Prevalence and risks of asymptomatic bacteriuria among HIV-positive pregnant women

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The objective of the study was to determine whether the prevalence of asymptomatic bacteriuria (ASB) and subsequent complications are higher in HIV-positive than in HIV-negative pregnant women. A prospective controlled study of asymptomatic pregnant women was carried out. One hundred and twenty-five consecutive HIV-positive women and 247 HIV-negative controls were screened for asymptomatic bacteriuria. Treatment of positive cultures was by means of antibiotics as per protocol. Nine percent (n=11) of HIV-positive patients and 7.9% (n=19) of HIV-negative patients had positive urine cultures (p=0.68). Microorganisms were similar in both groups. The incidence of preterm labour was 6.7% in the HIV-positive cohort, versus 11.3% in HIV-negative control patients (p=0.17). The rate of prelabour rupture of membranes was significantly increased in HIV-positive patients compared to HIV-negative controls (17 HIV-positive versus 13 HIV-negative patients, 14.17% and 5.42%, respectively; RR 2.615, 95% CI, 1.314-5.204). CD4+ cell count level <200/mm^3 or ≥200/mm^3 did not influence the occurrence of ASB. The prevalence of ASB in HIV-positive study patients did not differ from HIV-negative controls.

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Introduction

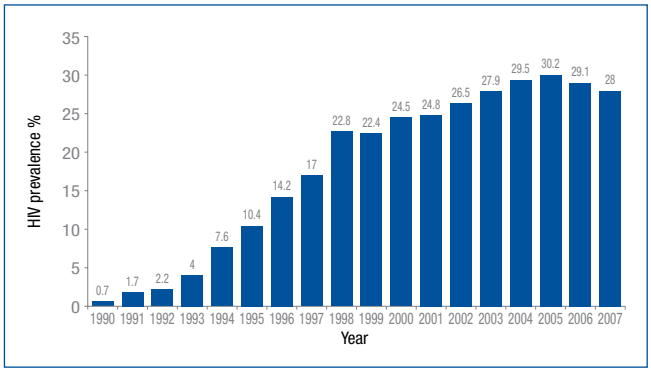
Urinary tract infection (UTI), which may be symptomatic or asymptomatic, is one of the most common bacterial infections requiring medical treatment during pregnancy.[1] Asymptomatic bacteriuria (ASB) affects 2-10% of pregnant women, depending on the patient population. If left untreated, as many as 30-50% will develop symptomatic UTI, often in the form of pyelonephritis.[2] The hormonal and mechanical changes of the upper and lower urinary tract during pregnancy contribute to development of bacteriuria and UTI.[3]

Antibiotic treatment, compared to placebo or no treatment, effectively eradicated ASB (RR 0.25, 95% CI 0.14-0.48), and reduced the incidence of pyelonephritis (RR 0.23, 95% CI 0.13-0.41) and the rate of low birth weight babies (RR 0.66, 95% CI 0.49-0.89).[2]

In 1991, a study involving 489 pregnant patients, performed at Tygerberg Hospital, found the prevalence of ASB to be 10%.[4] In a subsequent cohort study performed in 1996 at the same hospital, the prevalence of ASB was 6.2% (91/1,477 patients). In this study it was confirmed that patients with ASB had significantly increased risk of preterm labour and preterm premature rupture of membranes.[5]

The HIV epidemic is having a major impact on the health of pregnant patients in South Africa, with non-pregnancy-related infection being the leading cause of maternal deaths. The third comprehensive report on confidential enquiries into maternal deaths in South Africa from 2002-2004 showed that 37.8% of maternal deaths were due to non-pregnancy-related infections.[6] Figure 1 shows the high prevalence of HIV among patients who use public services for antenatal care in South Africa.[7]

Figure 1: Nationwide HIV prevalence among antenatal clinic attendees



Some studies have indicated that the risk of bacteriuria and UTI may be increased in HIV-infected patients and is inversely related to CD4+ lymphocyte counts.[8,9] UTI in HIV-positive patients tends to recur, requiring longer treatment and it is suggested that treatment should be culture-specific.[9] In the HIV Epidemiology Research Study (HERS) in the United States, it was found that the risk for UTI was not related to HIV infection but to viral load among the women who are infected with HIV.[10] A recent study conducted elsewhere in South Africa found the incidence of ASB among HIV-positive versus HIV-negative pregnant women to be 18.6% and 12.9%, respectively.[11]

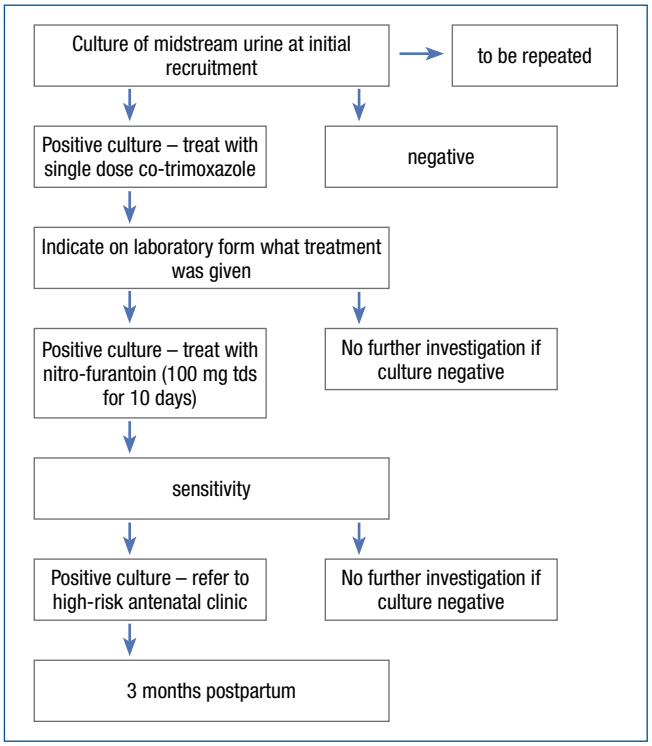
The primary aim of the study is to compare the prevalence of ASB in HIV-positive and HIV-negative pregnant women with the secondary aim to determine the efficacy of treatment of ASB in both groups and describe associated complications such as pyelonephritis and preterm labour. These aspects require urgent research to reduce maternal and neonatal morbidity and mortality.

Methods

A prospective controlled study was performed, whereby asymptomatic pregnant women who booked before 24 weeks gestation, were recruited at a community health centre, a primary care facility in the Tygerberg area. This centre, providing an ultrasound service for the surrounding antenatal clinics, was chosen as the place for recruitment. Recruitment commenced in March 2005 and was completed in October 2005. These patients are referred from all the antenatal clinics in the Cape Town Metropolitan area served by Tygerberg Hospital. Consecutive patients found to be less than 24 weeks pregnant on routine detailed foetal ultrasound or dating ultrasound examination, were included in the study, thus ensuring that gestational age was accurate. Patients received careful instruction on the manner of collecting a clean-catch urine specimen. The urine was immediately plated onto agar plates using 1 μl Quadloop loops. At the end of each day the agar plates were delivered to the laboratory where they were incubated and processed.

Growth of $\geq 10^5$ organisms on a single specimen was considered a positive culture. Urine results were followed up and management of positive cultures resumed according to flow diagram 1.

Flow diagram 1: Screening and management of ASB in pregnancy



Patients were contacted telephonically and requested to return to the antenatal clinic to collect treatment. Alternatively, treatment was given at the follow-up visit. By directly observing intake of a single dose of co-trimoxazole when given at the clinic, compliance was ensured. All contaminated samples (overgrowth of three different organisms) were repeated. Bacteriuria was considered persistent if a patient, who had ASB on initial urine sample and was known to have received treatment, had a follow-up urine sample yielding a positive culture.

Patients' data were collected post-partum where information was obtained from the antenatal card and hospital records. Patients who did not deliver at the local midwife obstetric units or Tygerberg Hospital were contacted telephonically to acquire information regarding location of hospital where delivery took place, date of delivery, weight of baby and outcome. Where possible, permission was obtained form the hospital where they delivered to view the patient record to complete the information.

HIV testing is routinely offered to all antenatal patients by means of universal counselling and voluntary testing. The screening programme consists of an HIV rapid test. If a positive result is obtained, this is confirmed by a second rapid test from a different supplier. Only patients with both tests positive are considered to be HIV-positive. CD4+ cell counts are determined for all HIV-positive patients. All of the patients with low CD4+ cell counts ($<200/mm^3$) received co-trimoxazole for *Pneumocystis carinii* pneumonia (PCP) prophylaxis and were placed on highly active antiretroviral therapy (HAART) after careful evaluation by the staff at the infectious disease clinic.

All HIV-positive patients received counselling and were dealt with according to Department of Health protocol with regard to prevention of mother-to-child transmission of HIV and management of HIV in pregnancy.[12]

Pyelonephritis was diagnosed if a patient presented with positive symptoms and signs such as rigors, fever, dysuria, frequency and costovertebral tenderness with a positive urine culture. Labour was considered preterm if there were regular uterine contractions (four per 20 minutes) associated with cervical change before 37 completed weeks of pregnancy. Prelabour rupture of membranes was defined as spontaneous rupture of membranes not followed within one hour by uterine contractions. A neonate was considered small for gestational age (SGA) if its mass was below the 10th percentile for gestational age. A percentile chart for birth weight derived by Theron and Thompson was used for reference.[13]

Sample size determination was done with EpiInfo Version 6. Using a 2:1 ratio between HIV-negative and HIV-positive patients, and assuming the ASB prevalence to be 5% among HIV-negative patients, 14% among HIV-positive patients and a type I error of 0.05, 250 HIV-negative and 125 HIV-positive patients were required to achieve 80% power. For the purposes of the study the sample size in the control arm was doubled as these patients could be recruited rapidly, and to improve the precision of ASB prevalence and related complications to be expected amongst HIV-negative patients.

Written consent was obtained from all patients. The study was approved by the Committee for Human Research at the Department of Health Sciences of the University of Stellenbosch.

The data were analysed using the SPSS statistical programme. Proportions were compared with the chi-square and Fisher's exact test with small numbers which would apply to the subanalysis of the main results. Means of normally distributed data were compared using the Student's t-test. The medians of data that did not have a normal distribution were compared using the Mann Whitney U-test.

Results

A total of 125 HIV-positive patients and 247 HIV-negative control patients were recruited. Five of the HIV-positive and seven of the HIV-negative patients were lost to follow-up. Eighteen patients in total delivered at facilities other than Tygerberg Hospital or the two midwife obstetric units that refer to Tygerberg Hospital. Medical records were obtained for seven of these patients. The remaining 11 patients delivered at hospitals remote from Cape Town and were interviewed telephonically. These data were included in the final analysis. At the time of urine specimen collection none of the patients were on PCP prophylaxis or antiretroviral treatment. Characteristics of the two groups are illustrated in Table 1.

Table 1: Summary data of study patients

	HIV-positive	HIV-negative	p value
Patients	120	240	
Age*	25.9 [16-37]	24.2 [15-40]	0.003
Parity#	0 [1-6]	0 [1-6]	0.69
GA at booking (weeks)*	15.1	14.3	0.15
GA at first ultrasound (weeks)*	19.5	18.2	0.01
GA at delivery (weeks)*	38.5	38.6	0.74
Birth weight (grams)*	2928	2985	0.44
Caesarean section	27 [22.5%]	30 [12.5%]	0.01
Normal vaginal delivery	89 [74%]	204 [85%]	0.018

*Mean [range] #Median [range] Abbreviation: GA, gestational age

CD4+ lymphocyte counts were known in 115 of the 125 HIV-positive patients. The distribution of CD4+ lymphocyte counts is shown in Table 2.

Table 2: CD4+ cell count distribution

CD4 + cell count	No. of patients (% of total)
<200/mm^3	9 (7.2%)
200-499/mm^3	64 (51.2%)
≥500/mm^3	42 (33.6%)
Unknown	10 (8%)

ASB was detected in 11 HIV-positive and 19 HIV-negative patients (9.2% vs 7.9%, p=0.69). The frequency and types of microorganisms were similar between the two groups (Table 3), with *Escherichia coli* the most commonly cultured organism, detected in the urine of seven HIV-positive and 13 HIV-negative patients (63.6% vs. 68.4%, p=1; Fisher's exact test). There were 9.6% and 9.3% of contaminated urine specimens in the HIV-positive and HIV-negative groups, respectively. Persistent bacteriuria after initial conventional treatment with single dose of co-trimoxazole was found in three of the 11 HIV-positive patients, and three of the 19 HIV-negative patients with ASB (p=0.45; Fisher's exact test). The overall clearance rate in 30 positive urine cultures was 80%.

The frequency of ASB among patients according to the various levels of CD4+ cell counts is illustrated in Table 4. The mean CD4 cell count of those HIV-positive patients with ASB was 381/mm^3 (standard deviation 165/mm^3). In those without ASB the mean CD4 cell count was 466 (standard deviation 254/mm^3). This was statistically different [p=0.0002, 95% CI of difference = (-128.80, -41.20)].

Table 3: Microorganisms cultured from patients with ASB

	HIV-positive (% of total)	HIV-negative (% of total)
Escherichia coli	7 (63%)	13 (68%)
Proteus mirabilis	2 (18%)	2 (10%)
Klebsiella pneumoniae	0 (0%)	1 (5%)
Staphylococcus saprophyticus	1 (9%)	1 (5%)
Enterococcus faecalis	0 (0%)	1 (5%)
Staphylococcus aureus	1 (9%)	1 (5%)

Table 4: Frequency of ASB in CD4+ cell count strata

CD4 cell count	ASB-positive (n=11)	ASB-negative (n=109)	
<200/mm^3	2 (18%)	7 (6%)	
≥200/mm^3	9 (82%)	97 (89%)	p= 0.20
Unknown	0 (0%)	5 (5%)	

Preterm labour occurred in eight HIV-positive and 27 HIV-negative patients (6.67% vs 11.25%, respectively; RR 0.593, 95% CI, 0.278 to 1.265). This difference was not statistically significant. The presence of HIV did not increase the risk for preterm labour. Of the eight HIV-positive patients that went into preterm labour, one patient had ASB. In the HIV-negative group, of 27 patients with preterm labour, three patients had ASB (p=1; Fisher's exact test).

A significantly larger number of HIV-positive patients had pre-labour rupture of membranes. This occurred in 17 HIV-positive versus 13 HIV-negative patients (14.17% and 5.42%, respectively; RR 2.615, 95% CI, 1.314 to 5.204). ASB was present in four out of 17 HIV-positive (23.5%) and two out of 13 HIV-negative patients (15.4%) who had prelabour rupture of membranes. The presence of ASB in the HIV-positive group did not increase the risk for prelabour rupture of membranes (RR 1.529; 95% CI, 0.329 -7.107).

Pyelonephritis developed in two patients in the study. Both of these patients were HIV-negative and neither had ASB. There were no cases of clinical sepsis antenatally or postnatally in either group of patients.

There was no difference in the number of patients admitted antenatally (17 HIV-positive and 47 HIV-negative, p=0.20). The reasons for antenatal admission were similar in both groups, with preterm labour (eight vs 27, p=0.17), pregnancy-induced hypertension (eight vs 18, p=0.77) and pre-eclampsia (seven vs nine, p=0.36) forming the most common indications for admission. Gestational diabetes was present in two of the HIV-negative patients.

Elective deliveries became necessary in 13 HIV-positive and 19 HIV-negative patients. Indications were similar, with pre-eclampsia, pregnancy-induced hypertension and post-dates the most common reasons for elective delivery. As shown in Table 1, HIV-positive patients underwent significantly more Caesarean sections (22.5% vs 12.5%, p=0.01). Indications for Caesarean section were similar between the two groups, except for significantly more HIV-positive patients having Caesarean section for failed induction of labour (14% vs 3.3% in HIV-negative patients). Wound sepsis after Caesarean section developed in two of the 27 HIV-positive patients, and in none in the HIV-negative group. There was no difference in the occurrence of other post-partum complications such as puerperal sepsis, haemorrhage and fever between the two groups.

Small for gestational age infants were present in 16 HIV-positive and 37 HIV-negative patients (13.3% vs 15.4%, p=0.59). One of these HIV-positive and five of these HIV-negative patients had ASB (p=0.65). The number of newborns with Apgar scores below 7 at five minutes was four in the HIV-positive group and three in the HIV-negative group (p=0.22, Fisher).

Neonatal outcomes were normal in most cases. In the HIV-positive group, two pregnancies ended with intra-uterine deaths, there were three neonatal deaths and one infant death. There were two intra-uterine deaths, and one neonatal death in the HIV-negative group.

Discussion

UTIs result from a complex interaction of host factors and the infecting organism. Defense mechanisms preventing urinary infection are the vaginal and urine pH, the normal vaginal flora, 'wash-out' effect of flowing urine and the mucopolysaccharide lining produced by the urothelium.[14,15] Other important factors are the secretion of immunoglobulin A (IgA) and blood group antigens, which inhibit bacterial adherence. There are few CD4+ lymphocytes in the normal urinary mucosa, and the role of these cells in protection from UTI is not completely understood.[10,15]

Pioneering work by Edward Kass in the 1950s and 1960s already revealed the relationship between ASB, pyelonephritis and adverse pregnancy outcomes such as preterm birth, and how treatment of ASB could prevent these complications.[16] Treatment of ASB is known to clear bacteriuria in 75% of cases, reduce the incidence of pyelonephritis by 77% and decrease low birth weight deliveries by 34%.[2] However, it has been questioned whether screening for ASB using a urine culture, which is relatively expensive, is cost-effective. In low ASB prevalence areas of 2%, it has been found not to be cost-effective.[17] On the other hand, in areas where the prevalence of ASB approaches 10%, the cost-effectiveness and cost-benefit ratios are increased markedly.

Previous studies done at Tygerberg Hospital showed the prevalence of ASB to be 6.2% and 10%, but due to the current study taking place at a peripheral low-risk clinic, the prevalence of ASB for HIV-negative pregnant women was assumed to be lower, at 5%.[4,5] This is the value used in the sample size calculation. The prevalence of ASB among HIV-positive patients was derived from a study performed in South Africa where ASB in 70 HIV-positive patients was determined and found to be 18%. The prevalence of ASB in 163 HIV-negative controls was 12.9% in this study (p=0.35; statistical analysis performed by authors).[11] Both of these percentages are noticeably higher than the incidence of ASB studied previously at our hospital.[4,5] We expected the prevalence of ASB among our HIV-positive population to be less than the other published study as the level of immune-compromise is less in the Western Cape. Therefore an ASB prevalence of 14% was expected. In the current study the overall prevalence of ASB was 8.3%, with no statistical difference found between the 9.2% in HIV-positive and 7.9% in HIV-negative patients.

Among female commercial sex workers in Nairobi, bacteriuria was present in 25% (13/52) of HIV-negative women and 21% (37/170) of HIV-positive women.[18] It was concluded in this study that HIV infection was unrelated to significant bacteriuria. However, the women in both groups were highly sexually active and this on its own is known to increase the occurrence of bacteriuria. Immune status did not affect the rate of bacteriuria, which was similar in the three subgroups of patients of CD4+ cell counts below 200/mm^3, between 200 and 499/mm^3 and above 500/mm^3.

A reason for the large difference in the prevalence of ASB in the index study compared to the population in the other South African study mentioned, may be that the patients had much lower CD4+ cell counts overall. Twenty-two percent of their patients had CD4+ counts less than 200/mm^3, compared to 7.2% in the index study.[11] The prevalence of HIV among antenatal patients is lowest in the Western Cape where this study took place, namely 15.7% at the end of 2005. In comparison the highest prevalence is in the province of KwaZulu-Natal where 39.1% of pregnant patients are HIV-positive.

Most patients in our study were referred to the ultrasound unit where they were recruited, shortly after booking. At this stage, results of CD4+ cell counts were not known and it is for this reason that none of the patients were on co-trimoxazole for PCP prophylaxis or HAART at the time of urine collection.

In our study population, mean CD4+ cell counts differed significantly between HIV-positive patients with and without ASB. We tried to determine if there was a certain level of CD4+ cell count at which the prevalence of ASB increased significantly, but did not identify such a level. As is illustrated in Table 4, at a CD4+ cell count level cut-off of <200/mm^3 or ≥200/mm^3 there is no significant difference in prevalence of ASB (p=0.20). In our study population there was therefore no significant relationship between CD4 cell count and prevalence of ASB; however, the numbers are small and a general conclusion cannot be made.

We feel that a likely reason for the lack of difference in ASB prevalence between HIV-positive and HIV-negative pregnant women in our study is associated with the fact that the HIV-positive patients were not immune-compromised to the same degree as patients in the other study mentioned.[11]

The HERS was a multi-centre prospective cohort study conducted in the United States, involving 871 HIV-positive and 439 HIV-negative women, to evaluate the possible effect of HIV on the prevalence and incidence of UTI in women.[10] The study found the risk for UTI not to be associated with HIV infection. As expected, pregnancy increased the risk for UTI (RR 3.79, 95% CI 2.67-5.37). In the HIV-positive patient group, 17.1% of patients had CD4+ cell counts <200/mm^3 and 36.5% of all HIV-positive patients were using antiretrovirals during the study. No association was found between UTI, HIV status or CD4+ cell count. However, an increased risk for UTI was found with increasing viral loads. PCP prophylaxis was used by 52.8% of the HIV-positive patients. PCP prophylaxis may be a confounding factor in studies assessing ASB or UTI in HIV-positive populations.

Preterm labour was not associated with HIV status or presence of ASB in the index study. It is known that untreated ASB increases the risk for preterm labour.[19] Conversely, it has been shown that treatment of ASB can decrease the incidence of preterm labour by 40%.[2] It must be noted that the ASB was treated, and this intervention possibly influenced this decrease in risk.

The finding of significantly increased rates of prelabour rupture of membranes in the pregnant patients with HIV is important. Perinatal transmission of HIV is directly related to duration of

rupture of membranes. A meta-analysis published in 2001 before the advent of HAART found the risk for HIV transmission to double if membranes were ruptured longer than four hours.[20] For every hour of ruptured membranes there is a 2% increase in HIV transmission up to 24 hours. At the time of the studies included in this meta-analysis not many patients were on antenatal HAART therapy. It is expected that the intake of HAART with altered viral loads has affected these findings subsequently. There is some evidence in the setting of preterm prelabour rupture of membranes with expectant management, that the risk of mother-to-child-transmission (MTCT) is not increased. However, the number of patients in the studies is small.[21,22] Notably the patients in the above studies where MTCT occurred were not on HAART antenatally, which is also true for most of our HIV-positive patients with CD4 cell counts ≥200/mm^3. Subclinical chorio-amnionitis is associated with prelabour rupture of membranes and may be increased in patients with HIV, thereby explaining the increased rate of prelabour rupture of membranes in this group of patients.

The prevalence of prelabour rupture of membranes was not found to be increased in the subgroup of HIV-positive patients who had ASB. The numbers of patients is small in this group. There is a known association between subclinical microbial invasion of the placenta and membranes by means of ascending infection and prelabour and premature rupture of membranes.[23,24]

It was shown in our study that a significantly higher number of HIV-positive patients did deliver by Caesarean section ultimately (Table 1). We deduced that this difference is most likely due to a lower threshold to perform Caesarean sections in HIV-positive patients. More patients having Caesarean sections for failed inductions of labour supports this fact. At our institution Caesarean section in HIV-positive patients is performed for obstetric indications only. Routine Caesarean section is not done for HIV. In our study population, post-operative complications were not increased in HIV-positive patients. Other studies have suggested that HIV-positive patients are at increased risk of post-operative complications with level of immune compromise affecting complication rates.[25]

Some of the limitations of the study include the loss of patients to follow-up as well as delay in giving treatment for ASB due to administrative and transport difficulties. We only included patients at less than 24 weeks gestation and thus our findings can apply only to this patient group.

Conclusion

The overall prevalence of ASB in our study population was found to be 8.3%. There was no difference in prevalence of ASB between HIV-positive and HIV-negative patients despite previous reports indicating an increased risk of ASB in HIV.

Preterm labour was not increased in HIV and was not associated with ASB. However, there was the intervention of treatment of ASB in our study group and this may have resulted in an altered outcome. This intervention also decreased the occurrence of pyelonephritis, with only two cases in the study.

Despite treatment of ASB, the rate of prelabour rupture of membranes was significantly increased in HIV-positive patients. This is clinically significant, as the rate of transmission of HIV to the foetus increases with longer duration of rupture of membranes.

Even though the mean CD4+ cell count among the group of HIV-positive patients with ASB was significantly lower, a CD4+ cell count level <200/mm^3 or ≥200/mm^3 did not influence the occurrence of ASB.

The relatively lower prevalence of ASB in our study group compared to the other South African study may be due to the lower percentage of HIV-positive patients with CD4+ cell counts below 200/mm^3 in our group. A factor influencing the prevalence of ASB and its complications may be where in the HIV epidemic a certain population is.

Larger population-based studies are needed to assess medical complications in HIV-positive patients in pregnancy with the focus on UTIs which are the most common infections seen in pregnancy in general.

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