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Pharmacotherapeutic options for kidney disease in HIV positive patients

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Abstract

Introduction: Since the development of combined antiretroviral therapy (cART), HIV-associated mortality and the incidence of HIV-associated end-stage kidney disease (ESKD) has decreased. However, in the United States, an increase in non-HIV-associated kidney diseases within the HIV-positive population is expected.

Areas Covered: In this review, the authors highlight the risk factors for kidney disease within an HIV-positive population and provide the current recommendations for risk stratification and for the monitoring of its progression to chronic kidney disease (CKD), as well as, treatment. The article is based on literature searches using PubMed, Medline and SCOPUS.

Expert opinion: The authors recommend clinicians (1) be aware of early cART initiation to prevent and treat HIV-associated kidney diseases, (2) be aware of cART side effects and discriminate those that may become more nephrotoxic than others and require dose-adjustment in the setting of eGFR ≤ 30ml/min/1.73m^2, (3) follow KDIGO guidelines regarding screening and monitoring for CKD with a multidisciplinary team of health professionals, (4) manage other co-infections and comorbidities, (5) consider changing cART if drug induced toxicity is established with apparent eGFR decline of ≥ 10ml/min/1.73m^2 or rising creatinine (≥0.5mg/dl) during drug-drug interactions, and (6) strongly consider kidney transplant in appropriately selected individuals with end stage kidney failure.

Keywords

APOL1; antiretroviral medications; dialysis; HIV; HIVAN; HIVICK; nephrotoxicity

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1. Introduction

In 2018, there were over 37 million people in the world living with human immunodeficiency virus (HIV), of whom approximately 36 million were adults and 1.7 million were children under the age of 15 (1). The Joint United Nations Program on HIV/AIDS (UNAIDS) reported that approximately 1 million people died from acquired immunodeficiency syndrome (AIDS)-related illnesses by the end of 2018. With the advent of combined antiretroviral therapy (cART), there have been significant improvements in HIV-associated mortality, and the worldwide prevalence of HIV continues to grow despite the decrease in incidence of HIV, of which the highest prevalence has been reported in eastern and southern Africa (1).

In addition to improved overall mortality, where cART averted approximately 1 million deaths worldwide as of 2016 (2), cART has also been associated with decreased incidence of HIV-associated end-stage-kidney-disease (ESKD). In the United States (US) alone, mortality in HIV-associated ESKD individuals initiating dialysis declined by 70% in 2009–2011 compared to 1989–1992, but mortality has remained at least 2.5- to 3-times higher than patients with ESKD from non-HIV-associated causes. (3). In line with this trend, an increase in non-HIV-associated kidney disease amongst patients with HIV is expected from the growing number of people living longer, improved testing, and ongoing pharmaceutical managements. The US Renal Data System (USRDS) reported 14,719 persons living with HIV and ESKD between 1989 to 2011 with significant reduction between 2006 to 2011 (893 in 2006 and 525 in 2011)(3). One review reported the prevalence of CKD in the US as high as 15.5% based on reduced estimated glomerular filtration rate (eGFR) and presence of proteinuria (4, 5). In a retrospective cohort of 437 biopsy-confirmed cases of HIV-positive individuals in the modern era from Columbia University between 2010 and 2018, 58% were blacks, 25% were whites, 17% were Hispanics, <1% were Asian, median proteinuria was 3.6 g/d (IQR, 1.7–6.9), and 191 patients (44%) had nephrotic range proteinuria (6). HIVAN with collapsing nephropathy was once the predominant diagnosis for HIV-associated disease and up to 60% of biopsy-related diagnosis in CKD individuals (7); however, more recent biopsy series are demonstrating CKD associated with non-HIVAN and non-collapsing focal segmental glomerulosclerosis (FSGS) renal diseases (6, 8, 9). The Kidney Disease: Improving Global Outcomes (KDIGO) group has published guidelines for risk stratifying adults living with HIV into low versus high risk for CKD and propose different monitoring regimens based on the risk (10). Similarly, the Infectious Diseases Society of America (IDSA) guidelines from 2014 propose close monitoring of kidney function and HIV status and maintenance of cART in people living with HIV (PLWH) (11). This expert review aims to highlight risk factors for kidney disease in PLWH and current recommendations regarding risk stratification for monitoring of progression and treatment of CKD.

2. Methods

We performed a comprehensive literature search using the PubMed database from January 1st, 1988 to August 1st, 2020, 2019. For our search strategy, we used the combination of the mesh terms “HIV,” “HIVAN,” “HIVICK,” “adults,” “children,” “nephrotoxicity,” “kidney

disease," "nephropathy," "CKD", "dialysis," and "transplantation." We limited our search to only include articles written in English.

3. Risk Factors for Kidney Disease in the HIV-positive Population

In the pre-cART era, kidney disease in PLWH was driven mostly by physiological complications from the retrovirus itself (e.g. HIVAN). With improvement in mortality from HIV, the spectrum of kidney disease in PLWH has diversified to include not only HIVAN, but also kidney diseases secondary to chronic nephrotoxic anti-retroviral exposures and other causes of kidney diseases of chronicity, common to the general population. Furthermore, research in the last 10 years has identified genetic risk for kidney disease in regions with high HIV prevalence.

3.1 HIV-Associated Nephropathy (HIVAN)

There is an 18- to 50-fold increased risk of developing kidney disease among PLWH of African descent aged between 20 and 64 years compared with their European descent counterparts (5). In one of the largest kidney-biopsy in PLWH, HIVAN was the most common disease in patients not on anti-retroviral therapy, and 94% were African Americans, suggesting an underlying genetic role in this particular glomerulopathy (6).

HIVAN commonly presents with progressive kidney dysfunction, heavy proteinuria, microcystic tubular dilatation, mild-to-moderate interstitial inflammation, and importantly, collapsing FSGS. Presentation generally includes proteinuria. The prevalence of +1 proteinuria is approximately 30% by urinalysis (13) and IDSA guidelines report higher on urinalysis or 24-hour measurements (7). A major limitation to the studies to the studies referenced in the IDSA guidelines in 2005 by Gupta et al. are in regard to the absence of kidney biopsies that would show the degree of destruction and correlations to proteinuria. HIVAN is thought to be related to the "infection" of kidney epithelial cells, resulting in injured podocytes, which then promote sclerotic lesions. Figure 1 displays characteristic pathological features of HIVAN on kidney biopsy.

Many children with HIVAN have a classical FSGS with or without mesangial hyperplasia, microcystic tubular dilation, and interstitial inflammation. This pathophysiological change differs from adults in whom the collapsing variant is more commonly observed. Immune complex deposition with mesangial proliferative lesions can also be seen (14). Among children, approximately 15–30% of them can have biopsy proven HIVAN and collapsing FSGS (15).

The management strategies deployed for the treatment of HIVAN, in either children or adults, prior to the cART were predominantly focused on steroids and renin-angiotensin system (RAAS) blockade for proteinuria. There are no randomized controlled trials (RCTs) for either treatments, instead the literature is predominantly comprised of several observational studies (16). Initial studies in 1994 and 1996 showed that patients treated with steroids for proven HIVAN had an overall improvement in both serum creatinine and proteinuria despite the increased risk of serious infections (17, 18). One of the earliest studies on RAAS blockade was a retrospective study conducted in 1996 where 18 patients

with biopsy proven HIVAN were treated with captopril versus placebo; the authors found much lower progression of kidney disease in the RAAS blockade arm compared to the placebo arm (19). Subsequently, there were multiple retrospective studies with RAAS blockade therapy that demonstrated similar results concerning progression of kidney disease requiring renal replacement therapy (RRT), proteinuria, and affecting overall survival (20, 21). Based on the limited available data on steroid and RAAS blockade, the IDSA guidelines designated a weak recommendation for the use of steroids as an adjunct therapy to RAAS blockade and cART for HIVAN treatment (11).

The IDSA guidelines from 2014 strongly recommended closer monitoring of kidney function, HIV load, and proteinuria in addition to the initiation of cART in PLWH to reduce the risk of progression to ESKD (11). These guidelines also suggest trying to initiate and maintain patients on cART in this population. Table 1 lists the diversity of cART that have been approved and marketed. The first report of HIVAN and cART management was from France in which they retrospectively analyzed data from 57 patients with biopsy proven HIVAN and treatment with cART, and the results showed a median renal survival of 40 months (22). In a large, prospective, longitudinal study tracking PLWH, the incidence of HIVAN (based on clinical criteria only) was decreased by 60% with cART management (23). Factors that have been demonstrated to be associated with worse renal outcomes included: severity of kidney dysfunction, increased sclerotic glomeruli in biopsy pathologies, and the time lapse for diagnosis of HIVAN (4, 24). Co-infections with either hepatitis B infection (HBV) or hepatitis C infection (HCV) were associated with even worse outcomes in another cohort of 36 patients with biopsy proven HIVAN, where 26 patients received cART compared to 10 patients who did not receive cART (25). Outcomes of kidney survival were significantly better for the cART group (adjusted HR [aHR] 0.30, 95% CI 0.09–0.98). In a South African study, in patients undergoing kidney biopsy pre- and post-cART initiation have interestingly demonstrated rapid and sustained clinical response with significant rise in the eGFR and rapid regression of proteinuria, irrespective of the histology (26). Similarly, the START trial demonstrated that immediate cART in the short-term, was associated with a slightly higher eGFR and lower proteinuria risk compared to the group with delayed cART therapy (27).

3.2 Genetic Susceptibility

ESKD risk was approximately 6 times higher in black adults living with HIV compared to their white counterparts (28). Furthermore, the association of HVIAN with blacks was suggestive of an underlying genetic risk. This strong association of HIVAN with blacks living with HIV was ultimately elucidated in 2010 seminal study demonstrating the association of two risk alleles (G1 and G2) in the C-terminal region of *APOL1* gene with increased susceptibility to HIVAN and FSGS in those of African descent (29). It was subsequently estimated that the prevalence of *APOL1* high-risk genotype, defined as the presence of two risk alleles (G1 or G2 variants), in the general African American population is approximately 13% compared to 62% in HIVAN and non-HIVAN FSGS(12, 30). As such, *APOL1* high-risk genotype is a strong predictor of HIVAN, although only 20% with high-risk variants develop the disease (12). Furthermore, HIVAN has also been documented in individuals with no risk alleles suggesting perhaps other factors triggering this disease (12).

APOL1 high-risk genotype has also been linked to incident proteinuria, hypertension attributable nephrosclerosis, and non-diabetic CKD. In general, the odds of proteinuria has been greater than 5-fold among African Americans living with HIV of (OR 5.04, 95% CI 2.45–10.37) (31). In individuals with high-risk *APOL1* genotypes, the incidence of proteinuria was significantly higher at 68% compared to 50% in individuals in the low-risk genotypes (32).

APOL1 risk variants have also been linked to progression of kidney disease in hypertension and diabetes (33). Other studies demonstrated association with prevalent kidney disease but not with prevalent cardiovascular disease (34, 35). Mechanisms by which *APOL1* risk variants increase risk for kidney disease remain unclear but antisense oligonucleotide strategy has been successful in *APOL1-G1* animal model by targeting *APOL1* mRNA resulting in decreased *APOL1*gene expression in the kidney preventing the development of proteinuria in this model (36).

3.3 HIV-Associated Immune Complex Kidney Disease (HIVICK)

HIVICK and its pathogenesis is not clearly understood. However, HIVICK represents a broader group of kidney disorders compared to HIVAN (37). HIV related antigens like p24 and gp120 have been identified in kidney pathology with immune complex deposits. These immunoreactants circulate in the blood and deposit in the glomerulus to precipitate immunopathogenic events, causing complement activation and tissue injury. It has been suggested that host factors, such as genetic variants, might modify kidney and systemic responses and natural killer T cells (38). Figure 2 displays common pathological findings of HIVICK on kidney biopsies. Spectrum of HIVICK includes IgA nephropathy, lupus-like glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, and immunotactoid glomerulonephritis (39–45). Diagnosis requires evidence of IgM, IgG, IgA, and complement (e.g. C3, C4 and C1q) deposits on immunofluorescent microscopy(38). In a large kidney biopsy series inPLWH, it was demonstrated that individuals with HIVICK were likely to be older, have hypertension,, higher HIV RNA ≥400 copies/ml, a higher eGFR, and lower degree of proteinuria (1+ on dipstick), compared to individuals with HIVAN(37). The study also suggested that African American race was not a risk factor for the development of HIVICK.

In contrast to the beneficial kidney outcomes seen in HIVAN with early cART initiation, the data on cART use in HIVICK has been controversial. An observational study (46) of 89 patients with biopsy proven HIVICK and a case-control study (37) of 83 biopsy proven HIVICK, cART therapy was not associated with improved kidney function. In contrast, in a multicenter that included 65 biopsy proven HIVICK, (47) a beneficial association of cART on kidney function was demonstrated Despite the conflicting data, the use of cART is now the standard of care for all PLWH at the time of HIV diagnosis, regardless of the underlying kidney diseases and comorbidities. While there are no specific guidelines regarding treatment of HIVICK, current management involves cART initiation, treatment of HCV or other coinfection, RAAS blockade, and optimal blood pressure control. Of note, RAAS blockade medications have been associated with decreased progression of scarring and fibrosis in this population and those with other immune complex diseases (48, 49).

3.4 Thrombotic Microangiopathy (TMA)

The other major manifestation of kidney disease in PLWH is TMA, which consists of a combination of clinical characteristics (e.g. thrombocytopenia, elevated lactate dehydrogenase, lower haptoglobin, schistocytes on peripheral smear) and kidney histological evidence (e.g. arteriolar or arterial thrombi, fibrinoid necrosis, endothelial swelling in glomeruli or arterioles, marked glomerular red cell congestion). Historically, in the early 1980s, the incidence of TMA in PLWH was estimated at less than 10%. In the cART era data suggests an incidence of 0.3% as demonstrated in a prospective analysis of 6022 PLWH between 1997 and 2003 (50). HIV associated TMA are more likely to have concurrent infections and severe thrombocytopenia compared to TMA in HIV-negative patients (51).

If TMA is suspected, the first step is to determine the disintegrin and metalloproteinase with a thrombospondin type-1 motif, member 13 (ADAMTS-13) activity. In the case of an ADAMS-13 activity less than 5%, patients are likely to present with severe thrombocytopenia and less kidney involvement. On the other hand, patients with adequate ADAMTS-13 activity should be investigated in detail for secondary causes of TMA (e.g. viral/bacterial infections, cocaine use, chemotherapeutic agents, malignancy, complement disorders, and connective tissue disorders).

Disease-specific therapy in addition to supportive care, plasma exchange, and potentially other immunomodulating agents are recommended after diagnosis of TMA with defective ADAMSTS-13 activity. Survival of less than 2 years post TMA diagnosis has been reported among HIV populations prior to the cART era (52, 53). However, post cART era includes many beneficial strategies for improving outcomes of HIV associated TMA, such as treatments with eculizumab (a monoclonal antibody C5 inhibitor of the alternative complement pathway), plasma exchange, steroids, and Rituximab (a monoclonal antibody against CD20 on B-cells) (54).

3.5 HIV-Treatment Associated Nephrotoxicity

3.5.1 Proximal Tubular Disease from cART—Nucleoside reverse transcriptase inhibitors (NRTI)'s bind to recipient mitochondrial DNA polymerase, particularly in the epithelium of the kidney, resulting in tubular damage that progresses to tubulointerstitial fibrosis (55). Tenofovir disoproxil (TDF) is a very important NRTI, reducing the risk of HIV infection in high-risk populations. Despite its efficacy in the treatment of HIV, TDF usage has been strongly associated with increase the risk of acute kidney injury and CKD(56). Furthermore, Scherzer and colleagues demonstrated a 34% increased yearly risk of proteinuria with cumulative TDF exposure after adjustment for age, gender, and race (56).

Exposure to TDF has been specifically associated with proximal tubulopathy, leading to Fanconi syndrome, decline in eGFR, lactic acidosis, reduced bone mineral density, and higher risk of fractures(57, 58). Spanish and Japanese cohorts have demonstrated rapid decline in eGFR as early as 3 months post TDF initiation (59, 60). Risk factors for TDF nephrotoxicity included lower body weight, lower eGFR, longer dose duration of TDF use, and combination of protease inhibitor [PI] use. Proximal tubular toxicities with Fanconi syndrome have been corroborated in in several other studies particularly when TDF was

concomitantly used with PI medications (61–63). Nephrotoxicity is likely due to the changes in the efflux affecting the clearance of the drug resulting in proximal tubular mitochondrial dysfunction. Recovery of both tubular injury and eGFR has been incomplete after discontinuation of TDF (64). Moreover, TDF has been associated with reduction in bone mineral density via reduction in the bone turnover processes in the hip and spine (57, 65, 66). For example, in a large international HIV cohort, exposure to TDF, but not other cART, was an independent risk factor for fractures (57). We recommend avoidance of TDF in high-risk patients, such as the elderly, those with proteinuria, co-morbid conditions, underlying kidney disease, or with eGFR ≤ 70ml/min/1.73m^2 (10, 67) Table 2 lists all the cARTs associated with side effects and the dosing of the medications based on the eGFR.

Compared with TDF, tenofovir alafenamide fumarate (TAF) has been shown to be less nephrotoxic because of its enhanced stability in plasma with less exposure to Tenofovir-diphosphate (TFV-DP) and thereby reduced risk of proximal tubulopathy (58, 68, 69). It is postulated that lower plasma levels of TFV-DP, results in lower need for glomerular filtration of TFV-DP and less tubular exposure. Despite its favorable nephrotoxic profile, TAF has been reported to induce proximal tubular injury under certain circumstances and one must be cautious in entirely dismissing its potential nephrotoxicity (70). Figure 3 demonstrates mitochondrial toxicity from TAF, a pathological classification of nephrotoxicity that can be confirmed through kidney biopsy.

3.5.2 Other Causes of Tubular Injury— Acute kidney injury (AKI) episodes commonly occur from drugs other than cART, including, but not limited to antibiotics (i.e. aminoglycosides, Sulfamethoxazole-trimethoprim [SMX-TMP], pentamidine), antivirals (i.e. acyclovir, foscarnet, cidofovir), antifungals (i.e. amphotericin), and nonsteroidal anti-inflammatory drugs (NSAIDs). These medications can cause hemodynamic fluctuations, direct toxicity such as acute tubular injury (ATI), acute interstitial nephritis (AIN), crystalline-related nephropathy, and urinary obstruction from drug-induced nephrolithiasis. Medications that use the CYP 3A4 pathway (e.g. statins, phenytoin, carbamazepine, phenobarbital) should be monitored carefully due to their known interaction with antiretroviral therapy. Cobicistat, ritonavir, and SMX-TMP are drugs that block tubular secretion of creatinine, resulting in elevation of serum creatinine without necessarily causing true kidney injury (67). As mentioned in this review and previous HIV reviews (67, 71, 72), most of the traditional antiretroviral medications (i.e. indinavir, atazanavir, TDF) are associated with significant long-term kidney dysfunction. The new generation of cARTs, such as novel integrase inhibitors, are less known to cause kidney dysfunction, but long-term data is currently unavailable.

3.5.3 Acute interstitial nephritis (AIN)— AIN has been cited as the third most common diagnosis of kidney injury in PLWH (73, 74). Given its frequency, AIN should be considered in any patient presenting with AKI. Additional risks factors include: exposure to drugs linked with AIN and increased risk for infections/inflammation, such as immune reconstitution inflammatory syndrome (IRIS), diffuse infiltrative lymphocytosis syndrome (DILS), and interstitial inflammation caused by HIV itself (73). Among PLWH, infections

associated with AIN are Tuberculosis, Cryptococcus, Epstein-Barr virus and Adenovirus (Table 3) (75–77). The gold standard for diagnosis is a kidney biopsy.

Treatment of AIN involves removal of the offending agent/instigator. In cases of isolated AIN in whom the offending agent is withdrawn early, recovery of kidney function to baseline or near baseline is expected within a few weeks. Although there are no RCTs to support the use of steroids, there are studies demonstrating that early treatment, within one week, with 1mg/kg/day of oral steroids for two to three weeks followed by a taper over three to four weeks is beneficial(18, 78, 79). We recommend early diagnosis and treatment with steroids in drug induced AIN. For patients without HIV who do not respond to steroids, treatment with immunosuppressants, including mycophenalate mofetil or cyclophosphamide, have been considered. However, these immunosuppressants have not be studied in PLWH and AIN in light of potential risk of complications in this population(80, 81).

3.5.4 Crystal Nephropathy—PIs, most notably indinavir and atazanavir, can crystalize in the kidney tubules, leading to nephropathy, AIN with subsequent AKI, acute on CKD, or progression of CKD (82, 83). Crystalluria occurred in 20% and nephrolithiasis in 3% in a large cohort of PLWH on indinavir (84). Indinavir also has been associated with kidney papillary necrosis (85) and atrophy (86). A Japanese case-control study suggested that certain genes, with single nucleotide polymorphism (SNP) in the UGT1A-3'-UTR, were associated with atazanavir-induced nephrolithiasis (87). Other risk factors include alkaline urine, reduced urine output in areas with warm climates, and the higher dosage of indinavir at 1000mg or more twice daily. Indinavir is no longer used in developed countries but individuals with prior exposure are now left with CKD and should be managed closely for kidney disease progression.

3.6 Other Causes of CKD in the HIV-positive Population

cART has substantially changed the prognosis of HIV. As such, HIV is currently considered a chronic disease and the PLWH are increasing. As this group of patients age, the incidence of chronic diseases, such as hypertension, diabetes, and CKD, is expected to increase. Some studies estimate that the prevalence of CKD in PLWH is between 2.5% in Europe and 7.4% in North America by 2016 (88) and likely higher into 2020. However, the true prevalence of patients with CKD remains difficult to estimate since most of the studies are based on eGFR equations which may not been adequately validated in the PLWH (89).

3.6.1 Hypertension & Diabetes—With the advent of an unprecedented global effort to increase cART treatment in HIV-positive populations, life expectancy has improved, at the expense of increasing challenges with noncommunicable diseases, especially hypertension and diabetes. Nephropathy from hypertension, which is commonly attributed as a leading cause of progression to ESKD may be the result of APOL1 high-risk genotype in this population. In HIV-positive patients in Malawi, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine and PI were both associated with higher risk of CKD in those patients who had hypertension (OR 2.79, 95% CI 2.16–3.35 and OR 2.15, 95% CI 1.52–3.02, respectively) (90). In another observational study among HIV-positive patients in

Kenya, noncommunicable diseases accounted for approximately 11.5% of PLWH, with 343 (87.5%) people with hypertension, which was the most common noncommunicable disease (91). A study from Zimbabwe evaluated the projection of noncommunicable diseases in HIV positive patients, and they found that the most prevalent noncommunicable diseases between 2015 and 2035 are hypertension, CKD, depression, and ever having been diagnosed with (any) cancer (92).

The incidence of diabetes among HIV positive patients in the Multicenter AIDS Cohort Study was reported at 4.7 cases per 100 person-years of follow-up (93). Similarly, a Canadian study reported higher incidence of diabetes in older HIV-positive patients compared to the general population (94). Diabetes is the second leading cause for progression to ESKD in the general population. However, diabetes is not necessarily the second leading cause of ESKD in the HIV-positive populations. In the study by Achwoka et al, only 2.1% (95% CI 0.9–4.7) of PLWH with noncommunicable diseases had documented diabetes mellitus (91). In another study, the incidence of new-onset diabetes in HIV-positive persons was significantly higher with an incidence rate of 5.72 per 1,000 person-years (95% CI 5.31–6.13) (95). In particular, higher incidence of diabetes is associated with use of PI (96). Thus, current management of diabetic kidney disease in PLWH is similar to the general population with RAAS blockade and blood pressure control. To our knowledge, no studies have specifically explored the use of sodium glucose transporter 2 inhibitors (SGLT2) in PLWH. SGLT2 inhibitors may offer beneficial kidney and cardiac effects that far outweigh their potential adverse reactions.

Moreover, HIV and the noncommunicable diseases listed above are independent risk factors for cardiovascular disease (CVD) and CVD events, such as stroke and myocardial infarction, CKD, neurocognitive decline, and other comorbidities (97).

4. Dialysis in HIV populations with ESKD

PLWH on cART are recommended to continue such therapy after dose adjustment while on dialysis. Survival appears to have slightly improved among PLWHon dialysis (98). The median survival was longer for those initiating dialysis during the cART era, at 16 months, than for those initiating dialysis before at nine months, and this trend was similar pre and post cART in those PLWH with HCV coinfection versus PLWH without coinfections (99, 100). However, a larger study demonstrated improved survival among PLWH who initiated RRT in post-cART era during 1999-2000, compared with those who started RRT in pre-cART era prior to 1990 (HR 0.49, 95% CI 0.40-0.60) (101). PLWH on continuous ambulatory peritoneal dialysis (CAPD) are at increased peritonitis risk, although HIV did not increase the risk for CAPD catheter failure rate at 18 months (102). European studies, on the other hand, do not suggest worse outcomes in mortality with RRT use among those with and without HIV (74, 103, 104). Table 4 further lists previous studies.

5. Transplantation among HIV populations

Both in the US (105) and in Europe, transplantation was once considered a contraindication in PLWH to due to concerns of HIV disease progression in the setting of

immunosuppression (106, 107). For example, the number of PLWH receiving kidney transplantation was 43 in the late 1990s with a slight increase to 208 by 2006 (108). The higher prevalence of ESKD among PLWH has historically been associated with increased mortality among those with decreased access to kidney transplantation. Overall, the difference in mortality was 80% higher between those with access and those without access to transplantation (104, 109). Initial experience demonstrated a positive 3-year survival advantage of approximately 94% in PLWH with ESKD who underwent kidney transplantation (110). With the HIV organ Policy Equity Act (HOPE) of 2013 which allows PLWHi to donate and receive organ transplantation nationally, there has been a significant rise in transplantation among PLWH(111).

Rejection rates in PLWH after transplantation has been reported higher than in the general population,. In a large prospective study of 150 HIV-positive kidney-transplant recipients followed for 3 years, risk of graft loss was increasingly associated with treated rejection (aHR 2.8, 95% CI, 1.2 to 6.6; P=0.02), and antithymocyte globulin induction (aHR, 2.5, 95% CI, 1.1 to 5.6; P=0.03) (112). Yet, transplant rejection in PLWH has not been associated with complications from opportunistic infections (109, 112). Instead, higher rejection rates were demonstrated in patients with biopsy proven HIVAN, which is the one of the predominant causes of ESKD in PLWH (113). The exact mechanism of rejection in this population remains unclear, but possible risk factors include altered immune activation, and induction-related medications (114). Other studies have demonstrated the presence of HIV in podocytes and tubular cells despite undetectable viral loads along with increased inflammatory cells, which may all represent subclinical cellular rejection; yet, the significance of these findings is currently unclear (115, 116).

One theory behind lower graft survival is the *APOL1* risk allele status among donors as these risk alleles travel with the donated organ. Transplanted kidneys from both deceased and live donors with *APOL1* risk alleles had slightly worse survival compared to those without risk alleles (117).

Another risk factor is drug-drug interactions between immunosuppression medications and cART. PI medications, such as ritonavir, are potent CYP 450 inhibitors that raise calcineurin inhibitor (CNI) exposure, and PI medication dose adjustments are often needed to achieve safe therapeutic CNI levels (118). The NNRTI class of medications have variable effect on CNI level. Interactions with the immunosuppressive medications are also common with efavirenz and nevirapine, which are inducers of CYP 3A4 and will reduce levels of CNIs (119). The medications that have the least interactions with immunosuppressive medications include integrase strand transfer inhibitors (INSTI) (120). Due to the complexities of the kidney diseases and disease in transplantation, an ideal therapeutic regimen has not been established for HIV-positive kidney transplant recipients (106, 121). We recommend a multidisciplinary team of physicians with expertise in these areas to be involved in the management of these patients because of the complexity of disease and management of pharmacokinetic interactions. Second, medical optimization and screening for common co-infections in PLWH prior to transplantation. Third, additional care must be given to the donated organ; living allografts are preferable to cadaveric donation for improved overall survival.

6. Conclusion

Several studies looking at the pathology from kidney biopsies have reported diagnoses of FSGS, HIVICK, and diabetic nephropathy in comparison to earlier studies predominant in HIVAN (4, 8, 122). Since the development of cART, the incidence of ESKD associated with HIV infection has decreased and mortality has improved. The aging cohort of HIV-positive patients is expected to have a continued increase in prevalence of non-HIV-related kidney diseases (4). Table 5 briefly outlines some of pharmacotherapy studies in the HIV populations affecting both children and adults.

7. Expert Opinion

HIV has been associated with HIVAN, HIVICK, and other kidney disease including cART-associated nephrotoxicities. Kidney biopsy remains the gold standard to ultimately characterize most of the associated kidney diseases in PLWH. The KDIGO pathology-working group helped in further classifying and grouping pathologies from series of biopsies surrounding PLWH s (10). Using these KDIGO classifications, a recent observational 9-year study of 437 kidney biopsies revealed a change in the spectrum of kidney diseases with decline in TDF nephrotoxicity and an apparent increase in the frequency of FSGS and diabetic nephropathy (6). Other serum and urine biomarkers are valuable in of the evaluation of concomitant diseases (i.e. HCV, HBV, TMA, AIN, etc.) in this patient population.

Thus, we recommend routine monitoring of PLWH by specialists and a multidisciplinary team (i.e. primary care, nephrologists, infectious disease specialists, pharmacist, rheumatologists, transplant specialists). Clinicians are required to: (1) be aware of the importance of early initiation with cART to prevent and treat specific HIV-associated kidney diseases, (2) be aware of cART medication associated adverse reactions and discriminate those that are more nephrotoxic than others and require dose-adjustment in the setting of declining eGFR and among those with eGFR ≤ 30ml/min/1.73m^2, (3) follow KDIGO guidelines regarding screening and monitoring for CKD, (4) manage other co-infections and comorbidities, (5) consider changing cART if drug induced toxicity is established (i.e. TDF, CNIs, etc.) by either kidney biopsy or by significant eGFR decline of ≥ 10ml/min/1.73m^2 or rising creatinine (≥ 0.5mg/dl), (6) consider drug-drug interactions, and (6) strongly consider kidney transplantation in appropriately selected patients with ESKD. Specifically, longitudinal monitoring of kidney function, proteinuria, viral loads are recommended at least twice annually, if not more depending on the severity of CKD. Individuals with non-HIVAN diseases need to be treated for their underlying etiology (i.e. lupus, infection, HBV/HCV, TMA, antihypertensive and diabetic medications) and managed by the multidisciplinary team. Kidney biopsies can help guide acute management (i.e. use of steroids, plasmapheresis, immunosuppression, antibiotics) and long-term management (i.e. immunosuppression, dialysis, transplantation).

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Abbreviations

ADAMTS-13	metalloproteinase with a thrombospondin type-1 motif, member 13
AIN	acute interstitial nephritis
AKI	acute kidney injury
APOL1	apolipoprotein-1
ATI	acute tubular injury
HBV	hepatitis B infection
HCV	hepatitis C infection
cART	combined antiretroviral therapy
CKD	chronic kidney disease
CNI	calcineurin inhibitor
CVD	cardiovascular disease
DILS	diffuse infiltrative lymphocytosis syndrome
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FSGS	focal segmental glomerulosclerosis
HIVAN	HIV associated nephropathy
HIVICK	HIV associated immune complex disease
HTLV	human T cell leukemia virus
IDSA	Infectious Disease Society of America
INSTI	integrase strand transfer inhibitors
HOPE	HIV organ Policy Equity Act
IRIS	immune reconstitution inflammatory syndrome
KDIGO	The Kidney Disease: Improving Global Outcomes
MRP	multidrug resistance proteins
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors

OAT	organic anion transporters
PI	protease inhibitors
PLWH	people living with HIV
PrEP	pre-exposure prophylaxis
RAAS	renin-angiotensin system
SGLT2	sodium glucose transporter 2 inhibitors
SNP	single nucleotide polymorphism
START	Strategic Timing of Antiretroviral Treatment
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate
TFV-DP	tenofovir diphosphate
TMA	thrombotic microangiopathy
US	United States
USRDS	United States Renal Data System
ZDV	zidovudine

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Article highlights

- For HIV-positive individuals and those at risk of kidney disease, expanding literature on genomics, including APOL1 disease, is likely to play a role in modified screening and monitoring regimens.
- Advances in antiretroviral therapy have led to improvement in increased survival among HIV-infected individuals, but the growing HIV-population faces the burden of comorbidities especially cardiovascular disease and acute and/or chronic kidney disease.
- Antiretroviral medications can be used as early as during childhood among patients with HIV, but children will have longer exposure to the side effects of the medications.
- Providers need to be vigilant regarding potential nephrotoxic effects and drug-drug interactions of antiviral medications and dose medications appropriately based on eGFR.
- Antiretroviral medications can be used in ESKD patients undergoing renal replacement therapy.
- Transplantation from HIV-positive donors became a successful landmark medical management, but the short-term and long-term outcomes are under investigation.

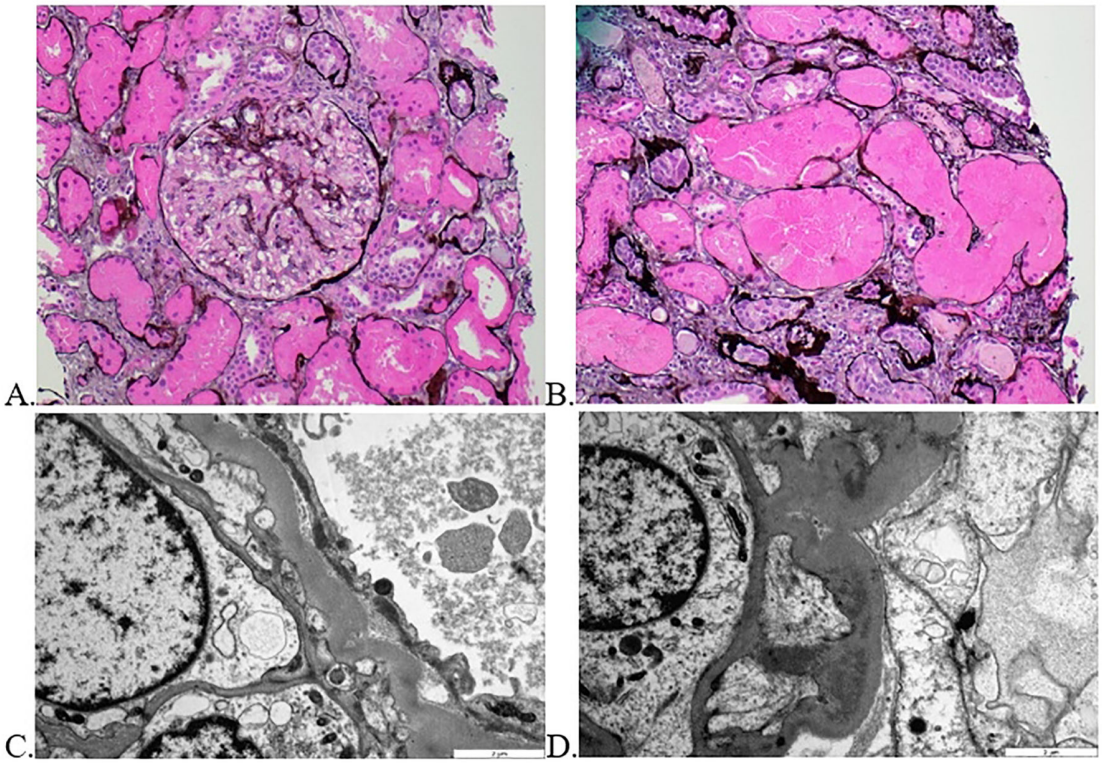

Figure 1.

A. LM 400X, silver stain. Glomerular capillary with collapsed basement membrane and glomerular tuft with podocyte hypertrophy and hyperplasia, and microcystic dilatation of tubules. B. LM, PAS. Excessing protein deposition and tubular cystic dilatation.

C & D. EM. Extensive podocyte foot effacement and frequent tubuloreticular inclusions in endothelial cells. Podocyte effacement is present.

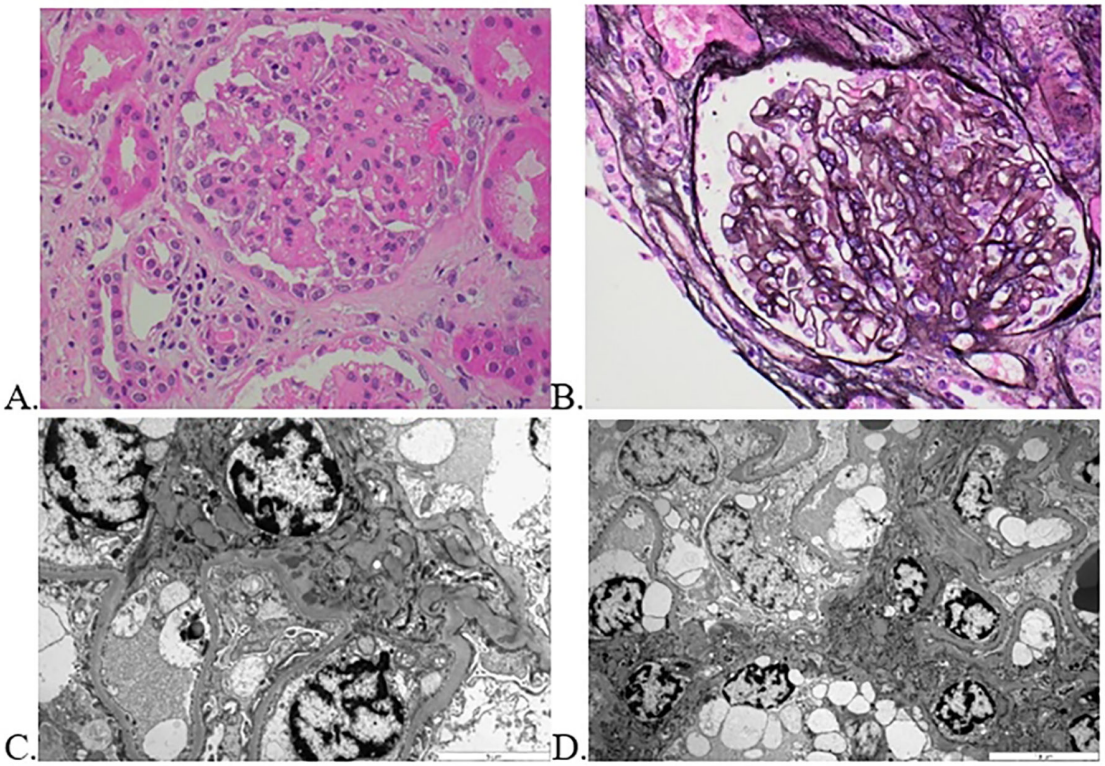

Figure 2.

A. LM at 400X, H&E stain. Severe mesangial proliferation.

B. LM at 400X, silver stain. Glomerulus with severe mesangial proliferation and collapsing glomerulopathy.

C. & D. EM. Diffuse podocyte effacements, depositions in basement membranes.

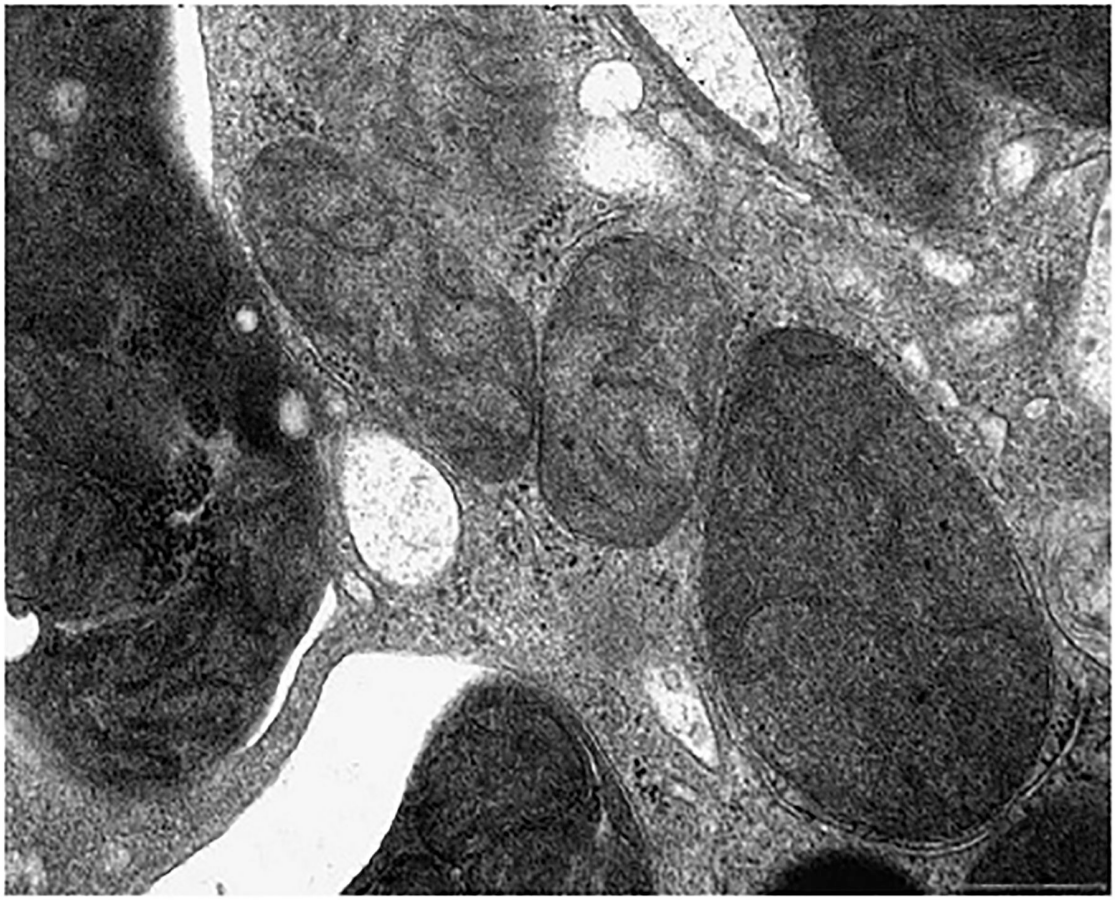

Figure 3.
EM. Tenofovir alafenainide fumarate (TAF) induced mitochondrial toxicity in proximal tubule.

Table 1.

History of Antiretroviral Therapies and Timing of the Food and Drug Administration (FDA) Approvals

Antiretroviral class	Names	FDA approved dates
Nucleoside reverse transcriptase inhibitors (NRTI)	Zidovudine (AZT)	1987
	Didanosine (ddl)	1991
	Zalcitabine (ddC)	1994
	Stavudine (d4T)	1995
	Lamivudine (3TC)	1998
	Abacavir (ABC)	2001
	Tenofovir (TDF)	
	Tenofovir Alafenamide (TAF)	2003
	Emtricitabine	
Protease inhibitors (PIs)	Saquinavir (SQV)	1995
	Indinavir (IDV)	19961996
	Ritonavir (RTV)	1997
	Nelfinavir (NFV)	1999
	Amprenavir (APV)	2000
	Lopinavir	2003
	Atazanavir	2003
	Fosamprenavir	2005
	Tipranavir (TPV)	2006
	Darunavir	
Non- nucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine (NVP)	1996
	Efavirenz (EFV)	1997
	Etravirine	1998
	Rilpivirine	2008
	Nevirapine XR	2011
	Doravirine	2018
Fusion inhibitors	Enfuviritide	2003
Integrase strand transfer inhibitors (INSTI)	Raltegravir	2007
	Elvitegravir	2012
	Bictegravir	2013
	Dolutegravir	
CCR5 inhibitor	Maraviroc	2007
Fixed-dose combination	Kaletra	2000
	Trizivir	
	Epzicom	2004
	Truvada	
	Atripla	2006
	Complera	2011
	Stribild	2012

Antiretroviral class	Names	FDA approved dates
	Triumeq	2014
	Evotaz	2015
	Genoya	
	Prezocobix	
	Descovy	2016
	Odefsey	
	Juluca	2017
	Biktarvy	2018
	Cimduo	
	Delstrigo	
	Symfi	
	Symfi Lo	
	Symtuza	
	Temixys	
	Dovatao	2019

Table 2.

Commonly reported antiretroviral therapies in clinical practice, their recommendations and their side effects

Antiretroviral	Class	Formulations	Dosing	Dosing based on eGFR	Side effects
Emtricitabine	NRTI	Solid, Liquid	200 mg daily	200 mg every 48 hours for moderate renal dysfunction (eGFR <50), but population based pharmacokinetic studies have shown lower AUC for moderate renal function patients with every 48 hour dosing (1).	Diarrhea, skin discoloration. Severe side effects include lactic acidosis and hepatotoxicity. Infection is high in children.
Lamivudine	NRTI	Oral Solid	150 mg twice daily of 300 mg daily	200 mg daily for mild renal impairment.(2).	Pancreatitis (higher in children), nausea, GI upset hepatic dysfunction, infection, and lactic acidosis.
Tenofovir disproxil fumarate (TDF)	NRTI	Oral	300 mg once daily	eGFR 30–49 every 48 hours, eGFR <30 not recommended. HD every 7 days. DHHS guidelines to avoid if eGFR <30 (3).	Renal dysfunction includes proximal tubule dysfunction (Fanconi syndrome), mitochondrial dysfuction, ATI, CKD, nephrogenic DI. Loss of bone mineral density.
Tenofovir Alafenamide (TAF)	NRTI	Oral	10 mg or 25 mg daily	eGFR <30 not recommended.	Headache Possible effects of mitochondrial dysfunction.
Etravirine	NNRTI	Oral	200 mg twice daily	No dose reduction required based on eGFR (4).	Rash, hyperglycemia, hypercholesteremia, significant interactions with other antiretrovirals (ex.dolutegravir).
Rilpivirine	NNRTI	Oral	25 to 50 mg	No dose adjustments for renal function. Coformulations with TDF and TAF needs to be adjusted for renal function (3).	>10% reported depression, drowsiness, nausea, hypercholesteremia, decreased cortisol, elevated liver enzymes.
Atazanavir	PI	Oral	400 mg daily or 300 mg daily if used with ritonavir or cobicistat.	No dose adjustments required for renal function (5).	Nephrolithiasis(6) and higher incidence of CKD(7). Rash, hypercholesteremia, nausea, cough (in children).
Dolutegravir	INSTI	Oral	50 mg daily or twice daily if suspected INSTI resistance	No dose adjustments necessary (5).	Increase in creatinine and drop in eGFR with no influence on true eGFR.(8). Hyperglycemia, weight gain, elevated liver enzymes.

Abbreviations: DHHS, Department of Health and Human Services; ATI, acute tubular injury; CKD, chronic kidney disease; DI, diabetes insipidus; NRTI, Nucleoside reverse transcriptase inhibitors; NNRTI, Non-nucleoside reverse transcriptase inhibitors; Protease inhibitors; INSTI, Integrase Strand Transfer Inhibitor

Table 3.

Pharmacotherapy and infections in HIV patients associated with interstitial nephritis

Medications	Infections	Immunologic/Inflammatory
Abacavir	Cryptococcus	
Atazanavir	Tuberculosis	Diffuse infiltrative lymphocytosis syndrome (DILS)
Beta lactams	Adenovirus	
Foscarnet	Epstein-Barr virus	Immune Reconstitution Inflammatory Syndrome (IRIS)
Indinavir	Polyomavirus	
NSAIDs	Cytomegalovirus	
Rifampin	Candida	
Sulfonamides		

Table 4.

Short summary of studies showing use of antiretroviral medications among patients on dialysis

Study	Year	Outcome
(101) Ahuja et al.	2002	From 1990 to 1999, 1-yr survival of HIV-infected patients on dialysis improved from 56 to 74%. The hazard ratio (HR) declined significantly in patients who initiated dialysis in years 1999–2000 compared with patients who initiated dialysis < or = 1990 (HR, 0.49; 95% confidence interval, 0. 40 – 0.60).
(99) Rodriguez et al.	2003	33% of the cohort initiating dialysis during the combined antiretroviral therapy (cART) era were receiving cART at dialysis initiation, and mean CD4 count at initiation of dialysis, which was a strong overall predictor of mortality, was no different among patients who initiated dialysis during *versus* before the ART era.
(46) Szczech et al.	2004	Study described the clinical and demographic characteristics, the dosing regimens for antiretroviral medications, and the frequency of renal biopsy of HIVAN receiving renal replacement therapy in five medical centers.
(12) Izzedine et al.	2003	Further analyzed the data and dosing of antiretroviral drugs from Szczech et al.(11) to demonstrate the importance of correctly dosing cART medications for patients undergoing hemodialysis.
(82) Izzedine et al.	2003	Recommended tenofovir be administered once a week in patients with ESRD based of a case report, where a patient with HIV and lamivudine-resistant coninfection with HBV was being treated.
(103) Tourret et al.	2006	The 2-yr survival rate of HIV-infected hemodialysis patients has dramatically improved since the beginning of the HIV infection epidemic. The main mortality risk factors were viral load and the history of opportunistic infection. cART was efficient and significantly increased survival in hemodialysis patients. Therefore, hemodialysis itself may be an indication of ART among HIV-infected patients.
(98) Atta et al.	2007	Older age, lower serum albumin level, lower CD4 cell count, and the lack of ART are independent predictors of poor survival among African Americans infected with HIV-1 undergoing renal replacement therapy (RRT) in a resource-limited urban area. RRT survival was similar in the pre-cART and cART eras, likely reflecting inadequate HIV treatment in this population.
(100) Butt et al.	2008	The HCV-HIV-coinfected subjects were younger, male, more likely to be black race, had a lower body mass index and spent shorter time durations on dialysis. There are differences in the patterns and frequency of various medical and psychiatric comorbidities and substance abuse between HCV and HCV with HIV-coinfection persons on dialysis.
(123) Gupta et al.	2008	No dosing adjustments are necessary in treatment-naive patients undergoing hemodialysis. However, caution should with the 400mg/100mg twice daily regimen in those who are on efavirenz and Protease inhibitors.
(124) Cramer et al.	2010	Results did not show a statistically significant difference in the timing and dosing at 200mg BID of Nevirapine for patients on dialysis because the plasma levels did not change from dialysis days when compare to non-dialysis days.
(104) Trullas et al.	2011	Medium-term survival of HIV-infected patients on dialysis was lower than that of matched HIV-negative patients. Being on effective cART improves survival.
(125) Aleman et al.	2015	HIV-positive patients with HBV coinfection on peritoneal dialysis may be adequately treated for with tenofovir disoproxil at 245 mg on a 2-weekly regime.
(126) Slaven et al.	2016	HIV patients on hemodialysis should be receiving either Tenofovir disoproxil fumarate at 300 mg once per week or emtricitabine 200mg twice per week to sufficiently prevent HIV acquisition and maintain therapeutic, non-toxic levels of the antiretroviral medications.
(102) Ndlovu et al.	2017	HIV infection in ESKD patients managed by continuous ambulatory peritoneal dialysis (CAPD) was associated with increased peritonitis risk; however, HIV infection did not increase the risk for CAPD catheter failure rate at 18 months.
(74) Sawinski et al.	2019	HIV/HCV-coinfected dialysis patients face many challenges, but renal transplantation and cure of HCV infection with antiretroviral therapy can positively impact their long-term survival. There are many drug-drug interactions to consider when treating HCV in this patient population, but most patients can be cured successfully.

Table 5.

A short summary of some pharmacotherapy studies in the pediatric and adult populations with HIV

	Reference	Study Design	Sample	Age	Duration	Exposure	Outcome
Children							
1	(127)	Case report	N=3	1–3 yrs	N/A	Zidovudine, lamivudine, and ritonavir	Resolution of cardiomyopathy, red cell aplasia, or nephropathy
2	(128)	Prospective cohort	N=30	>3 mos	96 wks	Indinavir, zidovudine, and lamivudine	Higher cumulative incidence of elevated serum creatinine/ leukocyturia in those < 5 yrs of age
3	(129)	Case report	N=1	12 yrs	N/A	Tenofovir, lopinavir-ritonavir, and didanosine	Tenofovir-related nephrogenic diabetes insipidus, renal insufficiency, and Fanconi-like syndrome
4	(130)	Prospective cohort	N=27	4.9–18 yrs	96 wks	Tenofovir	No significant change in serum creatinine, phosphorus and bicarbonate, urine protein, albumin, and microglobulin
5	(131)	Prospective cohort	N=2102	Median age 6.3	Median 6 yrs	Tenofovir and/or indinavir	Significant increased hazard of renal dysfunction (measured by serum creatinine and urine protein)
6	(132)	Nested case-control	N=456	2–18 yrs	Median 18 mos	Tenofovir disoproxil fumarate (TDF)	Significant increase in odds of hypophosphatemia
7	(133)	Prospective cohort	N=40	8–17 yrs	Median 77 mos	TDF	Significant decrease in serum phosphorus and potassium. No significant change in serum creatinine
8	(134)	Prospective cohort	N=26	4.9 to 17.4 yrs	60 mos	TDF	No proteinuria, hypophosphatemia, nor glycosuria. One case of moderate eGFR reduction
9	(135)	Randomized control trial	N=87	12 to <18 yrs	48 wks	TDF	No significant change in renal function or bone mineral density
10	(136)	Case report	N=1	Infant	N/A	Lopinavir, ritonavir	Immune reconstitution syndrome with nephrotic syndrome that resolved with prednisone, Lisinopril, and low-molecular-weight heparin
11	(137)	Prospective cohort	N=49	9–18 yrs	2 yrs	TDF	Significant decrease in eGFR and phosphatemia
12	(138)	Prospective cohort	N=448	Mean age 11.5 yrs	0 to >3 yrs of tenofovir exposure	Tenofovir	Significant increase in odds of proteinuria with greater than 3-year duration of tenofovir use
13	(139)	Randomized control trial	N=81	12–17 yrs	Median 96 wks	TDF	Virologic response
Adults							
1	(140)	Retrospective case-control	N=30	Median age 45	5 yrs	Atazanavir (ATV)	Increased odds of urolithiasis and bilirubin
2	(141)	Single center prospective	N=105	Mean age 38	1 yr	Indinavir	Incidence of urolithiasis was 12.5 %. Indinavir still used in resource limited settings and has been off the market in western countries
3	(142)	Multicenter prospective cohort	N= 22063	Median age 39	5 yrs	Tenofovir, Ritonavir boosted lopinavir,	Incidence of chronic renal impairment increased with all these three combinations.

Children							
	Reference	**Study Design**	**Sample**	**Age**	**Duration**	**Exposure**	**Outcome**
						Ritonavir boosted atazanavir	
4	(143)	Randomized controlled trial	N=707	Mean age 38	96 wks	Elvitegravir, cobicistat, emtricitabine, TDF	<1 % had medication stopped due to increase in creatinine. No proximal tubulopathy seen at 96 weeks. Blockade of creatinine secretion by Cobicistat.
5	(89)	Randomized double blind non- inferiority	N= 411	Median age 37	48 wks	Raltegravir vs Dolutegravir with ABC/3TC or TDF/FTC	Both groups had asymptomatic increase in creatinine with no statistically significant changes in eGFR at 48 weeks.