Chapter

Urinary Tract Infection in HIV/AIDS Patients

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Abstract

Urinary tract infection (UTI) is a common condition around the world, even affecting immunocompromised hosts such as people with human immunodeficiency virus (HIV) infection or acquired immuodeficiency syndrome (AIDS). Due to the anatomical conditions of the urogenital tract, women are more susceptible to UTI. Risk factors throughout life are determinants in the appearance of UTI. The frequency increases especially in women and is associated with sexual activity and pregnancy. In older adults and the elderly, again the frequency of UTI in both genders increases. In women, it is usually related at anatomical and functional sequelae due to parity and gyneco-obstetric surgeries. In old men, prostatic enlargement is an important concern. Chronic degenerative diseases such as diabetes mellitus with complications explain the high frequency of UTI in this population. Currently, the increase in violence and accidents are the leading cause of traumatic injuries with neurological damage, which leads the use of permanent urinary catheter. In patients infected with HIV/AIDS, the disease can be severe and is associated with more complications. The etiology in this population can be diverse, including fungi, parasites, and virus; antimicrobial resistance is a therapeutic challenge. This chapter is a comprehensive review of the epidemiology, pathophysiology, clinical presentation, diagnosis approach, and current treatment of UTIs in HIV/AIDS patients.

Keywords: urinary tract infection, UTIs, HIV, AIDS, HIV/AIDS

1. Introduction

UTI is defined as the presence of some pathogenic microorganism that induces a local or systemic inflammatory response. The infection can affect any structure of the urinary tract including the renal parenchyma, pelvic, ureters, bladder, and urethra. In general, infections located above the ureterovesical junction are considered as high infections and below this junction are considered as low. High-location UTIs are considered more severe but less frequent, and their exact location is often difficult to determine. UTI is considered the most common bacterial infection, estimated to affect more than 150 million people annually [1]. From 15 to 50 years of age, UTI is practically nonexistent in men, while in women, it has a prevalence that can reach up to 3% of the population [2]. Approximately, one in three women suffers an uncomplicated UTI before the age of 24 years old, and 30–44% develop a recurrent disease [3].

People living with HIV are more likely to develop UTIs due to the suppression of their immunity. AIDS is considered the late stage of HIV infection, when the number of the CD4 cells falls below 200 cells/mm^3 or when patients develop one or more opportunistic infections regardless of their low CD4 count. The incidence of UTI is increased in HIV patients, but there is a significant variance in the reported prevalence. Evidence suggests that HIV infection is associated with UTIs and abnormalities of bladder function, which is demonstrated by urodynamic studies [4, 5]. However, it is unclear whether HIV/AIDS imposes an additional risk of urinary conditions beyond the normal risk associated with age or other risk factors.

The urinary tract may be susceptible to complications of HIV infection [6], with *Escherichia coli* and *Enterobacter* spp. being found to be the dominant pathogens associated with UTIs [7]. Unusual germs such as *Salmonella* and *Acinetobacter* have also been reported. Other atypical pathogens such as fungi, *Toxoplasma gondii*, mycobacteria, cytomegalovirus (CMV), and adenovirus are often disseminated at the time of urinary tract infection, usually when CD4 counts are <100/mm^3 [8–10].

Opportunistic infections are well described in patients with HIV infection, but infections that do not define AIDS are relatively understudied. The diversity of microorganisms that can cause UTIs and the magnitude of drug resistance may cause treatment choices to be significantly limited. Improving knowledge on the prevalence, uropathogen spectrum, and associated factors of UTIs could substantially improve the current diagnostic and treatment guidelines for better prognosis of people living with HIV/AIDS.

2. Epidemiology

UTI is a disease of high prevalence worldwide, accounting for 150 million infections per year [11], and UTI hospital-acquired infections account for 40% of all hospital infections worldwide [12]. Indwelling urinary catheterization is the most common risk factor for hospital-complicated UTI [13].

Age and gender are conditions that impact the frequency of UTIs prominently. Risk factors are variable at certain stages of life; women suffer from UTIs more often than men, with nearly half of women developing UTIs throughout their lives [14]. Anatomical and physiological differences, such as a shorter urethra and hormone fluctuations, explain the high frequency of UTIs in women [15]. This pronounced increase in susceptibility in women is more remarkable in adolescents, pregnant women, and adults under 50 years of age. In populations older than 65 years, the prevalence of bacteriuria and UTI increases substantially in men to almost equal that of elderly women [16, 17].

HIV/AIDS continues to be a major problem throughout the world. New infections continue to occur in a significant way in conjunction with other sexually transmitted diseases (STIs) such as syphilis, papillomavirus, viral hepatitis, and many others. The ignored pandemic, alcoholism, drug addiction, sexual promiscuity, and violence has caused the increase and appearance of many diseases, including the emerging monkeypox infection and other diseases previously mentioned. This scenario has brought fatal consequences on the health and economy of many countries. Poverty and mental health issues (depression) are an important part of this vicious circle.

According to World Health Organization (WHO) data, there were an estimated 38.4 million (33.9–43.8 million) people living with HIV at the end 2021, two-thirds of whom were in the African region. In 2021, 650,000 people died of HIV-related causes,

and 1.5 million (1.1–2.0 million) people acquired HIV. In our current time frame, it is estimated that 40.1 million people have died from HIV-related causes [18]. There are many reports on the prevalence of UTI in HIV/AIDS-infected patients, some with a small number of patients and with limitations in the design of their studies. Most of the information comes from observational studies conducted over some period or cross-sectionally. As patients' ages are diverse, it is difficult to separate the inherent risk associated with their age and gender. Most studies do not include a control group (people who do not have HIV infection) to determine the risk.

The most cited research is the article published by Miles and associates [19], where they refer to an incidence of 17% of UTIs; however, the article was published in 1989. Due to the little information and the absence of well-designed studies to establish this knowledge, Miles' article is still taken as the main reference. The article was done retrospectively in a hospital in Detroit, Michigan, USA, with 120 patients seen from 1984 to 1987, practically at the beginning of the HIV pandemic. Only 16% of the patients had some urinary symptom, and at least one urine culture was performed in 56 of 120 patients, in which 17 (14%) were positive.

There is a consensus that people with lower CD4 have a high risk of developing UTIs as well as other opportunistic infections. The female sex constitutes an additional risk to the immunological state. The number of partners and sexual orientation are surely additional factors of risk of UTIs; however, there are no publications that provide sufficient clarity in this regard.

In patients with HIV who are hospitalized for any cause, the prevalence of hospital-acquired UTI increases significantly. In a study with 96 patients, of which 78 (81%) were men who were divided by the diagnosis of AIDS or HIV infection, the prevalence in patients with AIDS was 50% and in patients with HIV infection was 13.6%. From 18 women, 67% suffered from UTIs versus 35% of men ($p = 0.03$). The study included a control group without HIV in which the prevalence of UTI was 11.7% [7]. Studies on UTI prevalence in HIV/AIDS patients are shown in **Table 1**.

Author (year)	Ref	Patient number	Age range (y)	CD4 < 200 (%)	CV $<10^5$ log (%)	UTI number (%)
Miles (1989)	[19]	120	N.A.	N.A.	N.A.	17 (14)
Schönwald S. (1999)	[7]	96 (74 AIDS, 22 HIV)	16–68 (100%)	N.A.	N.A	(50) AIDS (13.6) HIV
Omoregie R. (2009)	[20]	421 (317 HIV vs. 104 non HIV)	N.A.	30	N.A.	(27) HIV (13) non HIV
De Pinho A. (1994)	[21]	415 (151 AIDS, 94 HIV, 170 non HIV)	18–50 (100%)	N.A,	N.A.	10 (6.6) in AIDS, none in both HIV and non HIV
Yepes A. (2010)	[22]	237	20–50 (70%)	61.5	76.9	13 (5.4)
Boaitey Y. (2012)	[23]	800 (500 HIV vs. 300 non HIV)	20–50 (61%)	N.A.	N.A.	5 (1) in HIV and 2 (0.7) in non HIV
Mota L. (2022)	[24]	57	20–30 (70%)	N.A	N.A.	30 (53)

N.A. = not available.

Table 1.
Prevalence of UTI in HIV/AIDS patients.

In a recent systematic review and meta-analysis about the magnitude and associated factors of UTIs among adults living with HIV in Ethiopia, seven studies were selected with 2257 participants that met the selection criteria. All were observational studies with an overall prevalence of 12.8% (range 10.3–18% for all studies). Additionally, it analyzed some risk factors such as gender, diabetes mellitus, history of catheterization, and CD4 counts. Those with CD4 counts larger than 200 had a lower risk of UTI than those with CD4 counts less than 200 (OR: 0.36, 95% CI: 0.06–2.35) with statistical significance of P = 0.001 [25].

3. Pathogenesis

Urinary tract infections usually migrate through the urethra, and microorganisms colonize the periurethral region**.** In a simple case, microorganisms can arrive in the urinary tract through the blood in the presence of a systemic disease such as perinephric abscess, renal tuberculosis, and some mycoses. A UTI may involve any site of the urinary tract, including renal parenchyma, renal pelvis, ureters, bladder, and urethra. Infection of the renal parenchyma is termed pyelonephritis. The infection of the upper urinary tract is usually associated with severe disease.

The ascent of bacteria colonizing the urethral meatus is more common in women due to the short urethra and bacterial colonization in adjacent vulvar and perianal regions [26]. Sometimes, a specific risk factor is present, such as pregnancy, indwelling catheter drainage or intermittent urinary catheterization of the bladder due to paraplegia, neurogenic bladder, bladder outlet obstruction, prostatism, urethral stricture, analgesic abuse neuropathy, or ureteral stricture from recurrent renal colic. Some of this risk factors can be inferred from proper questioning [27, 28]. The human body is host to a wide variety of microorganisms, establishing a well-known symbiotic relation [29]. Extensive studies on human microbiome have generated an unprecedented understanding of the microorganisms that colonize both the human body and its external environment [30].

Uropathogenic reservoirs often prevail within the urinary tract and the surrounding vaginal and gut microbiomes, causing recurrent UTIs in up to 30% of individuals within 6 months of the initial infection [31]. Urotypes in the female urobiome are commonly dominated by *Shigella*, *Lactobacillus*, *Enterococcus*, *Gardnerella*, *Prevotella*, and *E. coli.* The paradigm that has existed for years stating that urine is a liquid sterile under normal conditions has now been refuted by recent studies in which flora has been found in the bladder of adult woman [32, 33].

Specific virulence factors and various pathogens that cause UTIs have been studied extensively [34, 35]. Certain strains of *E. coli*, called uropathogenics, have been implicated as the most prevalent bacterium causing ITUs in different populations. *E. coli* adherence to uroepithelium is mediated by adhesins such as pili or fimbriae, interacting with specific receptors expressed on the surface of the uroepithelial cells. Fimbriated strains of *E. coli* account for 90% of pyelonephritis, and is the most predominant strain of bacteremic cases. Cell wall O antigens, capsular polysaccharide K antigens, and the flagellar H antigens have been associated with UTI severity. Other bacterial virulence factors associated with UTIs include aerobactin, hemolysins, and cytotoxic necrotizing factors [34, 35].

However, a high rate of UTIs has been described in patients with advanced HIV [7, 21]. Bacteriuria with the consequent risk of UTI has been found in >30% in patients living with HIV who have CD4 < 200 cell/mm^3 [36]. A routine study in this

population is recommended specially in advanced disease. Urine cultures may be negative because the patient is taking prophylactic antimicrobials against opportunistic infections. Urine should be cultured for mycobacteria, and the use of special culture media and stains, blood cultures, and viral titers should be considered [9, 37]. Intravenous pyelogram, renal ultrasound, or abdominal computed tomography may be very useful, and tissue biopsies may be necessary to establish a diagnosis, for example, CMV cystitis [8, 38].

Immune status is decisive in the occurrence of opportunistic infections; the critical levels associated with the occurrence of opportunistic infections are below 200 CD4/mm^3 cells in the blood. Following initial infection, HIV spreads to regional lymph nodes within 3–6 days due to the large population of HIV-targeted CD4+ T cells and constant cell trafficking by lymphatic vessels; systemic dissemination occurs, and studies suggest that the lymph node reservoir may be established within the first 2 weeks of infection (6–25 days) [39–41]. Viral replication is associated with a decline in the CD4 cell count and immune system deterioration. High viral load and low CD4 cell count are associated with a greater risk of opportunistic infections and progression to AIDS. HIV has been isolated from blood and many other fluids and secretions [37].

Therapeutic interventions that decrease plasma HIV RNA levels are associated with an improved prognosis [42, 43]. Since the first antiretroviral (ARV) was produced three decades ago, ARV therapy has transformed HIV infection from inevitable immune collapse and death into a chronic disease that can now be treated and prevented with a pill taken once a day [44]. Despite these advances, the definitive cure is still pending [45, 46].

4. Clinic presentation and risk factors

The clinical presentation of UTIs in patients with HIV/AIDS infection does not appear to be different from that described in the general population; the infection would be expected to be more severe in immunosuppressed patients, and signs and symptoms of UTI may be mild because there is no inflammatory response to infection. The specific clinical manifestations may be more related to the etiology and location of the UTI where variations in the clinical presentation are to be expected. The health consequences of UTI among HIV-infected patients can be severe, resulting in acute and chronic kidney diseases [47], infertility, cancer, sepsis, and neurologic complication, which lead to urinary stasis [48].

Fever, dysuria, and polyuria are the most frequent symptoms of UTIs; the presence of any of these symptoms is indicative of a UTI in about 50% of cases. The combination of symptoms increases the probability of a UTI to over 90% [49]. Low-location UTIs such as cystitis are the most frequent, least aggressive, and least related to factors that are predisposed to recurrences. On the other hand, high-location UTIs (such as pyelonephritis) are usually less frequent but more aggressive and can include sudden onset with bacteremia and high fever and may be present with signs and symptoms such as costovertebral pain and macroscopic hematuria [19, 50]. Both cystitis and pyelonephritis are complicated when they occur in the presence of a condition that increases the risk of recurrence or when are caused by resistant pathogens.

Cystitis can be defined as an infection of the urinary bladder accompanied by symptoms of dysuria, frequency, and urgency. Chronic pyelonephritis is commonly found in association with other renal diseases, such as chronic obstruction, uric acid

nephropathy, analgesic abuse, and hypokalemic nephropathy. Acute bacterial prostatitis generally presents with abrupt onset of fever, chills, dysuria, frequency, urgency, as well as perineal pain with symptoms of irritative and obstructive voiding dysfunction. Relapsing episodes of UTIs, either cystitis or pyelonephritis, are common [51].

Urosepsis may be defined as symptomatic bacteremia of urinary tract origin. It is a rare but life-threatening complication of UTI. Community-acquired urosepsis in an otherwise healthy host typically arises from acute pyelonephritis or renal abscess [52]. Hemorrhagic cystitis is characterized by hematuria, dysuria, frequency, and urgency, and in severe cases, blood clots can result in bladder outlet obstruction. This condition is generally associated with BK virus, adenovirus infection in bone marrow, and kidney transplant recipients, and it occurs in the early transplant period [53–55].

Clinical manifestations, etiology, and recurrence can also change widely in relation to host conditions, such as pregnancy, malformations of the urinary tract, and presence of lithiasis or tumor. Aging affects the function of all organs and systems and the urinary tract is not an exception. Prostate growth, neurogenic bladder with urinary retention, and increase frequency of asymptomatic bacteriuria are common at this stage of life [52]. An important part of the population living with HIV are people over 65 years of age who, like the rest of the population, suffer from chronic degenerative diseases.

In a previous cohort [56] of 33,336 male veterans with UTI, 234 (0.7%) were diagnosed with HIV infection. Patients with HIV were significantly younger than those without HIV (56.5 vs. 68.0 years; $P < .001$). Among the assessed comorbidities known or hypothesized to be associated with UTI, several differences between patients with HIV versus patients without HIV were observed (**Table 2**). Although this study represents a very specific population, it allows to consider the most common comorbidities that can be associated with UTIs in men who are non-HIV-infected compared with those who are HIV-infected.

Catheter-associated urinary tract infection (CAUTI) is defined as the new appearance of bacteriuria or funguria at a concentration greater than 10^5 CFU mL

Comorbidity	NonHIV (33,102)	HIV infected (n = 234)	*P* value
Diabetes mellitus	34.7	23.1	<.001
Benign prostatic hypertrophy	33.1	19.2	<.001
Prior UTI	30.9	27.3	.25
Incontinence	16.3	13.2	.20
Chronic kidney disease	10.8	11.5	.72
Prostate cancer	11.1	7.7	.10
Urethral stricture	7.8	4.3	.047
Urinary calculi	7.0	9.0	.24
Spinal cord injury	4.0	3.4	.32
Prostatitis	2.6	5.1	.02
Vesicoureteral reflux	0.1	0	.63

Adapted from: Drekonja et al. [56].

Table 2.
Percent of comorbidities associated with UTIs among non-HIV and HIV infected male patients.

according to the Centers for Disease Control and Prevention. More than 75% of hospital-acquired or nosocomial urinary tract infections are initiated by urinary catheters, which are used during the treatment of 15–25% of hospitalized patients. Infection occurs in 10–50% of patients undergoing non-Foley or short-term urinary catheterization (7 days), but virtually all patients undergoing Foley or long-term catheterization (>28 days) become infected [57]. There are different risk factors for CAUTI; one of the main reason for this condition is the material used in the fabrication of urinary catheters that allows colonization by microorganisms and subsequent bacteriuria and infection, especially for long-term catheterization [58]. Although there is a large amount of research on CAUTI, the ideal catheter with biocompatible, antimicrobial, and antifouling materials has not yet been developed [58].

The clinical manifestations of a patient with CAUTI may pass unnoticed or be present in a severe way. Evidence suggests that the diagnosis of CAUTI based on clinical signs varies widely among clinicians and is often inaccurate when compared to published guidelines [59, 60]. Clinical practice guidelines identify several such indicators, including fever, suprapubic tenderness, flank tenderness, and delirium [13]. Unfortunately, standardized procedures to assess some of these indicators have not yet been described in the literature, and information about the consistency of some of these assessment findings from one clinician to another is yet to be reported [61]. In a study of CAUTI assessment profile, three clinical manifestations, fever, suprapubic tenderness, and delirium, had acceptable and statistically significant consistency between three nurse rates, while flank tenderness did not [62].

Infection is a common precipitating factor for delirium, particularly in the elderly [63, 64]. Delirium is defined as an acute change in cognitive status resulting from an underlying medical, psychiatric, environmental, or multifactorial cause. This manifestation of CAUTI has four indicators: acute onset with a fluctuating course, inattention, disorganized thinking, and altered level of consciousness. In a study of 210 admissions, 72 (15%) HIV-infected patients had higher rates of infection compared with their overall nosocomial rates of 6.9%. This study showed that the use of urinary catheters, gastrointestinal procedures, and vascular access were the risk factors for hospital-acquired infection [65].

In a prospective cohort between February 1998 and October 1999 in a Brazilian infectious disease unit, 257 HIV-infected patients were matched with a control group of 204 HIV-negative patients by age, diagnosis, severity of illness, and prior hospitalization. The rates of hospital acquired infections (HAI) in the studied group were 8.16 for HIV-positive patients and 3.94 for HIV-negative patients per 1000 patient days ($P = .01$). Bloodstream infections, UTIs, vascular infections, and pneumonia were the most common diseases. Three UTIs were detected in HIV-positive patients and 7 in HIV-negative patients. Although HIV-positive patients were more likely to use a urinary tract catheter, there was no difference between both groups regarding the incidence of UTIs. No clinical picture and CD4 data were provided [66]. The education of competent healthcare workers is essential in CAUTI prevention. Its effectiveness is shown especially in comprehensive and contain information course about correct procedures of urinary bladder catheterization [67]. A well-working team of HAI prevention experts in hospitals with high-quality and comprehensively provided nursing care is essential [68].

Asymptomatic bacteriuria is a clinical syndrome defined as the isolation of $\geq 10^5$ CFU/ml of bacteria from an appropriately collected clean urine specimen [69]. By definition, a positive culture of two urine specimens for the same bacteria is required in women, whereas a single urine culture is required in men [52].

Studies have shown a 4–7% prevalence of bacteriuria during pregnancy, compared to 1–3% prevalence in young nonpregnant women [70, 71]. Another risk population is diabetics over 70 years of age and those that use permanent or intermittent urinary catheters [72–75]. Screening and treatment of asymptomatic bacteriuria is only recommended in pregnant women, prior to prostate surgery or an invasive urological procedure [76]. Studies have shown a high prevalence of asymptomatic bacteriuria in HIV-infected pregnant women than among uninfected pregnant women [77–79]. In men infected with HIV/AIDS with a CD4 count <200, bacteriuria can reach up to 30% [36].

5. Etiology in different scenarios

UTIs in HIV patients are generally caused by the same gram-negative bacterial uropathogens that cause infections in healthy hosts, with *E. coli* being the predominant pathogen isolated. HIV status had no significant impact on the uropathogens that caused UTI in any setting [80]. However, the resistance of *E. coli* isolates demonstrated significantly higher resistance to co-trimoxazole compared to isolates from known HIV-negative patients (95% vs. 72%) (P: 0.001). Antimicrobial resistance has already emerged to most oral agents in the world including HIV- and non-HIV-infected patients.

Enterobacteriaceae, especially *E. coli*, is the major aerobic organism residing in the intestine and is the most reported cause of UTI [81, 82] being a common fecal contaminant, accounting for more than 60% of urinary isolates in HIV-infected patients. *Klebsiella*, *Enterococcus*, *Enterobacter*, and *Proteus* species are the next most common pathogens isolated [7, 22]. *Salmonella* and *Neisseria gonorrhoeae* can rarely cause prostatitis [42].

The exact etiology of UTIs is difficult to know. Most of the studies are retrospective in which clinical records or databases were analyzed. Many are already very old and have the limitation that the identification of the etiological agent is focused on bacteria, and routine tests are not included to identify other microorganisms such as fungi, parasites, and virus. In most centers, molecular DNA amplification tests were not used to identify organisms of fastidious growth. **Table 3** shows us the relevant information from selected studies on the etiology of UTIs in HIV-infected patients.

Reference author	**[83] Vignesh**	**[7] Schönwald**	**[84] Tessema**	**[85] Klapaczyńska**	**[86] Marami**
Year	2008	1999	2000	2018	2019
Country	India	Croatia	Esthiopia	Poland	Ethiopia
Analysis	Retrospective	Retrospective	Retrospective	Retrospective	A cross-sectional
N. patients	85	96	23	141	63
Female (%)	28.0	18.7	86.9	51.8	73.0
CD4 (cells/μl)	NA	NA	≥200 (74%)	139 (mean)	<200 (55.6%)
E. coli	42.3	22	69.6	82 (58.2)	24 (38.1)
S. aureus	21.2	0.0	8.7	1 (0.7)	7 (11.1)
K. pneumoniae	17.6	7.5	8.7	2 (1.4)	15 (23.8)

Reference author	[83] Vignesh	[7] Schönwald	[84] Tessema	[85] Klapaczyńska	[86] Marami
Enterococcus sp	8.2	26	0.0	18 (12.8)	2 (3.2)
Pseudomonas sp	3.5	15	4.3	5 (3.5)	4 (6.4)
Proteus sp	3.5	5.5	0.0	3 (2.1)	0.0
S. epidermidis	3.5	1.8	0.0	7 (5.0)	0.0
Other CONS*	0.0	0.0	0.0	3 (2.1)	5 (7.9)
Enterobacter sp	0.0	5.5	8.7	1 (0.7)	0.0
Acinctobacter sp	0.0	5.5	0.0	1 (0.7)	0.0
Providencia sp	0.0	3.7	0.0	0.0	0.0
S. agalactie	0.0	0.0	0.0	4 (2.8)	0.0
Streptococcus sp	0.0	0.0	0.0	3 (2.1)	0.0
C. albicans	0.0	0.0	0.0	1 (0.7)	0.0
S. emteritidis	0	1.8	0.0	0.0	0.0
S. maltophilia	0.0	0.0	0.0	1 (0.7)	0.0
M. morganii	0.0	0.0	0.0	1 (0.7)	0.0
Serratia odorifera	0.0	0.0	0.0	1 (0.7)	0.0
Sin cultivo	NA	NA	NA	NA	NA
Mixed patogen	0.0	0.0	0.0	4 (2.8)	0.0
Other	0.0	0.0	0.0	3 (2.1)	0.0

**Coagulase-negative Staphylococci; ND = not done.*

Table 3.
Studies showing the frequency of organisms causing UTIs in HIV infected patients.

5.1 Hospital-acquired UTIs

HIV-infected patients may be at a greater risk of HAI. In a study of 210 subjects, a rate of 15% of HAI was found in HIV-infected patients compared with only 6.9% of their overall nosocomial rates [65]. More than 75% of hospital-acquired UTIs are initiated by urinary catheters, which are used during the treatment of 15–25% of hospitalized patients. Common bacteria associated with CAUTI are *Staphylococcus aureus*, *E. coli*, *Pseudomonas aeruginosa*. *P. mirabilis*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Klebsiella pneumoniae* [57].

A retrospective cohort study [87] was carried out in an academic health system in New York City, which included 10,575 (697 UTIs) HIV-positive discharges from four hospitals over a period from 2006 to 2014. The rates of HAIs among HIV-infected patients are likely to be higher than those among HIV-uninfected patients; the risk factors were similar. The main organisms isolated in UTIs were *Acinetobacter baumannii*, *E. faecalis*, *K. pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Further research is required to address how patients' CD4 counts and viral loads affect their susceptibility to HAIs. Strategies to prevent nosocomial infections among HIV-infected patients are the same control measures used in HIV-uninfected patients [88].

In a Brazilian study, the overall incidence of HAIs was 5.90 per 1000 patient-days. The rates of HAI were 8.16 for HIV-positive and 3.94 for HIV-negative patients (P = 0.01). The most common HAIs were bloodstream infection in 44%, followed by UTIs with 18%, vascular infections in 14%, and pneumonia in 11%. Common etiologic agents were *A. baumanii*, *E. coli*, *E. faecalis*, *K pneumoniae*, *P. aeruginosa*, and yeast. Only three UTIs were detected in HIV-positive patients and 7 in HIV-negative patients [66].

5.2 AIDS with low CD4 count

HIV patients with a CD4 count <200 cells/μL are reported by some authors to be at a higher risk for UTIs, while others report that CD4 count is not associated with UTIs [36, 89, 90]. Few studies report the CD4 averages of patients with UTIs, and in some cases, etiology analysis is performed, separating patients with CD4 greater or less than 200 cells, in which no major differences have been reported in terms of isolated organisms. However, there are few reports of AIDS patients in very advanced stages, including some autopsy studies. In patients with AIDS, infections by atypical pathogens include fungi, parasites, mycobacteria, and viruses. These organisms are often widely disseminated at the time of urinary tract involvement and are usually associated with CD4 counts of <100/mm^3 [39, 91].

In patients with AIDS and disseminated *Cryptococcus neoformans* infection, prostate involvement may serve as a hidden site of persistent infection [92]. Fungal etiology is uncommon in immunocompromised and diabetic patients with chronic prostatitis [93].

The most illustrative study is by Miles et al. [19], which was carried out very early in the AIDS pandemic (1984–1987) in 120 patients, when there was still no antiretroviral treatment. They found a UTI prevalence of 14% (17 patients); only 9 had standard bacterial urinary infections. In the remaining 8 patients, 1 had gonorrhea, and 7 had positive urinary cultures that considered a manifestation of the systemic disease (6 with CMV and 1 with *Cryptococcus*). Autopsies were performed in 22 males and 1 female; the predominant urogenital finding was the absence and/or reduction of spermatogenesis in 17 patients. CMV was noted in the adrenal glands in 12 cases, one in bladder and prostate, respectively. Kaposi's sarcoma occurred in 4 cases. Numerous genitourinary sites involved with CMV and Kaposi's sarcoma suggested the systemic nature of these illnesses.

Renal tuberculosis has been detected in about 6–23% of AIDS patients by autopsy; a significant proportion of these cases were asymptomatic [42, 94, 95]. *Mycobacterium tuberculosis* is the most common species reported, followed by *Mycobacterium avium* and *Mycobacterium intracellulare*. Renal tuberculosis initially affects the kidney and by descending matter involves the ureters and lower urinary tract structures. When renal tuberculosis is suspected, polymerase chain reaction may be useful as a rapid assay to detect *M. tuberculosis*-specific DNA or RNA materials in urine [96, 97].

5.3 Asymptomatic HIV patients

A study with 317 asymptomatic HIV patients (89 men, 228 women), the prevalence of UTI did not differ significantly from those with a CD4 count less or high of 200 cells/μL. Females showed significantly higher prevalence of asymptomatic UTI than males [20]. The microbiology findings of urine culture are showed in **Table 4**, and the susceptibility of the isolated pathogens is showed in **Table 5**.

Organisms	NonHIV (n = 104)	HAART naive (n = 101)	On HAART* (n = 216)
Escherichia coli	6 (31.5)	4 (12.9)	6 (9.4)
Klebsiella species	0 (0.00)	1 (3.2)	5 (7.8)
Proteus species	0 (0.00)	1 (3.2	3 (4.7)
Staphylococcus aureus	6 (31.5)	8 (25.8)	17 (26.6)
Coagulase-negative Staphylococci	4 (21.5)	5 (16.1)	10 (15.6)
Enterococcus faecalis	0 (0.00)	1 (3.2)	8 (12.5)
Candida albicans	3 (15.8)	7 (22.6)	15 (23.4)
Trichomonas vaginalis	0 (0.00)	4 (12.9)	0 (0.00)
Total	19 (16.7)	31 (27.2)	64 (56.1)

**On HAART = ARVs use for three to six months.*
Modified from Omoregie and Eghafona [20].

Table 4.
Pathogens isolated from urine culture in asymptomatic HIV patients.

Antibacterial agents (μg/disc)	Organisms					
	E. coli (n = 16)	*Klebsiella* sp. (n = 6)	*Proteus* sp. (n = 4)	*S. aureus* (n = 31	CONS* (n = 19)	*E. faecalis* (n=9)
Amoxicillin (30)	1 (6.2)	1 (16.7)	1 (25.0)	10 (32.2)	6 (31.6)	4 (44.4)
Amoxicillin/clav (30)	6 (6.2)	1 (16.7)	2 (50.0)	11 (35.5)	5 (26.3)	4 (44.4)
Gentamicin (10)	3 (18.7)	0 (0.0)	1 (25.0)	5 (16.1)	5 (26.3)	4 (44.4)
Co-trimoxazole (25)	1 (6.2)	1 (16.7)	0 (0.0)	1 (3.2)	1 (5.3)	0 (0.0)
Tetracycline (25)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	1 (11.1)
Nitrofuratoin (300)	9 (56.2)	1 (16.7)	2 (50.0)	16 (51.6)	12 (63.2)	6 (66.7)
Nalidixic acid (30	3 (18.7)	0 (0.0)	0 (0.0)	ND	ND	ND
Ciprofloxacin (5)	6 (37.5)	2 (33.3)	2 (50.0)	10 (32.2)	8 (42.1)	5 (55.6)
Ofloxacin (5)	6 (37.5)	0 (0.0)	1 (25.0)	5 (16.1)	6 (31.6)	3 (33.3)

**Coagulase-negative* Staphylococci*; ND = not done.*
Adapted from Omoregie and Eghafona [20].

Table 5.
Susceptibility of bacterial isolates (number and percent).

6. Susceptibility drugs and therapy

Bacterial resistance is a major public health problem, which mainly affects developing countries. The irrational and indiscriminate use of antibiotics and deficient surveillance programs on antibiotic use are common in these countries [98, 99]. According to the etiological tendency, clinicians should know these changes for effective treatment of UTIs and to avoid antibiotic misuse.

In a recent study in Southern Ethiopia [84] of 224 study participants, bacteria have been isolated from 23 patients, 11 (4.9%) with symptomatic and 12 (5.4%) with asymptomatic UTI; most of participants were females (58.5%). Twenty-one (91.3%)

Antibacterial agents (μg/disc)	Organisms				
	E. coli (n = 16)	*K. pneumoniae* (n=2)	*E. aurogenes* (n = 2)	*Pseudomonas* spp. (n = 1)	*S. aureus* (n = 2)
Ampicillin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Ciprofloxacin (30)	14 (87.5)	2 (100)	2 (100)	1 (100)	2 (100)
Cotrimoxazole (30)	6 (37.5)	2 (100)	1 (50)	0 (0.0)	0 (0.0)
Gentamicin (10)	15 (93.8)	2 (100)	2 (100)	1 (100)	2 (100)
Meropenem (25)	14 (87.5)	2 (100)	2 (100)	1 (100)	NA
Nitrofuratoin (300)	16 (100)	2 (100)	2 (100)	0 (0.0)	2 (100)
Amoxicillin/clav	11 (68.8)	0 (0.0)	1 (50)	1 (100)	NA
Cefriaxone	16 (100)	1 (50)	1 (50)	1 (100)	NA
Norfloxacin	14 (87.5)	2 (100)	2 (100)	0 (0.0)	2 (100)
Ceftazidime	8 (50)	2 (100)	1 (50)	1 (100)	NA
Tetracycline	5 (31.3)	1 (50)	1 (50)	0 (0.0)	0 (0.0)
Clindamycin	NA	NA	NA	NA	2 (100)
penicillin	NA	NA	NA	NA	2 (100)
erythromycin	NA	NA	NA	NA	2 (100)
Cefoxitin	NA	NA	NA	NA	2 (100)

Modified from Tessema et al. [84].

Table 6.
Susceptibility of bacterial isolates from UTIs of HIV infected patients (number and percent).

of isolates were gram-negative bacteria where *E. coli* was the most predominant isolate. Drug testing was done by the Kirby-Bauer disk diffusion method; susceptibility findings are shown in **Table 6**. Most of the bacterial isolates were susceptible to ciprofloxacin, ceftriaxone, gentamicin, nitrofurantoin, and norfloxacin. The isolates were resistant to ampicillin, tetracycline, and co-trimoxazole. Multidrug resistant bacteria were common in this study [84].

In another study published in 2019, *E. coli* was resistant to ampicillin (95.8%), ceftazidime (95.8%), cotrimoxazole (95.8%), amoxicillin (91.7%), ceftriaxone (87.5%), and tetracycline (87.2%); 46% were multidrug resistant. On other hand, *E. coli* and the rest of the gram-negative bacilli were sensitive to quinolones (ciprofloxacin, norfloxacin) as well as gentamicin in about 75%. *S. aureus* exhibited a high proportion of resistance (85.7%) to each of ampicillin, amoxicillin, and cotrimoxazole. Coagulase-negative *Staphylococcus* were 100% resistant to each of ampicillin and amoxicillin and 80% to chloramphenicol. However, it is important to note that antibiotics such as carbapenems, piperacillin tazobactam, tigecycline, and other new antibiotics were not tested for gram-negative bacteria and that third-generation cephalosporins, vancomycin, linezolid, and tigecycline were also not tested for gram-positive bacteria [86].

E. coli isolates from known HIV-positive patients demonstrated significantly higher resistance to co-trimoxazole. HIV status did not affect resistance patterns to the other antimicrobials that were examined. Resistance of *E. coli* to ampicillin and co-trimoxazole was greater than 60%; authors recommended that these agents should not be used as empiric treatment for UTI. Additionally, given that there was greater than

20% resistance to ciprofloxacin, its use would otherwise be inappropriate as an empiric agent in the context of Botswana [80].

6.1 Treatment of UTIs in HIV infected patients

Like the general population, the treatment of UTIs should be individualized; in patients with AIDS, a culture-specific treatment is recommended. To select a specific treatment, it is advisable to follow the international treatment guidelines. It is recommended that the guidelines be recent [100, 101], according to how the epidemiology of UTIs and resistance evolve in specific populations. Despite clear guidelines, practice patterns vary widely with numerous studies showing substantial discrepancies between clinical practice guidelines and antibiotic-prescribing practices [102].

In the selection of empirical therapy of UTIs, it is necessary to define if the patient had some risk factor for complicated UTI. The evidence suggests that HIV-infected patients had the same or almost the same behavior as non-infected HIV population. Microbiology studies show that enterebocateriaceae, especially *E. coli*, are primarily implicated. This may apply to different populations of HIV patients, including the most common complicated UTIs, such as hospital-acquired UTIs, associated or not with the use of a urinary catheter, pregnant patients, elderly patients, and in cases of asymptomatic bacteriuria.

On recent guidelines [100] for urological infections, the following tables show the suggested therapy for different scenarios: Uncomplicated cystitis (**Table 7**), uncomplicated pyelonephritis (**Table 8**), parenteral antimicrobial therapy in uncomplicated pyelonephritis (**Table 9**), urosepsis (**Table 10**), and chronic bacterial prostatitis (**Table 11**).

The diagnostic approach varies according to clinical suspicion; at best, a general urine examination accompanied by a urinary culture with antimicrobial sensitivity tests is reasonably chosen for its already recognized activity against urinary pathogens. Many sites are using obsolete panels containing useless antimicrobial agents such as tetracyclines, chloramphenicol, and others, without the new useful antimicrobial

Antimicrobial	Daily dose	Duration of therapy	Comments
First-line women			
Fosfomycin trometamol	3 g SD	1 day	Recommended only in women with uncomplicated cystitis
Nitrofurantoin macrocrystal	50–100 mg	5 days	
Nitrofurantoin monohydrate/ macrocrystals	100 mg b.i.d.	5 days	
Nitrofurantoin macrocrystal prolonged release	100 mg b.i.d.	5 days	
Pivmecillinam	400 mg t.i.d.	3–5 days	
Alternatives			
Cephalosporins (e.g. cefadroxil)	500 mg b.i.d.	3 days	Or comparable
If the local resistance pattern for *E. coli* is < 20%			
Trimethoprim	200 mg b.i.d.	5 days	Not in the first trimenon of pregnancy
Trimethoprimsulfamethoxazole	160/800 mg b.i.d.	3 days	Not in the last trimenon of pregnancy

Antimicrobial	Daily dose	Duration of therapy	Comments
Treatment in men			
Trimethoprim/ sulfamethoxazole	160/800 mg b.i.d.	7 days	Fluoroquinolones can also be prescribed in accordance with local susceptibility testing.

SD = single dose; b.i.d. = twice daily; t.i.d. = three times daily.
Adapted from Bonkat et al. [100].

Table 7.
Suggested regimens for antimicrobial therapy in uncomplicated cystitis.

Antimicrobial	Daily dose	Duration of therapy	Comments
Ciprofloxacin	500–750 mg b.i.d.	7 days	Fluoroquinolone resistance should be less than 10%
Levofloxacin	750 mg q.d.	5 days	
Trimethoprim sulfamethoxazol	160/800 mg b.i.d.	14 days	If such agents are used empirically, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered
Cefpodoxime	200 mg b.i.d.	10 days	
Ceftibuten	400 mg q.d.	10 days	

b.i.d. = twice daily; q.d. = every day.
Adapted from Bonkat et al. [100].

Table 8.
Suggested regimens for empirical oral antimicrobial therapy in uncomplicated pyelonephritis.

Antimicrobials	Daily dose	Comments
First-line treatment		
Ciprofloxacin	400 mg b.i.d.	
Levofloxacin	750 mg q.d	
Cefotaxime	2 g t.i.d.	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftriaxone	1–2 g q.d.	Lower dose studied, but higher dose recommended.
Second-line treatment		
Cefepime	1–2 g b.i.d.	Lower dose studied, but higher dose recommended
Piperacillin/ tazobactam	2.5–4.5 g t.i.d.	
Gentamicin	5 mg/kg q.d.	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d.	
Last-line alternatives		
Imipenem/ cilastatin	0.5 g t.i.d.	Consider only in patients with early culture results indicating the presence of multi-drug resistant organisms.
Meropenem	1 g t.i.d.	
Ceftolozane/ tazobactam	1.5 g t.i.d.	

Antimicrobials	Daily dose	Comments
Ceftazidime/ avibactam	2.5 g t.i.d.	
Cefiderocol	2 g t.i.d.	
Meropenem-vaborbactam	2 g t.i.d.	
Plazomicin	15 mg/kg o.d.	

b.i.d. = twice daily; t.i.d. = three times daily; q.d. = every day; o.d. = once daily.
Adapted from Bonkat et al. [100].

Table 9.
Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis.

Antimicrobials	Daily dose	Duration of therapy
Cefotaxime	2 g t.i.d.	7–10 days Longer courses are appropriate in patients who have a slow clinical response
Ceftazidime	1–2 g t.i.d.	
Ceftriaxone	1–2 g q.d.	
Cefepime	2 g b.i.d.	
Piperacillin/ tazobactam	4.5 g t.i.d.	
Ceftolozane/ tazobactam	1.5 g t.i.d.	
Ceftazidime/ avibactam	2.5 g t.i.d.	
Gentamicin*	5 mg/kg q.d.	
Amikacin*	15 mg/kg q.d.	
Ertapenem	1 g q.d.	
Imipenem/ cilastatin	0.5 g t.i.d.	
Meropenem	1 g t.i.d.	

**Not studied as monotherapy in urosepsis, b.i.d. = twice daily; t.i.d. = three times daily; q.d. = every day.*
Adapted from Bonkat et al. [100].

Table 10.
Suggested regimens for antimicrobial therapy for urosepsis.

Antimicrobial	Daily dose	Duration of therapy	Comments
Floroquinolone	Optimal oral daily dose	4–6 weeks	
Doxycycline	100 mg b.i.d	10 days	Only for *C. trachomatis* or *Mycoplasma* infections
Azithromycin	500 mg once daily	3 weeks	Only for *C. trachomatis* infections

Antimicrobial	Daily dose	Duration of therapy	Comments
Metronidazole	500 mg t.i.d.	14 days	Only for *T. vaginalis* infections

b.i.d. = twice daily; t.i.d. = three times daily.
Adapted from Bonkat et al. [100].

Table 11.
Suggested regimens for antimicrobial therapy for chronic bacterial prostatitis.

agents. It is not uncommon that in a culture where an *Acinectobacter baumannii* grows, sensitivity to antibiotics such as colistin and tigecycline is not included in the report. The laboratory and the medical engineers who manufacture part of these supplies should also be advised about these queries.

Patients with complicated infections or recurrent infections, both infected or not by HIV, require additional studies that in many cases are aimed to find the cause of the recurrence; sometimes, it can be obvious such as pregnancy or the use of urinary catheter. Other factors for recurrence of UTIs such as malformations of the urinary tract, bladder ureter reflux, retentionist bladder, and the presence of a tumor or lithiasis are usually not in sight and require additional diagnostic tests such as plain film of the abdomen, ultrasonography, computed tomography, magnetic resonance, and cystography to detect correctable structural or functional abnormalities. Urodynamic findings in HIV patients included acontractile hypoactive bladder and detrusor-sphincter dyssynergia [4]. In patients with urinary retention, hypocontractility of the bladder was observed in 35–45% and prostatic enlargement in only 18%. Many of these patients required intermittent catheterization [103].

6.2 Treatment of UTIs for non-bacterial causes

Patients with AIDS, especially those with <100 CD4 cells/mm^3, the etiology of UTIs may be related to the spread of infections; the etiological agents may be diverse as they have already been described in this population [9, 42]. These patients require cultures and sensitivity tests not only for bacteria but also for cultures and stains for fungi and mycobacteria. Parasites should be searched, and molecular tests should include viruses such as CMV and adenovirus; GeneXpert for *M. tuberculosis,* which is a widespread test, is accessible and with high diagnostic value. The diagnostic approach may also vary according to the microbial epidemiology of each country and the accessibility of diagnostic tests. Fungal pathogens are related to a weakened immune system due to diseases such as HIV, cancer, organ transplantation, or by the use of certain drugs, resulting in the body's inability to fight infection. Long-term use of antifungal drugs can easily lead to fungal resistance; more than 90% of fungus-related deaths are caused by *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*, and *Pneumocystis* [104].

To choose the treatment in cases of UTIs by a fungal pathogen, it is necessary to have knowledge of the various therapeutic options, especially some pharmacological principles about the spectrum of antifungals, the safety of their use, and the possibility of resistance. Hospital-acquired UTIs and overall those associated with long-term urinary catheter use in AIDS patients with very low CD4 counts have a high risk for *Candida* and other fungi UTIs [105]. **Figure 1** shows the current antifungals and their modes of action, and **Table 12** shows the generalities about the spectrum of antifungal agents by family.

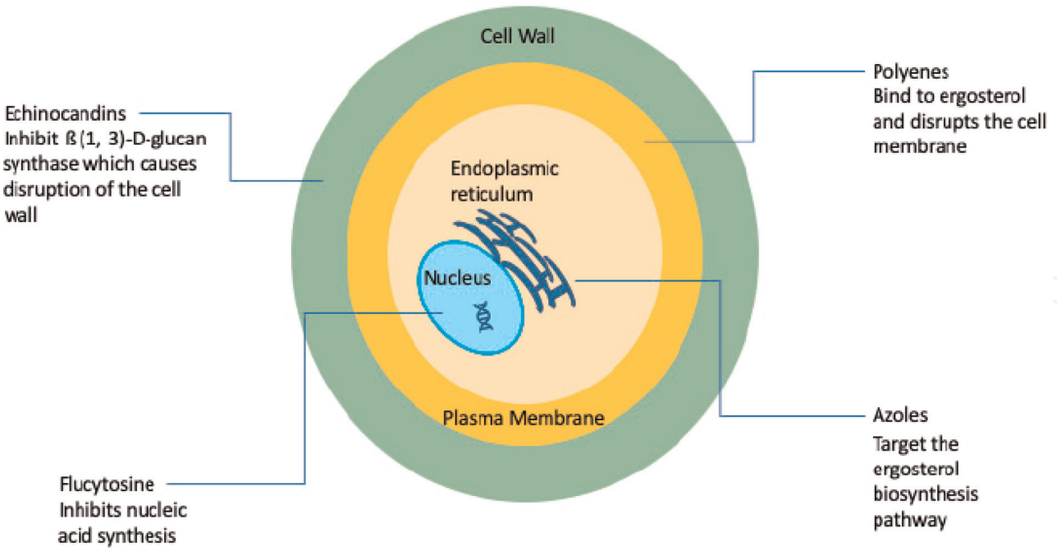

Figure 1.
Simplified schematic diagram depicting the current antifungals and their modes of action. Adapted with permission from: Wall and Lopez-Ribot [105].

Antifungal class	Biological effect	Spectrum of action
Polyenes	Fungicidal	Broad spectrum antifungal in treatment of invasive fungal infections; resistance is rare.
Flucytosine	Fungicidal against *Cryptococcus* spp.	Almost exclusively used for cryptococcal meningitis, but resistance is extremely common so never used in monotherapy.
Azoles	Mostly fungistatic	As a class they display broad spectrum against yeasts and filamentous fungi, although some species display intrinsic resistance to commonly used derivatives; secondary resistance can often develop during treatment.
Echinocandins	Fungicidal against *Candida* spp., but fungistatic against *Aspergillus* spp.	First line of defense for candidiasis and used in aspergillosis when refractory to other treatments; resistance is emerging.

Modified from: Wall and Lopez-Ribot [105].

Table 12.
Agent classes for the treatment of invasive fungal infections.

Candida UTI can be caused by a hematogenous spread following candidemia or by retrograde route via the urethra. Fluconazole is the treatment of choice for symptomatic infections, having a high urine concentration. Other antifungal azoles and echinocandins do not reach sufficient urinary levels. Amphotericin B deoxycholate (AmB) is the recommended therapy in cases of intolerance or resistance to fluconazole. **Table 12** shows the treatment of UTIs caused by Candida species [106].

In 1990, Fluconazole became available and is now the most used azole for systemic fungal infections, particularly those caused by yeast (i.e., *Candida*, *Cryptococcus*). Emerging fungi such as *Aspergillus* show intrinsic resistance to fluconazole, requiring the use of itraconazole or voriconazole. Mucorales are another group of aggressive fungi that cause systemic infections and for which posaconazole and more recently

isavuconazole have been used. Azole resistance is common during treatment due to various mechanisms, including mutations in the ERG11 target gene and overexpression of efflux pumps [107]. Despite resistance, azoles are still some of the most used antifungal drugs.

Fluconazole is one of the few antifungals with a good elimination by urine, reaching a concentration of about 80% of the drug in unchanged form. The use of fluconazole may have some limitations due to drug interactions, liver toxicity, QT prolongation, and resistance of some non-*Candida albicans* species such as *C. glabrata* and *C. krusei*. Treatment of *C. glabrata* infections may require high doses (800 mg/day) or definitive use of AmB as an alternative if the isolate is highly resistant to fluconazole [108, 109]. Other azole antifungals are poorly eliminated in the urine, which limits their use in cystitis. For example, itraconazole achieves a concentration of only <1%, voriconazole <5%, and posaconazole <1% [110]. Isavuconazole also has negligible urinary excretion and is unlikely to be useful for the treatment of UTIs [111]. Posaconazole and voriconazole are well concentrated in renal tissue and may be effective in the treatment of *Candida* pyelonephritis [110]. The echinocandins (caspofungin, anidulafungin, and micafungin) are only <2% concentrated in urine, so they are not recommended for the treatment of lower urinary tract infections, but they can reach high concentrations in the renal parenchyma [112]. There are some reports of cases that were successfully treated with echinocandins as rescue in complicated UTIs [113–115]. Caspofungin was the first echinocandin to be approved for use in humans in 2001; subsequently, two other echinocandins (micafungin in 2005 and anidulafungin in 2006) were approved [116, 117]. As a consequence of increased drug exposure, there has been an increase in the development of resistance mostly in strains different to *C. albicans* [116].

The major problem with amB has always been its toxicity presenting itself as chills, fever, dyspnea, hypokalemia, and nephrotoxicity that can lead to kidney failure. Thus, several lipid formulations of amB, including liposomal amB, amB lipid complex, and amB colloidal dispersion, have been developed, which generally show decreased toxicity and improved pharmacokinetic parameters that depend to a large extent on the composition and particle size of the nanoformulations [118]. The Infectious Diseases Society of America (IDSA) recommends deoxycholate AmB but not lipid formulations for the treatment of Candida UTI [109, 112].

Reactivation of latent CMV infection (usually acquired during childhood) occurs in >40% of patients with AIDS. UTI caused by CMV is often asymptomatic, but rare cases of symptomatic CMV cystitis have been reported; antiviral agents, for example, ganciclovir or foscarnet, can be necessary in the treatment of this disease [19, 42]. In 1989, ganciclovir became the first anti-CMV agent approved by the US Food and Drug Administration for the treatment and prevention of CMV infection and disease, followed by foscarnet, cidofovir, and valganciclovir. New agents with a novel mechanism of action such as letermovir and possibly maribavir are brought to clinical use; combination therapy for the treatment of CMV infection and disease becomes, for the first time, a possibility, especially in serious clinical presentations [119].

Treatment of tuberculosis in HIV-infected patients represents great challenges. Drug interactions and adverse events must always be taken as a risk, and a close monitoring must be carried out to avoid complications and clinical worsening. Per se, the standard (first-line) anti-TB therapy is already associated with adverse events and even intolerance. The interaction between rifampicin and many ARV drugs requires adjustment from a standard ARV regimen to a modified one. In addition, there is a risk of developing resistance when tuberculosis is treated using intermittent therapy.

The treatment recommendation for HIV-infected patients receiving ARVs who have drug-sensitive tuberculosis consists of a 6-month regimen, of which during the first 2 months (intensive phase), 4 drugs are given daily: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB), which is usually given as compacted tablets that are calculated by weight. In the continuation phase, only two drugs (INH and RIF) are used and are administered every third day for 4 months. In the rare situation where HIV-infected patients do not receive ART during TB treatment, the recommendation is to extend the continuation phase with INH and RIF for an additional 3 months (i.e., a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy) [120]. Pyridoxine (vitamin B6) is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfed infants; persons infected with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or those who are of advanced age) [121, 122].

The use of intermittent tuberculosis treatment regimens in HIV-infected patients has been associated with high rates of relapse and the emergence of drug resistance [123, 124]. Relapse and resistance were associated with low CD4 lymphocyte counts, as all recurrences occurred in patients with baseline CD4 lymphocyte counts of <100 cells/μL. Lower plasma concentrations of rifabutin and INH were identified as key risk factors for acquiring rifamycin resistance [125]. ART should ideally be started within 2 weeks for those patients with a CD4 count of <50 cells/μL and by 8–12 weeks for those with a CD4 count of ≥50 cells/μL [126]. The concurrent administration of ARV and rifamycin is a major therapeutic challenge. RIF can modify the concentration of some drugs in the treatment of HIV infection, especially protease and integrase inhibitors [127, 128].

Late-stage HIV patients with CD4+ cell counts of <50 cells/μL who initiate ARV therapy are at high risk of developing immune reconstitution inflammatory syndrome (IRIS) [129]. IRIS can present with high fever and generalized lymphadenopathy or with localized manifestations including respiratory symptoms, infiltrates or pleural effusions, abdominal pain, retroperitoneal abscesses, headache, seizures, and focal neurological deficits. M. tuberculosis, Toxoplasma, P. jirovecii, and *C. neoformans* are the main pathogens involved [130]. For more severe cases of IRIS, treatment with corticosteroids is effective. In a placebo-controlled trial of prednisone for patients with moderate IRIS, prednisone 1.25 mg/kg/day significantly reduced the need for hospitalization or surgical procedures [131].

7. Conclusion

UTI is considered the most common bacterial infection, mainly affecting women. From 15 to 50 years of age, UTI is practically nonexistent in men, but in those older than 65 years, the prevalence of bacteriuria and UTI increases substantially in men to almost equal that of elderly women. The prevalence of hospital-acquired UTI increases significantly in AIDS patients, mainly in patients with <200 CD4 cells/mm^3. Asymptomatic bacteriuria is more prevalent in HIV-infected pregnant women than among uninfected pregnant women. Bacteriuria can reach up to 30% in AIDS patients.

A specific risk factor for UTI can be present, including sexual activity, pregnancy, indwelling catheter drainage, neurogenic bladder, prostatism, and urethral stricture, among many others. Some of these risk factors can be inferred from proper questioning. There is a consensus that people with lower CD4 have a high risk of developing UTIs as well as other opportunistic infections. However, it is unclear whether HIV/AIDS imposes an additional risk for UTI.

UTIs in HIV patients are generally caused by the same gram-negative bacteria that cause infections in healthy hosts, with *E. coli* being the predominant pathogen isolated. *Klebsiella*, *Enterococcus*, *Enterobacter*, and *Proteus* species are the next most common pathogens isolated. In AIDS patients, especially those with <100 CD4 cells/mm^3, the etiology of UTIs may be diverse and associated with disseminated infections by atypical pathogens including CMV, adenovirus, *Cryptococcus*, *Candida*, *M. tuberculosis*, and Kaposi's sarcoma. **Figure 2** summarizes the most relevant aspects of this chapter.

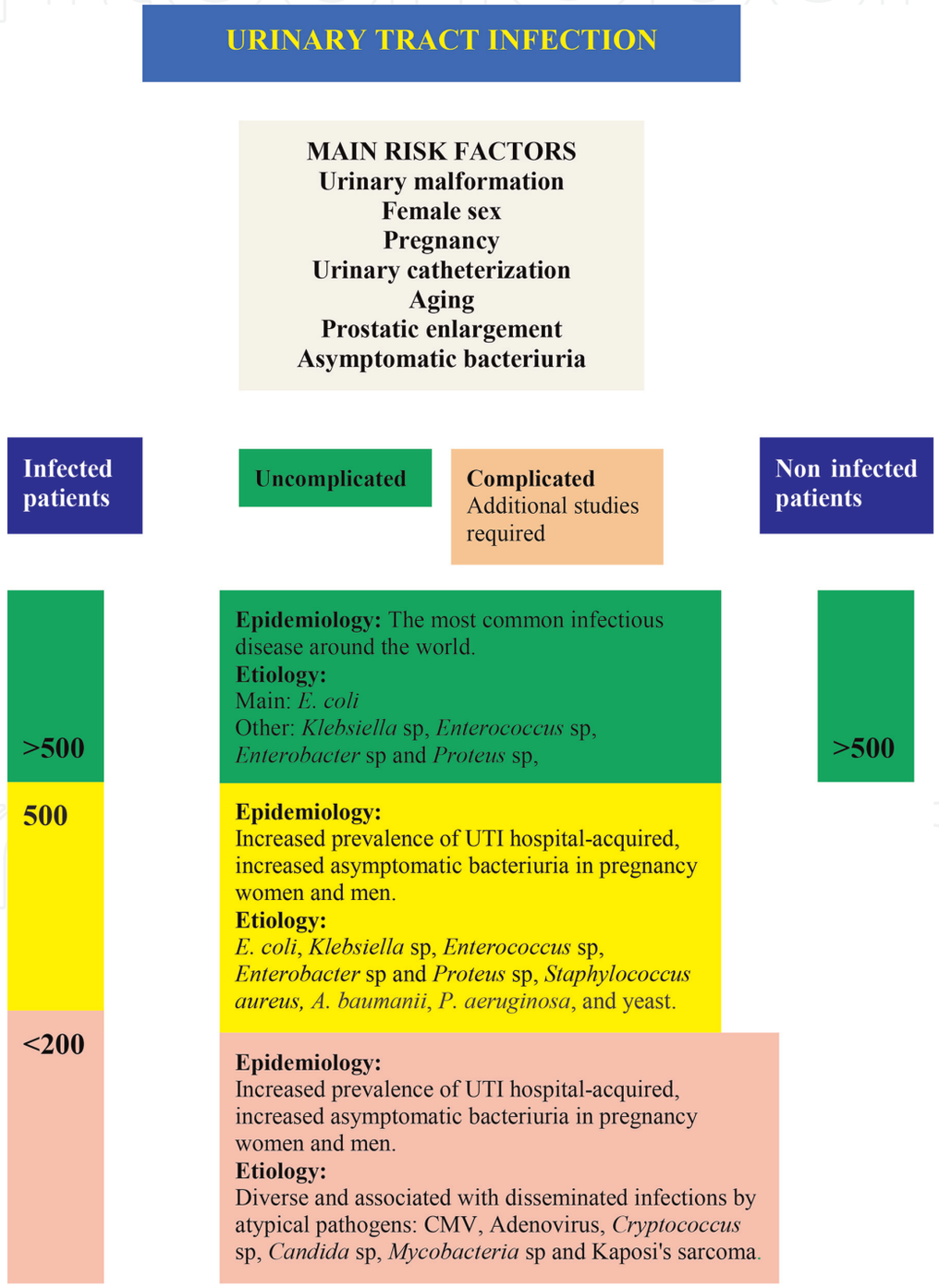

Figure 2.
Summary of the most relevant features of UTI in HIV/AIDS patients.

The diagnostic approach may also vary according to the microbial epidemiology of each country and the accessibility of diagnostic tests such as molecular techniques. Like the general population, the treatment of UTIs should be individualized; an etiology determination is recommended in AIDS patients in order to select a specific treatment; it is advisable to follow the international treatment guidelines.

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Conflict of interest statement

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