with varying levels of success.

However, the results also suggest that missed opportunities for retesting continue to exist due to lack of understanding of the importance of early and sustained antenatal clinic attendance on the part of clients, as well as a lack of retesting even when clients have come to antenatal clinic when eligible for a retest. Our first manuscript reported that 23.4% of all women (22.2% of women who had initially tested HIV-negative) only had one ANC clinic visit. We also found that being unmarried and aged 20 or younger was associated with an increase in mean gestational age of first visit by 2.52 weeks (95% CI: 1.56, 3.48) and a 2.59 odds (95% CI: 1.90, 3.54) of failing to return to clinic, compared to those who were married and over 20 years of age. These data were corroborated by one nurse, who commented that "especially the young girls, they really tend to hide… their main worry is not how the baby will be [but] it is just what people will say." This trend is concerning, especially since young women bear a disproportionately high burden of new HIV infections compared to their male peers and older women.[81]

Interestingly, the first and second manuscripts differed in terms of their findings on the impact that village distance from the clinic has on ANC attendance. While our qualitative data suggested that transportation or lack thereof was a significant barrier to visiting antenatal clinic, our quantitative data found that women who lived at a greater distance were more likely to come earlier for their first appointment and return for at least one more visit. Although these two results may seem contradictory, they may simply represent different phenomena. For example, our quantitative manuscript included subgroup analyses of the women living far from clinic, showing that they were more likely to have prior knowledge of their HIV-positive status. We hypothesized that they may have been more aware of their need to begin ANC attendance early in their pregnancy to prevent perinatal HIV transmission and that they may have already been in HIV care and thus used to accessing health services. HIV-related stigma or unavailability of HIV care services close to their village may have been associated with traveling further to antenatal clinic. This does not invalidate the reality that many women who live far from antenatal clinics may only come once for ANC – or perhaps they may never come at all and thus would not have been recorded in clinic records.

Our first manuscript found the incidence rate of HIV during pregnancy to be 4.4 per 100 person-years at a large district hospital in southwestern Kenya. While the size and representativeness of our sample may limit the generalizability of the results, this estimate was in line with results of a meta-analysis of incidence rates in sub-Saharan Africa, which reported a pooled rate of 4.7 (95% CI 3.3, 6.1) per 100 person-years.[7] Our estimate was slightly lower than a 2010 study of combined incidence in the Nyanza and Nairobi regions of Kenya to be 6.8 (95% CI: 5.1, 8.8) per 100 person-years,[19] but slightly

higher than more recent estimates from the Nyanza region showing incidence rates among pregnant women to be 3.1 per 100 person-years among women who newly tested positive during antenatal care,[39] and 2.35 per 100 person-years among women who were documented HIV-negative three months prior at an initial antenatal care HIV test.[40] All these incidence estimates suggest that sexually active women of reproductive age are acquiring HIV at a rate higher than the western Kenyan population at 1.9 per 100 person-years.[82] Unfortunately, we found that women newly diagnosed as being HIV-positive in ANC were significantly less likely to return to clinic – a crucial group to focus on for the prevention of MTCT and linkage to care for their own health.[83]

When the cumulative incidence rate of HIV during pregnancy, defined as the proportion of all pregnant women who seroconverted and distinct from the number of women who seroconverted per 100 person-years, dropped below 1% in our cost-effectiveness model, we found that repeat HIV testing may no longer be cost-effective under the WHO rubric for willingness to pay based on Kenyan GDP *per capita*. Based on our estimate of the cumulative incidence of HIV during pregnancy of 1.5% at a large district hospital in southwestern Kenya, it is possible that retesting is a cost-effective strategy in this region. Caution should be taken, however, when extending the conclusion of cost-effectiveness of the repeat HIV testing strategy across all Kenyan provinces, regardless of local incidence rates.

Parallels were also present in our second and third manuscripts. In particular, both explored how decisions made at the level of the health system can impact the reality of repeat HIV testing on the ground. Our qualitative manuscript described how cost and supply chain limitations resulted in an insufficient number of HIV test kits. Our economic

analysis manuscript demonstrated that the long-term cost of antiretroviral therapy was an important consideration in cost-effectiveness calculations, and that costly ART may tip the scales in favor of the no-retesting strategy in some settings.

Overall, our third manuscript found that retesting may not only be a cost-effective strategy, but that it may also avert infant HIV infections and reduce maternal and child mortality and morbidity. Since research has shown that individuals who know their HIV-positive status are empowered to initiate antiretroviral therapy and initiate HIV care services,[64] we anticipate that retesting may have the additional benefit of reducing new HIV infections among the future sexual partners of women who tested positive on retest, further amplifying the benefits of a retesting strategy. However, policymakers should carefully weigh the merits of retesting versus other strategies to eliminate MTCT and avert horizontal transmission, such as interventions that prevent HIV infections among reproductive-aged women, or perhaps even investments in HIV programs with other objectives unrelated to preventing HIV transmission.

Strengths and Limitations

The three papers comprising this dissertation present a unique constellation of strengths. In particular, our prospectively-collected longitudinal quantitative data spanned the years before and after the implementation of repeat HIV testing guidelines, allowing us to observe change over time. Our qualitative data were gathered from three sites in rural southwestern Kenya from a range of participants including nurses, community health workers, health educators, HIV testing counselors, laboratory technicians, facility coordinators, program technical advisors, trained lay healthcare workers, and

administrative staff involved in finances and procurement. This allowed us to explore barriers and enablers to retesting at multiple socioecological levels and represent a range of stakeholder perceptions. Finally, our cost-effectiveness model incorporated a unique state-transition model that was able to track the outcomes of both mother and child, and utilized stochastic simulations to model joint uncertainty in all the parameters at once.

This dissertation has limitations, in particular limited generalizability resultant from having quantitative data from a single large hospital and qualitative data from a relatively small sample of participants in one region of Kenya. Thus, caution should be taken when extending the results of these analyses beyond rural southwestern Kenya. Data were also primarily collected from government clinics supported by Family AIDS Care Education and Services, a program that provides a level of mentoring and support for HIV care and ANC services that other neighboring facilities may not have. Our cost-effectiveness model had limitations pertaining to its ability to accurately represent reality, including our decision to not model transmission of HIV from the women to their HIV-negative sexual partners or from HIV-positive children to their future sexual partners.

Conclusion

This dissertation supports the conclusion that HIV incidence during pregnancy among women in southwestern Kenya remains high and while HIV retesting rates have increased since guideline dissemination, implementation efforts appear to have lagged in some subgroups, leaving high-risk young, unmarried women less likely to get retested. Implementation of repeat HIV testing in high HIV-prevalence areas of Kenya is cost-

effective and likely to avert substantial new pediatric infections, but will require a multi-sector commitment to capitalize on community strengths.

Results from this dissertation suggest that there is a societal willingness to invest in the complete elimination of perinatal HIV transmissions in order to reap the lifelong benefits of an AIDS-free generation. In the words of one of our interview participants, "[We] feel motivated and say 'Eh kumbe hata sisi we' – [meaning] we are able to do it."

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APPENDIX A

UNIVERSITY OF ALABAMA AT BIRMINGHAM INSTITUTIONAL REVIEW BOARD APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on January 24, 2017. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator:	TURAN, JANET M
Co-Investigator(s):	CHAMOT, ERIC A M CUTTER, GARY R
Protocol Number:	**X140304009**
Protocol Title:	*A Home-Based Couples Intervention to Enhance PMTCT and Family Health in Southern Nyanza, Kenya*

The IRB reviewed and approved the above named project on 4-9-14. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 4-9-14

Date IRB Approval Issued: 4-9-14

IRB Approval No Longer Valid On: 4-9-15

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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OMB No. 0990-0263
Approved for use through March 31, 2018

Protection of Human Subjects
Assurance Identification/IRB Certification/Declaration of Exemption
(Common Rule)

Policy: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the Common Rule. See section 101(b) of the Common Rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the Common Rule. Institutions must have an assurance of compliance that applies to the research to be conducted and should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Name of Federal Department or Agency and, if known, Application or Proposal Identification No.
[ ] ORIGINAL [X] CONTINUATION [ ] EXEMPTION	[X] GRANT [ ] CONTRACT [ ] FELLOWSHIP [ ] COOPERATIVE AGREEMENT [ ] OTHER:_____	
4. Title of Application or Activity A Home-Based Couples Intervention to Enhance PMTCT and Family Health in Southern Nyanza, Kenya		5. Name of Principal Investigator, Program Director, Fellow, or Other TURAN, JANET M

6. Assurance Status of this Project *(Respond to one of the following)*

[X] This Assurance, on file with Department of Health and Human Services, covers this activity:
Assurance Identification No. FWA00005960, the expiration date 11/08/2021 IRB Registration No. IRB00000196

[ ] This Assurance, on file with *(agency/dept)*_____, covers this activity.
Assurance No._____, the expiration date_____ IRB Registration/Identification No._____*(if applicable)*

[ ] No assurance has been filed for this institution. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

[ ] Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph_____.

7. Certification of IRB Review (Respond to one of the following IF you have an Assurance on file)

[X] This activity has been reviewed and approved by the IRB in accordance with the Common Rule and any other governing regulations.
by: [ ] Full IRB Review on (date of IRB meeting) _____ or [X] Expedited Review on (date) 1/10/17
[ ] If less than one year approval, provide expiration date _____

[ ] This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the Common Rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments	Title X140304009
Protocol subject to Annual continuing review.	A Home-Based Couples Intervention to Enhance PMTCT and Family Health in Southern Nyanza, Kenya

IRB Approval Issued: 1/10/17 IRB Approval No Longer Valid On: 1/10/18

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed until study closure and certification will be provided.	10. Name and Address of Institution
11. Phone No. *(with area code)* (205) 934-3789 12. Fax No. *(with area code)* (205) 934-1301 13. Email: irb@uab.edu	University of Alabama at Birmingham 701 20th Street South Birmingham, AL 35294
14. Name of Official Expedited Reviewer DE Linn	15. Title IRB Member
16. Signature	17. Date 1/10/17

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APPENDIX B

KENYA MEDICAL RESEARCH INSTITUTE SCIENTIFIC AND ETHICAL REVIEW UNIT APPROVAL

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel (254) (020) 2722541, 2713349, 0722-205901, 0733-400003; Fax: (254) (020) 2720030
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KEMRI/RES/7/3/1 August 1, 2014

TO: PROF. ELIZABETH BUKUSI,
PRINCIPAL INVESTIGATOR

THROUGH: DR. WILLIE SANG,
ACTING DIRECTOR, CMR,
NAIROBI

forwarded on 05.08.14

Dear Madam,

RE: SSC PROTOCOL NO. 2797 (*RESUBMISSION*): A HOME-BASED COUPLES INTERVENTION TO ENHANCE PMTCT AND FAMILY HEALTH IN SOUTHERN NYANZA, KENYA.

Reference is made to your letter dated 25th July, 2014. The ERC Secretariat acknowledges receipt of the revised protocol on July 28, 2014.

This is to inform you that the Ethics Review Committee (ERC) reviewed the documents submitted and is satisfied that the issues raised at the 228th meeting of the KEMRI ERC on 24th June, 2014 have been adequately addressed.

The study is granted approval for implementation effective this **1st August, 2014**. Please note that authorization to conduct this study will automatically expire on **July 31, 2015.** If you plan to continue with data collection or analysis beyond this date, please submit an application for continuing approval to the ERC Secretariat by **June 19, 2015**.

Any unanticipated problems resulting from the implementation of this protocol should be brought to the attention of the ERC. You are also required to submit any proposed changes to this protocol to the SSC and ERC prior to initiation and advise the ERC when the study is completed or discontinued.

You may embark on the study.

Yours faithfully,

MR. AMBROSE RACHIER,
THE CHAIR,
KEMRI/ETHICS REVIEW COMMITTEE

KENYA MEDICAL RESEARCH INSTITUTE

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KEMRI/RES/7/3/1 **July 01, 2016**

TO: **PROF. ELIZABETH BUKUSI,**
CO-PRINCIPAL INVESTIGATOR

THROUGH: **THE DIRECTOR, CMR,**
NAIROBI

Forwarded 11/7/2016
DR. C. B.

Dear Madam,

RE: **SSC PROTOCOL NO. 2797 *(REQUEST FOR ANNUAL RENEWAL):* A HOME-BASED COUPLES INTERVENTION TO ENHANCE PMTCT AND FAMILY HEALTH IN SOUTHERN NYANZA, KENYA**

Thank you for the continuing review report for the period **July 22, 2015** to **May 30, 2016**.

This is to inform that during the 252nd Committee C meeting of the KEMRI/Scientific and Ethics Review Unit (SERU) held on the **30th June 2016**, the Committee **conducted the annual review and approved** the above referenced application for another year.

This approval is valid from **July 22, 2016** through to **July 21, 2017**. Please note that authorization to conduct this study will automatically expire on **July 21, 2017**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to SERU by **June 09, 2017.**

You are required to submit any amendments to this protocol and other information pertinent to human participation in this study to SERU for review prior to initiation.

You may continue with the study.

Yours faithfully,

for

DR. EVANS AMUKOYE,
ACTING HEAD,
KEMRI/SCIENTIFIC AND ETHICS REVIEW UNIT