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Taking a hard look at the pathogenesis of childhood HIV-associated nephropathy

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Abstract

Childhood human immunodeficiency virus-associated nephropathy (HIVAN) is defined by the presence of proteinuria associated with mesangial hyperplasia and/or global-focal segmental glomerulosclerosis, in combination with the microcystic transformation of renal tubules. This review discusses the pathogenesis of childhood HIVAN and explores how the current pathological paradigm for HIVAN in adults can be applied to children. The Human Immunodeficiency virus-1 (HIV-1) induces renal epithelial injury in African American children with a genetic susceptibility to develop HIVAN. The mechanism is not well understood, since renal epithelial cells harvested from children with HIVAN do not appear to be productively infected. Children with HIVAN show a renal up-regulation of heparan sulphate proteoglycans and a recruitment of circulating heparin-binding growth factors, chemokines, and mononuclear cells. Macrophages appear to establish a renal HIV-reservoir and transfer viral particles to renal epithelial cells. All of these changes seem to trigger an aberrant and persistent renal epithelial proliferative response. The paradigm that viral products produced by infected renal epithelial cells per se induce the proliferation of these cells is not supported by data available in children with HIVAN. More research is needed to elucidate how HIV-1 induces renal epithelial injury and proliferation in HIV-infected children.

Keywords

Heparin-binding growth factors; HIV-associated nephropathy; Infection of renal tubular epithelial cells; Pediatric AIDS; Renal disease

Introduction

During the pre-HAART (highly active antiretroviral therapy) era, approximately 40% of all children infected with the human immunodeficiency virus-1 (HIV-1) in the USA presented renal complications [1–5]. Among them, 10–15% of all children who acquired the HIV-1 through vertical transmission developed a renal disease named HIV-associated nephropathy (HIVAN) [2–5]. The study of HIVAN attracted significant attention because it was considered a new renal disease induced directly by HIV-1. In addition, HIVAN bears a significant impact on the quality of life, treatment, and survival of HIV-infected children [2–5]. African Americans show a unique susceptibility to develop this renal disease. Over 80% of the estimated 2.1 million HIV-infected children under 15 years of age are living in the sub-Saharan Africa [1]. Based on these data, if the USA data from the pre-HAART era were extrapolated to Africa, approximately 300,000 children without access to antiretroviral therapy could

develop HIVAN [5]. Thus, it is necessary to understand the pathogenesis and risk factors for the development of childhood HIVAN and to develop new treatments to prevent the progression of this renal disease. This article discusses research findings that are relevant for the pathogenesis of childhood HIVAN and explores how the current pathological paradigm for HIVAN in adults can be applied to HIV-infected children.

Definition of HIVAN

In 1984, two groups of physicians from New York and Miami reported the presence of HIVAN in adult African American patients [6,7]. HIVAN was initially described as a clinical and renal histological syndrome characterized by heavy proteinuria and rapid progression to end stage renal disease. The renal histology showed a combination of glomerular and tubular lesions involving global or focal segmental glomerulosclerosis (FSGS), microcystic transformation of renal tubules, and interstitial inflammation. It should be noted that the initial reports suggested that the glomerular lesions were similar to those seen in patients addicted to heroin [6,7]. The identification of HIVAN in young children subsequently provided key evidence to support the notion that HIV-1 per se was capable of inducing renal disease independently of other confounding variables present in HIV-infected adults [2,3].

Follow-up reports in adult patients with HIVAN identified the presence of glomerular capillary collapse associated with a remarkable hyperplasia of podocytes [8,9]. Collapsing glomerulopathy (CG) is nowadays considered to be a typical feature of HIVAN, but it can also be seen in patients not infected with HIV-1 [10,11] and, in fact, many children with HIVAN do not develop CG. Therefore, what is considered as unique histological feature of childhood HIVAN is the presence of mesangial hyperplasia and/or classic FSGS in combination with microcystic tubular dilatation and interstitial inflammation [2–5] (Fig. 1). Alternatively, HIV-infected children can develop mesangial proliferative lesions secondary to immune complex deposits [2–5]. These patients show a different clinical and renal histological pattern and are not included in the definition of HIVAN. Overall, the study of the pathogenesis of childhood HIVAN provides a unique opportunity to define how HIV-1 induces direct renal injury in the absence of immune complex disorders and other confounding variables present in HIV-infected adults.

The HIV-1 virus

Previous review articles have discussed in detail the structure of the HIV-1 virus and the function of its viral products [12,13]. Here, only a few basic concepts considered to be important to understanding the pathogenesis of HIVAN are summarized. The HIV-1 virus is a member of the genus *Lentivirus* in the *Retroviridae* family, and called a retrovirus because its RNA genome must be reverse transcribed to DNA within the cells using the viral enzyme reverse transcriptase (RT). In permissive cells, the DNA enters the nucleus, integrates into the chromosomes, is transcribed to messenger RNA, and is subsequently translated into viral proteins [12,13] (Fig. 2c). HIV-1 may also enter cells without necessarily establishing a productive or latent infection.

Viral proteins

HIV-1 contains at least nine genes that generate viral proteins [12,13]. By convention, the viral proteins (p) are designated with a number corresponding to the protein size ($\times 1000$) and are categorized as structural, regulatory, or accessory proteins. The three structural proteins are Gag, Pol, and Env (Fig. 2a). The Gag precursor polyprotein is processed by the viral protease (PR) to generate the Gag proteins: (1) matrix (MA, p17), which forms the inner shell just below the viral membrane; (2) capsid (CA, p24), which forms the conical core enclosing the viral genomic RNA; (3) nucleocapsid (NC, p7), which interacts with viral RNA inside the capsid

(Fig 2a). The Pol precursor polyprotein gives rise to the viral enzymes RT, PR, and integrase (IN), which provide enzymatic functions essential to the viral life cycle [13]. The *env* gene codes for the HIV proteins gp120 and gp41, which constitute the viral envelope and form the surface unit of HIV-1 as it “buds” out of cells. Two regulatory proteins, Tat and Rev, are also needed for HIV infection and replication. Tat is a transcription factor that is essential for viral replication, but it can also be released in the extracellular space and taken up by uninfected cells. Rev plays a key role regulating the splicing of HIV RNA transcripts [12,13]. Finally, four accessory viral proteins, named Nef, Vif, Vpu, and Vpr, perform relevant accessory functions that enhance HIV replication and infectivity [12,13] (Fig. 3).

Role of HIV genes in HIVAN

At least four HIV genes, *env*, *tat*, *nef*, and *vpr*, have been linked directly to the pathogenesis of the renal disease in HIV-transgenic (Tg) rodents [14–20]; however, their contribution to the pathogenesis of HIVAN in humans is less clearly understood. The HIV-1 genes *nef* and *vpr* have strong renal pathogenic roles in HIV-Tg mice [18–20] and can induce the de-differentiation and proliferation of cultured murine podocytes by interacting with several signaling pathways in these cells [21,22]. Based on these data, along with the detection of HIV-1-specific proviral DNA and mRNA in the renal tubular epithelium of patients with HIVAN [23,24], many investigators postulate that *nef* and *vpr* play a key role in the pathogenesis of HIVAN in adult humans [22–26]. These findings have yet to be reproduced in renal sections or cultured epithelial cells harvested from children with HIVAN.

Role of genetic factors in HIVAN

Genetic host factors play an essential role in the pathogenesis of HIVAN in both humans and HIV-Tg mice [26–28]. African Americans show an 18- to 50-fold increased risk for developing HIVAN [26,27]. Mutations in the *CD2AP* gene, which is abundantly expressed in podocytes, have been found in African Americans with HIVAN [29]. Most recently, two different groups of investigators found a significant association between a genetic variation in the *MYH9* gene and the presence of FSGS in African Americans with HIVAN [30,31]. The *MYH9* gene encodes the non-muscle myosin heavy chain IIA protein, which is also expressed in podocytes [32]. More studies are needed to identify the causal sequence variation in the *MYH9* gene and to determine additional genetic or environmental factors that may interact with *MYH9* to cause HIVAN [30,31].

HIV-Tg mice

Studies on HIV-Tg mice have provided important information towards establishing the current pathological paradigm for HIVAN in adults. Tg-mice expressing high levels of HIV-1 genes in renal tubular epithelial cells and/or podocytes develop the full HIVAN phenotype [17–20]. In contrast, targeted expression of viral genes to lymphocytes and lymphoid tissue induces renal disease but does not reproduce the full human HIVAN phenotype [14]. Therefore, it appears that HIV-1 genes must be expressed in podocytes to reproduce the full HIVAN phenotype [17–20]. Nevertheless, because the infection process is bypassed in all HIV-Tg mice, these findings should be interpreted with caution. For example, these mouse models can not be used to exclude the possibility that circulating cytokines and/or viral proteins (i.e. Tat, gp120) play a role in the pathogenesis of HIVAN. Both gp-120 and Tat are released into the circulation of HIV-infected patients, and play essential roles modulating the host immunological response [33–35] and the infection of peripheral blood mononuclear cells that infiltrate renal tissues [12,13,36]. These essential clinical features of the pathogenesis of HIVAN in humans are bypassed in HIV-Tg mice.

Pathological paradigm for HIVAN in adults

Most investigators agree that the response of the renal epithelial cells to HIV-1 infection appears to be the critical step in the pathogenesis of HIVAN [23–26]. Because collapsing glomerulopathy is considered to be the typical feature of HIVAN in adults, most research studies have attempted to define how HIV-1 induces the de-differentiation and proliferation of podocytes [18–22]. One proposed mechanism to explain the pathogenesis of HIVAN in susceptible adults is that HIV-1 induces a productive infection of podocytes, which is sufficient per se to cause de-differentiation and proliferation of these cells, leading to the collapse of glomerular capillaries [22,25,26]. However, several pathogenic mechanisms that are important to validate this paradigm remain unknown (Table 1). The most relevant one is that we do not know how HIV-1 induces a productive infection of human podocytes. Key studies demonstrating that cultured human podocytes can undergo a productive infection leading to their de-differentiation and proliferation are missing, and two studies failed to infect cultured human podocytes [37,38]. Only cultured immortalized mouse podocytes can undergo de-differentiation and proliferative changes when infected with pseudotyped viral vectors carrying HIV-1 genes, including *nef* and/or *vpr* [21,22]. Alternatively, renal sections from patients with HIVAN [10], or from HIV-Tg mice that express HIV-1 genes selectively in podocytes [19], show a remarkable proliferation of glomerular parietal epithelial cells. Thus, some investigators have argued that the proliferation of parietal epithelial cells, rather than of podocytes, plays a key role in this process [10].

Studies in cultured human podocytes that were not infected with HIV-1 support the alternative notion that HIV-Tat release into the extracellular space, in synergy with fibroblast growth factor-2 (FGF-2), can induce the de-differentiation and proliferation of these cells [39]. A more recent study concluded that HIV-Tat may enhance the permeability of renal glomeruli by reducing the expression of nephrin in podocytes [40]. Moreover, selective expression of the angiogenic vascular permeability factor VEGF-A in podocytes can induce CG in transgenic mice [41,42]. All of these angiogenic factors play a role in the pathogenesis of other proliferative disorders in patients with the acquired immunodeficiency syndrome (AIDS) [43]. Therefore, if similar pathogenic events are confirmed in human kidneys, a different pathological paradigm for HIVAN in adults could emerge.

Pathological paradigm for childhood HIVAN

African American children with HIVAN show a higher prevalence of mesangial hyperplasia and a lower prevalence of CG than adults (Table 1). The reasons for the different renal histological lesions are unknown. Many factors can be considered to explain these findings, including an immature glomerular function, immunological factors, different susceptibility and regenerative capacity of intrinsic renal cells in response to HIV-1, environmental or infectious co-factors, and/or the use of illegal drugs in adults. Nevertheless, the study of childhood HIVAN provides a unique opportunity to understand how HIV-1 induces mesangial hyperplasia in combination with tubulointerstitial changes in the absence of other confounding variables present in adults.

Pathogenesis of mesangial hyperplasia

HIV-infected children with mesangial hyperplasia show a slower rate of progression of the renal disease when compared to children with the classic or collapsing FSGS variants [2,3]. Mesangial hypercellularity may be an early event in the pathogenesis of childhood HIVAN [2], but this hypothesis has never been tested. Unfortunately, the pathogenesis of mesangial hyperplasia in children with HIVAN has not been explored in depth. HIV-Tg mice provide clinical evidence in support of a unifying hypothesis that could explain the pathogenesis of mesangial hyperplasia and proteinuria in children with HIVAN. More specifically, Tg mice

that express HIV genes selectively in podocytes can develop podocyte injury, proteinuria, and mesangial hyperplasia [19]. The mechanism by which injured podocytes may cause mesangial hyperplasia is not clearly understood, but this event is not restricted to the pathogenesis of HIV-renal diseases; other transgenic model systems that are not relevant for HIVAN show similar changes [44]. Both human glomerular endothelial and epithelial cells produce endogenous heparin-like substances that can inhibit the growth of mesangial cells [45]. Thus, when these cells are injured by HIV-1, the synthesis and release of these inhibitory factors may be suppressed. Alternatively, injured podocytes and endothelial cells can release heparin-binding growth factors, such as FGF-2, which can enhance the proliferation of mesangial cells harvested from HIV-infected children [46].

An important issue that should be taken into consideration to explain the pathogenesis of mesangial hyperplasia in HIV-infected children is whether mesangial cells can be productively infected by HIV-1. Three different groups of investigators showed that cultured human mesangial cells can be infected by HIV-1 [37,38,47]. One group found that the chemokine receptor GPR1 plays an important role in this process [47], while another showed that infected mesangial cells release cytokines that are potentially able to induce FSGS [37]. In contrast, two different groups of investigators were unable to infect cultured mesangial cells [48,49], and their studies in renal sections from patients with HIVAN did not support the notion that mesangial cells are productively infected by HIV-1 [49,50].

HIV-Tg rats carrying a replication-defective HIV-1 proviral DNA develop mesangial hyperplasia during the early stages of the renal disease, but only glomerular and tubular epithelial cells express viral transcripts in the kidneys of these rats [51]. Only one study done in HIV-Tg mice carrying a different replication-defective HIV-1 provirus showed that restricted expression of HIV genes in vascular smooth muscle or mesangial cells can induce the proliferation of these cells [52]. However, these changes were associated with a remarkable recruitment of inflammatory cells, and it is unclear whether the HIV-1 genes per se, or the cytokines released by the inflammatory cells, were responsible for the proliferative changes [52]. In summary, the results of all of these studies suggest that the HIV-cytokine milieu—alone or in combination with endogenous factors released by injured glomerular cells—can cause mesangial hyperplasia without necessarily inducing a productive infection of these cells.

Pathogenesis of the tubulointerstitial lesions and infection of renal tubular epithelial cells

A central question that remains to be answered is whether renal tubular epithelial cells from children with HIVAN can be productively infected in vivo. HIV-1 infects mononuclear cells by sequentially interacting with CD4, its primary receptor, and a co-receptor, usually either CCR-5 or CXCR-4 (Fig. 2c). The HIV-1 receptor and co-receptors are recognized by the HIV-1 envelope gp120 glycoprotein (Fig. 2c) [12,13]. However, previous studies failed to detect mRNA and protein expression of CD4, CCR-5, and CXCR-4 in intrinsic glomerular and tubular epithelial cells from renal biopsies harvested from adult patients with HIVAN [50]. Thus, it is unclear how renal epithelial cells could become productively infected in vivo by HIV-1. In contrast, HIV-infected macrophages express abundant HIV-receptors and co-receptors [12, 13], and for this reason, they probably constitute the renal HIV reservoir.

The rationale for proposing that HIV-infected macrophages can establish the critical renal HIV reservoir, is based on their ability to undergo latent and productive infections [12,13]. Macrophages harvested from children with HIVAN release viral proteins, can transfer mature viral particles to renal epithelial cells (Fig. 4), and maintain their infection capability after 3 weeks in culture [53]. In contrast, primary renal epithelial cells harvested from the urine of children with HIVAN do not release mature viral particles and do not produce viral proteins

unless they are infected in vitro with a high viral load [53]. Therefore, as shown in Fig. 4, we propose that the cell-to-cell contact between HIV-infected macrophages and renal tubular epithelial cells may trigger the rapid release of viral particles into the enclosed space formed between the “donor” mononuclear cells and the “acceptor” renal epithelial cells [53]. Mature virions released into this space (Fig. 4, black arrows) can be subsequently trapped in vesicles inside renal epithelial cells by a mechanism that is yet not understood (Fig. 4, open arrows). This Trojan horse-like mechanism of viral entry may explain how HIV-1 infects renal tubular epithelial cells harvested from children with HIVAN [53]. However, this process appears to bypass the fusion entry step and can not explain how renal tubular epithelial cells become productively infected with HIV-1 [53]. Nevertheless, studies carried out in cultured human intestinal epithelial cells have shown that similar cell-to-cell contact interactions can facilitate the transfer of membrane-derived microparticles containing HIV-1 co-receptors (i.e. CCR-5) [54]. This mechanism may allow the fusion of HIV-1 to the cell membrane, resulting in the productive infection of intestinal epithelial cells [54]—but this hypothesis remains to be tested in renal epithelial cells. If correct, and the cell-free culture supernatants harvested from children with HIVAN do contain similar membrane-derived microparticles, this mechanism may explain the modest productive infection observed in renal tubular epithelial cells exposed to these samples [53]. Alternatively, only one study has shown that cultured primary renal tubular epithelial cells harvested from HIV-negative adult donors can become infected by a CD4-mediated mechanism [55]. However, RT-PCR and immunohistochemistry studies have shown that primary renal tubular epithelial cells harvested from children with HIVAN express only low mRNA levels of CD4, CXCR4, and CCR-5 and that they do not express detectable levels of these proteins on their cell surface [56]. In summary, HIV-infected macrophages appear to establish a critical renal HIV reservoir and induce renal tubular injury in HIV-infected children.

Induction of renal tubular epithelial injury by HIV-1

Another question that remains unanswered for the pathogenesis of childhood HIVAN is how HIV-1 can cause renal epithelial injury without inducing a productive infection of these cells. Several studies suggest that HIV-1 can induce direct renal epithelial injury [57,58]. Renal tubular epithelial cells from developing HIV-Tg₂₆ kidneys undergo apoptosis when the expression of HIV-1 genes is activated by ultraviolet light [57]. The induction of renal tubular epithelial injury during the early stages of renal disease in HIV-Tg₂₆ mice is correlated with the highest levels of HIV-1 gene expression in these cells [58]. Cultured renal epithelial cells harvested from the urine of children with HIVAN and exposed to HIV-infected supernatants show decreased growth and survival rates when compared to control mock-infected cells [53]. Finally, viral proteins and cytokines released by HIV-1 infected cells may induce renal tubular injury without necessarily causing a productive infection of these cells [26,36,59–61].

A recent study showed that the envelope glycoprotein gp120 can bind to the glycosphingolipid globotriaosylceramide (Gb₃) located on renal tubular epithelial cells [62]. Gb₃ is the functional receptor for the Shiga-like toxins, and renal sections harvested from children and HIV-Tg₂₆ mice with renal disease show a remarkable upregulation of Gb₃ in dilated renal tubules and microcysts [63,64]. In addition, gp-120 has an affinity for galactosyl ceramide, and this glycosphingolipid, alone or together with Gb₃, can enhance the binding and/or entry of HIV-1 in the absence of CD4 [65]. All of these interactions have the potential to enhance the viral infectivity and cytotoxic effects of HIV-1 in renal tubular epithelial cells. Further studies are needed to elucidate the role of glycosphingolipids and gp-120 in the pathogenesis of childhood HIVAN and to define how HIV-1 can injure renal tubular epithelial cells.

Role of heparin-binding growth factors

Studies done in renal tubular epithelial cells harvested from the urine of children with HIVAN show that very few colonies are positive for HIV-1, based on PCR results [4,53]. Since these cells represent the pool of tubular epithelial cells that are probably undergoing active proliferative changes in vivo, these findings strongly suggest that other mitogenic factors acting either alone or in association with HIV-1 should be responsible for inducing the tubulointerstitial proliferative lesions characteristic of HIVAN. For example, renal tubular epithelial cells harvested from the urine of children with HIVAN produce and release high levels of heparin-binding growth factors, including an FGF-binding protein (BP-1) that enhances the release and mitogenic activity of several members of the FGF's family [66,67]. High plasma levels of FGF-2 have been found to be correlated with the progression of AIDS in adults [68], and FGF-2 levels are elevated in the plasma and urine of HIV-infected children with HIVAN [46]. FGF-2 released into the circulation could be trapped in injured renal tissues bound to renal heparan sulphate proteoglycans (HSPG) [58]. In this manner, FGF-2 can increase the attachment of HIV-infected mononuclear cells to renal epithelial cells [61], enhance the expression of hypoxia-inducible genes in these cells [69], induce renal microcysts [70], and/or cause FSGS [71], depending on the experimental and rodent model system. In addition, HSPG can act as low-affinity receptors for the uptake of HIV-1 [72] and other heparin binding factors, such as VEGF-A [73], chemokines [60,73,74], and the viral proteins gp-120 [34] and Tat [59,75]. In support of this notion, HIV-infected children and HIV-Tg₂₆ mice with renal disease (Fig. 5) show a remarkable up-regulation of renal HSPG in correlation with the progression of their renal disease and the accumulation of heparin-binding growth factors [36,58,66,67]. Thus, the excessive release and accumulation of heparin-binding factors in children with HIVAN may induce an aberrant renal tubular regenerative response and induce tubular proliferative lesions.

Treatment of childhood HIVAN

Despite the scientific progress that has been made during the last years, no controlled randomized trials have been performed to determine the best treatment for children with HIVAN. Nevertheless, based on isolated reports describing the clinical experience of many pediatricians, the new anti-retroviral therapies (ART) are considered the best treatment for HIVAN [36,76]. Although ART probably improve the outcome of HIVAN by reducing the viral load [77], the protease inhibitors saquinavir and indinavir also have potent anti-angiogenic activity [78]. Thus, it is tempting to speculate that these drugs are also able to decrease the renal activity of heparin-binding growth factors, such as FGF-2 and vascular endothelial growth factor-A. Corticosteroids, in combination with ART, may also improve the outcome of childhood HIVAN by decreasing the renal interstitial inflammation [79]. However, the risks associated with their long-term use in HIV-infected children, especially in countries with a high prevalence of tuberculosis, should be balanced against their potential benefits [5]. No controlled studies have been published to date showing that corticosteroids can improve the long-term outcome of children with HIVAN. Alternatively, angiotensin-converting enzyme inhibitors have been used successfully to ameliorate the progression of HIVAN in adults [80]. Captopril also improves the outcome of the renal disease in HIV-Tg₂₆ mice [81] and HIV-Tg rats, probably by reducing the proteinuria, the activity of renal fibrogenic cytokines, and/or the hypertension frequently seen during the late stages of the renal disease [51]. Nevertheless, these drugs should be used with caution in HIV-infected children with hypoalbuminemia, salt-wasting disorders, and gastrointestinal problems. These conditions can induce extracellular fluid volume contraction and, therefore, blocking the renal angiotensin system under these clinical circumstances could induce further renal injury. Hopefully, new and more effective treatments will become available during the next years.

Summary

We propose that HIV-1 induces continuous and progressive renal epithelial injury in African American children with a high viral load and a genetic susceptibility to develop HIVAN. The exact mechanisms by which HIV-1 induces renal epithelial injury in HIV-infected children are not currently understood, since renal epithelial cells harvested from children with HIVAN do not appear to be productively infected with HIV-1. The paradigm that viral products produced by infected renal epithelial cells per se are sufficient to induce the proliferation of these cells can not be supported by the data generated in renal sections or primary epithelial cells harvested from children with HIVAN (Table 1). Nevertheless, HIV-infected macrophages appear to establish a renal HIV reservoir, and they are capable of releasing mature viral particles, viral proteins, and cytokines in close proximity to glomerular and tubular epithelial cells. These events may facilitate the transfer of viral particles to renal epithelial cells and to perpetuate the renal injury process. The renal injury is associated with an up-regulation of renal HSPG and the recruitment of heparin-binding growth factors, chemokines, and HIV-infected cells in the kidney. These changes could trigger an aberrant, progressive, and diffuse proliferative response of glomerular and tubular epithelial cells. Highly active antiretroviral therapy may ameliorate the development of HIVAN not only by decreasing the viral load, but also by reducing the release of viral proteins, cytokines, and heparin-binding growth factors. More research is needed to elucidate the basic mechanisms involved in all these processes and to test new treatments aimed at preventing the progression of the renal disease.

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Fig. 1.
Representative hematoxylin and eosin staining of a renal biopsy from a child with human immunodeficiency virus-associated nephropathy (HIVAN). Original magnification $\times 150$

Fig. 2. Structure and viral cycle of HIV-1 in productively infected cells. **a** Diagram of the HIV-1 virus. The viral proteins (*p*) are designated with a *number* corresponding to the protein size ($\times 1000$). **b** Electron micrograph picture of mature viral particles ($\times 100,000$). **c** Representative diagram of the viral cycle in productively infected cells. *MA* Matrix protein, *CA* capsid, *NC* nucleocapsid, *RT* reverse transcriptase, *PR* protease, *IN* integrase, *CD4* HIV-1 receptor, *CXCR-4*, *CCR-5* HIV-1 co-receptors, *HSPG* heparan sulfate proteoglycans

Fig. 3.

Function of HIV-1 viral proteins. This picture was reproduced with modifications from Ray et al. [36] (used with permission)

Fig. 4.

Electron micrographs showing the transfer of viral particles from HIV-infected macrophages (*M*) to cultured primary renal tubular epithelial cells (*RTEc*) harvested from a child with HIVAN. **a** Viral particles released into the interstitial space between cells and trapped inside *RTEc* (*black and open arrows*, respectively). **b, c** Higher magnification view of the viral particles show in **a**. Magnification: **a** $\times 10,000$, **b** $50,000$, **c** $70,000$. These pictures were reproduced with modifications from Ray et al. [53] (used with permission)

Fig. 5. ^{125}I -fibroblast growth factor-2 (FGF-2) binding to representative renal sections harvested from normal wild-type mice (**a**) and HIV-Tg₂₆ mice with renal disease (**b**). Renal sections were exposed to ^{125}I -FGF-2 in the presence of heparin (30 $\mu\text{g}/\text{ml}$) as described previously [58]. HIV-Tg₂₆ mice with renal disease show increased binding of ^{125}I -FGF-2 to the renal cortex and medulla [58]. Original magnification $\times 20$

Table 1Pathological features of HIV-associated nephropathy in adults, children, and HIV-Tg₂₆ mice^a

HIVAN	Adults	Children	HIV-Tg ₂₆ mice
Classic FSGS	Common	Common	Very common
Collapsing glomerulopathy	Common/typical	Less common	Less common; atypical
Mesangial hyperplasia	Less common	Common	Less common
Renal tubular microcysts	Common/typical	Common/typical	Common/typical
HIV-1 viremia and immunosuppression	High/present	High/present	Absent/absent. Infection is bypassed
Role of genetic and host factors	Necessary	Necessary	Necessary
Infection of cultured renal tubular epithelial cells	Yes, CD4-dependent mechanism ^b	Yes, unknown mechanism	No
Infection of cultured podocytes	No	Unknown	No
In vivo detection of HIV-1 proteins in renal epithelial cells	No	No	HIV-Rev
In vivo detection of HIV-1 mRNA in renal epithelial cells	Yes, glomerular and tubular cells	Unknown	Yes, glomerular and tubular cells
Additional evidence to suggest that renal epithelial cells can be productively infected in vivo	Viral envelope sequences only in dissected tubules	Unknown	No
HIV genes considered essential for development of HIVAN	<i>Nef</i>	Unknown	<i>Nef, vpr</i>
Pathological paradigm in susceptible hosts	Productive infection of renal epithelial cells causes direct proliferative lesions and release of inflammatory cytokines	Renal recruitment of HIV-infected mononuclear cells causes epithelial injury. Heparin-binding factors and cytokines induce proliferative lesions	Up-regulation of HIV-genes in renal epithelial cells causes epithelial injury and proliferative lesions. Cytokines also play a role in this process
Most effective treatment	HAART	HAART	Others

HAART Highly active antiretroviral therapy, FSGS focal segmental glomerulosclerosis, HIVAN human immunodeficiency virus-associated nephropathy

^aThe information provided in this table is based on the results of published studies cited in this article. "Unknown" indicates that no studies have been published so far to document this feature^bOnly one study found detectable CD4 protein on the cell surface of cultured renal tubular epithelial harvested from HIV-negative adults [55]