Published in final edited form as:

J Acquir Immune Defic Syndr. 2007 October 1; 46(2): 208–215. doi:10.1097/QAI.0b013e318141fcc0.

Morbidity Among HIV-1–Infected Mothers in Kenya:

Prevalence and Correlates of Illness During 2-Year Postpartum Follow-Up

Judd L. Walson, MD, MPH^{*,†}, Elizabeth R. Brown, ScD[‡], Phelgona A. Otieno, MBChB, MMed, MPH^{*}, Dorothy A. Mbori-Ngacha, MMed, MPH[§], Grace Wariua, MBChB[§], Elizabeth M. Obimbo, MBChB, MMed, MPH[§], Rose K. Bosire, MBChB, MPH^{||}, Carey Farquhar, MD, MPH^{†,¶}, Dalton Wamalwa, MBChB, MMed, MPH[§], and Grace C. John-Stewart, MD, PhD^{†,§,¶}

^{*}Centre for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya

[†]Department of Medicine, University of Washington, Seattle, WA

[‡]Department of Biostatistics, University of Washington, Seattle, WA

[§]Department of Pediatrics, University of Nairobi, Nairobi, Kenya

^{||}Centre for Public Health Research, Kenya Medical Research Institute, Nairobi, Kenya

[¶]Department of Epidemiology, University of Washington, Seattle, WA

Abstract

Background—Much of the burden of morbidity affecting women of childbearing age in sub-Saharan Africa occurs in the context of HIV-1 infection. Understanding patterns of illness and determinants of disease in HIV-1–infected mothers may guide effective interventions to improve maternal health in this setting.

Methods—We describe the incidence and cofactors of comorbidities affecting peripartum and postpartum HIV-1–infected women in Kenya. Women were evaluated by clinical examination and standardized questionnaires during pregnancy and for up to 2 years after delivery.

Results—Five hundred thirty-five women were enrolled in the cohort (median CD4 count of 433 cells/mm³) and accrued 7736 person-months of follow-up. During 1-year follow-up, the incidence of upper respiratory tract infections was 161 per 100 person-years, incidence of pneumonia was 33 per 100 person-years, incidence of tuberculosis (TB) was 11 per 100 person-years, and incidence of diarrhea was 63 per 100 person-years. Immunosuppression and HIV-1 RNA levels were predictive for pneumonia, oral thrush, and TB but not for diarrhea; CD4 counts <200 cells/mm³ were associated with pneumonia (relative risk [RR] = 2.87, 95% confidence interval [CI]: 1.71 to 4.83), TB (RR = 7.14, 95% CI: 2.93 to 17.40) and thrush. The risk of diarrhea was significantly associated with crowding (RR = 1.86, 95% CI: 1.19 to 2.92) and breast-feeding (RR = 1.71, 95% CI: 1.19 to 2.44). Less than 10% of women reported hospitalization during 2-year follow-up; mortality risk in the cohort was 1.9% and 4.8% for 1 and 2 years, respectively.

Conclusions—Mothers with HIV-1, although generally healthy, have substantial morbidity as a result of common infections, some of which are predicted by immune status or by socioeconomic factors. Enhanced attention to maternal health is increasingly important as HIV-1–infected mothers transition from programs targeting the prevention of mother-to-child transmission to HIV care clinics.

Keywords

HIV/AIDS; HIV-1 progression; maternal health; morbidity; postpartum; pregnancy; prevention of mother-to-child transmission; women

Women of reproductive age represent half of all infected HIV-1– individuals worldwide and more than half of HIV-1 infections in Africa.¹ Improving maternal health has been targeted as the Fifth Millennium Development Goal, endorsed by 189 countries.² HIV-1 infection has been shown to increase the risk of direct complications of pregnancy such as sepsis and hemorrhage. In addition, other illnesses such as tuberculosis (TB), pneumonia, and malaria are all increased significantly in pregnancy and in the postpartum period.^{3–6} A study conducted in Zambia found that postpartum HIV-infected women were significantly more likely to experience moderate to severe morbidity than HIV-uninfected women.⁷ HIV-1–infected women may initiate medical care only as a result of pregnancy, delivery, or early postpartum visits. Such encounters may present a unique opportunity to reduce morbidity and mortality in HIV-1–infected women by facilitating early HIV-1 diagnosis and providing access to HIV-1 care and treatment.

HIV/AIDS seems to increase the risk of maternal mortality in Africa. Countries most severely affected by the HIV epidemic have seen marked increases in rates of maternal mortality.^{8,9} HIV-1 infection may be responsible for as many as 1300 excess maternal deaths per 100,000 live births.^{10–12} Among postpartum women in Zimbabwe, HIV-seropositive women were 10 to 30 times more likely to die from TB, pneumonia, meningitis, or sepsis than HIV-seronegative postpartum women.³ The World Health Organization (WHO) is now considering revising the definition of maternal death to include late deaths occurring up to 1 year postpartum, given accumulating evidence that increases in maternal mortality risk extend far beyond the traditionally defined 42-day post-partum period.^{11,13}

Pregnancy results in significant immune alterations, including decreases in cell-mediated immune function, T helper cells, and natural killer cells, which may increase the risk of infection and result in more severe clinical outcomes during pregnancy and in the postpartum period.¹⁴ In a previous study conducted by our group, mortality during 2-year postpartum follow-up was 6.0% and seemed to be mainly attributable to AIDS-related illnesses, including Kaposi sarcoma, wasting syndrome, TB, cryptococcal meningitis, pneumonia, and diarrheal diseases.¹⁵ In Zimbabwe, TB, pneumonia, and meningitis accounted for two thirds of all mortality in the 24-month postpartum period.³ Although much of this mortality is directly attributable to AIDS-related illnesses, comorbidities such as diarrhea, malaria, sexually transmitted diseases (STDs), and other respiratory illnesses may occur frequently in HIV-1–infected postpartum mothers.

There are limited data on prevalence or patterns of these illnesses in this population. Because many women are diagnosed with HIV-1 during pregnancy and subsequently followed in prevention of mother-to-child transmission (PMTCT) programs, it is important for maternal health as well for PMTCT program planners to quantify the burden of illness in this population and the cofactors predictive of morbidity. As part of a study evaluating postpartum maternal health among women with HIV-1, we collected data on illnesses occurring during 2-year follow-up in these women to determine the incidence of various morbidities and cofactors for the development of these illnesses.

METHODS

Study Setting and Population

These data were collected as part of a prospective cohort study conducted in Nairobi, Kenya from July 1999 to June 2005.¹⁶ Briefly, pregnant HIV-1–seropositive women were referred from Nairobi City Council clinics to the study clinic at Kenyatta National Hospital. Initially, 216 women were enrolled with a follow-up period of 12 months. Subsequently, an additional cohort of 319 women was included with a predefined follow-up period of 24 months. Immunologic and viral markers and mortality were evaluated in the latter group of women with 2-year follow-up, and these parameters were compared in breast-feeding versus formula-feeding women as previously published.¹⁶ For analyses of morbidity, data from both cohorts were used, and thus included 535 women. Written informed consent was obtained from all subjects. Human experimentation guidelines of the US Department of Health and Human Services were followed, and approval was obtained from the Institutional Review Board of the University of Washington and the Ethical Review Committee of the Kenya Medical Research Institute (KEMRI).

Clinical Procedures

Baseline sociodemographic and medical information was collected for all women using a standardized questionnaire at enrollment. The risk of HIV-1 transmission through breast-feeding was explained to all women, and formula was provided to women who chose to formula-feed. Women received instruction in the proper preparation of formula, including appropriate ratios for mixing and use of clean water. All women also received iron and multivitamin supplementation in the first 6 postnatal months. Women with severe immunosuppression (CD4 count <200 cells/mm³) were provided with cotrimoxazole prophylaxis and referred to HIV treatment programs providing antiretroviral therapy.

Women received standard antenatal care, including short-course zidovudine, according to the Centers for Disease Control and Prevention (CDC) Thai regimen to reduce the risk of HIV-1 transmission to the baby.¹⁷ Women were examined, and blood was collected for T-cell subset analysis and hemoglobin and HIV-1 RNA levels at 32 weeks of gestation. Blood was collected at delivery for HIV-1 RNA measurements.

Women enrolled in the study were followed with routine scheduled visits as directed by clinic staff. Between 1999 and 2002, women were followed monthly for 12 months after delivery of a baby. From 2002 until 2005, all enrolled participants were followed monthly for the first 12 months and then every 3 months for an additional 12 months after delivery. Blood was collected for T-cell subset analysis and HIV-1 RNA levels at postpartum months 1, 3, 6, 9, and 12 for all women and at 18 and 24 months postpartum in the women followed for the extended study period. In addition, women in the cohort with health complaints occurring between scheduled visits were seen in clinic on an as-needed basis.

Laboratory Procedures

Measurement of lymphocyte counts and CD4 cell percentages was conducted at the University of Nairobi using a FACScan flow cytometer (Becton Dickinson, Mountain View, CA).¹⁸ Plasma HIV-1 RNA levels were quantified in Seattle at the Fred Hutchinson Cancer Research Center using a transcription-mediated amplification assay developed by Gen-Probe (San Diego, CA), which has been shown to quantify the subtypes of HIV-1 prevalent in Kenya.¹⁹

Definitions of Morbidities

Diagnoses of illness were based on self-reported history of illness and clinical examination findings at each clinic visit. Historical diagnoses were recorded after asking women if they had been diagnosed with specific syndromes (eg, malaria, pneumonia, TB) or symptoms (eg, fever, cough, diarrhea). Clinical determination of illness was based on WHO diagnostic guidelines in use at the clinic site by study physicians (RB, CF, EO, PO, DW, and GW).²⁰

STATISTICAL ANALYSIS

Outcome measurements for this analysis included self-reported and clinically diagnosed illnesses at scheduled and unscheduled (as needed) visits. All data were analyzed using Statistical Package for Social Sciences (SPSS-Windows, Chicago, IL) and R (R Development Core Team; Gnu project, Boston, MA).²¹ Maternal baseline characteristics were summarized using means for continuous variables and proportions for categorical variables. Continuous variables were compared using Student *t* tests for means, and categorical variables were compared using χ^2 tests.

Calculation of Incident Morbidity

Because interim missing visits could bias the calculation of at-risk time, follow-up time was split into 60- and 90-day intervals. A woman's at-risk time was defined as the number of intervals in which she had a visit times the length of the interval. Therefore, if a woman missed visits for many months in a row and could not contribute to incidence calculations, she would also not contribute disproportionately to follow-up time. Incidence (in 100 person-years) over a year was defined as the number of incident illnesses over the year, divided by the total number of at-risk intervals for the cohort, multiplied by the number of intervals in a year (4 for 90 days and 6 for 60 days) times 100. Incidence was calculated for scheduled visits alone and for scheduled plus unscheduled visits. Associations with baseline variables and time trends were estimated and tested using generalized estimated equations (GEEs) with a log-link (robust correlated Poisson regression). Associations between baseline variables and outcomes were restricted to scheduled visits because of the potential bias associated with including unscheduled visits, whose probability of occurring may be related to the outcome and the baseline covariates. Women were censored at reported second pregnancy, initiation of highly active antiretroviral therapy (HAART), or death. Individual definitions of morbidity incidence were calculated as follows.

If a participant reported a history of upper respiratory tract infection (URTI), pneumonia, malaria, diarrhea, pelvic inflammatory disease (PID), thrush, bronchitis, genital ulcers, STD, urinary tract infection (UTI), or mastitis at a visit and there was no record of the same diagnosis made at a previous visit within 30 days, the event was counted as a new episode. If fever was recorded at a visit and the last visit with a recorded fever was more than 14 days prior, it was counted as a new fever. Any reported episode of TB within a 7-month period (210 days) was counted as a new episode of TB. AIDS-defining illness was defined using WHO clinical staging guidelines.²²

RESULTS

Enrollment and Follow-Up

Of 535 women enrolled, 501 (93.6%) were followed to delivery, 489 (97.6%) of whom had data from at least 1 visit after delivery and were included in this analysis. During the follow-up period, 12 women initiated antiretrovirals (ARVs) and 21 women died. Thirty-two women became pregnant with another child (second pregnancy), and 1 woman became pregnant and started ARVs (Fig. 1). The data included in this analysis represent 7746

person-months of follow-up. Three hundred twenty-eight (67%) women completed 1 year of follow-up, and 102 (32%) of 319 women completed 24 months of planned follow-up. Women who completed follow-up tended to be younger and were less likely to breast-feed than those who were lost to follow-up. The women who completed 2 years of follow-up were also more likely to have plasma viral loads higher than the median at baseline.

Overall, data were collected on 7147 separate encounters in the first 2 years postpartum (an average of 14.6 visits per woman). The women completed an average of 11.5 scheduled follow-up visits and 3.1 as-needed visits for clinical care. In the first year, there were 5635 encounters by 488 women, representing 11.4 visits per woman. In the second year, there were 1536 encounters by 353 women, representing 4.4 visits per woman. Among the 485 women who attended a scheduled visit in the first year, the mean time between scheduled visits in the first 390 days was 31.5 days.

Baseline Characteristics of the Women in the Cohort

Women were enrolled into the study at approximately 32 weeks of gestation. Baseline characteristics of the cohort are presented in Table 1. At the enrollment visit, 69 women (14.1%) reported a history of STD and 41 (8.4%) reported having been diagnosed with TB in the past. In addition, 67 women (13.7%) reported a history of fever, 43 (8.8%) reported having had malaria, 29 (5.9%) reported having had diarrhea, and 7 (1.4%) reported having had oral thrush during their current pregnancy. Prior use of multivitamins in pregnancy was reported by 169 women (34.6%), and 107 (21.9%) reported having used an antibiotic during their pregnancy.

CD4 cell counts were available for 466 women at enrollment (95.3%), and HIV-1 RNA levels were available for 451 women (92.2%). The median CD4 count was 433 cells/mm³, and 10.6% of the women had a CD4 count <200 cells/mm³ at enrollment. The median HIV-1 RNA level at enrollment in this cohort was 4.71 log₁₀ copies/mL (see Table 1).

Follow-Up

Cofactors associated with an increased likelihood of coming for an unscheduled (as needed) visit included having a CD4 count <200 cells/mm³, having an HIV-1 RNA level higher than the median, being formula-feeding, being older than the median, not having a flush toilet, and not being primigravida (Table 2).

Over the first year of follow-up, 11.4% (IQR: 8.1, 14.6) of subjects who had a CD4 count >200 cells/mm³ at baseline and who had follow-up CD4 measurements had at least 1 CD4 count less than 200 cells/mm³. At 24 months of follow-up, the percentage of participants with at least 1 CD4 count less than 200 cells/mm³ increased to 17.5% (IQR: 12.6, 22.1) (Fig. 2). Time between visits (scheduled and as needed) was similar when comparing subjects with CD4 counts greater than and less than 200 cells/mm³ (1 day more for those with a CD4 count <200 cells/mm³). Women with a CD4 count <200 cells/mm³ had 42 days fewer total scheduled follow-up time than women with higher CD4 counts ($P = 0.002$), however. Baseline viral load was not associated with time between visits. There was no association between baseline viral load and total follow-up time.

Hospitalization

During follow-up, 42 women were hospitalized a total of 44 times. Information on the cause of illness leading to hospitalization was available for 39 of these hospitalizations (88.6%). These included 9 episodes of malaria, 7 episodes of pneumonia, 6 episodes of TB, 6 episodes of typhoid fever, 5 episodes of diarrhea, 4 episodes of chest pain, and 1 episode each of shingles and yellow fever. There was no correlation between baseline CD4 cell

count, log₁₀ HIV RNA level, or prior history of AIDS-defining illness and the risk of hospitalization in this cohort. The incidence of hospitalization did not increase over time during the follow-up period.

Mortality

Twenty-one women were confirmed to have died during the course of the study period. The estimated mortality at 12 months was 1.9% (95% confidence interval [CI]: 0.6% to 3.2%), and it was 4.8% (95% CI: 2.3% to 7.3%) at 24 months. The cause of death was reported as “AIDS related” in 15 women (71.4%). Mortality was associated with a higher viral load and immunosuppression at baseline (hazard ratio for viral load higher than median = 3.02 (IQR: 0.972, 9.35); $P = 0.06$ and hazard ratio for CD4 count <200 cells/mm³ = 13.6 (IQR: 5.06, 36.5); $P < 0.001$).

Incidence and Correlates of Illness in the Cohort

During the first year of follow-up postpartum, frequent causes of morbidity included URTIs, malaria, and diarrhea (Table 3). At scheduled visits during the first year, 204 women reported fever since their last visit (41.7%), 122 reported diarrhea (24.9%), 89 reported malaria (18.2%), and 78 reported a history of pneumonia (16.0%). Fever, URTI, malaria, and diarrhea all occurred at more than 50 cases per 100 person-years during the first year of follow-up. UTI, genital ulcers, STD, thrush, and PID were all reported less frequently at rates of <25 cases per 100 person-years of follow-up during this period. Incidence rates of morbidity were calculated for all visits (scheduled and as needed) and were similar between the first and second years of follow-up in this cohort (see Table 3). Women were rarely diagnosed with more than 1 serious morbidity at a single visit (4 visits with diarrhea and pneumonia and 2 visits with diarrhea and TB reported).

The incidence of common morbidities such as pneumonia, TB, and malaria seemed to remain relatively stable over the follow-up period, whereas the incidence of diarrhea seemed to increase in a linear fashion (Fig. 3). These trends in morbidity incidence over the first year of follow-up were stratified by CD4 count (>350 cells/mm³ and <350 cells/mm³). Pneumonia incidence increased significantly over the follow-up period in the women with CD4 counts <350 cells/mm³ but remained stable in those women with higher CD4 counts, whereas the incidence of TB remained stable regardless of CD4 cell count over the first year of follow-up. The increasing incidence of diarrhea in the cohort was independent of CD4 cell count (see Fig. 3).

Upper Respiratory Tract Infections and Pneumonia

URTIs were the most commonly reported illnesses in the cohort, with an incidence of 161 episodes per 100 person-years and 145 episodes per 100 person-years of follow-up in the first and second years, respectively. Primigravid status was associated with a significantly reduced risk of URTI during the first year of follow-up (relative risk [RR] = 0.68, 95% CI: 0.55 to 0.85). This effect remained after adjusting for maternal age.

Pneumonia was diagnosed with an incidence of 33 cases per 100 person-years in the first year of follow-up and 29 cases per 100 person-years in the second year. Cofactors significantly associated with developing pneumonia in the first year of follow-up included age older than the median (RR = 1.75, 95% CI: 1.15 to 2.68), CD4 count <200 cells/mm³ (RR = 2.87, 95% CI: 1.71 to 4.83), and viral load higher than the median (RR = 1.77, 95% CI: 1.15 to 2.73).

Tuberculosis

The incidence of pulmonary TB was 11 cases per 100 person-years in the 2 years of follow-up. A CD4 count <200 cells/mm³ at baseline was associated with an increased risk of TB during the first year postpartum (RR = 7.14, 95% CI: 2.93 to 17.40). Having a viral load greater than the median was also associated with a significantly greater risk of TB in the first year postpartum (RR = 3.37, 95% CI: 1.23 to 9.23).

Diarrheal Disease

During the first year postpartum, diarrhea incidence was 63 cases per 100 person-years. This risk increased throughout the first year. Incidence of diarrhea was slightly less in the second year (49 episodes per 100 person-years). Having only 1 room in the home was associated with an increased risk of diarrhea (RR = 1.86, 95% CI: 1.19 to 2.92), and there was a trend toward an association between diarrhea and not having a flush toilet. In addition, breast-feeding was significantly associated with maternal diarrhea when compared with formula-feeding (RR = 1.71, 95% CI: 1.19 to 2.44). The association between diarrhea and breast-feeding seemed to be independent of level of education or socioeconomic status (as measured by having more than 1 room and having a flush toilet) when included in a multivariate analysis (RR = 1.48; $P = 0.053$).

Mastitis

In the first year of follow-up, the incidence of clinical mastitis was 25 per 100 person-years, declining to 4 per 100 person-years in the second year. Breast-feeding was associated with an increased risk of developing mastitis in this cohort (RR = 5.65, 95% CI: 2.47 to 12.96). Older age and higher socioeconomic status seemed to be associated with a lower risk of developing mastitis.

AIDS-Defining Illnesses

During the first year of follow-up, 59 women presented with an illness consistent with WHO stage III or IV HIV disease. After adjusting for baseline CD4 cell count, having a viral load higher than the median was associated with the development of an AIDS-defining illness (RR = 1.87, 95% CI: 1.02 to 3.43; $P = 0.04$).

Other illnesses

The incidences of other morbidities, including malaria, PID, oral thrush, bronchitis, genital ulcers, STD, and UTI, are presented in Table 3. Cofactors for these morbidities are presented in Table 4.

DISCUSSION

The results of this analysis suggest that in the 2-year period after delivery of a baby, HIV-infected Kenyan women experience a high incidence of URTIs, diarrhea, pneumonia, and TB. Respiratory infections, diarrhea, and TB are among the top 10 causes of death in sub-Saharan Africa and were important causes of morbidity in this cohort.²³ Given the high rates of disease and relatively low mortality observed in this cohort, this analysis suggests that much of the illness leading to death in HIV-1-infected postpartum women may be preventable with access to appropriate health care. This finding underscores the importance of integrating routine HIV care with peripartum and postnatal care programs in resource-limited settings.

Few studies have evaluated morbidity among women in Africa beyond the immediate postpartum period. Incidence rates of pneumonia, TB, malaria, and diarrhea are likely to be

higher in HIV-infected postpartum mothers than in their HIV-uninfected counterparts. A study of HIV-seropositive and -seronegative postpartum women in Zambia found that HIV seropositivity increased the risk of moderate to severe postpartum morbidity by almost 2-fold (adjusted odds ratio [OR] = 1.63) over a 16-week period.⁷ In Zimbabwe, HIV-infected postpartum women with similar median CD4 cell counts to those included in this analysis experienced incidence rates of URTI, pneumonia, TB, malaria, and diarrhea that were lower than we report.³ Other studies evaluating rates of illness in adult HIV-1-infected African populations have shown highly variable incidence estimates for pneumonia (0.8 to 44.3 per 100 person-years), TB (0.6 to 16.2 per 100 person-years), malaria (6.5 to 34.1 per 100 person-years), and diarrhea (3.1 to 53.0 per 100 person-years), however.^{24–26} All these studies included participants with lower median CD4 counts (median CD4 counts 300 cells/mm³) than the women included in our analysis. We report incidence rates that are in the higher range of previously reported morbidities. The reasons for the higher incidence rates reported in our analysis may be attributable to different ascertainment or follow-up intervals or to biologic consequences resulting from changes during or after pregnancy.²⁷

URTIs, pneumonia, and pulmonary TB accounted for a large proportion of the reported morbidity in this analysis. This finding is consistent with other studies, which have shown that respiratory complaints are common among HIV-infected individuals in Africa, with reported incidence rates of 71.5 to 217.3 cases per 100 years of follow-up.^{24,26} Among postpartum women in Zimbabwe, URTIs were the most common cause listed for attending a sick visit by HIV-1-positive women during the first postpartum year and TB and pneumonia were the 2 leading causes of death.²⁸ It is possible that our finding that multigravid women experienced higher rates of URTI may reflect greater exposure to common pathogens among women with other children in the household.

Globally, TB is the leading cause of infection-related death in women aged 15 to 44 years and is a major nonobstetric cause of mortality in Africa, with 25% to 34% of maternal deaths attributable to TB.^{3,5,27,29} The observed incidence of TB (11 cases per 100 years of follow-up) and the 7-fold increase in risk of TB associated with severe immunosuppression (CD4 count <200 cells/mm³) seen in this study are consistent with other reports from Africa. The CD4 cell count in HIV-infected individuals has been shown to be a dominant risk factor for the development of TB in sub-Saharan Africa, with a reduction in the risk of developing TB of approximately 25% for each 100-cell/mm³ increase in the CD4 count.³⁰ In addition, pregnancy may increase the risk of developing active TB among infected women.³¹ Untreated TB has a case fatality rate as high as 90% in HIV-1-infected individuals.^{31–34} TB was the most common cause of death among HIV-positive women followed postpartum in Zimbabwe and South Africa and was the third leading cause of maternal death after sepsis and hypertensive disorders of pregnancy. In addition, coinfection with HIV and TB increased the risk of death in women more than 3-fold compared with that in women with TB and no HIV infection.^{3,6} Our study adds to the evidence that HIV-infected women with lower CD4 cell counts would benefit from increased vigilance for TB, and potentially from empiric isoniazid (INH) prophylaxis.

After respiratory diseases, diarrhea was the most common morbidity reported in this cohort. This may reflect overcrowded living conditions and lack of adequate sanitation experienced by this urban cohort of women. Most of the episodes of diarrhea seemed to be of relatively short duration, consistent with the higher CD4 cell counts of the women in the cohort. In addition, the risk of diarrhea seemed to increase over the follow-up period. Breast-feeding was also associated with an increased risk of diarrhea, an effect that remained after controlling for education and markers of socioeconomic status. Women in the formula-feeding arm may have benefited from the education regarding safe water. The observed increase in diarrhea risk over time also supports this hypothesis, because hygiene practices

may have waned over time, resulting in increasing exposure to pathogens. Breast-feeding and formula-feeding mothers may benefit from enhanced sanitary education in the context of PMTCT programs in these settings.

These data suggest that in the extended postpartum period, women seem to have an appreciable risk of developing a variety of common infections. In this analysis, women with more advanced immunosuppression were at increased risk of oral thrush, pneumonia, and TB. The risk of other common illnesses such as URTI and diarrhea seemed to be independent of CD4 cell count, however. Having only 1 room in the home was associated with an increased risk of developing diarrhea, thrush, and mastitis. This cofactor seemed to be a marker for low socioeconomic status in this cohort and may be an easily identifiable risk factor to target as a marker of increased risk of disease in these women. Expanding current PMTCT programs to provide more intensive education and follow-up to these women may result in important health benefits to women and their children. In addition, many of the morbidities reported in this analysis are potentially preventable with cotrimoxazole prophylaxis. Further studies are warranted to determine if HIV-infected women in the postpartum period may benefit from extended cotrimoxazole prophylaxis, regardless of CD4 cell count.

There are several important strengths and limitations to this analysis. The study was designed to evaluate disease progression in a cohort of women followed during the third trimester of pregnancy and after delivery. Frequent scheduled follow-up visits allowed documentation of thorough history and physical examination findings. In addition, the inclusion of unscheduled visits allowed us to capture events that might otherwise be missed. Despite these strengths, it is important to note that this study was not designed to evaluate morbidity as a primary outcome measure. Measures of morbidity were collected using standardized questionnaires by clinical staff and did not include microbiologic or radiographic confirmation. Although we cannot exclude bias attributable to misclassification, the rates of illness observed in this study were consistent with those from other published studies.^{3,6,24–26}

This analysis further demonstrates that identifying HIV-1–infected women during pregnancy and in the postpartum period may have direct effects on maternal health. As programs scale up PMTCT and other maternal-child health care programs in Africa, efforts should be made to incorporate longitudinal follow-up and care of HIV-infected mothers. The time surrounding childbirth and delivery represents an important and unique opportunity to improve the health of HIV-1–infected mothers and their babies. Further studies are needed to define the most effective screening programs and interventions for HIV-1–infected women in resource-limited settings.

Acknowledgments

Supported by US National Institutes of Health (NIH) research grants (RO1 HD 23412 and AI27757) and the University of Washington Center for AIDS Research. P. A. Otieno, E. M. Obimbo, R. K. Bosire, D. Wamalwa, G. Wariua, and C. Farquhar were scholars in the University of Washington AIDS International Research and Training Program, which is supported by an NIH Fogarty International Center grant (D43-TW00007).

References

1. United Nations Program for HIV/AIDS/World Health Organization. UNAIDS/02.46E. Geneva, Switzerland: UNAIDS; 2002. AIDS Epidemic Update—December 2002.
2. Sachs JD, McArthur JW. The Millennium Project: a plan for meeting the Millennium Development Goals. *Lancet*. 2005; 365:347–353. [PubMed: 15664232]

3. Zvandasara P, Hargrove JW, Ntozini R, et al. Mortality and morbidity among postpartum HIV-positive and HIV-negative women in Zimbabwe: risk factors, causes, and impact of single-dose postpartum vitamin A supplementation. *J Acquir Immune Defic Syndr*. 2006; 43:107–116. [PubMed: 16885772]
4. Pillay T, Khan M, Moodley J, et al. The increasing burden of tuberculosis in pregnant women, newborns and infants under 6 months of age in Durban, KwaZulu-Natal. *S Afr Med J*. 2001; 91:983–987. [PubMed: 11847922]
5. Ahmed Y, Mwaba P, Chintu C, et al. A study of maternal mortality at the University Teaching Hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause of maternal death. *Int J Tuberc Lung Dis*. 1999; 3:675–680. [PubMed: 10460099]
6. Khan M, Pillay T, Moodley JM, et al. Maternal mortality associated with tuberculosis-HIV-1 co-infection in Durban, South Africa. *AIDS*. 2001; 15:1857–1863. [PubMed: 11579249]
7. Collin SM, Chisenga MM, Kasonka L, et al. Factors associated with postpartum physical and mental morbidity among women with known HIV status in Lusaka, Zambia. *AIDS Care*. 2006; 18:812–820. [PubMed: 16971293]
8. Bicego G, Boerma JT, Ronsmans C. The effect of AIDS on maternal mortality in Malawi and Zimbabwe. *AIDS*. 2002; 16:1078–1081. [PubMed: 11953479]
9. Fawcus SR, van Coeverden de Groot HA, Isaacs S. A 50-year audit of maternal mortality in the Peninsula Maternal and Neonatal Service, Cape Town (1953–2002). *BJOG*. 2005; 112:1257–1263. [PubMed: 16101605]
10. Le Coeur S, Khlata M, Halembokaka G, et al. HIV and the magnitude of pregnancy-related mortality in Pointe Noire, Congo. *AIDS*. 2005; 19:69–75. [PubMed: 15627035]
11. Ronsmans C, Graham WJ. Maternal mortality: who, when, where, and why. *Lancet*. 2006; 368:1189–1200. [PubMed: 17011946]
12. Sewankambo NK, Gray RH, Ahmad S, et al. Mortality associated with HIV infection in rural Rakai District, Uganda. *AIDS*. 2000; 14:2391–2400. [PubMed: 11089628]
13. Hoj L, da Silva D, Hedegaard K, et al. Maternal mortality: only 42 days? *BJOG*. 2003; 110:995–1000. [PubMed: 14592584]
14. Goodrum LA. Pneumonia in pregnancy. *Semin Perinatol*. 1997; 21:276–283. [PubMed: 9298716]
15. Nduati R, Richardson BA, John G, et al. Effect of breastfeeding on mortality among HIV-1 infected women: a randomised trial. *Lancet*. 2001; 357:1651–1655. [PubMed: 11425369]
16. Otieno PA, Brown ER, Mbori-Ngacha DA, et al. HIV-1 disease progression in breast-feeding and formula-feeding mothers: a prospective 2-year comparison of T cell subsets, HIV-1 RNA levels, and mortality. *J Infect Dis*. 2007; 195:220–229. [PubMed: 17191167]
17. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet*. 1999; 353:773–780. [PubMed: 10459957]
18. Kiarie JN, Richardson BA, Mbori-Ngacha D, et al. Infant feeding practices of women in a perinatal HIV-1 prevention study in Nairobi, Kenya. *J Acquir Immune Defic Syndr*. 2004; 35:75–81. [PubMed: 14707796]
19. Emery S, Bodrug S, Richardson BA, et al. Evaluation of performance of the Gen-Probe human immunodeficiency virus type 1 viral load assay using primary subtype A, C, and D isolates from Kenya. *J Clin Microbiol*. 2000; 38:2688–2695. [PubMed: 10878065]
20. WHO HIV Department–IMAI Project. Integrated Management of Adolescent and Adult Illness. 2004. Available at: http://www.who.int/hiv/pub/imai/en/acutecarerev2_e.pdf
21. Chompook P, Todd J, Wheeler JG, et al. Risk factors for shigellosis in Thailand. *Int J Infect Dis*. 2006; 10:425–433. [PubMed: 16997593]
22. Interim World Health Organization. Clinical Staging of HIV/AIDS and HIV/AIDS Case Definitions for Surveillance, African Region. World Health Organization; Geneva, Switzerland: 2005.
23. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006; 367:1747–1757. [PubMed: 16731270]

24. van Oosterhout JJ, Laufer MK, Graham SM, et al. A community-based study of the incidence of trimethoprim-sulfamethoxazole-preventable infections in Malawian adults living with HIV. *J Acquir Immune Defic Syndr*. 2005; 39:626–631. [PubMed: 16044018]
25. Watera C, Todd J, Muwonge R, et al. Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1-infected adults attending an HIV/AIDS clinic in Uganda. *J Acquir Immune Defic Syndr*. 2006; 42:373–378. [PubMed: 16810124]
26. Mwachari CW, Shepherd BE, Cleopa A, et al. Mortality and burden of disease in a cohort of HIV-seropositive adults in Nairobi, Kenya. *Int J STD AIDS*. 2004; 15:120–126. [PubMed: 15006075]
27. McIntyre J. Mothers infected with HIV. *Br Med Bull*. 2003; 67:127–135. [PubMed: 14711759]
28. Zvandasara P. Primary school children's knowledge of health and illness in The Gambia: its implication for teaching children about disease. *J Trop Pediatr*. 1987; 33:110–112. [PubMed: 3586097]
29. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*. 1997; 349:1269–1276. [PubMed: 9142060]
30. Lawn SD, Myer L, Bekker LG, et al. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS*. 2006; 20:1605–1612. [PubMed: 16868441]
31. Gilks CF, Brindle RJ, Otieno LS, et al. Extrapulmonary and disseminated tuberculosis in HIV-1-seropositive patients presenting to the acute medical services in Nairobi. *AIDS*. 1990; 4:981–985. [PubMed: 2261127]
32. Juneja Y, Goel U, Sood M. Changing trends in maternal mortality over a decade. *Int J Gynaecol Obstet*. 1994; 46:265–269. [PubMed: 7805994]
33. Ray A. Maternal mortality in a subdivisional hospital of eastern Himalayan region. *J Indian Med Assoc*. 1992; 90:124–125. [PubMed: 1517613]
34. Raviglione, M.; Nunn, P.; Kochi, A., et al. The Pandemic of HIV-Associated Tuberculosis. Mann, JM., editor. Oxford University Press; United Kingdom: 1996. p. 87-96.

FIGURE 1.

Trial profile. Over the course of the study period, 12 women initiated ARVs, 32 became pregnant again, 21 died, and 1 became pregnant again and initiated ARVs.

FIGURE 2.

CD4 cell count decline over 2 years of follow-up. Survival curve for time to CD4 count <200 cells/mm³. The vertical axis is the percentage of patients not yet having met the endpoint, and the horizontal axis is time in months. Overall, most women were not severely immunosuppressed at enrollment; however, over the follow-up period, the number of women meeting criteria for the initiation of ARVs (based on CD4 cell count) increased significantly.

FIGURE 3.

Individual morbidity increase over the first year of follow-up. The vertical axis shows the number of cases reported per 100 person-years of follow-up. Participants are stratified by CD4 cell count at enrollment. Participants with CD4 counts < 350 cells/mm³ were significantly more likely to develop pneumonia and TB during the follow-up period than those with higher CD4 cell counts. The CD4 cell count did not seem to affect the risk of developing diarrhea.

TABLE 1**Demographic and Clinical Characteristics of the Cohort**

	n	Median	(IQR) or n (%)
Mother's age	485	25.0	(22.0, 28.0)
Years of education	480	8.0	(8.0, 12.0)
Marital status	485		
Single		42	9%
Monogamous marriage		385	79%
Polygamous marriage		44	9%
Widowed		3	1%
Divorced/separated		11	2%
Uses alcohol	482	22	5%
Uses tobacco	483	5	1%
Age at first sex	484	17.0	(16.0, 19.0)
No. lifetime sex partners	484	3	(2, 4)
No. prior pregnancies	449	1	(1, 2)
History of prostitution	482	10	2%
CD4 cell count	466	433.0	(303.2, 617.5)
Log ₁₀ HIV-1 RNA	451	4.71	(4.17, 5.24)
MUAC	368	25	(24, 27)
BMI	451	24.5	(22.6, 26.2)

BMI indicates body mass index; IQR, interquartile range; MUAC, mid-upper arm circumference.

TABLE 2

Predictors of an As-Needed Visit in the First Year

	RR (95% CI)	P
Viral load > median	1.16 (1.00 to 1.35)	0.047
CD4 count <200 cells/mm ³	1.28 (1.08 to 1.53)	0.005
Breast-feeding	0.71 (0.62 to 0.81)	<0.001
Age > median	1.20 (1.04 to 1.38)	0.011
Education > primary	1.14 (0.99 to 1.31)	0.073
1-room	0.91 (0.78 to 1.07)	0.268
Flush toilet	0.86 (0.75 to 1.00)	0.046
Primigravida	0.80 (0.66 to 0.98)	0.032

TABLE 3
Incidence of Morbidity During the First and Second Years of Postpartum Follow-Up (Numbers per 100 Person-Years of Follow-Up)

Diagnosis	First Year			Second Year		
	Scheduled Visit	As-Needed Visit	Estimated Overall	Scheduled Visit	As-Needed Visit	Estimated Overall
Fever	83	—	83	83	—	83
URTI	104	55	159	55	85	139
Pneumonia	18	14	33	10	17	27
Malaria	36	17	54	26	22	48
Diarrhea	49	12	61	32	16	49
PID	12	5	17	6	5	10
TB	3	3	6	6	6	9
Thrush	12	—	12	14	—	14
Mastitis	22	3	25	3	1	4
Bronchitis	15	7	22	3	6	9
Genital ulcers	3	—	3	2	—	2
STD	0	5	6	1	5	6
UTI	—	20	20	—	22	22
Hospitalization	7	—	7	5	—	5

TABLE 4
Cofactors for Overall Morbidity Among HIV-1-Infected Women During the First Year Postpartum

	Pneumonia	Diarrhea	TB	URTI	Thrush	Mastitis	Hospitalization
Age > median	2.01 ^{**} (1.23 to 3.27)	0.96 (0.71 to 1.32)	1.75 (0.75 to 4.08)	1.01 (0.84 to 1.21)	1.95 [*] (1.02 to 3.73)	0.58 [*] (0.34 to 0.98)	0.80 (0.38 to 1.68)
Education > primary	0.98 (0.58 to 1.63)	0.76 (0.55 to 1.05)	0.89 (0.37 to 2.10)	0.99 (0.82 to 1.20)	1.34 (0.69 to 2.60)	0.88 (0.50 to 1.54)	1.01 (0.48 to 2.14)
1 room in home	1.00 (0.56 to 1.81)	1.79 [*] (1.09 to 2.93)	1.29 (0.44 to 3.76)	0.99 (0.80 to 1.24)	0.49 [*] (0.25 to 0.96)	4.50 ^{**} (1.71 to 11.82)	0.95 (0.41 to 2.21)
Flush toilet	0.83 (0.51 to 1.37)	0.77 (0.57 to 1.05)	0.97 (0.42 to 2.24)	0.98 (0.81 to 1.18)	1.46 (0.76 to 2.82)	0.40 ^{**} (0.23 to 0.69)	0.87 (0.41 to 1.82)
Primigravida	0.77 (0.41 to 1.45)	0.78 (0.50 to 1.22)	0.37 (0.09 to 1.58)	0.71 ^{**} (0.55 to 0.90)	0.57 (0.24 to 1.39)	0.95 (0.48 to 1.89)	0.74 (0.25 to 2.18)
Breast-feeding	0.69 (0.40 to 1.20)	1.83 ^{**} (1.25 to 2.67)	0.72 (0.30 to 1.74)	1.06 (0.86 to 1.32)	0.93 (0.41 to 2.14)	6.11 ^{**} (2.47 to 15.10)	1.12 (0.49 to 2.60)
CD4 count <200 cells/mm ³	2.39 ^{**} (1.33 to 4.29)	0.89 (0.58 to 1.37)	5.09 ^{**} (2.16 to 11.97)	1.07 (0.78 to 1.47)	5.95 ^{**} (2.97 to 11.94)	0.94 (0.38 to 2.32)	2.18 (0.85 to 5.55)
Viral load > median	1.70 [*] (1.01 to 2.87)	1.12 (0.81 to 1.54)	3.76 [*] (1.25 to 11.30)	1.07 (0.89 to 1.30)	2.89 ^{**} (1.36 to 6.12)	0.68 (0.40 to 1.16)	1.94 (0.91 to 4.18)

Only scheduled visits contribute to incident visits.

RRs from independent regressions are shown with 95% CIs.

Significant values are noted as:

^{*} *P* 0.05,

^{**} *P* 0.01.