HIV and kidney: a dangerous liaison

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SUMMARY

Kidney disease represents an important health concern among HIV-infected individuals, with an esti-
mated prevalence ranging between 2.4 and 17%. The widespread use of antiretroviral drugs has changed
the epidemiology of kidney disease in the HIV positive population, drastically reducing the percentage of
patients affected by HIV-associated nephropathy (HIVAN), a complication characterized by apoptosis and
de-differentiation of renal epithelial cells and podocytes. However, impaired kidney function remains an
important issue among HIV-infected patients because of their long-term exposure to antiretroviral drugs
and the growing burden of traditional risk factors associated with chronic renal disease. Furthermore,
since HIV infects renal epithelial cells, kidney is a potential reservoir site that needs to be considered in
future eradication studies. This review summarizes the main risk factors associated with chronic kid-
ney disease in HIV-infected patients and discusses the contribution of viral infection and antiretroviral
therapy to the pathogenesis of renal damage, emphasizing the need to monitor kidney status during the
follow-up of HIV-infected patients.

INTRODUCTION

Over the last two decades, the natural history of HIV infec-
tion has changed from that of an acute disease to a chron-
ic manageable condition (Deeks et al., 2013; Maartens et
al., 2014). Indeed, following the introduction of combina-
tion antiretroviral therapy (cART), AIDS-related morbidi-
ty and mortality have been effectively reduced, and the life
expectancy of HIV-infected individuals has significantly
increased (Antiretroviral Therapy Cohort 2008; Coquet et
al., 2010; May and Ingle 2011; Sabin 2013). Nevertheless,
cART is not curative, and HIV-infected individuals need
lifelong therapy in order to maintain viral suppression
(Chun et al., 1997; Wong et al., 1997; Siliciano et al., 2003).
In this scenario, the occurrence of organ-specific lesions
as well as systemic syndromes related to viral persistence
and immune activation is rising (Deeks and Phillips 2009;
Hernandez and Sherman 2011; Rodriguez-Penney et al.,
2013; Lucas and Nelson 2015). Similarly, the aging of the
HIV population has important consequences, including a
growing burden of age-related comorbidities (Guaraldi et
al., 2011; Costagliola 2014). Finally, the cumulative toxic
effect due to antiretroviral drug exposure is gaining grow-
ing importance in the monitoring of HIV-infected patients
(Schambelan et al., 2002). In the long run, several organs

and apparatuses might be damaged, resulting in a signif-
icant decrease in the quality of life of HIV-infected indi-
viduals. In this regard, a substantial body of evidence in-
dicates that HIV-infected individuals are at higher risk of
developing chronic kidney disease (CKD), which occurs in
a large percentage of HIV patients. This paper reviews the
interplay between HIV and kidney, describing the major
renal syndromes observed in HIV patients, the contribu-
tion of virus-specific factors and antiretroviral-associated
nephrotoxicity to the pathogenesis of CKD, and the possi-
ble role of kidney as a viral reservoir.

HIV-ASSOCIATED CKD

Renal impairment was identified as a possible complica-
tion of HIV infection early after the start of the HIV ep-
idemics. In 1984, the first study investigating the preva-
lence of kidney disease among HIV patients described
several cases in which renal function impairment was as-
sociated with focal or segmental collapsing glomeruloscle-
rosis (Rao et al., 1984). Nowadays, more than twenty years
after the introduction of cART, the spectrum of HIV-re-
lated nephropathies has changed, but renal pathologies
continue to be among the leading co-morbidities in HIV
infection (Campbell et al., 2009; Rodriguez-Penney et al.,
2013). Similarly, although the incidence of end-stage renal
disease (ESRD) in HIV-positive individuals has decreased
over time, they are still more likely to develop ESRD than
HIV-negative individuals (Bickel et al., 2013; Rasch et al.,
2014; Abraham et al., 2015).
The complex three-dimensional structure of the filtration
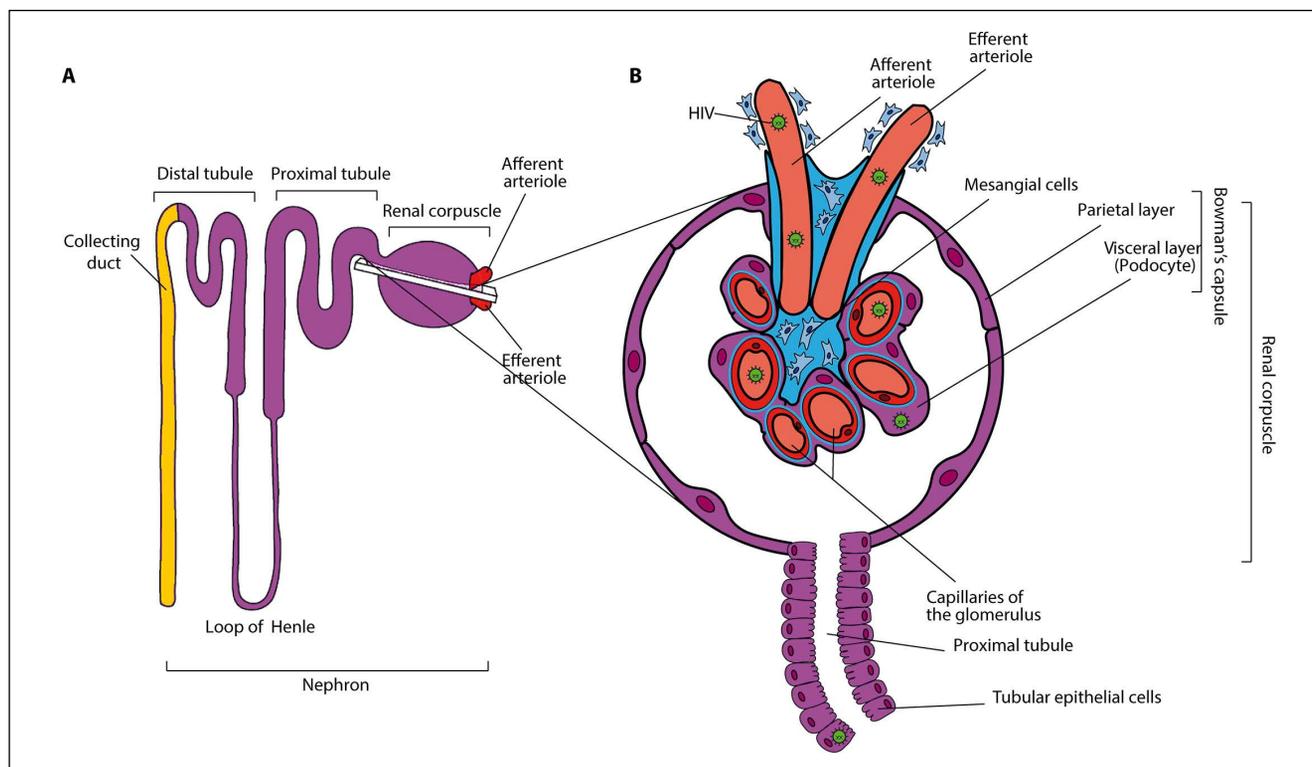barrier is pivotal to maintain kidney function and is criti-

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Figure 1 - *A) Organization of the nephron. B) Section of renal corpuscle showing the complex interplay between different structures and cell lineages. HIV-mediated kidney damage can result from exposure to viral antigens or from infection of cells belonging to renal parenchima.*

cally dependent on the integrity of each of its components. Within the nephron, the filtration barrier is constituted by the fenestrated endothelium of the glomerular capillaries, the basal lamina of the endothelial cells of the capillaries and the slit diaphragms of the podocytes and allows the passage of water and ions from the bloodstream to Bowman's capsule, while preventing the loss of high molecular weight proteins. The filtration process generates an ultrafiltrate, which is eventually converted into urine by selective reabsorbing processes, which take place in the renal tubule (*Figure 1*). Alterations to renal function indicating tubular damage, such as proteinuria and albuminuria, as well as a decline in the glomerular filtration rate (eGFR) are considered reliable indicators of renal damage. Generally, chronic kidney disease (CKD) is defined by reduction of kidney function lasting for at least three months. However, most of the studies performed so far in the HIV-infected population based the diagnosis of CKD on a single measurement of proteinuria or eGFR. Similarly, although the CKD Epidemiology Consortium (CKD-EPI) equation is considered the GFR estimate with the highest accuracy (Inker *et al.,* 2012; Gagneux-Brunon *et al.,* 2013), most epidemiological studies were based on older GFR estimates. Due to these diagnostic caveats and significant differences in the prevalence of risk factors among different regions and study populations, the epidemiology of kidney disease among HIV patients varies substantially among studies and countries.

Spectrum of CKD manifestations in the HIV population
Although their specific pathogenesis has not been fully elucidated, HIV patients may suffer a broad spectrum of kidney disorders, often presenting as glomerular and tubulointerstitial pathology (Nebuloni *et al.,* 2009; Muraka-

mi *et al.,* 2014; da Silva *et al.,* 2016). The most common HIV-related conditions include HIV-associated nephropathy (HIVAN) and immune complex mediated disease (HIVICD), both affecting the renal parenchyma.
HIVAN is a unique syndrome that affects up to 27% of seropositive individuals and is characterized by glomerulosclerosis accompanied by prominent interstitial injury (Gerntholtz *et al.,* 2006; Wyatt *et al.,* 2012). Collapsing glomerulosclerosis with podocyte hypertrophy and proliferation, endothelial cell tubuloreticular inclusions, microcystic tubular dilatation, and a large infiltration mainly composed of CD8+ T lymphocytes are pathognomonic findings of HIVAN (Wyatt *et al.,* 2008; Fogo *et al.,* 2016b). In the absence of cART, HIVAN rapidly progresses towards ESRD, a profound impairment of kidney function that requires dialysis and eventually kidney transplant.
HIVICD is the second most common kidney dysfunction diagnosed in HIV patients, and presents with glomerulonephritis accompanied by a variety of histological changes (Booth *et al.,* 2016; Fogo *et al.,* 2016a). The immune complex glomerulonephritis found in HIV-infected patients includes IgA nephropathy, post-infectious glomerulonephritis (PIGN), lupus-like glomerulonephritis, cryoglobulinaemic glomerulonephritis, and membranoproliferative glomerulonephritis (MPGN) (Nobakht *et al.,* 2016). Common to all these manifestations is the deposition of immunocomplexes, either circulating or formed in situ, in the mesangial and paramesangial regions of the glomeruli.
Besides HIVAN and HIVICK, a wide variety of kidney abnormalities related to or independent of viral infection can be observed among HIV-positive patients, including, among others, cART-induced acute kidney damage, proximal tubular dysfunction, crystalluria and urolithiasis.

Risk factors in the HIV population

Traditional CKD risk factors as wells as HIV-related factors are major determinants of the prevalence of CKD among HIV-infected individuals (*Figure 2*). General risk factors associated with CKD are diabetes mellitus, hypertension, older age, black race, and hepatitis C virus coinfection (Sorli *et al.*, 2008; Flandre *et al.*, 2011; Menezes *et al.*, 2011; Cao *et al.*, 2013; Morlat *et al.*, 2013; Banerjee *et al.*, 2014; Ryom *et al.*, 2014). The D:A:D study, a large prospective cohort including patients from the US, Europe, and Australia, found these risk factors were associated with CKD as well as with advanced chronic disease and ESRD (Ryom *et al.*, 2014; Mocroft *et al.*, 2015).

Both diabetes and hypertension are considered risk factors for the development of CKD due to their impact on the integrity of blood vessels. Several studies reported a marked decline of the eGFR and an increased risk of progression to ESRD among diabetic HIV patients compared to otherwise healthy infected individuals (Jotwani *et al.*, 2012; Ryom *et al.*, 2014; Abraham *et al.*, 2015). Of note, several reports indicate a role for HIV infection in accelerating the aging process, thereby increasing the overall risk of co-morbidities for the HIV population (Guaraldi *et al.*, 2011; Kooman *et al.*, 2014; Pathai *et al.*, 2014).

Similarly to what was observed in the general population, the prevalence of non-communicable diseases (NCD), including CKD, among HIV-infected individuals is sex and gender dependent. A recent study investigating the epidemiology of NCD in HIV patients over a 13-year period showed that the risk of CKD is higher in both men and women of black ethnicity compared to non-black men (Wong *et al.*, 2016a). Although these disparities are in part explained by differences in retention in care, it is well known that genetic background plays an important role in determining the susceptibility to CKD. A number of studies have reported a significantly higher incidence of HIVAN and a higher likelihood of progression to ESRD in black compared to white patients, regardless of the aetiology of kidney disease (Choi *et al.*, 2007; Lucas *et al.*, 2008; Alves *et al.*, 2010; Banerjee *et al.*, 2014; Achhra *et al.*, 2015). Linkage disequilibrium

and association studies pointed out the involvement of the ApoL1 locus in determining this increased susceptibility (Fine *et al.*, 2012; Wasser *et al.*, 2012). A recent South African study, enrolling 120 HIV-infected individuals in whom HIVAN was diagnosed on renal biopsy material, confirmed a skewed distribution of ApoL1 alleles among patients experiencing kidney disorders, with homozygous high-risk alleles conferring an 89 fold odds for HIVAN (Kasembeli *et al.*, 2015). Interestingly, the ApoL1 alleles associated with a higher susceptibility to CKD confer survival advantage in areas where *Trypanosoma brucei rhodesiense* is endemic. Indeed, serum containing variants of the gene product ApoL1 is able to lyse this parasite conferring protection against African sleeping sickness (Genovese *et al.*, 2010). The association between kidney disease and ApoL1 high-risk alleles has also been observed among children. A study enrolling paediatric patients showed that individuals harbouring the high-risk genotypes had a 4.1 fold increased odds of developing CKD compared to those with low-risk genotypes (Purswani *et al.*, 2016). These findings have important implications, in particular for the sub-Saharan region, where more than 90% of the AIDS paediatric population is located and where access to antiretroviral therapy is still limited (World Health Organization 2013). For HIV-ICK, data regarding a possible association with ethnicity are unclear. Initial evidence reported a higher incidence of HIVICK in the white population, but these observations were not confirmed by subsequent studies (Foy *et al.*, 2013; Booth *et al.*, 2016).

A higher incidence of acute kidney injury (AKI) is an additional factor contributing to the CKD risk among HIV-infected individuals. Occurrence of AKI was the factor most strongly associated with CKD development in a French prospective cohort of HIV patients (Flandre *et al.*, 2011). Furthermore, multiple epidemiological reports indicate a relationship between AKI and CKD progression and overall kidney-related mortality. A large retrospective analysis showed that the 5-year cumulative probability of death in patients experiencing AKI was 31.3%, compared with 16.5% in patients without AKI (Lopes *et al.*, 2013).
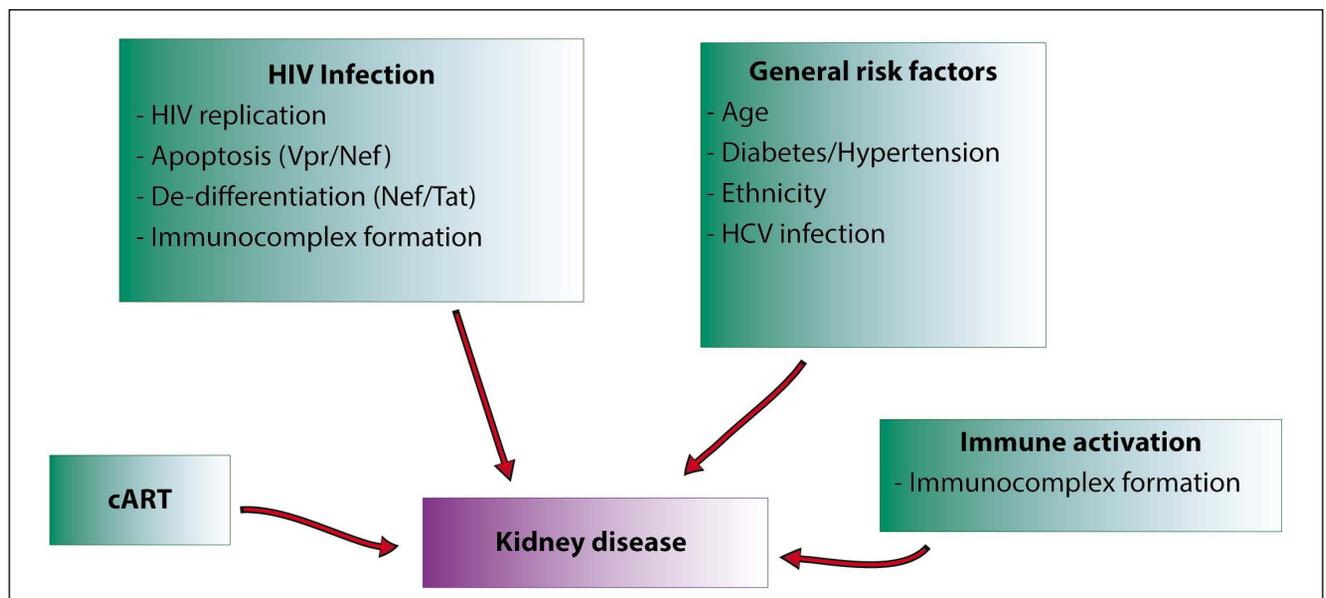
Figure 2 - *Factors associated with the development of chronic kidney disease in HIV infected patients.*

Finally, studies carried out in HIV patients co-infected with HCV showed a significant decrease of eGFR and a higher risk of progression to CKD compared to patients infected with HIV alone, underlining the role of HCV co-infection in promoting kidney disease (Tsui *et al.,* 2009; Kurbanova and Qayyum 2015; Fabrizi *et al.,* 2016).

As demonstrated by the drop in incidence of HIVAN following the widespread introduction of cART (Mallipattu *et al.,* 2014), HIV itself constitutes a risk factor for the development of kidney disease and active replication is detrimental for renal tissue. The following sections describe the mechanisms mediating HIV-induced toxicity in the kidney and the potential issues associated with the long-term use of antiretroviral agents.

PATHOGENESIS OF CHRONIC KIDNEY DAMAGE: THE ROLE OF HIV INFECTION

A growing body of literature demonstrates that besides inducing a progressive decay in the number of CD4 lymphocytes, HIV infection also affects many other cell types and lineages. HIV progressively hampers the homeostasis and functionality of cells belonging to the central nervous system, bone, cardiovascular system and kidney either through infection or via indirect mechanisms (Gibellini *et al.,* 2008; Carter *et al.,* 2011; Gibellini *et al.,* 2011; Nazari-Shafti *et al.,* 2011; Bordoni *et al.,* 2013; Butler *et al.,* 2013; Mbita *et al.,* 2014; Morini *et al.,* 2016; Tauber *et al.,* 2016).

In vivo and in vitro studies have shown that the pathogenesis of both HIVAN and HIVICK is mediated by the exposure of renal cells to viral antigens. The formation and deposition of the immunocomplex is pivotal to the onset of HIV-ICK. The presence within the kidney of viral antigens deriving from HIV replication, including p24 and gp120, is likely to increase the chance of immunocomplex formation, possibly acting as trigger for the disease (Kimmel *et al.,* 1993). In the case of HIVAN, observations made in biopsies taken from HIV-infected individuals and in murine models suggest that the histopathological findings characterizing this syndrome result from massive apoptosis and loss of renal cell differentiation, notably podocytes (Bodi *et al.,* 1995; Barisoni *et al.,* 1999). HIV transgenic mice expressing HIV envelope and accessory proteins display a range of features recapitulating HIVAN, such as severe collapsing focal segmental glomerulosclerosis and massive proteinuria (Kopp *et al.,* 1992; Bruggeman *et al.,* 1997; Barisoni *et al.,* 2000; Dickie 2000; Dickie *et al.,* 2004; Zhong *et al.,* 2005). In murine models, disease severity was associated with viral transgene levels, providing evidence that the renal expression of HIV is responsible for the HIVAN phenotype (Bruggeman *et al.,* 1997). Further studies, in which specific viral proteins were selectively expressed or inactivated, identified the viral protein r (Vpr) as the major factor responsible for triggering glomerulonecrosis (Dickie *et al.,* 2004). Other accessory proteins, including Nef and Tat, are not essential to induce glomerular lesions, but they appear to enhance the damage resulting from Vpr expression (Kajiyama *et al.,* 2000; Zuo *et al.,* 2006). Interestingly, the murine model developed by Zhong *et al.,* in which HIV proteins are selectively expressed in podocytes, displays a phenotype reminiscent of HIVAN, emphasizing the central role of this cell population in HIV-mediated kidney disease (Zhong *et al.,* 2005).

Together with glomeruloscleoris, tubulointerstitial injury is a prominent feature of kidney damage in HIV patients (Wyatt *et al.,* 2008). Apoptosis and toxicity mediated by the interaction with HIV proteins also affect tubular epithelial cells. In addition, a number of studies have established that HIV can infect tubular epithelial cells both *in vivo* and in vitro (reviewed in the following sections). HIV infection mediates the damage of tubular cells directly through its cytopathic effect and indirectly by inducing a cytokine cascade, which in turn leads to inflammation (Faulhaber and Nelson 2007). Upregulation of inflammatory response, in particular the nuclear factor kappa B cascade, has been observed in both epithelial cells and podocytes, and inhibition of pro-inflammatory mediators improves the HIVAN phenotype in mice models of kidney disease (Ross *et al.,* 2006; Faulhaber and Nelson 2007).

HIV-induced apoptosis in renal cells

One of the hallmarks of HIV infection is the ability of the virus to induce apoptosis, which results both from viral replication and from the interaction of HIV proteins with host cell components (Mbita *et al.,* 2014; Shah *et al.,* 2016). The typical features of apoptosis, namely cell shape rounding, cell detachment, nucleus shrinkage, and fragmentation were found to occur in primary proximal tubular epithelial cells infected in vitro (Conaldi *et al.,* 1998). Further studies performed on the HK2 human renal epithelial cell line (RTEC) implicated Vpr in the disruption of apoptotic pathways (Marras *et al.,* 2002; Snyder *et al.,* 2010). Mechanistically, Vpr is thought to induce apoptosis via activation of the DNA damage response pathway, as shown by the increase in the levels of phosphorylated histon 2A.X variant response to Vpr overexpression detected both in HK2 cells and in renal tissue from a transgenic mouse model (Rosenstiel *et al.,* 2008). In addition, a study by Snyder et al., suggests that sustained Vpr-mediated activation of the ERK pathway in RTEC is responsible for activation of caspase 8, which results in induction of apotosis via mitochondrial damage and caspase 9 activation (Snyder *et al.,* 2010). Interestingly, transgenic expression of Vpr was also associated with upregulation of the ubiquitin like protein FAT10, which in turn is essential for Vpr-induced apoptosis (Snyder *et al.,* 2009).

The HIV envelope protein gp120 is also able to trigger apoptosis in several cell populations, including cell types that are not susceptible to HIV infection (McCloskey *et al.,* 1997; Ahr *et al.,* 2004; Gibellini *et al.,* 2008; Gibellini *et al.,* 2011). Consistently, exogenous expression of gp120 in HK2 cells was shown to induce cellular injury in a time-dependent manner, reflecting the higher apoptosis rate of transduced cells compared to controls. Gp120 expression was associated with higher levels of both Fas and FasL, whereas pretreatment with anti-FasL antibody partially inhibited tubular cell apoptosis, indicating that Gp120 mediates apoptosis through the extrinsic pathway (Vashistha *et al.,* 2008). Interestingly, we observed a similar Gp120 induction of apoptosis in a series of experiments where immortalized podocytes (obtained by courtesy of Dr. Moin Saleem, University of Bristol, UK) were challenged with HIV laboratory strains (unpublished data). Although undetectable levels of HIV DNA and RNA suggested the absence of viral replication, podocytes were triggered to cell death, from day 3 onwards, stressing the importance of apoptosis in the pathogenesis of kidney disease.

Podocyte de-differentiation

Podocyte proliferation and loss of differentiation markers, such as synaptopodin, Wilm's tumour (WT-1), podocalyxin, common acute lymphoblastic leukemia antigen (CALLA)

and ezrin, are central for the pathogenesis of HIVAN (Barisoni *et al.*, 1999; Barisoni *et al.*, 2000). Numerous studies have shown that exogenous expression of Nef in podocytes phenocopies the podocyte alterations observed in renal biopsies from HIVAN patients (Husain *et al.*, 2005). Downregulation of CALLA and ezrin expression as well as impaired cytoscheletal organization, both indicative of de-differentiation, have also been specifically associated with Nef expression (Sunamoto *et al.*, 2003; Tan *et al.*, 2013). Nef-mediated proliferation of podocytes has been observed both in vitro and in vivo, and has recently been associated with a deregulation of the Notch pathway (Schwartz *et al.*, 2001; Sunamoto *et al.*, 2003; Husain *et al.*, 2005). The pathogenetic role of the Notch pathway has been demonstrated in vitro, where treatment with the specific Notch inhibitor GSIXX blocks Nef-dependent proliferation (Sharma *et al.*, 2013). Doublier et al., showed that another HIV accessory protein, Tat, is also involved in the pathogenesis of HIVAN in podocytes (Doublier *et al.*, 2007; Xie *et al.*, 2014). Extracellular Tat altered the expression of nephrin and cytoskeleton organization in human cultured podocytes. Similarly to what was observed for Nef, Tat-induced in vitro hyperproliferation and dedifferentiation depend on the integrity of Notch signalling pathway (Sharma *et al.*, 2013).

HIV replication in the kidney compartment

The evidence supporting a role of the interaction between HIV and renal cells in the pathogenesis of HIVAN has raised the question of whether the virus can infect kidney cells. Available literature suggests that kidney cells, and in particular glomerular and tubular epithelial cells, are able to support viral replication (Marras *et al.*, 2002; Li *et al.*, 2016). HIV RNA, DNA, and extrachromosomal circular DNA, the latter indicative of active replication, have been detected in renal cells (Cohen *et al.*, 1989; Tanji *et al.*, 2006), even in the absence of detectable HIV RNA in peripheral blood (Bruggeman *et al.*, 2000).

Several studies have tried to identify the mechanisms of HIV entry in renal epithelial cells, defining a list of possible cellular receptors and molecules that might interact with the virus (Husain and Singhal 2011). Although isolated reports provided evidence for the presence of CD4 in this cell population (Karlsson-Parra *et al.*, 1989), it is generally believed that these cells do not express the classic HIV receptor and coreceptors. In the absence of CD4, other membrane proteins, such as DEC-205, and Globotriaosyl ceramide (Gb3) have been proposed as possible counterparts for HIV entry (Hatsukari *et al.*, 2007; Khan *et al.*, 2009). Alternatively, cell-to-cell transmission, mainly involving helper T cells, has often been implicated in HIV infection of renal epithelial cells (Phillips and Bourinbaiar 1992; Mikulak *et al.*, 2009; Chen *et al.*, 2011; Blasi *et al.*, 2014). Chen *et al.*, described the virological synapses that allow HIV to pass from infected T cells to renal tubular cells. Consistent with the cell-to-cell transmission scenario, viral transmission occurred more efficiently when cells were infected in the presence of T cells, compared to cell-free viral inoculum. Uptake of the virus was further enhanced in the presence of two specific heparan sulfate proteoglycans, syndecan 1 and agrin, although their role in absence of viral envelope engagement is not clear (Chen *et al.*, 2011).

Several studies have reported the infection of podocytes (Bruggeman *et al.*, 2000; Marras *et al.*, 2002; Tanji *et al.*, 2006; Khatua *et al.*, 2010; Li *et al.*, 2016). These cells express, albeit at low level, both CD4 and a number of the members of the CCR and CXCR families of chemokine receptors necessary for the entry of the virus (Huber *et al.*, 2002). Consistently, we showed the presence of the HIV receptor and co-receptors on the surface of immortalized podocytes by means of flow cytometry (unpublished observations). Nevertheless, some reports suggest that HIV entry in podocytes might also be mediated by interaction of the virus with other cellular molecules (Mikulak and Singhal 2010; Mikulak *et al.*, 2010).

Kidney as a viral reservoir

In humans, in situ HIV RNA hybridization experiments revealed spliced and unspliced viral mRNA both in tubular and glomerular epithelial cells, regardless of cART treatment and viral suppression (Bruggeman *et al.*, 2000; Winston *et al.*, 2001). These observations, together with the findings described in the previous sections, are consistent with a model in which infected CD4 T lymphocytes deliver the virus to kidney cells (Chen *et al.*, 2011). Once integration has occurred, renal cells can produce and transfer new viral particles to the neighbouring cells as well as to CD4 T lymphocytes, in a contact-dependent way (Blasi *et al.*, 2014).

Of note, phylogenetic analysis of envelope sequences showed that viral variants derived from renal tubules cluster separately from those derived from PBMCs of the same patient, suggesting that kidney might serve as a separate replication site (Marras *et al.*, 2002). Analyzing biopsies from HIV patients who underwent kidney transplantation, Canaus et al., showed the presence of viral DNA and RNA both in podocytes and in epithelial cells, supporting the notion that HIV infection of kidney cells could occur even during complete virological suppression (Canaud *et al.*, 2014). These data strengthen the role of kidney as a reservoir for local or systemic viral rebound.

PATHOGENESIS OF CHRONIC HIV KIDNEY DISEASE: THE ROLE OF ANTIRETROVIRAL-ASSOCIATED NEPHROTOXICITY

Despite the benefits of cART for the treatment and prevention of HIV infection, the use of antiretroviral drugs has been associated with a number of adverse effects. These include mitochondrial toxicity, lipodystrophy syndrome, dyslipidemias, insulin resistance, cardiovascular disease, osteopenia, and renal toxicity (Kohler and Lewis 2007; Anuurad *et al.*, 2009; Calza 2012; Calvo and Martinez 2014; Negredo *et al.*, 2015; Moran *et al.*, 2016; Non *et al.*, 2016). Given that current guidelines recommend the early start of cART, and medications need to be taken life-long, monitoring the cumulative toxic effects of antiretroviral drugs is of the utmost importance for the management of HIV-infected individuals (Antinori *et al.*, 2016; European AIDS Clinical Society 2016). cART impact on renal functions can result in different conditions, depending on the specific drugs included in the antiretroviral regimen and the presence of concomitant risk factors. Nephrotoxicity has been reported for almost all the classes of antiretroviral drugs and it is recommended to monitor patients constantly, especially those who present risk factors associated with impaired kidney function (Achhra *et al.*, 2016). Characterization of the mechanisms mediating cART-associated nephrotoxicity is needed to develop validated protocols to identify individuals at high risk for kidney damage, in particular in view of the possible implementation of pre-exposure prophylaxis (PrEP) across large HIV-uninfected populations.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Prolonged use of NRTIs, notably zidovudine, stavudine and didanosine, is generally associated with mitochondrial toxicity (Kohler and Lewis 2007). Although renal toxicity associated with members of this class is uncommon, several studies have reported an association between Tenofovir (TFV) and a decline in kidney function. When administered in the prodrug form tenofovir disoproxil fumarate (TDF), secretion of TFV requires glomerular filtration and active tubular secretion. The latter process involves TFV internalization in proximal tubule cells through basolateral organic anion transporters (OAT1 and OAT3) and its excretion through the multidrug resistance protein 4 (MRP-4) and 7 (MRP-7) (Ray et al., 2006; Imaoka et al., 2007). Consistently with TDF's known mitochondrial toxicity and its accumulation in the tubules, Fanconi syndrome, a severe form of proximal tubulopathy, has been reported in multiple studies involving patients receiving TDF-based regimens (Karras et al., 2003; D'Ythurbide et al., 2007; Woodward et al., 2009). Moreover, studies comparing TDF-based regimens with regimens based on other NRTIs have documented a time-dependent decline in eGFR associated with the use of TDF (Gallant et al., 2005; Mauss et al., 2005). Proteinuria and rapid eGFR decline were observed in subsequent studies, along with the onset of CKD (Cooper et al., 2010; Mocroft et al., 2010; Scherzer et al., 2012; Ryom et al., 2013). The D:A:D study enrolled cART-treated patients with normal baseline eGFR (≥90 mL/min) evaluating eGFR evolution over a median period of 7.2 years. Although the cumulative incidence of renal damage in this cohort was low, nephrotoxicity was more frequent among patients receiving TDF and the risk of CKD was associated with the duration of exposure, supporting a cumulative toxic effect (Mocroft et al., 2016).

Tenofovir alafenamide (TAF) is an alternative formulation of the Tenofovir prodrug with a better renal and bone safety profile compared to TDF. Preliminary studies suggest that TAF, which is not a substrate of OAT1 and OAT3, reduces the risk of nephrotoxicity as it does not accumulate in renal proximal tubular cells (Cihlar et al., 2009). Clinical trials assessing the safety and efficacy of switching from a baseline therapy to a TAF-containing therapy confirmed the non-inferior virological efficacy and the improvements in the renal function parameters (Markowitz et al., 2014; Sax et al., 2014; Sax et al., 2015; Mills et al., 2016; Pozniak et al., 2016; Wohl et al., 2016). A phase II randomized, double-blind, double-dummy, multicentre trial compared an active-controlled arm where patients received a regimen based on elvitegravir, cobicistat, emtricitabine, and TDF with a study arm where patients received elvitegravir, cobicistat, emtricitabine, and TAF. The virological suppression and the safety were comparable between the two prodrugs. Moreover, at week 24, patients in the TAF arm experienced a smaller decrease in creatinine clearance and reduced proteinuria, while showing comparable virological suppression and general safety (Sax et al., 2014). Hence, the FDA approved TAF administration to patients with a creatinine clearance ≥30 mL/min, albeit advising continued monitoring of kidney function during therapy (Gilead press statement 2015). In patients with mild to moderate renal impairment, switching to a regimen including TAF was associated with an improvement in kidney function, namely decreased proteinuria and improved proximal tubular function (Pozniak et al., 2016). Interestingly, these trials reported an alteration in lipid parameters in patients receiving a regimen including TAF, who showed a greater increase of the low-density lipoprotein cholesterol levels compared to patients receiving TDF (Sax et al., 2014; Mills et al., 2016). The implications of these alterations remain to be fully elucidated, hence dose-adjustments of the antiretroviral therapy according to patient response are strongly recommended.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

In general, drugs from the NNRTI class show a safe renal profile. Sporadic cases of urolithiasis were reported with efavirenz (Wirth et al., 2006), even though this drug is usually associated with mitochondrial dysfunction and toxicity (Lopez et al., 2004).

Protease inhibitors (PI)

Protease inhibitors (PI) are a large class of drugs which inhibit viral replication by preventing the cleavage of HIV polyproteins by the viral protease. Because of their similarities in terms of structure and binding pattern, regimens including PI usually share similar side-effects (Lv et al., 2015). PI-induced metabolic syndromes include lipodystrophy/lipoatrophy, dyslipidemia, insulin-resistance as well as cardiovascular diseases (Carr et al., 1998; Barbaro and Iacobellis 2009). Urolithiasis, nephrolithiasis and other forms of AKI such as acute tubular injury and tubulo-interstitial nephritis have been sporadically reported in patients treated with PI, in particular indinavir, lopinavir and atazanavir (Doco-Lecompte et al., 2004; Hamada et al., 2012; Lafaurie et al., 2014; Lin et al., 2015). Observational studies suggested that long-term exposure to ritonavir-boosted atazanavir or lopinavir might also be associated with CKD (Mocroft et al., 2010; Albini et al., 2012; Young et al., 2012; Bagnis and Stellbrink 2015; Gianotti et al., 2016). However, it is debated whether the reported effects of PI on CKD development are independent, or result from its frequent co-administration with TDF. In this regard, a metanalysis including 24 randomized clinical trials did not provide evidence of the association of lopinavir/ritonavir or atazanavir/ritonavir with progression to either CKD or ESRD, while confirming the increased risk of acute renal function impairment (Bagnis and Stellbrink 2015). Similarly, the European observational cohort RE-MAIN, observed no significant decline in renal function among naïve patients starting a atazanavir/ritonavir-based regimen over a period of 5 years (Teofilo et al., 2016).

Integrase inhibitors (INSTIs)

Integrase inhibitors are a new class of molecules acting as catalytic inhibitors of integrase, which have been successfully introduced in clinical practice in recent years (Andreoni et al., 2015; Wong et al., 2016b). Drugs belonging to this class have generally better safety profiles as they target integration, a process which occurs only in infected cells. Raltegravir (RTG) and, more recently, dolutegravir (DTG) have both been associated with increased serum creatinine levels and small reductions of eGFR (Cahn et al., 2013; Gupta et al., 2013; Raffi et al., 2013). The SPRING-2 and VIKING studies, assessing the efficacy and safety of DTG, found that this increase in serum creatinine upon initiation of therapy seems to be non-progressive and reaches a plateau at week 4 (Eron et al., 2013; Raffi et al., 2013). Cobicistat (COBI) a pharmaco-enhancer licensed for use in combination with elvitegravir, is also known to increase serum creatinine levels (German et al., 2012). While the aetiology of the rise in

serum creatinine following treatment with RTG is unclear, DTG and COBI are thought to block the uptake and efflux of creatinine by inhibiting the organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion protein 1 (MATE1), respectively (Lepist *et al.*, 2014; Maggi *et al.*, 2014). However, aside from the reported effects on serum creatinine, the use of integrase inhibitors does not seem to be associated with mid and long-term declines in kidney function (Milburn *et al.*, 2016).

Pre-exposure prophylaxis

In recent years, pre-exposure prophylaxis (PrEP) has gained considerable attention as a possible large scale preventive measure among individuals at risk for HIV infection (Spinner *et al.*, 2016). In 2012, the FDA approved the use of TDF in combination with oral emtricitabine for PrEP to prevent HIV infection (FDA news realease 2012). Although some controversial points, such as suboptimal adherence and the risk of drug resistance arising from PrEP (Abbas *et al.*, 2011; Marcus *et al.*, 2016a; Marcus *et al.*, 2016b), have yet to be fully addressed, the open-label PrEP trials showed encouraging results (Grant *et al.*, 2014; Liu *et al.*, 2016). Nevertheless, the issue of potential toxicity of these regimens remains, in particular given the known adverse events associated with the use of TDF. Moreover, although PrEP is administered to HIV-uninfected individuals, large scale implementation of PrEP has to take into account the incidence of other risk factors associated with kidney disease, such as age and other co-morbidities. In a recent clinical trial, 15.5% of participants receiving PrEP were diagnosed with a reduction in eGFR (<70 mL/min/1.73 m^2) and 0.6% stopped PrEP due to renal toxicity. Decreased eGFR was associated with age, older (≥50 years) participants having a higher incidence than young individuals (Marcus *et al.*, 2016a). The iPrEx open-label-extension (OLE) trial enrolled HIV-negative MSM/transgender individuals with no restriction on current renal function who followed a PrEP regime based on tenofovir-disoproxil-fumarate/emtricitabine (TDF/FTC). A significant decrease in estimated creatinine clearance over time was observed, and this phenomenon was more relevant in those starting PrEP at older age (Gandhi *et al.*, 2016).

CONCLUSION

With the increased life expectancy of HIV-infected patients receiving cART, the epidemiology of kidney diseases has changed drastically. Kidney damage associated with HIV infection is due to multiple distinct mechanisms, including direct infection of renal cells, host response to specific viral antigens, and the long-term use of antiretroviral drugs. Given the wide range of possible interactions between HIV, individual predisposing factors, and cART, clinicians need to be aware of the possible kidney complications of HIV infection and to consider regular monitoring of patients exhibiting risk factors associated with CKD progression.

Besides its role in the pathogenesis of kidney disease, the observation that HIV can replicate in kidney cells makes this organ a potential reservoir site. This finding has profound implications for the achievement of sustained viral suppression and for HIV cure strategies, particularly in the light of the recent introduction of kidney transplant as a therapeutic option for HIV-infected individuals experiencing kidney failure.

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