HIV and Associated TB: A Lethal Association for Kidney Health?

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Human immunodeficiency virus (HIV) and tuberculosis (TB) are the leading infectious causes of death globally. The combined brunt of these diseases is experienced mainly in low-income and lower-middle-income countries. HIV/TB have devastating effects on the kidneys, leading to accelerated decline of kidney function as well as mortality. Managing the triad of TB/HIV and kidney disease is challenging. We discuss the epidemiology of HIV/TB coinfection and the kidney and the key mechanisms of kidney disease including genetic susceptibility. The clinical presentation and pathology, as well as the challenges of diagnosing CKD in these patients, also are discussed. The strategies to prevent and manage HIV/TB-related kidney disease such as proper assessment, avoiding nephrotoxic regimens, drug dose adjustments, kidney function monitoring, avoidance of drug–drug interactions, and other interventions are explored. We also briefly discuss the complexities around HIV/TB patients on dialysis and kidney transplantation. HIV/TB coinfection presents an increased risk for kidney-related morbidity and mortality; patients with this triad need to be given special consideration for future research and management.
Semin Nephrol 43:151470 © 2023 Elsevier Inc. All rights reserved.
Keywords: HIV, HIV/tuberculosis coinfection, kidney disease

When emerging and re-emerging infectious diseases are mentioned, one is largely drawn to viral diseases such as coronavirus-19 (COVID-19), Ebola, Marburg, and other related diseases. However, the origins of this term trace back to 1987. It currently is used to describe diseases that have increased in incidence over the past 2 decades, or are predicted to increase, and these also include tuberculosis (TB) and human immunodeficiency virus (HIV).[1]

People living in a low-income country are far more likely to die of a communicable disease than a noncommunicable disease. Despite the global decline, 6 of the top 10 causes of death in low-income countries are communicable diseases. Malaria, TB, and HIV/acquired immune deficiency syndrome (AIDS) all remain in the top 10. There was a significant decline for HIV/AIDS, with 59% fewer deaths in 2019 than in 2000 (161,000 and 395,000 respectively)[2]; however, there has been an increasing trend since the pandemic of COVID-19, which is worrying.

EPIDEMIOLOGY OF HIV INFECTION

HIV has its origins in Western Africa, spreading from West to East Africa, and finally developing an epicenter in Southern Africa.[3] By the early 1980s it had reached epidemic proportions. It remains a major global public health issue, having claimed 40.1 million lives to date, with some countries reporting increasing trends in new infections, which were previously on the decline. There were an estimated 38.4 million people living with HIV at the end of 2021, two thirds of whom (25.6 million) were from the World Health Organization (WHO) Africa Region.

In 2021, 650,000 people died from HIV-related causes and 1.5 million people acquired HIV. Although there is no cure for HIV infection, with access to effective HIV prevention, diagnosis, and treatment (including for opportunistic infections), HIV has become a manageable chronic disease, enabling People with HIV (PWH) to lead long and healthy lives.[4] Today, despite global efforts to control infection, the condition still represents an overwhelming proportion of disease burden. Action to tackle the inequalities driving AIDS urgently is required to prevent millions of new infections.[4]

EPIDEMIOLOGY OF TB

Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 (more than HIV/AIDS). In 2021, an estimated 10.6 million

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Financial disclosure and conflicts of interest statements: none.
1526-0550/02/$-see front matter
© 2023 Elsevier. All rights reserved. doi:10.1016/semnephrol.2023.151470
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https://doi.org/10.1016/j.semnephrol.2023.151470

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people had TB worldwide, 6 million men, 3.4 million women, and 1.2 million children. TB is present in all countries and age groups. Importantly, it is curable and preventable.[5]

The WHO End TB Strategy, approved by the World Health Assembly in 2014, mandated a 90% reduction in TB deaths and an 80% reduction in TB incidence rates by 2030.[6] Global improvements followed until the onset of the COVID-19 pandemic in 2020.

The Effect of COVID-19 on TB and HIV Targets

COVID-19 resulted in the deceleration, stalling, or reversal of global TB targets, which now are off track. There was a large global decrease in the reported number of people newly diagnosed with TB, peaking at 7.1 million in 2019, then decreasing to 5.8 million in 2020 (−18%), with a partial recovery to 6.4 million in 2021. Globally, the estimated number of deaths from TB increased between 2019 and 2021, reversing years of decline between 2005 and 2019. In 2021, there were an estimated 1.4 million deaths among HIV-negative people and 187,000 deaths among PWH, culminating in a combined total of 1.6 million. This was up from best estimates of 1.5 million in 2020 and 1.4 million in 2019. Other negative impacts on TB include a decrease between 2019 and 2020 in the number of people provided with treatment for rifampicin-resistant TB and multidrug-resistant TB from 181,533 to 150,469.

Unfortunately, the COVID-19 pandemic also displaced TB improvement targets in PWH. In 2020, the percentage of notified incident TB cases among PWH declined from the previous year (56% to 48%), the first time since 2004. In 2020, 42% of the estimated number of PWH with incident TB received antiretroviral therapy (ART), compared with 49% in 2019.[7]

Recovery of all essential health service delivery is critical after pandemics and other disasters—this includes services for health promotion, disease prevention, rehabilitation, and palliation. The lack of these services may have even greater adverse health effects than the pandemic itself, especially among vulnerable populations. Intensified efforts backed by increased fundings urgently are required to mitigate and reverse the negative impacts of the COVID-19 pandemic on HIV/TB programs.[8]

What Makes TB- and HIV Infection−Related Kidney Disease Neglected and Lethal?

The sustainable development goal target 3.3 of ending the HIV epidemic by 2030 requires that 95% of all PWH should have a diagnosis, 95% of those should be taking life-saving ART, and 95% of those on treatment should achieve a suppressed viral load.[4]

To achieve the TB sustainable development goal target for 2030 it has been suggested that US $13 billion is needed annually for TB prevention, diagnosis, treatment, and care.[5] These targets may not be easy to achieve, especially in low-resource settings, with resultant complications of organ dysfunction including kidney disease. Kidney disease in HIV is a great immunosuppressant that contributes to the development of TB resulting from vitamin D deficiency, deranged cellular immunity, and malnutrition.[9] In Figure 1, we show the prevalent cases per 100,000 of TB, HIV, and kidney disease for adults of both sexes ages 15 to 49 years in 2019, and the annual percentage change from 1990 to 2019. It is clear that this triad is concentrated in low-income and lower-middle-income countries.

HIV/TB Coinfection

TB is the most common opportunistic infection seen in HIV. The risk of TB increases by 2- to 5-fold in early HIV-1 infection, and by more than 20-fold in advanced HIV-1 disease.[10] HIV-1 infects $CD4^+$ T cells and macrophages. *Mycobacterium tuberculosis* primarily infects macrophages, which require $CD4^+$ T cells to augment intracellular clearance of microbial pathogens. Hence, the depletion of $CD4^+$ T cells that is associated with HIV-1 infection is thought to have a major role in the increased risk of TB in individuals infected with HIV-1.[10]

In addition, the introduction of ART can exacerbate the immunopathology of TB, giving rise to immune reconstitution inflammatory syndrome (IRIS). IRIS is an inflammatory disorder associated with either paradoxical unmasking or worsening of opportunistic infections after ART initiation. TB-IRIS is the most common manifestation with the potential to affect the kidney.

HIV/TB and Kidney Disease

Figure 2 describes how HIV and TB can affect the kidney, leading to chronic kidney disease (CKD). Kidney disease in the setting of HIV is common, with a wide range of possible causes including acute kidney injury, HIV-associated nephropathy (HIVAN), immune-complex kidney disease, diabetic kidney disease, and hypertensive nephrosclerosis.[11] It also may be caused by opportunistic infections, of which TB is the most common, as well as the drugs used to treat TB.[12-14] There now have been several studies reporting on a change in the spectrum of kidney disease in PWH since the ART era.[12,15,16] HIVAN is declining in regions where ART initiatives were commenced early in the HIV epidemic. Two recent biopsy series from South Africa also reported an increase in the proportion of biopsy specimens with tubulointerstitial disease, which has been influenced in part by granulomatous interstitial nephritis (GIN) in the setting of HIV/TB coinfection.[13,15]

Figure 3 describes how TB effects the kidney and genitourinary tract. TB can affect the kidney in two

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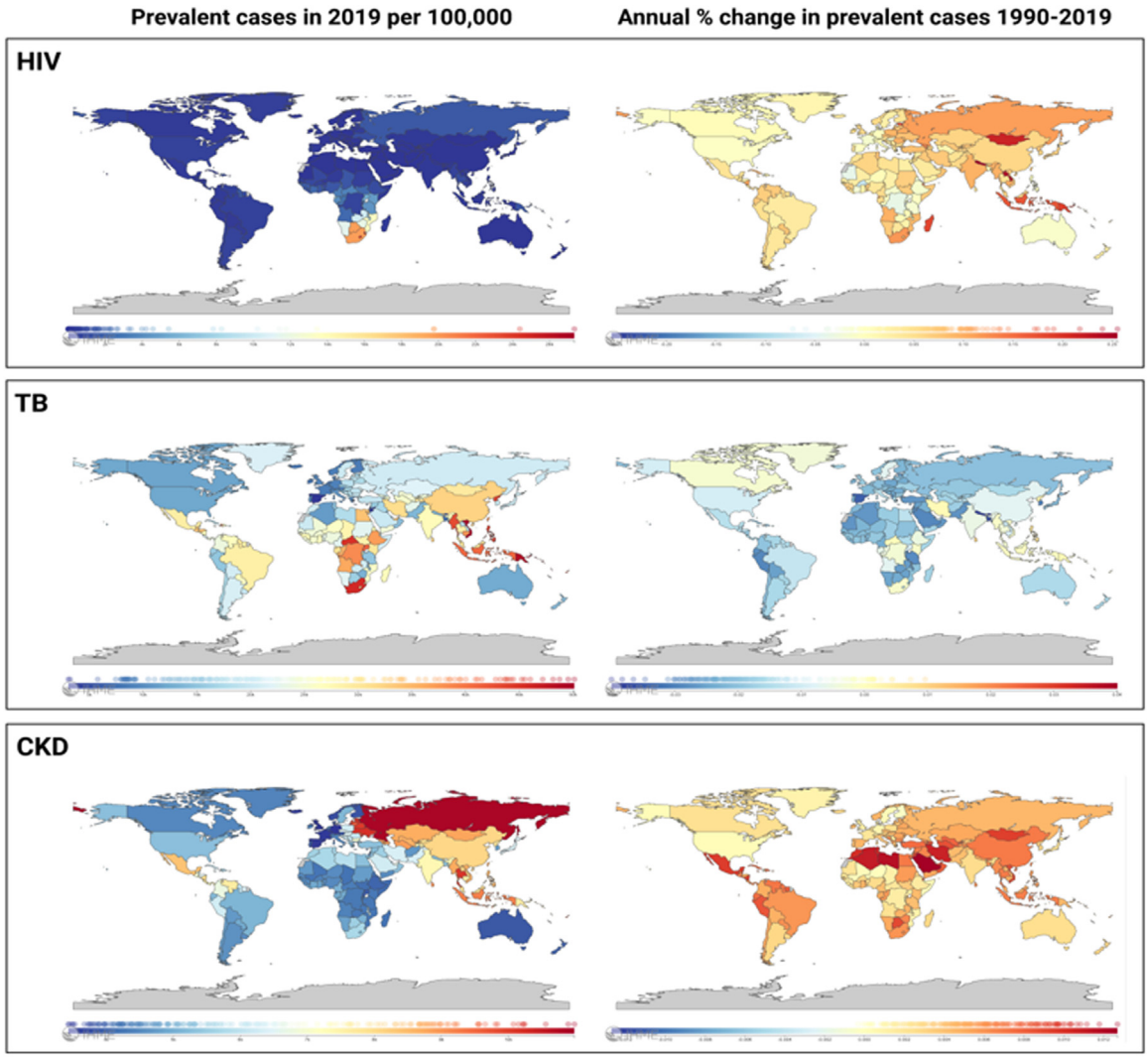

Figure 1. Prevalence and annual changes in prevalence for human immunodeficiency virus (HIV), tuberculosis (TB), and chronic kidney disease (CKD). Derived from the Institute for Health Metrics and Evaluation GBD 2019. ©2023 University of Washington (https://www.thelancet.com/lancet/visualisations/gbd-compare). The data presented are the prevalent cases per 100,000 for adults of both sexes, ages 15 to 49 years in 2019, and then the annual percentage change from 1990 to 2019.

major ways, first by causing genitourinary TB (GU-TB), and, second, in the form of GIN. Autopsy series describing TB involvement in the kidney of PWH in the pre-ART from India, Mexico, and Cote D'Ivoire have reported a frequency of 59%, 23%, and 60%, respectively.[11,17,18] In a biopsy series of PWH from Cape Town, South Africa, the prevalence of GIN was 10 to 29 times higher (14.2% vs 0.5%-1.37%) than the rate of GIN observed in other reported studies from developed countries. TB accounted for most of these cases (55.5%).[19]

TB-renal IRIS may manifest in the form of TB-GIN or acute interstitial nephritis.[19,20] ART restores the host's ability to form granulomata.[21] A kidney biopsy often is required to establish the diagnosis and guide therapeutic management.

Mechanisms of HIV/TB-Associated Kidney Injury

The mechanisms of TB/HIV injury to the kidney could be a direct effect from the infections, gene expression, chronic inflammation or immunologic dysfunction, comorbidities, aging, coinfections, and from the drugs used to treat these conditions (Table 1).

Direct HIV Injury

The kidney has no CD4, C-C chemokine receptor type 5 (CCR5), or C-X-C chemokine receptor type 4 (CXCR4) coreceptors required for HIV entry into cells, yet without ART, kidney disease rapidly progresses to kidney failure (KF) in PWH. The interaction between HIV-infected CD4+ T cells, macrophages, and renal tubular epithelial

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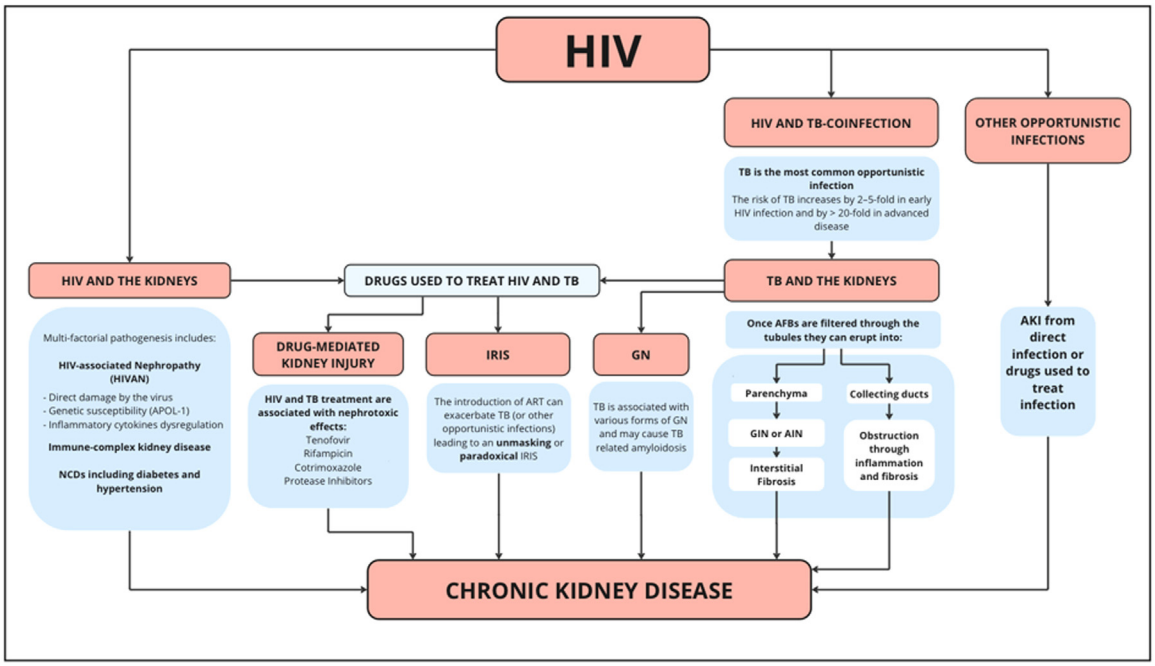

Figure 2. The relationship between human immunodeficiency virus (HIV), tuberculosis (TB), and chronic kidney disease (CKD). Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; APOL-1, apolipoprotein L1; GIN, granulomatous interstitial nephritis; GN, glomerulonephritis; IRIS, immune reconstitution inflammatory syndrome; NCD, noncommunicable disease.

cells contribute to HIV-associated kidney disease, particularly HIVAN.[22,23] Furthermore, HIV gene products Nef and Vpr induce podocyte proliferation[24] and apoptosis, respectively,[25] which may accelerate kidney disease. The ongoing damage to the glomerular and tubular epithelial cells leads to a collapsing glomerulopathy with ultimate glomerulosclerosis, proteinuria, and tubulointerstitial damage.

Cytokines as Inflammatory Mediators

Cytokines play an important role in immune modulation, however, HIV infection causes dysregulation of both proinflammatory and anti-inflammatory mediators.[26] Cytokines may play an important role in HIV-associated kidney disease progression. In one study, the mesangial and tubular cell production of interleukin-6 and tumor necrosis factor-α stimulated HIV replication.[27] Virus multiplication also causes kidney damage through inflammatory mediators.

Genetic Susceptibility

The *APOL1* gene was first identified in Black Americans in the United States.[28] It later was noted that indigenous people from West Africa had the highest levels of *APOL1*, which is present in up to 40% of the population.[29] The variants of *APOL1* evolved to protect individuals from African trypanosomiasis, conferring a greater risk of developing focal segmental sclerosis and HIVAN among PWH. Two variants (G1 and G2) are associated with an increased risk of kidney disease compared with wild type (G0). The G1 allele encodes two missense mutations in the APOL1 protein, whereas G2 encodes a two−amino acid deletion. APOLI-associated kidney disease is mediated through cytotoxicity, cell lysis, and apoptosis.[30] *APOL1* potentiates HIVAN and can cause accelerated kidney disease in patients without ART. It has been noted that not all people with *APOLI* double variants develop disease. This has led to the second-hit theory, postulating the need for high levels of inflammatory markers and interferon γ to promote kidney damage in high-risk *APOLI* risk variants. HIV is a high-risk second hit.[31,32] As an example, *APOL1* combination risk variants (G1 and G2) had 89-fold increased odds of developing HIVAN compared with HIV+ controls. In 120 patients with HIVAN and CKD and 108 controls from a South African Black population, Kasembeli et al[33] found that 79% of patients with HIVAN and 2% of the controls carried two risk alleles (APOL1 G1 and G2 variants).

Data from patients with kidney transplants suggest that the presence of *APOL1* high-risk variants in the organ donor, rather than in the transplant recipient, determines the risk of subsequent disease.[34,35] Together, these reports strongly suggest that in those with high-risk *APOL1* variants, kidney injury is likely to be mediated locally, within the kidney. The kidney has been noted to be a site of HIV replication and persistence in HIV+ kidney transplant recipients.[36-40] The kidney also can be a

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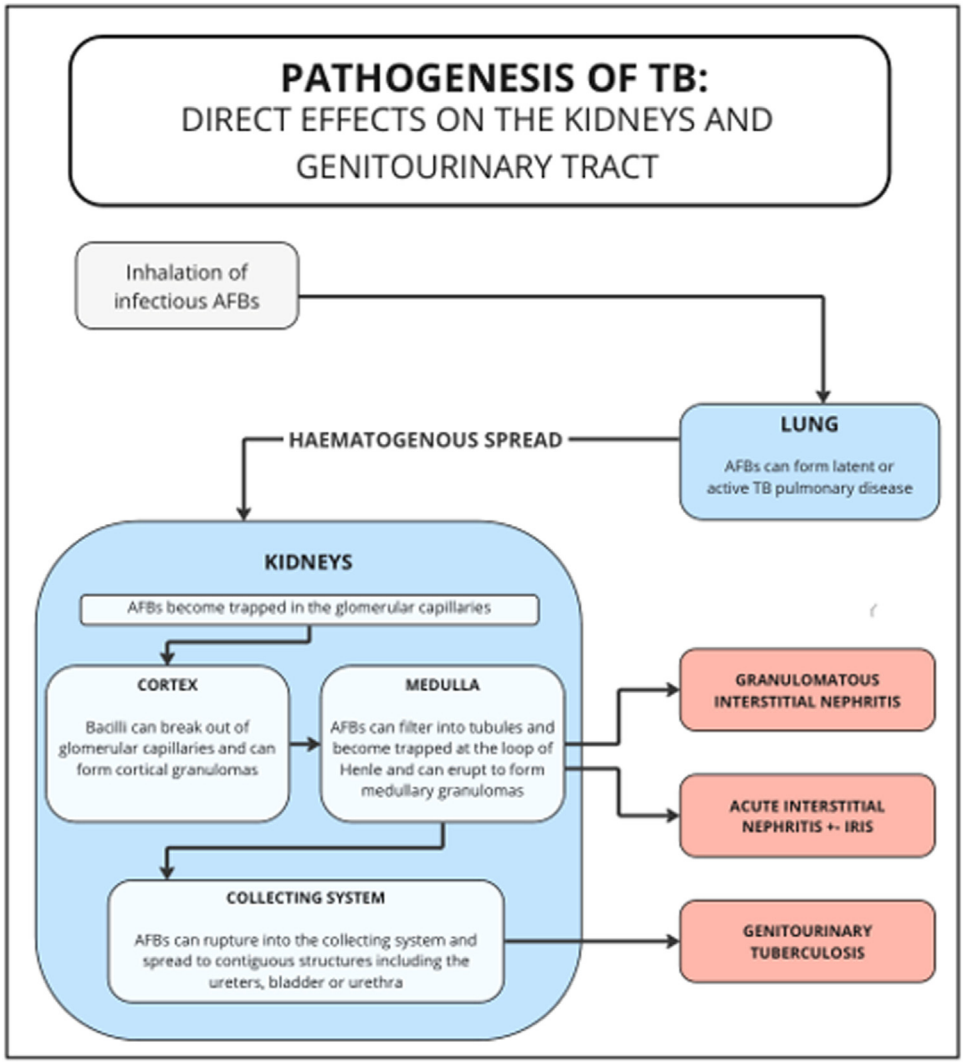

Figure 3. Pathogenesis of tuberculosis: direct effects on the kidney and genitourinary tract. Abbreviations: AFB, acid fast bacilli; IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis.

reservoir for HIV after kidney transplantation. In a study of 19 transplant recipients with undetectable HIV viral loads who received noninfected kidneys, the kidneys later were confirmed to have active HIV infection despite undetectable viremia in the recipients.[38]

Table 1. Mechanisms of HIV/TB Kidney Injury

Direct HIV injury
Inflammatory cytokines
Opportunistic infections and the kidney
Genetic susceptibility
TB direct injury, localized genitourinary disease, granulomatous interstitial nephritis, TB–immune reconstitution inflammatory syndrome, and acute interstitial nephritis

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

Opportunistic Infections, Comorbidities, and the Kidney

Opportunistic infections such as TB, *Cryptococcus neoformans*, cytomegalovirus, and their treatment increase the risk of developing kidney disease among PWH.[14,41] With the advent of ART, PWH are living longer, thereby increasing the risk of comorbidities such as diabetes mellitus, hypertension, and other cardiovascular diseases. The presence of comorbidities, as well as their treatment, predispose to the development of kidney disease through accelerated inflammation, toxicities, and apoptosis (Fig. 2).[42-45]

Direct TB Injury and TB-IRIS

Tuberculosis directly can involve the glomerulus, tubules, or the interstitial space of the kidneys. TB forms caseating granulomas in the glomeruli that may erupt

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and discharge bacilli into the tubules. Tuberculomas in the cortex may calcify or rupture into the pelvis and subsequently into the tubules and along the urinary system, subsequently causing spread of bacilli to the urinary bladder and the urethra, leading to GU-TB (Fig. 3). TB also is associated with various forms of glomerulonephritis and may cause TB-related amyloidosis[46] (Fig. 2). On the other hand, patients with a low CD4 count and high HIV viral loads are predisposed to TB-IRIS. TB-IRIS reflects recovery of the innate immune inflammatory responses to *M tuberculosis*, which may be exacerbated by the recirculation of *M tuberculosis*−reactive T cells and failure of the normal homeostatic control of inflammatory responses,[47] leading to kidney damage.[11,19,48,49]

Patients with KF show a highly inflammatory plasma profile (glycosylation) and an activated cellular state (monocyte activation) compared with those without KF, which may explain the high risk of latent TB reactivation seen in this population.[50]

Drug-Mediated Kidney Injury

HIV and TB therapies are associated with nephrotoxic effects.[14,51-54] Although rare, rifampicin has been associated with life-threatening KF through antibody-mediated hemolysis, leading to release of the nephrotoxic heme pigment.[54] In the Wistar rat model, a combination of isoniazid, rifampicin, and pyrazinamide caused an increased number of reactive oxygen species with increased enzymatic antioxidants and alteration in anti-apoptotic genes promoting apoptosis.[55]

Nephrolithiasis attributed to protease inhibitors (PIs) mainly results from crystallization, dehydration, and alkaline urine, and is aggravated by concomitant use of other drugs, urinary stasis, or the presence of urinary tract infections.[56] The presence of CKD affects the choice and dosing of ART when cleared by the kidneys. The greatest culprits are PIs (indinavir and atazanavir, boosting ritonavir) and tenofovir disoproxil fumarate (TDF). TDF toxicity can result in tubular injury with hypophosphatemia, glycosuria, proteinuria, and an increased creatinine concentration.[56] TDF causes kidney dysfunction through organic transporter interference, and proximal tubular dysfunction (mitochondria injury), with or without decreased kidney function.[57,58] This injury may be aggravated in the presence of PIs (such as ritonavir and lopinavir), which inhibit the membrane receptor protein-2 on the luminal side of the tubule.[59]

Some ARTs (dolutegravir, raltegravir, elvitegravir, and cobicistat) may cause falsely increased creatinine concentrations through interference with the tubular secretion of creatinine without any evidence of significant kidney injury.[60] Second-line injectable drug −related adverse drug reactions are common among Extensively Drug-Resistant (XDR-TB) patients and should be avoided if other alternatives are available.[61]

THE DIAGNOSES OF HIV/TB COINFECTION AND CKD

Clinical Presentation

Presentation of genitourinary-TB

GU-TB often is missed owing to lack of awareness, its insidious onset, chronic nonspecific symptoms, and variable clinical manifestations. A high degree of suspicion therefore is warranted.[62-65] GU-TB can present at any age, however, the presentation is uncommon in children because of the long latency period. Active disease may present only 5 to 15 years after the primary infection.[66] Many patients can be asymptomatic during the early stages and have nonlocalizing symptoms and signs often disguised under differing diagnoses.[63,64,67] The clinical presentation can vary widely from asymptomatic to nonspecific symptoms and signs to obstructive uropathy and KF.[68] The presentation of GU-TB in the setting of HIV also may differ in that there may be a predominance of systemic symptoms and disseminated disease with a lower frequency of involvement of the collecting system.[69]

Dysuria, urinary hesitancy, and frequency are common findings in kidney, bladder, and prostatic TB. Patients with kidney involvement also may have associated flank or renal angle tenderness and often are misdiagnosed with acute bacterial urinary tract infections. In these cases, urinalysis often shows a sterile pyuria (negative culture), and microscopic or macroscopic hematuria.[68] Regardless of HIV status, a delay in diagnosis results in disease progression, tissue and organ damage, and possible obstructive uropathy that ultimately may lead to KF (Fig. 3).

Presentation of GIN

In the setting of HIV in TB endemic areas, GIN is a common finding in biopsy specimens. In a South African cohort of 316 PWH, 45 biopsy specimens showed GIN (14.2%), with TB being the likely cause in 27 (60%), and 9 (20%) attributed to a drug. TB-GIN was associated with low CD4 levels, less than 200 cells/mm^3, and the granulomas typically were formed poorly. Proteinuria was the most prominent finding on urine dipstick in 38 of 40 (84%), followed by hematuria in 27 (60%). Sterile pyuria was present in 16 (35.6%) patients.[19] The difficulty in identifying granulomas in the kidney parenchyma in immunodeficient patients has been documented previously.[70] Poorly formed granulomas have been attributed to impaired CD4+ cell function in HIV, thereby changing cytokine secretion, causing a

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switch from cell-mediated immunity (Th1) to humoral immunity (Th2).[71]

In the South African HIV cohort, 6 of 45 patients fit the clinical entity of TB-IRIS associated with GIN. This typically occurred within 8 to 12 weeks of ART initiation, a similar timeframe to other forms of IRIS.[72] ART treatment restores the host's ability to form granulomata, often resulting in an intense paradoxical reaction.[21] There have been few published case reports describing kidney biopsy−proven IRIS-related TB-GIN.[19] A more recent publication on IRIS-related acute interstitial nephritis adds to the existing literature.[20] Chronic inflammation as a result of GIN may lead to interstitial fibrosis and progression of CKD.

Investigations and other modalities

A comprehensive history and clinical examination raising suspicion for GU-TB should be followed by targeted diagnostic investigations. The definitive diagnosis of GU-TB remains difficult and usually is made by demonstration of *M tuberculosis* in clinical samples through smear microscopy using Ziehl-Neelsen staining of acid-fast bacilli (AFB), culture, or genetic amplification assays.[68] These diagnostic tests can be applied to various specimens, including urine, semen, vaginal fluid, kidney histology, and bladder tissue, all of which have varying yields, specificity, and sensitivity.

Urine samples generally are pauci-bacillary and on microscopy leukocytes and erythrocytes may be present.[73] The gold standard for diagnosis remains mycobacterial culture, however, because of the slow growth of bacilli it can take 6 to 8 weeks to obtain results. These tests are expensive and require specialist laboratory facilities that may be unavailable in high-burden settings.[74,75] In addition, urinary mycobacterial cultures have a low sensitivity, with a reported yield of 2% to 46% in HIV-negative patients.[73,74] Comparatively, in PWH, one study showed a yield of up to 77%.[76] Nonetheless it still has limited use in accurately making an early diagnosis.[76,77]

Nucleic acid amplification tests, endorsed by the WHO since 2010, including the Xpert MTB/RIF assay (Cepheid Inc.) have assisted in reducing delays in diagnosis.[78] They have the added benefit of simultaneous detection of both *M tuberculosis* and rifampicin drug resistance. In a Cochrane meta-analysis that included 1,199 samples from 13 studies including both PWH and negative patients, the Xpert had a pooled sensitivity of 82.7% (69.6%-91.1%) and a specificity of 98.7% (94.8%-99.7%) compared with traditional urine culture.[79]

Xpert MTB/RIF Ultra (Xpert Ultra), is the newer-generation assay, which was developed to improve sensitivity and increase the accuracy of rifampicin resistance detection and has an eight-fold lower analytical limit of detection than Xpert.[78,80] Xpert Ultra has shown improved sensitivity in patients with low-bacillary burdens. The diagnostic performance of Xpert compared with Xpert Ultra on urine has yet to be evaluated rigorously in the literature.[75]

Biopsy specimens of bladder and kidney tissue may assist with diagnosis in specific cases.[75] Typical biopsy findings show a tubulointerstitial nephritis and granuloma formation, with or without the presence of AFBs.[70] The yield of AFBs on kidney histology is not high in PWH. In a study of 45 biopsy specimens in PWH from South Africa, multiple predominantly poorly formed granulomata were seen in 16 (35.6%) of the specimens. Ziehl-Neelsen staining for AFB was performed in 23 patients, with only two positive results (4.4%). There was no evidence of caseous necrosis identified in any of the biopsy specimens.[19] Chronic interstitial nephritis, papillary necrosis, and fibrosis also can been seen on kidney histology.[73] Xpert and Xpert Ultra, although used on other tissues such as lymph nodes, has been investigated minimally on kidney biopsy and genitourinary tract tissue samples.

Because of an increasing need to enhance diagnostic methods, TB biomarkers such as lipoarabinomannan (LAM), a component of the mycobacterial cell wall, have been investigated to assist with same-day diagnosis and drug initiation. The presence of a positive urinary LAM is explained in part by TB infection of the kidney, but it also is positive in other forms of disseminated TB, signifying other nonexplained mechanisms for urinary LAM positivity.[81] In the systematic review by Gupta-Wright et al,[82] detectable urinary LAM was an independent risk factor for mortality among patients receiving treatment for HIV/TB.

The Alere Determine TB LAM Ag assay (AlereLAM-Abbot) is a point-of-care bedside test that tests a urine sample and provides a result in less than 30 minutes.[83] This test has limited sensitivity in all populations, however, in PWH, the sensitivity improves with lower CD4 counts.[83] The WHO strongly recommends the use of the AlereLAM in HIV-positive inpatients with signs and symptoms of TB, who are seriously ill or with advanced HIV disease, and any patient with a CD4 count less than 200 cell/mm^3.[84] There are fewer data with regard to the outpatient use of AlereLAM; the WHO suggests that there is possible benefit in testing patients who are seriously ill and those with a CD4 count less than 100 cell/mm^3.[84] Newer assays, including FujiLAM (Fujifilm), which has two monoclonal antibiotics targeting LAM and an additional silver particle amplification step, shows superior sensitivity compared with the AlereLAM.[85]

Imaging can aid in the diagnosis, assist with detection of complications, and guide further surgical management if indicated.[68,73] Ultrasound, X-ray, computerized tomography, magnetic resonance imaging, and isotope studies all can be used on a case-by-case basis.[86] Radiologic findings supporting TB in the kidney are

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hypoattenuated cortical lesions and calcifications as well as a moth-eaten appearance of the calyx. Findings suggestive of GU-TB include the following: multiple strictures, localized hydrocalycosis, cavitary lesions, low-capacity thimble bladder, pipe-stem ureter, calcifications, and calculi.[86]

THE MANAGEMENT (TREATMENT) OF HIV/TB COINFECTION AND CKD

Overview of Therapies for HIV/TB

Since the introduction of zidovudine for the treatment of HIV in 1987, numerous ART classes have emerged, including nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), PIs, integrase strand transfer inhibitors, fusion inhibitors, CCR5 antagonists, and novel agents such as CD4 postattachment inhibitors (ibalizumab), gp-120 attachment inhibitors (fostemsavir), and capsid inhibitors (lenacapavir). Current WHO guidelines (2021) recommend the initiation of ART in all PWH, with the combination of dolutegravir (DTG) and an optimized NRTI backbone tenofovir disoproxil fumarate (TDF) and either lamivudine (3TC) or emtricitabine (FTC) as the preferred first-line regimen, with TDF/3TC (lamivudine)/efavirenz (EFV as an alternative).[9] Tenofovir alafenamide (TAF) may be considered in place of TDF in patients with mild CKD or with use of concomitant nephrotoxic agents because of its lower risk of nephrotoxicity and equal efficacy to TDF in PWH.[87]

In HIV/TB coinfection, timing of ART initiation should be within 2 weeks of starting anti-TB therapy (but delayed by at least 4 weeks after starting anti-TB treatment for TB meningitis).[9] Rifampicin is a potent inducer of the cytochrome P450 enzyme system, giving rise to drug interactions with multiple ARTs when co-administered. DTG administration in the setting of concomitant rifampicin use thus requires increasing the DTG dose to 50 mg twice a day throughout the duration of rifampicin therapy, and up to 2 weeks after stopping rifampicin.[9] DTG dose adjustment is not required if rifabutin or rifapentine is used in place of rifampicin.

Rifampicin also can decrease concentrations of PIs, nevirapine, and TAF. No dose adjustment is required if rifampicin is co-administered with EFV. Co-administration of newer anti-TBs such as bedaquiline and delamanid with PIs should be performed with caution owing to the risk of prolongation of the QT interval.[9]

ART and the Kidney

Special considerations need to be made when prescribing ART to PWH with comorbid CKD because some ARTs predominantly are excreted renally whereas others are nephrotoxic. TDF generally should be avoided in patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min, and should be substituted with another ART if there is a greater than 25% decline in eGFR or a reduction in GFR to less than 60 mL/min with its use.[88] However, in settings where there is no alternative to TDF use, a dose adjustment may be considered.[47] Co-administration of TDF with ritonavir-boosted PIs as well as with cobicistat may increase the risk of TDF-associated nephrotoxicity.[47] Rapid eGFR decline also has been observed with use of the PIs atazanavir and lopinavir-ritonavir, with improvement in kidney function noted when these drugs were substituted with boosted darunavir.[47]

Apart from abacavir, other NRTIs will require dose adjustment in patients with CKD (Table 2). No dose adjustment is required for NNRTIs, PIs, DTG, or bictegravir in the setting of CKD.[14,51]

TB Therapies and the Kidney: Special Considerations

First-line anti-TB therapy for susceptible *M tuberculosis* strains remains the combination of rifampicin, isoniazid, pyrazinamide, and ethambutol in the intensive phase of treatment, and rifampicin/isoniazid in the continuation phase. Metabolites of pyrazinamide such as pyrazinoic acid may accumulate in patients with advanced KF, whereas approximately 80% of ethambutol is excreted via the kidneys; these drugs thus require dose adjustment in CKD.[89] Dose reduction of these two agents may lead to impaired treatment efficacy owing to reduced peak serum levels; experts thus recommend increasing the time interval between doses rather than a dose reduction among patients with an eGFR less than 30 mL/min and those on hemodialysis[89] (Table 3). These frequency-adjusted treatment schedules have been shown to be efficacious among patients with CKD.[90]

For patients with advanced CKD who require second-line anti-TB treatment, adjustment of treatment frequency to two to three times a week is required for levofloxacin, cycloserine, streptomycin, capreomycin, amikacin, and kanamycin.[89] The newer anti-TB agent bedaquiline is excreted predominantly via feces and does not require a dose adjustment in mild to moderate kidney disease.[91] However, caution is advised when used in advanced kidney disease and in patients on hemodialysis, owing to limited data on its efficacy and safety in this subset of patients.[92]

HIV/TB and Dialysis

NNRTIs are removed by hemodialysis, thus ART should be administered after hemodialysis sessions. Fixed-dose combination tablets are not recommended with an eGFR less than 60 mL/min because the various ARTs require a dose adjustment in CKD (Table 2).

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Table 2. Dose Adjustment of Commonly Used ARTs in Adults With Chronic Kidney Disease[14,103,104]

ART	eGFR				Intermittent Hemodialysis	Peritoneal Dialysis
	≥50 mL/min	30-49 mL/min	10-29 mL/min	<10 mL/min		
NRTIs						
Abacavir	300 mg q12h or 600 mg q24h	No dose adjustment required				
Emtricitabine	200 mg q24h		200 mg q72h	200 mg q96h	200 mg q24h	No data
Lamivudine	300 mg q24h	150 mg q24h	100 mg q24h	25-50 mg q24h	25-50 mg q24h	25-50 mg q24h
Tenofovir disoproxil fumarate	300 mg q24h	300 mg q48h	Not recommended If no alternative: 300 mg q72h-q96h	Not recommended If no alternative: 300 mg q7d	300 mg q7d	No data
Tenofovir alafenamide	25 mg q24h			No data	25 mg q24h	No data
Zidovudine	300 mg q12h			100 mg q8h	100 mg q8h	No data
NNRTIs						
Efavirenz	600 mg q24h	No dose adjustment required				
Nevirapine	200 mg q12h	No dose adjustment required			Additional 200 mg after dialysis	No dose adjustment
Rilpivirine	25 mg q24h	No dose adjustment required				
INSTIs						
Dolutegravir	50 mg q24h	No dose adjustment required				
Raltegravir	400 mg q12h or 1,200 mg q24h	No dose adjustment required				
PIs						
ATV/r	300/100 mg q24h	No dose adjustment required			Not recommended	No dose adjustment
DRV/r	800/100 mg q24h 600/100 mg q12h	No dose adjustment required				
LPV/r	400/100 mg q12h	No dose adjustment required				
Fusion inhibitor						
Enfuvirtide	90 mg SC q12h	No dose adjustment required				

Comprehensive renal function–adjusted dosing details for more ARTs can be accessed from the listed sources that were used to compile this table: https://eacs.sanfordguide.com/drug-drug-interactions-other-prescribing-issues/other-prescribing-issues/arv-dosing-renal-impairment and https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-characteristics-tables-renal-hepatic-insufficiency-full.

Abbreviations: ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; eGFR, estimated glomerular filtration rate; INSTI, integrase strand transfer inhibitor; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; q7d, every 7 days; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; q48h, every 48 hours; q72h, every 72 hours; q96h, every 96 hours.

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Table 3. Dose Adjustment of Anti-TB Therapies in Adults With Chronic Kidney Disease[6,47]

Drug	eGFR ≥60 mL/min	eGFR 30-59 mL/min	eGFR <30 mL/min	Intermittent Hemodialysis	Peritoneal Dialysis
Rifampicin	10 mg/kg q24h	No dose adjustment required			
Isoniazid	5 mg/kg q24h	No dose adjustment required			
Pyrazinamide	25-35 mg/kg q24h	25-35 mg/kg q24h	25-35 mg/kg 3 times per week	25-35 mg/kg 3 times per week after hemodialysis	No dose adjustment required
Ethambutol	15-25 mg/kg q24h	15-25 mg/kg q24h	15-25 mg/kg 3 times per week	15-25 mg/kg 3 times per week after hemodialysis	15 mg/kg q48h
Moxifloxacin	400 mg q24h	No dose adjustment required			
Prothionamide	15-20 mg/kg/d in divided doses	No dose adjustment required	eGFR ≥10 to 30: no dose adjustment eGFR <10: 250 mg q12h	250 mg q12h	250 mg q12h
Cycloserine	10-15 mg/kg/d in divided doses	250 mg q12h	250 mg q24h	250 mg q24h given after dialysis	250 mg q24h
Bedaquiline	400 mg q24h for 2 weeks then 200 mg 3 times per week	No dose adjustment required	Use with caution and consider therapeutic drug monitoring		
Linezolid	600 mg q24h	No dose adjustment required			
Para- aminosalicylic acid	8-12 g/d in divided doses	No dose adjustment required	4 g q12h	4 g q12h	4 g q12h
Streptomycin, amikacin, capreomycin	15 mg/kg/d	15 mg/kg individual doses with dosing interval extended to achieve an undetectable plasma trough level before each dose			
Clofazimine	100 mg q24h	No dose adjustment required			

Further details on anti-TB drug dosing can be accessed from the listed sources that were used to compile this table: https://www.health.qld.gov.au/__data/assets/pdf_file/0024/444507/tb-guideline-renal.pdf and https://pubmed.ncbi.nlm.nih.gov/27516382, and official American Thoracic Society/Center for Disease Control/Infectious Disease Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis.
Abbreviations: eGFR, estimated glomerular filtration rate; q12h, every 12 hours; q24h, every 24 hours; q48h, every 48 hours; TB, tuberculosis.

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Among the anti-TBs, pyrazinamide undergoes significant clearance via hemodialysis, with up to 45% recovered in dialysate fluid, compared with 9% for isoniazid, 4% for rifampicin, and 2% for ethambutol.[93] It thus is preferable to administer anti-TB therapy posthemodialysis to facilitate directly observed therapy, as well as to mitigate against hemodialytic clearance of pyrazinamide. Data on the effect of peritoneal dialysis on clearance of anti-TB agents are scarce, with a small study suggesting no dose adjustment is required for isoniazid, rifampicin, and pyrazinamide among patients on continuous ambulatory peritoneal dialysis.[94] Monitoring of serum drug levels of anti-TB drugs among dialysis patients may be considered to ensure adequate drug levels are maintained, while reducing the risk of drug toxicity owing to accumulation.[89]

HIV/TB and Kidney Transplant

The potential exists for clinically significant drug interactions between ARTs and transplant immunosuppressant drugs. NNRTIs such as EFV and nevirapine induce the metabolism of tacrolimus, with increased tacrolimus doses required to maintain required trough levels. On the other hand, PIs compete with tacrolimus for binding to CYP3A isozymes, inhibiting tacrolimus metabolism and increasing risk of its toxicity.[95] A reduction of the tacrolimus dose and even increasing the dosing interval to once every 7 days thus may be required when co-administered with PIs,[96] as well as more frequent therapeutic drug monitoring.

These drug interactions are not benign; HIV-positive kidney transplant recipients on PI-based regimens had higher rates of biopsy-proven calcineurin inhibitor toxicity compared with those on an NNRTI-based regimen.[96] There also are recent data implicating an increased risk of rejection for those on a PI regimen.[97] Use of integrase inhibitor−based regimens (unboosted integrase strand transfer inhibitor plus 2 NRTIs) thus is recommended in HIV-positive kidney transplant recipients owing to minimal risk of drug interactions, as well as higher rates of graft survival at 3 years.[98-100] A comprehensive ART immunosuppressant drug interaction table can be accessed at https://eacs.sanfordguide.com/drug-drug-interactions-other-prescribing-issues/drug-drug-interactions/immunosuppressants-arvs-interactions.

Among anti-TB agents, rifampicin induces cytochrome P450 enzymes, leading to reduced drug levels of calcineurin inhibitors as well as Mammalian target of rapamycin (mTOR) inhibitors. Kidney Disease: Improving Global Outcomes recommends close monitoring of these immunosuppressant drug levels during rifampicin use, or, alternatively, substituting rifabutin for rifampicin because of the lower risk of drug interactions.[101] A rifampicin-sparing regimen consisting of isoniazid/ethambutol/levofloxacin/pyrazinamide in the intensive phase and isoniazid/ethambutol/levofloxacin in the maintenance phase also has been used successfully among HIV-negative kidney transplant recipients.[102]

Prevention of Kidney Disease in HIV/TB Coinfections

Both HIV and TB present an increased risk for the development of CKD.[47] Because of the often-delayed diagnosis, patients present late for medical care. Kidney disease screening among high-risk individuals, such as those with diabetes mellitus and hypertension, is advocated routinely. [103,104] However, there are no specific screening protocols for patients with HIV/TB coinfection.[105] The majority of these patients present with chronic ill health, therefore it is very easy to attribute the occurrence of CKD to the primary disease of HIV/TB.[106] Moreover, once patients with KF get TB, they are more likely to spread it to other individuals during dialysis because they are in close proximity for up to 4 hours. In addition, there is triple immunosuppression in patients with HIV/TB and CKD, making it a very fertile ground for nosocomial spread of disease.[107]

It is therefore important that patients with HIV/TB coinfection are considered as a high-risk category for the development of CKD and screened routinely as well as before the initiation of drugs.[47]

Measuring baseline kidney function can help guide the selection of the drug combinations, thereby avoiding nephrotoxic agents such as PIs and TDF, as shown in Table 2.

Once the kidney function is established, drug dose adjustments can be made with recommendations to use individual ART and anti-TB drugs, as well as preferential use of newer kidney-friendly ART such as TAF.[87]

It is of paramount importance to monitor kidney function among patients with TB/HIV because of the increased risk of drug interactions, as well as additional exposure to nephrotoxic drugs used to treat opportunistic infections. Look out for drug−drug interactions, for example, rifampicin is a liver enzyme inducer that may affect ART levels similar to PIs, therefore such combinations should be avoided.[14,47,108]

It now is possible to offer kidney transplants to PWH, including those from HIV-positive donors.[109,110] Special consideration should be taken for PWH on dialysis and those with kidney transplants because they are at increased risk of developing TB and an increased risk of death.[107] Because of the high risk of complications, PWH should have TB treated before transplantation. Once transplanted, they should be kept on prophylaxis with isoniazid for the first 6 to 12 months after transplant.[111] In TB endemic regions, this also could be considered life-long. Table 4 contains a summary on preventive measures.

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Table 4. Principles of Prevention of Kidney Disease Among Patients With TB/HIV

Assessment and staging of kidney function
Avoid nephrotoxic agents
Drug dose adjustments
Separate fixed-dose combinations
Switching therapies when drug interactions or low eGFR
Monitor kidney function in patients on potential nephrotoxic agents
Consider drug–drug interactions
Special considerations for KRT patients
Other considerations such as vaccinations for flu, *Streptococcus pneumoniae, Hemophilus influenza*, COVID-19, and hepatitis B

Abbreviations: COVID-19, coronavirus disease-2019; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; KRT, kidney replacement therapy; TB, tuberculosis.

Current Gaps and Recommendations for the Future

The COVID-19 pandemic disrupted TB and HIV prevention and treatment programs, resulting in an increase in new infections and deaths in 2021. Eastern Europe, central Asia, the Middle East and North Africa, and Latin America all have seen increases in annual HIV infections over the past decade. Despite ART use, HIV-associated kidney disease still is present. Of the approximately 28.7 million PWH accessing ART in 2021, equal to 75% of all people living with HIV, 68% are reported to be virally suppressed, which is short of the recommended 95% targets.

Multidrug-resistant TB remains a public health crisis and a health security threat. Only approximately one in three people with drug-resistant TB accessed treatment in 2021. Third-line therapies for HIV infection also are hard to access.[112,113]

More efforts on public education, early diagnosis, and adherence to therapy, together with development of nontoxic therapeutic agents, are required to impact these devastating infections.

The WHO is developing a plan for pandemic preparedness, which in addition to improving nations' capacity to handle pandemics, may prevent its devastating effects on treatment of other infections and chronic diseases. Research on TB/HIV and kidney disease should be prioritized to generate evidence for dealing better with this highly lethal triad.

CONCLUSION

HIV/TB coinfection poses an increased risk for kidney-related morbidity and mortality that requires special consideration. GIN and GU-TB are underdiagnosed. Because the symptoms, signs, and imaging features can be nonspecific, it remains important to have a high index of clinical suspicion, especially in endemic regions. Further research remains for novel biomarkers and assays to improve sensitivity and specificity to make a timely diagnosis. There is great opportunity to combat this lethal triad through having a high index of suspicion for kidney disease among HIV/TB patients, active screening, and the use of appropriate and safer drug regimens coupled with regular follow-up evaluation. For patients on dialysis and those with kidney transplants, special caution is needed in their management. With proper care, patients with HIV/TB and kidney disease can live longer.

ACKNOWLEDGMENT

The authors would like to acknowledge Andrea L Conroy, who helped in the visualization of Figure 1.

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