Lower Urinary Tract Symptoms in Men Living with Human Immunodeficiency Virus: A Case-control Study

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What's known on the subject? and What does the study add?

Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) remains a global public health challenge, affecting populations worldwide. By the end of 2022, an estimated 39.0 million individuals were living with HIV, with approximately 1.3 million new infections reported that year. The widespread availability of contemporary antiretroviral therapy (ART) has significantly improved life expectancy among people living with HIV, leading to an increased prevalence of age-related comorbidities. Existing literature indicates that HIV-negative individuals have a lower risk of developing non-AIDS-related complications, including bone, cardiovascular, and renal diseases, compared to those living with HIV. While LUTS are prevalent in the general aging male population, research specifically examining their occurrence among males living with HIV (MLWH) is scarce. Addressing this gap is particularly important, as MLWH may be exposed to unique risk factors, such as chronic immune activation, systemic inflammation, and potential adverse effects of long-term ART, which could influence the development and progression of LUTS compared to HIV-negative individuals. The prevalence of all types of LUTS was higher among MLWH compared to HIV-negative controls. Statistically significant differences were noted for hesitancy, intermittency, reduced urinary flow rate, and sensation of post-void residual urine. The sensation of post-void residual urine was the most frequently reported LUTS among MLWH. The prevalence of moderate to severe LUTS was significantly higher in MLWH compared to HIV-negative controls. A significantly higher proportion of MLWH had OAB V8 scores of ≥11 compared to HIV-negative controls, indicating an increased likelihood of OAB in MLWH. All MLWH in our study were receiving ART, providing contemporary insights into the relationship between HIV and LUTS in the modern treatment era. Bictegravir-based ART was the most commonly used regimen among MLWH. No statistically significant differences were observed in LUTS prevalence across ART regimen subgroups.

Abstract

Objective: Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome constitutes a global pandemic affecting populations worldwide. There's a gap in data regarding lower urinary tract symptoms (LUTS) among men living with HIV (MLWH) during the antiretroviral therapy era. The aim of this study is to evaluate the potential influence of HIV status on the presence of LUTS.

Materials and Methods: Infectious Diseases and Clinical Microbiology Clinic, referred MLWH and HIV-negative men (control group) to Urology Clinic after their initial assessment. In both groups, International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms (ICIQ-MLUTS), International Prostate Symptom Score (IPSS), King's Healthcare Questionnaire, 8-item Overactive Bladder Questionnaire (OAB-V8), ICIQ-Short Form, Urogenital Distress Inventory 6 and 7 were used. The presence or absence of each LUTS was individually assessed.

Results: A total of 95 males (51 MLWH and 44 HIV-negative controls) were included. Both groups exhibited similar perceptions of general health. Scores of ICIQ-MLUTS, (for both voiding and incontinence scores), IPSS, and OAB-V8 were higher in the MLWH group. There were statistically significant differences between ICIQ-MLUTS and IPSS scores. The MLWH group exhibited a higher frequency of all types of LUTS. Statistical significance was observed in hesitancy, intermittency, decrease in urine flow rate, and sensation of incomplete bladder emptying between the MLWH group and the control group.

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Conclusion: LUTS were more commonly observed among MLWH compared to HIV-negative individuals. MLWH had more symptoms related to the emptying phase, as evidenced by higher scores on the IPSS and ICIQ-LUTS. While the results did not achieve statistical significance, there was a trend indicating a higher likelihood of OAB among MLWH. Continuing to explore this correlation within larger prospective cohorts, including comprehensive information on sexual behaviors, sexually transmitted diseases, and urodynamic data, might offer insights into the pathophysiological basis of this correlation.

Keywords: Functional urology, general urology, pathology, radiology, reconstructive urology

Introduction

Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) constitutes a global pandemic affecting populations worldwide. By the conclusion of 2022, there were an estimated 39.0 million individuals living with HIV, with approximately 1.3 million new HIV infections occurring worldwide during that year (1). As contemporary antiretroviral treatment (ART) options gained wide availability, people living with HIV started to live longer and confront age-associated illnesses (2). Data in the literature have already shown that HIV-negative controls were at lower risk for non-AIDS-related complications such as bone, heart, and renal diseases than patients living with HIV (3-6). There's insufficient data on lower urinary tract symptoms (LUTS) among men living with HIV (MLWH) during the ART era. Although LUTS are commonly observed in the general aging male population, there is a scarcity of studies specifically focusing on the prevalence of these symptoms among MLWH. This research gap is particularly important, as MLWH may face unique risk factors such as chronic immune activation, inflammation, and potential side effects of prolonged ART, all of which could exacerbate or modify the presentation of LUTS in comparison to HIVnegative men. The mechanisms by which HIV infection and ART influence the development and progression of LUTS remain largely unexplored. While ART is essential for extending life expectancy, it may carry side effects or long-term consequences for urinary health. Furthermore, limited research has examined the relationship between HIV-specific clinical markers such as CD4 count, viral load, and history of opportunistic infections and LUTS. Despite a general recognition that MLWH may have distinct healthcare needs, few studies have directly compared the prevalence, severity, and risk factors of LUTS between MLWH and matched HIV-negative controls. The aim of this study is to evaluate the potential influence of HIV status on the presence of LUTS.

Materials and Methods

The case-control study protocol was approved by the Institutional Review Board. Infectious Diseases and Clinical Microbiology Clinic (IDCMC) referred MLWH and HIV-negative men (control group) to Urology between August 2022 and June 2023. MLWH were under routine follow-up for HIV whereas the control group was composed of patients who presented to the IDCMC for long-term follow-up after completely recovering from non-genitourinary conditions such as upper respiratory tract infections or gastroenteritis, with no acute infectious symptoms.

Ages, laboratory test results (levels of CD4 T-lymphocytes and HIV RNA), types of ART and syphilis serology results (for MLWH group) were recorded. MLWH who defined themselves as "men who have sex with men (MSM)" were categorized and analyzed separately.

Exclusion criteria included non-native speakers, men receiving treatment and/or who underwent urological surgery due to LUTS, individuals with clinical or laboratory findings suggestive of urinary tract infection, those with uncontrolled diabetes mellitus, and those with a history of neurological disorder. Urinalysis and fasting serum glucose level measurements were conducted in the IDCMC for all patients. Patients with abnormal urinalysis findings (such as hematuria, pyuria, leukocyte esterase positivity, nitrite positivity) or abnormal fasting serum glucose levels were also excluded. Neurological disorders were screened during history taking or through measurable deficits, as outlined in International Continence Society (ICS) documents (7).

Table 1 was created based on the answers provided by the patients, regarding the presence or absence of a particular LUTS as defined by the Glossary of the ICS. These symptoms include hesitancy, intermittency, decrease in urine flow rate, sensation of post-void residual urine, urgency, urgency urinary incontinence, stress urinary incontinence, terminal dribbling, increased daytime urinary frequency, and nocturia.

MLWH and control groups were asked to complete the following native language-validated questionnaires: International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms (ICIQ-MLUTS), International Prostate Symptom Score (IPSS), King's Healthcare Questionnaire (KHQ), 8-item Overactive Bladder Questionnaire (OAB-V8), ICIQ-Short Form (ICIQ-SF), Urogenital Distress Inventory 6 and 7 (UDI 6 and UDI 7).

The ICIQ-SF score ranges indicating the severity of OAB were as follows: 1-5 (mild), 6-12 (moderate), and 13-21 (severe and very severe) (8). Responses to the initial item of the KHQ

were categorized into two groups for analysis: "very good" and "good" versus "fair", "poor", and "very poor". The threshold value denoting a high likelihood of OAB was set at 11 in the OAB V8 questionnaire (9). IPSS symptom severity was classified into three levels: mild (0-7), moderate (8-19), and severe (20-35) (10). Elevated scores on UDI 6 and UDI 7 indicated a higher level of disability associated with LUTS (11).

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Koç University Ethics Committee (approval number: 2023 127.IRB1.039, date: 03.04.2023). Written informed consent was obtained from all patients. Clinical Trial Registration ID NCT05964803.

Statistical Analysis

The sample size for each group has been calculated as 39 patients, with an approximate standard deviation of 3 units, a Type I error rate of α =0.05, and a study power of 1- β =0.80. Taking the dropout rate into consideration, 41 was the minimum number of patients to be included in each group (12). Sample size calculation was conducted using MedCalc Statistical Software version 19.1 (MedCalc Software bv, Ostend, Belgium; https:// www.medcalc.org; 2019). Statistical analyses were conducted using either Student's t-test or the Mann-Whitney U test for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables.

LUTS	MLWH group n=51 (%)	Control group n=44 (%)	р
Hesitancy	29/51 (56.8)	15 (34)	0.02*
ART including Bictegravir	21/29		
Other ART regimens	8/29		
Intermittency	32/51 (62.7)	18 (41)	0.03*
ART including Bictegravir	23/32		
Other ART regimens	9/32		
Decrease in urine flow rate	24/51 (47)	12 (27)	0.04*
ART including Bictegravir	17/24		
Other ART regimens	7/24		
Sensation of post-void residual urine	37/51 (72.5)	21 (47.7)	0.01*
ART including Bictegravir	27/37		
Other ART regimens	10/37		
Urgency	39/51 (76)	26 (59)	0.06
ART including Bictegravir	28/39		
Other ART regimens	11/39		
Urgency urinary incontinence	11/51 (21.5)	5 (11.3)	0.1
ART including Bictegravir	9/11		
Other ART regimens	2/11		
Stress urinary incontinence	5/51 (9.8)	2 (4.5)	0.3
ART including Bictegravir	4/5		
Other ART regimens	1/5		
Terminal dribbling	33/51 (64.7)	22 (50)	0.1
ART including Bictegravir	25/33	_	
Other ART regimens	8/33		
Increased daytime urinary frequency	28/51 (55)	17 (39)	0.1
ART including Bictegravir	22/28		
Other ART regimens	6/28		
Nocturia	25/51 (49)	13 (29.5)	0.06
ART including Bictegravir	19/25		

Results

A total of 95 males (51 MLWH and 44 HIV-negative controls) were included. A total of 40 patients were excluded based on exclusion criteria during the study period.

The median patient age in MLWH and HIV-negative groups was 40 (22-62) and 39 (24-67) years, respectively (p>0.05). The median CD4 T lymphocyte count of MLWH was 665 cells/ mm³ [interquartile range (IQR) 404.5], and all MLWH had non-detectable HIV RNA levels. The number of MLWH receiving tenofovir alafenamide fumarate + emtricitabine + bictegravir, emtricitabine + tenofovir alafenamide elvitegravir + cobicistat, and medications including dolutegravir was 38, 7, and 6, respectively.

Table 1 presents the comparative prevalence of LUTS in both the MLWH and control groups. The MLWH group exhibited a

higher frequency of all types of LUTS. Statistical significance was observed in hesitancy, intermittency, decrease in urine flow rate, and sensation of incomplete bladder emptying between the MLWH group and the control group (p<0.05). An additional subgroup analysis was performed regarding the effects of different ART regimens on LUTS within the MLWH group (Table 1). There were statistical differences between bictegravir-based ART and other regimens.

The comparison of questionnaire scores is outlined in Table 2. Both groups exhibited similar perceptions of general health, while scores of ICIQ-MLUTS (for both voiding and incontinence scores), IPSS, and OAB-V8 were higher in the MLWH group. Additionally, there were statistically significant differences between ICIQ-MLUTS and IPSS scores. Questionnaire scores recorded in the MSM group were analyzed separately and the results are presented in Table 2.

Table 2. Mean questionnaire scores recorded in MLWH and control groups						
Questionnaire & score	MLWH group (n=51)	MSM subgroup (n=24)	Control group (n=44)	р		
ICIQ-MLUTS (IQR; range)			I			
Voiding score	4.2 (4, 0-12)	3.9 (3; 0-11)	2.8 (4; 0-14)	0.01*		
Incontinence score	3 (3; 0-8)	3.5 (3.2; 0-8)	1.7 (1; 0-6)	0.002*		
ICIQ-SF						
Mean (IQR; range)	0.62 (0; 0-11)	0.7 (0; 0-11)	0.1 (0; 0-3)			
None	46	21	41			
Slight (1-5), n	3	2	3	0.3		
Moderate (6-12), n	2	1	-			
Severe-very severe (13-21), n	-	-	-			
IPSS			·			
Mean (IQR; range)	7.9 (5.5; 0-26)	7.2 (5.2; 0-18)	4.1 (5; 0-19)			
Mild (0-7), n	30	13	38	0.01*		
Moderate (8-19), n	19	11	6			
Severe (20-35), n	2	-	-			
КНО			·	·		
General health perception						
Mean total score %, (IQR; range)	23.5 (0; 0-50)	25 (0; 0-50)	16.1 (25; 0-50)	0.3		
Very good & good, n (%)	43 (84.3)	19 (79.1)	38 (86.3)			
Fair, poor and very poor, n (%)	8 (15.7)	5 (20.9)	6 (13.7)			
OAB V8			·	·		
Mean total score (IQR, range)	10 (6; 3-32)	9.4 (6; 3-24)	5.8 (3; 2-15)	0.05		
Scores ≥11, n (%)	14 (27.4)	7 (29.1)	5 (12.1)	0.05		
UDI-6 (IQR; range)	2.5 (4; 0-8)	2.8 (3.5; 0-8)	1.1 (2; 0-8)	NA**		
UDI-7 (IQR; range)	0.8 (0; 0-9)	0.7 (0; 0-9)	0.1 (0; 0-4)	NA**		

The scores recorded in the MSM subgroup of MLWH are shown as a separate column. P-value was calculated for the difference between MLWH and control groups. Mean scores were given on the table for each questionnaire scores, MLWH: Males living with HIV, MSM: Men having sex with men, ICIQ-MLUTS: International Consensus on Incontinence Male Lower Urinary Tract Symptoms, ICIQ-SF: International Consensus on Incontinence Short Form, IPSS: International Prostate Symptom Scale, KHQ: King's Healthcare Questionnaire, OAB V8: Overactive Bladder Version 8, UDI: Urogenital distress inventory, IQR: Interquartile range *: Statistically significant value

**: Not calculated

Out of 51 MLWH, 20 individuals (39.2%) tested positive for treponemal chemiluminescent microparticle immunoassay (CMIA). The median age for MLWH with positive and negative CMIA results was 39 (28-62) and 40 (22-55) years, respectively (p>0.05). There were no statistically significant differences in the presence of any type of LUTS between the MLWH and CMIA results.

Twenty-four of 51 MLWH (47%) defined themselves as MSM; 2 patients identified as heterosexual. The remaining 49.1% preferred not to answer the question related to sexual orientation. The median age of MSM was 38 (IQR 35.5-49.5) years. The mean age of the MSM subgroup did not significantly differ from that of other MLWH subgroups or the control group. Seven (29.1%) MSM had positive treponemal CMIA results. Eighty percent of MSM were under bictegravir treatment. The median ICIQ-MLUTS (Voiding), ICIQ-MLUTS (Incontinence), and IPSS scores were 3.5 (IQR 2-5), 3 (IQR 2-5.5), and 6 (IQR 3.5-9), respectively. Ten (41.6%) had IPSS scores over 7. Seven (29.1%) had OAB-V8 scores above 10. One had ICIQ-SF score above 5. The distribution of LUTS in the MSM subgroup and its comparison with the larger group of MLWH and HIV-negative controls is provided in Figure 1.

Discussion

The role of HIV status as an independent risk factor related to the presence or severity of LUTS in men receiving ART remains uncertain. Life expectancy and quality of life for MLWH have improved with modern ART options. Concurrently, there is an increasing focus on studying the health outcomes of the aging population affected by HIV (13,14). The relationship between HIV infection and LUTS was first assessed in a retrospective case series. In 1996, Kane et al. (15) documented that among 18 HIV-positive males with voiding dysfunction, the most prevalent urodynamic diagnoses were detrusor hyperreflexia (27.7%), detrusor-sphincter dyssynergia (27.7%), and detrusor areflexia (5.5%). Hermieu et al. (12) evaluated 39 HIV-positive patients (35 males, 4 females) with voiding symptoms. Only 5 (12.8%) of the patients had a normal urodynamic evaluation. The predominant urodynamic finding was the presence of uninhibited detrusor contractions (69.2%). Notably, among these patients, over 60% presented with coexistent neurological disorders (cerebral toxoplasmosis, HIV encephalitis, etc.) (12). The frequency of neurological disorders in these studies might have influenced urodynamic results. In our study, we excluded all males with neurological disorders to minimize confounding factors. We found a higher percentage of patients in the MLWH group scoring \geq 11 on the OAB V8 (27.4%) vs. 12.1%, p=0.05), which indicates a high likelihood of OAB. Moreover, to our knowledge, our study is the first to compare OAB symptoms between MLWH and an HIV-negative control group. Furthermore, we observed marginally elevated ICIQ-SF, UDI 6, and UDI 7 scores in MLWH. Total scores obtained from these questionnaires were quite low in both cohorts, suggesting that the differences remained minimal and possibly subclinical.

Our results revealed a higher prevalence of all types of LUTS in MLWH compared to the HIV-negative controls. The differences were statistically significant for hesitancy, intermittency, decrease in urine flow rate, and sensation of post-void residual urine. Sensation of post-void residual urine were the most common (72.5%) LUTS among MLWH in our study. Breyer et al. (3) surveyed 1507 HIV-negative and 323 HIV-positive



Distribution of LUTS

Figure 1. Distribution of LUTS among the MSM subgroup of MLWH, MLWH group in total, and HIV-negative controls. Percentages per symptom were given for all groups

LUTS: Lower urinary tract symptoms, PVR: Post-void residual urine, UI: Urinary incontinence, MSM: Men having sex with men, MLWH: Males living with HIV

MSM online using the IPSS in 2011. HIV status surfaced as an independent factor associated with the reporting of LUTS. In their study, HIV-positive males exhibited a higher prevalence of severe (11.4% vs. 4.2%) and moderate LUTS (33.2% vs. 29.2%) when compared to their HIV-negative counterparts (3). Similarly, our data showed the prevalence of moderate to severe LUTS was significantly more prevalent in MLWH (41.1% vs. 13.6%). Moreover, the ICIQ-MLUTS-Voiding scores corroborated the IPSS scores, revealing significantly higher prevalence of emptying phase-related symptoms among MLWH compared to the control group.

In our study, a relatively lower percentage of MLWH (47%, 24 out of 51 individuals) self-identified as MSM, while a smaller proportion (3.9%, 2 out of 51 individuals) self-identified as heterosexual. The sexual orientations of the remaining MLWH (25 out of 51 individuals) were unknown. Additionally, the individuals in the control group were not queried regarding their sexual behaviors or orientations. The predominant symptoms observed in our MSM subgroup were urgency (83.3%) and the sensation of post-void residual urine (70%). The questionnaire responses recorded in the MSM subgroup resembled those of MLWH. The small number of patients within the MSM subgroup might have hindered the interpretation of these results.

In the study conducted by Breyer et al. (3), the information regarding ART usage was absent. On the contrary, in our study all MLWH were receiving ART, which provides contemporary insights into the relationship between MLWH and LUTS in the modern era. Bictegravir-based ART was the most common (74.5%) modality among MLWH in our cohort. We observed no statistically significant differences among subgroups based on ART types regarding the presence of LUTS.

Larouche et al. (16) assessed 177 women living with HIV (WLWH) using the UDI-6. They found that stress urinary incontinence (UI) was the most prevalent urinary symptom, observed in 36.7% of the participants. Another study by Greene et al. (14), including 145 MLWH and 10 WLWH, reported a 25% prevalence of unspecified UI. This finding was associated with the relatively higher median age of patients (57 years). Similarly, in our study, with a median patient age of 40 years, 13 MLWH (25.4%) reported experiencing urinary incontinence, a rate that was higher than in the control group, but the difference remained statistically insignificant.

Potential risk factors for LUTS in HIV-positive individuals could encompass chronic urinary tract inflammation, a background of opportunistic infections, and other sexually transmitted infections, the direct impact of the virus on both the central and peripheral nervous systems, and potential toxicity associated with ART (3,16). In our study, we observed no statistically significant differences between CMIA positive, and negative MLWH, in terms of the presence and severity of LUTS. In another study, urinary tract infections, prostatitis, and gonorrhea were found to be an unlikely underlying cause of bothersome LUTS in HIV-positive individuals (3). Furthermore, the type of ART exhibited no discernible impact on the presence of LUTS or the scores recorded on questionnaires in our study. We speculate the likelihood of the virus and/or the ART, impacting the nervous system and contributing to the increased occurrence of LUTS in MLWH.

Study Limitations

The primary strength of our study was the utilization of multiple validated questionnaires to assess the existence and severity of LUTS among MLWH. Moreover, we compared these results with an HIV-negative control group. However, we omitted the analysis of factors such as sexual orientation/ behavior, clinical information, and serological titers related to sexually transmitted diseases in certain individuals with MLWH, but not in the control group. Furthermore, syphilis was solely assessed through CMIA sero-positivity, without conducting any further confirmatory tests in MLWH. Moreover, given its observational nature, our study lacked robust hypotheses that could substantiate our findings from pathophysiological and urodynamic perspectives. Unfortunately, we do not have additional information about comorbidities beyond those specified in the methodology section. This represents another important drawback of our study.

Conclusion

LUTS are more frequently observed in MLWH than in HIVnegative controls. A significantly higher number of MLWH reported symptoms related to the emptying phase as reflected by higher IPSS and MCIQ-LUTS scores. Although not reaching statistical significance, there was a greater tendency for OAB, in MLWH. Continuing to explore this correlation within larger prospective cohorts, including comprehensive information on sexual behaviors, sexually transmitted infections, and urodynamic data, might offer insights into the pathophysiological basis. This will enhance patient counseling, and management strategies for understanding and addressing of LUTS in MLWH.

Ethics

Ethics Committee Approval: This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Koç University Ethics Committee (approval number: 2023. 127.IRB1.039).

Informed Consent: Written informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Concept: E.K., Ö.A., S.T., Design: E.K., Ö.A., S.T., T.T., Data Collection or Processing: E.K., U.C.K., İ.C.A., S.T., Analysis or Interpretation: Ö.A., İ.C.A., T.T., Literature Search: E.K., U.C.K., Writing: E.K., T.T.

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