

Urinary tract infection in HIV-positive women

Infecção do trato urinário em mulheres soropositivas para o HIV

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ABSTRACT

Introduction: Urinary tract infections (UTI) are common in women and can cause systemic repercussions. In pregnant women, for example, the occurrence of UTI or asymptomatic bacteriuria (AB) can lead to premature birth and fetal death. The generalized immune depletion caused by HIV is related to the exacerbation of infections, and may be related to UTI. **Objective:** The objective of this review was to evaluate the characteristics of UTI in pregnant and non-pregnant HIV-positive women as well as the factors that interfere in its occurrence. **Methods:** By searching the databases PubMed, Web of Science, Scielo and Lilacs, we selected eleven articles that correlated UTI and HIV infection in women. **Results:** Our analysis showed that HIV-positive pregnant women have a higher predisposition to UTI than HIV-negative ones. The Viral Load (VL) is directly related to UTI and AB in HIV-positive non-pregnant women. TCD4 lymphocyte levels (TCD4) lower than 200 cells/mL and VL over 10,000 copies/mL are correlated with higher UTI and AB rates in HIV-positive pregnant women. There is a tendency for greater variability of pathogens in HIV-positive women and a predisposition to higher rates of antibiotic resistance in HIV-positive pregnant women. **Conclusion:** HIV-positive pregnant women have higher predisposition to urinary tract infection and its incidence is correlated with a high viral load and a low TCD4 count.

Keywords: urinary tract infections; HIV; pregnant women.

RESUMO

Introdução: As infecções do trato urinário (ITU) são comuns em mulheres e podem causar repercussões sistêmicas. Em mulheres grávidas, por exemplo, a ocorrência de ITU ou bacteriúria assintomática (BA) pode levar ao nascimento prematuro e à morte fetal. A depleção imunológica generalizada causada pelo HIV está relacionada à exacerbção de infecções e pode estar relacionada à ITU. **Objetivo:** O objetivo desta revisão foi avaliar as características da ITU em gestantes e não gestantes HIV-positivas, bem como os fatores que interferem na sua ocorrência. **Métodos:** Por meio de busca nas bases de dados PubMed, Web of Science, SciELO e LILACS, foram selecionados 11 artigos que correlacionavam ITU a infecção pelo HIV em mulheres. **Resultados:** Nossa análise mostrou que gestantes soropositivas têm maior predisposição à ITU do que gestantes soronegativas. A carga viral está diretamente relacionada a ITU e BA em mulheres não grávidas HIV-positivas. Os níveis de linfócitos TCD4 (TCD4) abaixo de 200 células/mL e a carga viral acima de 10.000 cópias/mL estão correlacionados a maiores taxas de ITU e BA em mulheres grávidas HIV-positivas. Há uma tendência para maior variabilidade de patógenos em mulheres HIV-positivas e uma predisposição para maiores taxas de resistência a antibióticos em mulheres grávidas HIV-positivas. **Conclusão:** Gestantes HIV-positivas apresentam maior predisposição à infecção do trato urinário e sua incidência está correlacionada com alta carga viral e baixa contagem de TCD4. **Palavras-chave:** infecções urinárias; HIV; gestantes.

INTRODUCTION

Urinary tract infections (UTI) are recurrent in women; estimates state that 60% of them will develop an UTI at least once in their lifetime. UTI is characterized by the presence of infectious agents in the urine in quantities greater than 100,000 colony-forming units per milliliter of urine (CFU/ml). The main symptoms of urinary infection are dysuria, pollakiuria, hematuria, urgency, and suprapubic pain. The condition can also manifest as urethritis, cystitis, or even pyelonephritis⁽¹⁾.

UTI is common during pregnancy, affecting on average 14.6% of pregnant women⁽²⁾. UTI in pregnant women, when untreated, can cause bacteremia, septicemia, septic shock and maternal death, in addition to an increased risk of prematurity, limited intrauterine growth and membrane rupture, which may lead to fetal death^(3,4).

About 6,000 women between the ages of 15 and 24 are infected by HIV every week⁽⁵⁾. The Human Immunodeficiency Virus (HIV) is a retrovirus transmitted by contaminated secretions during unprotected sexual intercourse, breastfeeding, syringe sharing, etc. This virus infects TCD4 lymphocytes, resulting in a generalized immune depletion, which leads to the occurrence of opportunistic infections. In addition, being HIV-positive is an independent risk factor for premature membrane rupture [OR=1.35, 95%CI 1.14–1.60]⁽⁶⁾.

Immunocompromised women, such as those HIV-positive, who simultaneously present UTI, are classified as having a complicated UTI⁽⁷⁾. Nevertheless, the relationship between changes in the immune system resulting from HIV and the pathophysiology of urinary infection in this population is still unknown. Therefore, a better comprehension of the bacteriological profile of this population would be of great value.

OBJECTIVE

In addition to the lack of studies correlating UTI and HIV infection in women, the existing research does not address all of the factors involved, such as epidemiology, causative pathogens, antimicrobial resistance and correlations with viral load (VL) and TCD4. Thus, this review aims to characterize the urinary tract infection in HIV-positive women and particularly in HIV-positive pregnant women.

METHODS

A literature search was conducted in the PubMed, Web of Science, Scielo, and Lilacs databases, using the following keyword combinations: (“Urinary Tract Infections” OR “Infecciones Urinarias” OR “Infecções Urinárias”) AND (HIV OR SIDA OR AIDS OR VIH OR “Acquired Immunodeficiency Syndrome” OR “Síndrome de Inmunodeficiencia Adquirida” OR “Síndrome de Imunodeficiência Adquirida”) AND (women OR woman OR

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mulher* OR mujer*). From the initial search, we retrieved 142 articles published between December 1976 and May 2019. After duplicate articles were removed, we obtained a total of 111 articles. The last search was made on November 10, 2019. The abstracts of the articles were analyzed by two members of the research team separately, and the differences in selection criteria were discussed until a consensus was reached. At this stage, we excluded articles not written in English, Portuguese or Spanish, as well as literature reviews or studies that did not mention comorbidity between UTI and HIV. A total of 94 articles were excluded from the search and 17 remained. One article was excluded because we were unable to obtain access to its full content. The 16 remaining articles were analyzed. After this analysis, five articles were also excluded; three were excluded for not correlating UTI with HIV infection, and the other two for not discriminating between female and male populations. Finally, a total of eleven articles were included in this review, according to the **Figure 1**.

RESULTS

Epidemiology

The incidence of symptomatic UTI in HIV-positive women in a retrospective study, with data from 1988 to 1992, was 18.5/100 patient-year, while the UTI annual incidence in HIV-negative women in the same region and period was estimated at 6.25⁽⁸⁾. A 2002 prospective study of 1,310 women found no statistically significant difference between the incidence of UTI in HIV-positive and HIV-negative women, only a tendency for higher risk of UTI in the HIV-positive group. However, at the time of the survey, the study excluded women with a history of AIDS, which may have interfered with the results. In addition, six of the 14 women who

were infected with HIV during this study developed UTI within the following six months. According to this study, it is unclear whether the UTI is a marker of sexual practices that predispose to HIV infection or if acute infection with the virus is a predisposing factor for UTI in women. The study did not discriminate asymptomatic bacteriuria (AB) from symptomatic infections, which may have influenced the results⁽⁹⁾.

As for pregnant women, a Nigerian study in 2016 showed that both pregnancy and HIV affect the rate of symptomatic UTI in women ($p < 0.05$)⁽¹⁰⁾. Another Nigerian study involving 563 HIV-positive pregnant women showed an 18.1% prevalence of AB, a higher rate than that reported for HIV-negative pregnant women in the same country⁽¹¹⁾. In a retrospective cohort study with US data from 2003 to 2012, HIV-positive pregnant women were three times more likely to develop UTI, regardless of symptoms (OR=3.02; CI95% 2.40–3.81; $p < 0.01$)⁽⁶⁾. A 2003 US study also showed a higher propensity to develop UTI in HIV-positive pregnant women when compared to HIV-negative ones (OR=1.75; CI95% 1.40–2.20)⁽¹²⁾. In addition, a Peruvian analysis of 237 elective cesarean sections in HIV-positive women between 2004 and 2012 showed that symptomatic or asymptomatic UTI was the most common complication in this group of pregnant women when compared to HIV-negative women (OR=4.5; CI95% 1.4–14.5)⁽¹³⁾. Finally, another study, conducted in Nigeria, analyzed co-infection of malaria and HIV in pregnant women, concluding that the population of women infected by these two pathogens presented higher risk for symptomatic and asymptomatic UTI (OR=1.89)⁽¹⁴⁾.

Pathogens

As for the causative agents, a Nigerian UTI survey of asymptomatic women published in 2009 showed distinct pathogen profiles among the three groups analyzed: HIV-negative women, HIV-positive women under Antiretroviral Therapy (ART), and HIV-positive women not under ART. In the first group, the most frequently isolated pathogens were *E. coli* and *S. aureus* (33.33%). In the group of HIV-positive individuals who did not undergo ART, *S. aureus* was the most frequent agent (26.67%). The group of HIV-positive patients under ART also had a higher prevalence of *S. aureus* (22.03%)⁽¹⁵⁾. In another study, *E. coli* was the most frequently isolated pathogen in all groups, and HIV-positive women have shown a tendency to have UTI caused by other pathogens. However, it is relevant to note that this study did not discriminate asymptomatic bacteriuria from those symptomatic, which may have influenced the results⁽⁹⁾.

In HIV-positive pregnant women, the main causative agents of AB were *E. coli* (44.3%), followed by *Proteus mirabilis* (21.6%), *S. aureus* (19.6%), and *K. pneumoniae* (15.5%)⁽¹¹⁾. A study on symptomatic and asymptomatic UTI in HIV-positive pregnant women, conducted in Tanzania in 2016, showed *E. coli* (57.7%) as the most frequently isolated pathogen, with *Klebsiella pneumoniae* as the second (23.1%)⁽¹⁶⁾. A Nigerian survey on co-infection between malaria and HIV showed that the number of organisms isolated in the HIV-positive group was three times that of the control group, and twice that of the malaria-infected group alone. The authors concluded that the co-infection increased the number and diversity of pathogens that cause UTI, regardless of the presence of symptoms⁽¹⁴⁾.

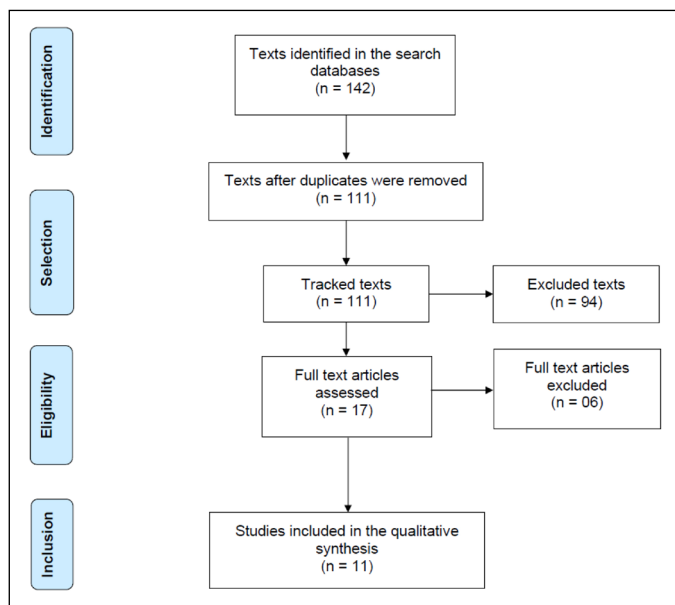


Figure 1 – PRISMA 2009 flowchart showing the inclusion of papers on narrative review about urinary tract infections in pregnant and non-pregnant HIV positive patients.

Antibiogram

In this review, we found no studies that addressed antibiotic resistance in UTI-causing pathogens in non-pregnant HIV-positive women.

An antibiogram of urocultures of pregnant women who were HIV-positive and had either symptomatic or asymptomatic UTI showed that *E. coli* and *K. pneumoniae* were the most prevalent pathogens. For isolated colonies of *E. coli*, 93.3% were resistant to Ampicillin, 90% to Sulfamethoxazole-trimethoprim, 16.7% to Nitrofurantoin, 10% to Gentamicin, 13.3% to Ceftriaxone, and 3.3% to Meropenem. About 8.2% of *E. coli* colonies produced extended-spectrum beta-lactamase. For *K. pneumoniae*, resistance rates were 100% for Ampicillin, 72.7% for Sulfamethoxazole-trimethoprim, 33% for Nitrofurantoin, and 0% for Ceftriaxone and Meropenem. Only two colonies of *S. aureus* were isolated and both were resistant to Penicillin, Sulfamethoxazole-trimethoprim, Tetracycline and Nitrofurantoin, but were sensitive to Erythromycin, Ciprofloxacin, Gentamicin and Vancomycin. The only isolated *Streptococcus agalactiae* colony showed resistance to Ampicillin, Sulfamethoxazole-trimethoprim, Nitrofurantoin and Erythromycin⁽¹⁶⁾. Despite these results, we draw attention to the fact that, regardless of the HIV status, resistance profiles may vary according to the location and health-care center.

When comparing data from previous studies, also conducted in Tanzania with HIV-negative pregnant women, there were higher rates of antibiotic resistance in isolated HIV-positive cultures, with the following rates: Sulfamethoxazole-trimethoprim (64.7 to 90.0%), Nitrofurantoin (5.9 to 16.7%) and Gentamicin (5.9 to 10.0%) in isolated *E. coli* colonies. One study points out that 17.9% of pregnant women were symptomatic and 13% were asymptomatic, but does not separate the results of the antibiogram according to the symptomatology⁽²⁾.

The empirical treatment for UTI, when it comes to *E. coli*, must be based on the local resistance rate. The use of Sulfamethoxazole-trimethoprim is indicated if local resistance rate is less than 20%, and the use of fluoroquinolones if the resistance rate is less than 10%. In addition, Phosphomycin and Nitrofurantoin are the first line of antibiotics for the treatment of uncomplicated UTI⁽¹⁷⁾.

Viral load and TCD4 levels

In a study with 1,310 US women, 871 of which were HIV-positive, there is evidence that the incidence of UTI, regardless of symptoms, is not related to low TCD4 lymphocyte rates. A hypothesis for the lack of a correlation between TCD4 and UTI levels would be the small amount of T lymphocytes in the urinary mucosa; thus, the systemic decrease of TCD4 lymphocytes caused by HIV infection would not significantly affect local immunity. However, a high value of viral load has shown correlation with an increased risk of UTI, symptomatic and asymptomatic, where there is a 30% increase in risk of urinary infection for each tenfold increase in the value of viral load (OR=1.31; 95%CI 1.03–1.63; p=0.01)⁽⁹⁾. This correlation may be associated with increased viral replication in the presence of bacterial infections.

A study conducted in Nigeria showed that TCD4 values lower than 200 cells/mL (OR=1.4; 95%CI 1.1–3.3; p=0.03) and VL above 10,000 copies/mL (OR=3.9; 95%CI 2.7–9.1; p<0.0001) increase

the incidence of AB in pregnant women⁽¹¹⁾. Research carried out in Tanzania corroborate with these results, demonstrating that low TCD4 values (<200 cells/mL) (OR=2.9; 95%CI 1.1–7.7; p=0.031) are an independent and predictive factor of UTI, regardless of symptoms, in HIV-positive pregnant women⁽¹⁶⁾.

DISCUSSION

The main results of this review are shown at **Table 1**.

The studies analyzed were controversial regarding the epidemiology of UTI and AB in HIV-positive non-pregnant women. While a 1995 study pointed to a higher incidence of symptomatic UTI in HIV-positive women⁽⁸⁾, another 2002 study found no statistically significant difference in the incidence of urinary bacteriuria between HIV-positive and HIV-negative women⁽⁹⁾. However, the second study excluded women with a history of AIDS and made no distinction between symptomatic infection and AB, which may have influenced the results. Among the causing bacteria, *E. coli*⁽⁹⁾ and *S. aureus*⁽¹⁵⁾ were identified as the most frequent. In addition, HIV-positive women have the propensity to present a broader spectrum of bacteria involved in these infections⁽⁹⁾.

The correlation between TCD4 and urinary bacteriuria is still controversial, and a 2002 study indicates that there is no correlation between the incidence of urinary bacteriuria and a low TCD4 count. However, it evidences a higher risk of urinary bacteriuria due to the increase in the VL value in HIV-positive women⁽⁹⁾. This increased prevalence of UTI in HIV-positive women is believed to be due to a generalized depletion of the immune system and a decrease in cytokine secretion⁽¹⁸⁾. The study that did not find this correlation justifies its results by the small amount of TCD4 lymphocytes in the urinary tract mucosa⁽⁹⁾.

In older studies, mainly conducted in the United States, researchers obtained different conclusions from those of more recent studies, which are mainly carried out in African countries, where HIV prevalence reaches high rates. This difference may also be related to low rates of ART use in African countries when compared to those of developed countries.

The studies analyzed showed a higher prevalence of AB and UTI in HIV-positive pregnant women^(6,11,12). These studies have shown that there is a tendency for this population to present a broader spectrum of causative bacteria⁽¹⁴⁾, with *E. coli* being the most prevalent^(11,16). Antibiotic resistance rates seem to be higher when compared to those of the population of pregnant women who do not carry the virus.

As for the prevalence of UTI and TCD4 lymphocyte count, there is a correlation between the decrease in TCD4 and the increase in

Table 1 – Main results.

HIV-positive women:
Tendency for higher risk of UTI
High values of VL are correlated with an increased risk of UTI
HIV-positive pregnant women:
Higher predisposition to UTI
TCD4 lower than 200 cells/ml and VL above 10,000 copies/ml are correlated with higher UTI and AB rates

UTI incidence in HIV-positive pregnant women^(11,16). A high level of VL is another factor related to higher UTI and AB rates in HIV-positive pregnant and non-pregnant women^(9,11).

Strengths

This article presents a comprehensive review of the correlation between urinary tract infection and HIV in female populations, a topic rarely addressed in the scientific literature. Thus, enabling a better understanding of how urinary tract infections affect the growing HIV-positive female population and helping to guide future treatments and research on this topic.

Limitation

This review presents limitations due to the diversity of methodologies applied in the selected studies, both for the pregnant and non-pregnant women. Moreover, the fact that these studies were conducted in different places with distinct prevalence rates of HIV infection may have biased the conclusions. Some studies^(6,9,12-14,16) do not separate their results according to the symptomatology of the patients. Another limiting factor is that in the literature used, it is unclear whether the AB evolved into a UTI or resulted in other complications in pregnant and non-pregnant HIV-positive women differently from HIV-negative women.

Therefore, more studies with pregnant and non-pregnant HIV-positive women with UTI should be conducted in order to clarify issues such as pathophysiology, incidence rates and possible correlation between UTI and AB with the use of ART. Due to higher antibiotic resistance rates in HIV-positive women, empirical antibiotic therapy should be investigated further.

CONCLUSION

There seems to be a tendency for higher risk of UTI in HIV-positive non-pregnant women. *S. aureus* and *E. coli* were the most prevalent pathogens in this population, whether under ART or not. Higher VL values are directly related to higher UTI and AB rates in HIV-positive non-pregnant women so far.

In the case of HIV-positive pregnant women, the studies have shown a higher predisposition to UTI than HIV-negative pregnant women. *E. coli* was more prevalent in this group. TCD4 lower than 200 cells/ml and VL above 10,000 copies/ml are correlated with higher UTI and AB rates in HIV-positive pregnant women.

Participation of each author

Newton Sérgio de Carvalho: conceived and designed the study, analyzed the selected research papers, wrote this review and approved the final version of this manuscript.

Beatriz Zaia Bertoldi: partook in the literature search and the selection of research papers, analyzed the selected research papers, wrote this review, and approved the final version of this manuscript.

Patricia da Cruz Russo: partook in the literature search and the selection of research papers, analyzed the selected research papers, wrote this review, and approved the final version of this manuscript.

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Conflict of interests

The authors declare no conflicts of interest.

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