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APOL1 risk variants and the development of HIV Associated Nephropathy

Rohan Goyal[1], **Pravin C. Singhal**[2]

[1]SUNY Downstate Health Sciences University, New York, USA

[2]Institute of Molecular Medicine, Feinstein Institute for Medical Research and Zucker School of Medicine at Hofstra-Northwell, New York, USA

Abstract

HIV Associated Nephropathy (HIVAN) remains a concern among untreated HIV patients, notably of African descent, as patients can reach end-stage renal disease within three years. Two variants (G1 and G2) of the *APOL1* gene, common in African populations to protect against African sleeping sickness, have been associated with an increased risk of several glomerular disorders including HIVAN, hypertension-attributed chronic kidney disease, idiopathic focal segmental glomerulosclerosis and are accordingly named renal risk variants (RRVs). This review examines the mechanisms by which APOL1 RRVs drive glomerular injury in the setting of HIV infection and their potential application to patient management. Innate antiviral mechanisms activated by chronic HIV infection, especially those involving type 1 interferons, are of particular interest as they have been shown to upregulate APOL1 expression. Additionally, the downregulation of miRNA 193a (a repressor of APOL1) is also associated with the up-regulation of APOL1. Interestingly, glomerular damage affected by APOL1 RRVs is caused by both loss and gain of function changes in the protein, explicitly characterizing these effects. Their intracellular localization offers a further understanding of the nuances of APOL1 variants effects in promoting renal disease. Finally, although APOL1 variants have been recognized as a critical genetic player in mediating kidney disease, there are significant gaps in their application to patient management for screening, diagnosis, and treatment.

Graphical Abstract

The collapsing variant of focal segmental sclerosis (cFSGS), a hallmark of HIVAN, is a consequence of interferons-mediated APOL1 expression in HIV-infected podocytes and parietal epithelial cells (PECs). G0 facilitates PECs transition, but G1/G2 lacks this function. G1/G2 not only exacerbates HIV-induced podocyte injury but also prevent their replacement. A gain of function in podocytes and loss of function in PECs results in the development of cFSGS in G1/G2-HIV patients.

Address for correspondence: Pravin C. Singhal, MD, 350 Community Drive, Manhasset, NY11030, Tel 516-465-3010, FAX 516-465-3011, psinghal@northwell.edu.

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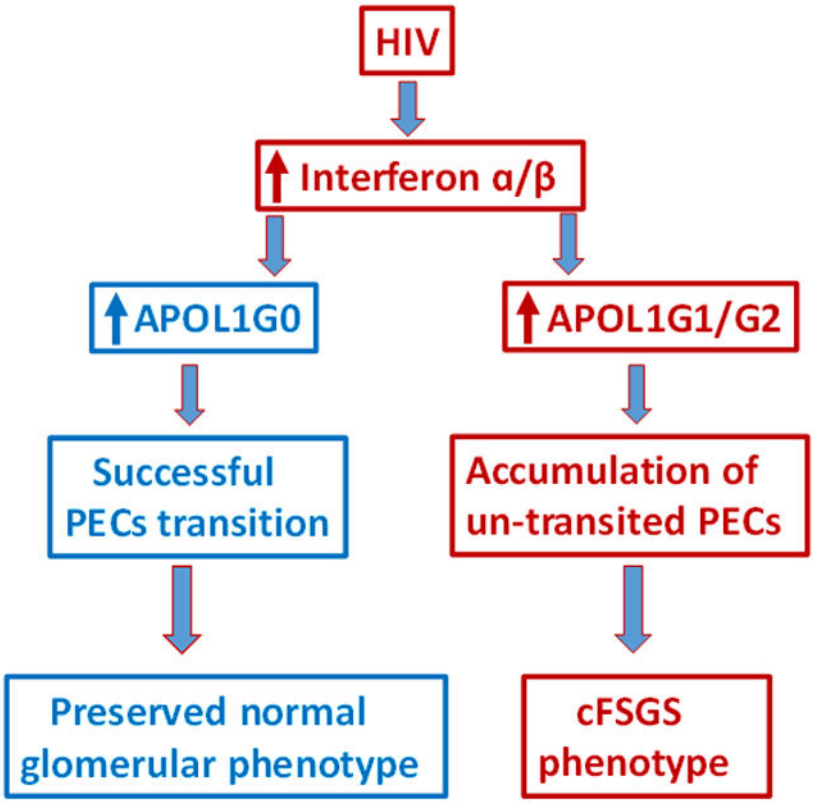

Keywords

Apolipoprotein (Apo)L1; HIVAN, Collapsing FSGS, Podocytes; Parietal epithelial cells

Introduction

Human Immunodeficiency Virus (HIV) has significantly contributed to the global public health burden for several decades. It is well recognized that in addition to its canonical role in causing acquired immunodeficiency, HIV can cause chronic disease in several organs. This is especially true of the kidney, where albuminuria has been reported in 10-15% of patients [1]. Kidney disease in HIV patients has been associated with direct pathogenic effects of the virus itself and long-term treatment with antiretroviral therapy (ART) [2-4]. Notably, 90% of classical HIV Associated Nephropathy (HIVAN) cases have been observed in African descent people. Although HIVAN was much more common before the introduction of ART, it remains of significant concern, especially in untreated patients, as patients can reach end-stage renal disease (ESRD) within three years. HIVAN generally initially presents as nephrotic syndrome and is characterized by light microscopy by the development of the collapsing subtype of focal segmental glomerulosclerosis (cFSGS) and microcyst formation in the tubulointerstitial region [1,5,6]. While HIVAN was known to more commonly occur in African descent persons, it was not well understood why it mainly affected this group.

An important clue came from identifying the *APOL1* gene, which has two key haplotypes that are significantly associated with chronic kidney disease development in general but HIVAN in particular. *APOL1* is located on chromosome 22 found exclusively in primates that codes for apolipoprotein L1 and was identified via a genome-wide association study in 2010 (misattributed initially to the *MYH9* gene) [7]. Apolipoprotein L1 (ApoL1), the protein product of *APOL1*, is mostly secreted into the serum by the liver and is found in high-density lipoprotein (HDL) or complexed to IgM; it is also expressed intracellularly in several organs, including the kidney, vasculature, lung, pancreas, prostate, spleen, and placenta [8,9]. While the normal function of the intracellular protein remains poorly understood, it is clear that the serum protein serves a vital role in maintaining intrinsic resistance to infection by the parasite *Trypanosoma brucei* by contributing to trypanosomal lysis during infection. The wild-type allele, G0, conferred resistance to most subspecies of *Trypanosoma brucei*. Two subspecies developed resistance to the G0 form of ApoL1—*Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*; both are recognized as the leading causes of African sleeping sickness. Within the last 10,000 years, African populations in West and East Africa, where these parasites are endemic, developed two variant alleles of *APOL1*, termed G1 and G2, to overcome this resistance [10-12].

APOL1 G1 and G2 alleles, termed renal risk variants (RRVs), have gained prominence in the past several years as key players in developing FSGS in Black populations globally. Elevated frequencies of APOL1 RRVs have also been identified in several Central American, Caribbean, and South American subpopulations with recent African genetic ancestry [13]. These variants have been of concern in developing the idiopathic focal segmental glomerular sclerosis (FSGS), hypertension-attributed renal disease, lupus nephritis, sickle cell kidney disease, and transplantation outcomes; they are also increasingly studied for their effects in other organs [14-18].

APOL1 RRVs have mostly been given attention in understanding the disparity of renal sequelae of HIV infection in persons of African descent. Both the G1 and the G2 alleles are inherited recessively, with G0 heterozygotes demonstrating relative protection from developing kidney disease. About 13% of African Americans carry two high-risk alleles (either G1/G1, G2/G2, or G1/G2), putting them at a 3- to 30-fold risk of developing future kidney disease. Notably, the presence of two RRVs confers a very high odds ratio, with an estimated odds ratio of 29.2 in the United States (89 in South Africa), for developing HIVAN and heterozygosity (mostly driven by G0/G1) confers a much lower odds ratio, approximately 1.8, for developing HIVAN [10,19,20]. However, most people with *APOL1* RRVs alleles do not develop kidney disease. The current understanding is that a "second hit," most likely an environmental trigger, is required to cause disease development [10,21].

This review will examine the mechanisms by which *APOL1* RRVs contribute to the development of HIVAN. Specifically, the mechanisms by which HIV induces *APOL1*-driven phlogogenic activity, the mechanisms by which ApoL1 causes kidney injury, and the possibility of incorporating *APOL1* variant status into patient management will be explored.

HIV upregulates APOL1 in podocytes

Despite the paramount understanding of ApoL1's function of providing serum innate immunity, serum apolipoprotein L1 is not significantly involved in renal disease [22, 23]. Instead, it seems to be *APOL1* expressed intrinsically within the kidney, especially in podocytes and parietal epithelial cells that has been associated with the development of glomerular disease [24, 25].

The most well-substantiated mechanism is that the innate immune response to HIV upregulates ApoL1 production (all alleles). Although multiple innate immune pathways (e.g., IL-1β and toll-like receptor 3 [TLR3]) have been shown to affect APOL1 levels, the most relevant to the case of HIV infection is signaling by type 1 interferons (IFN), specifically IFN-α and IFN-β [26, 27]. These interferons are part of the innate host defense against viruses and act in an autocrine or paracrine manner to induce several intracellular changes in response to viral infection to reduce the viral spread and induce apoptosis of infected cells [28]. Type 1 interferons have also been reported earlier to participate in the development of the glomerular disease. For example, Type 1 interferons have been previously implicated in podocytes' involvement in lupus nephritis [29, 30]. Notably, even before discovering *APOL1* RRVs, interferon-associated cFSGS was associated with African descent [31, 32]. The most apparent clinical evidence for type 1 interferons' role in upregulating APOL1 is that intravenous interferon infusion was associated with increased APOL1 levels and was associated with the development of cFSGS in patients with *APOL1* RRVs [27]. Other anecdotal evidence of interferon's role in precipitating kidney disease in patients with *APOL1* variants includes case reports showing cFSGS after infection with Parvovirus B19 and SARS-CoV-2 (the cause of COVID-19) in patients with *APOL1* RRVs [33-36].

One candidate mechanism by which *APOL1* is upregulated by interferons is via STING (Stimulator of interferon genes) mediation. cGMP-AMP synthase (cGAS) and interferon-inducible protein 16 (IFI16) have both been shown to activate STING in the setting of lupus nephritis; both are also sensors of HIV infection [37, 38]. STING acts to phosphorylate interferon-regulatory factor 3 (IRF3), which directly upregulates *APOL1* and IFN-β; IFN-β acts in an autocrine/paracrine manner to upregulate *APOL1* and IFI16, which then further enhance STING upregulation [39]. STING's role as a critical mediator of *APOL1* upregulation may have clinical importance; a case report showed very early onset of cFSGS in a patient with *APOL1* RRVs in the setting of SAVI (STING-associated vasculopathy with onset in infancy), a genetic disorder associated with increased STING expression [40].

Further evidence for this mechanism includes another study that showed that the upregulation of RIG-I and NF-κB was also associated with increased intracellular ApoL1 production [41]. RIG-I has been shown to "sense" HIV infection and mediates transcriptional activation of type 1 IFN, and IFN has been described as an activator of NF-κB [42]. The role of NF-κB may be of some importance, as *APOL1* is also upregulated via stimulation of toll-like receptor 3, which increases NF-κB signaling. A summary of interferon-mediated activation of *APOL1* may be found in Figure 1.

Although the innate viral immune response is a plausible mechanism by which *APOL1* upregulation occurs, some issues will need to be addressed. Anecdotal case reports, but no clinical studies, have been able to identify other viruses that cause similar kidney disease in patients with *APOL1* RRVs; if an innate antiviral response mediated the "second hit", similar effects ought to be seen with other viruses. Instead, the opposite is the case, with JC viremia being shown to protect against kidney disease in patients with APOL1 RRVs [43]. Future research will be required to establish better that type 1 interferon expression is sufficient to upregulate *APOL1* in HIV infection and establish a more robust mechanistic basis.

While interferon expression has been the central mediator of *APOL1* upregulation in the setting of HIV infection studied, other proteins have been shown to affect ApoL1 levels. For example, the ubiquitin-like protein UBD putatively targets ApoL1 variants for destruction, and circulating levels of soluble urokinase plasminogen activator receptor (suPAR) can modulate the APOL1 variant function [44, 45]. Other similar associations include CXCL4 and CXCL11 in the glomerulus and SNOR148 and MUC13 in the tubulointerstitium [46]. Additionally, p53, TNF-α, and vitamin D receptor (VDR) agonists have been reported to enhance the cellular expression of ApoL1. MicroRNA193a (miR193a) down-regulates the expression of APOL1. Both IFN-γ and VDR agonists have been shown to upregulate *APOL1* through the downregulation of miR193a [47]. The role of suPAR and other effects of miR193a dysregulation will be discussed later.

APOL1 may both directly cause and enhance HIV-mediated podocyte damage

Given that HIV infection serves as a "second hit" in two *APOL1* RRV carrying individuals, it is crucial to determine whether ApoL1's leading role is indirectly causing glomerular damage or in facilitating damage caused by HIV. This is very closely related to the ongoing debate as to whether APOL1 variants act as a "loss-of-function" (loss of protective effect of G0) versus "gain-of-function" (increased or new toxic functionality in G1/G2 variants) compared to the wild-type. Both factors are at play, and future research is required to elucidate the functional change in ApoL1, causing renal disease [25, 48].

Loss of G0 Protective Function

Since most mammals except humans and select primates do not carry *APOL1*, it suggests that *APOL1* is unlikely to have an essential physiologic role in the kidney. This notion was further supported by observations of no appreciable renal abnormality in *APOL1* null individuals [49]. However, *in vitro* studies have shown that G0 expression preserved the molecular phenotype of podocytes by stabilizing adherens complexes and preserving the actin cytoskeleton [50]. Additionally, optimal expression of G0 by podocytes keeps them in differentiated states; moreover, initiation of the expression of G0 in parietal epithelial cells (PECs) facilitates their transition to podocytes [25, 48]. In contrast, G1 and G2 expression lacked this property in PECs (unpublished observations). However, these effects of G0 and G1/G2 need to be validated *in vivo* studies. Nonetheless, this concept explains the lack of the development of HIVAN in African descent patients carrying G0 (an example

of sustaining successful podocyte homeostasis preventing the collapse of capillary loops). On the other hand, PECs could not transit fully in G1 and G2 milieus, resulting in their accumulation in Bowman's space, and lack of podocyte homeostasis resulted in collapsed capillary loops.

The G0 variant may also mitigate the deleterious effects of the G1/G2 variants. The G0 variant has been shown to localize to intracellular lipid droplets, whereas the G1 and G2 variants both showed a preference for the endoplasmic reticulum, as shown in Figure 2. Notably, the G0 variant was shown to promote lipid droplet localization of all APOL1 proteins, including RRVs, providing a possible explanation for reduced risk in G0 heterozygotes [51, 52]. The localization of *APOL1* RRVs in membranes, as opposed to droplets, is likely of importance as the RRVs has toxic effects in several membrane-bound organelles, as will be discussed shortly. Furthermore, the administration of endoplasmic reticulum stress inhibitors to human podocytes *in vitro* was shown to be protective against cytoskeletal damage and cell death [53]. Although this hypothesis is compelling, however, a recent *in vitro* study of ApoL1 localization in podocytes using anti-ApoL1 antibodies was unable to find any ApoL1 localization in lipid droplets; further study is required to determine the *in vivo* localization pattern of ApoL1 and to resolve this apparent contradiction between study results [54].

In the exceptional setting of HIV, the G0 variant's presence reduced podocyte damage compared to either the presence of the G2 variant or the absence of G0 in HIV-transgenic mice [55]. Further work in monocytes has demonstrated that the G0 variant of APOL1 targets HIV’s Gag protein for degradation and depletes the viral accessory protein Vif, thus reducing viral virulence and infectivity [56]. The antiviral activity of ApoL1 against HIV has been explored in detail by Kopp and colleagues [57]. The absence of this protective effect in patients with G1 and G2 alleles may potentiate other mechanisms of HIV-induced glomerular disease, which still require further exploration [3].

A gain of G1/G2 Toxic Function

High-risk *APOL1* variants have been shown to have a variety of direct toxic effects on podocytes. *APOL1* RRVs have been shown to have several deleterious effects on membranes and membrane-bound organelles. In mitochondria, overexpression of G1 and G2 variants markedly reduced the maximum respiration rate, reserve respiration capacity, and mitochondrial membrane potential [52, 58]. Additionally, while the G0 variant was shown to promote mitochondrial fusion, G1 and G2 variants promoted mitochondrial fission [59]. Expression of high-risk *APOL1* variants in *Drosophila melanogaster* showed cell-autonomous accumulation of the endocytic marker atrial natriuretic factor-red fluorescent protein with later development of nephrocyte loss, and expression of high-risk APOL1 variants in *Saccharomyces cerevisiae* showed impaired endosomal trafficking and vacuolar acidification [60]. *APOL1* RRVs also demonstrate enhanced ApoL1 complex formation with suPAR, activating $\alpha_v\beta_3$-integrin at the cell membrane of podocytes; the activity of $\alpha_v\beta_3$-integrin is necessary for cell detachment. This effect is modulated by circulating levels of suPAR [45].

The interaction of *APOL1* RRVs with the tightly regulated miR193a pathway may be of significance in explaining both cytoskeletal disruption and reduced podocyte differentiation. Among its many effects, the miR193a signaling pathway is involved in reducing the expression of nephrin, an adherens complex stabilizer, via downregulation of the Wilms tumor type 1 (WT1) protein, as well as downregulating autophagy via inhibition of phosphatidylinositol 3-kinase catalytic subunit type 3 (PI3KC3) [61, 62]. The *APOL1* RRVs, shown to destabilize adherens complexes and disorganize the actin cytoskeleton in podocytes, upregulate miR193a expression and reduce nephrin expression, thus contributing to cytoskeletal instability and changes in cellular morphology [50, 63]. miR193a has also been shown to suppress parietal epithelial cells' differentiation into podocytes; *APOL1* RRV induced upregulation of miR193a would accordingly inhibit podocyte regeneration [64, 65]. Additionally, G1 and G2 expression induce a blockade of podocyte autophagy by upregulating miR193a, favoring de-differentiation [62]. Since the HIV viral Nef protein also induces blockade of the later phases of autophagy, HIV infection will further exacerbate the de-differentiation of podocytes in *the APOL1* variant milieu [66]. An alternate cytoskeletal disruption mechanism is that APOL1 high-risk variants may inhibit the activation by APOL3 of the Golgi PI(4) kinase IIIB, an enzyme involved in actomyosin organization [67]. For clarification regarding the interaction between APOL1 variants and the miR193a signaling pathway, please refer to Figure 3.

Significantly, HIV is known to exacerbate cell death in podocytes expressing G1 and G2 [68]. HIV stimulates activation of inflammasomes, which induces pyroptosis even in podocytes carrying low-risk alleles [69]; however, APOL1RRVs have been demonstrated to induce pyroptosis in podocytes independent of HIV [70]. These effects of HIV and RRV expression has been reported both in vitro and in vivo studies. Thus, HIV likely exacerbates pyroptotic death in G1 and G2 podocytes. G1 and G2 have been shown to enhance K+ efflux resulting in the activation of the mitogen-activated protein kinase (MAPK) pathway and inflammasome activation [52, 70, 71]. In a recent report, bioinformatics studies suggested that G1 and G2 altered ion channels' structural configuration in plasma membranes, resulting in K^+ efflux [70]. The influx of sodium and calcium by cation-selective pores could also enhance K^+ efflux [72, 73]. Additionally, RRVs-induced opening of the mitochondrial permeability transition pore has also been demonstrated to cause cell death [74].

Future research in this area will require work on multiple fronts. APOL1 variants' status as "gain of function" versus "loss of function" is ultimately situational; given the range of potentially implicated metabolic pathways identified, determining which are most significant in causing glomerular disease is paramount. Thus far, the disjointed nature of mechanisms fails to connect intracellular changes caused by high-risk variants to the presenting phenotype; this deficiency may potentially be ameliorated by incorporating systems biology and computational approaches to account for the disparate mechanisms that may be contributing to disease. Such approaches can also help determine the extent to which synergistic effects between the direct actions of HIV and APOL1 variants may contribute to disease; such findings may be significant in explaining the high odds ratio of developing the cFSGS phenotype after HIV infection.

Superimposition of collapsing glomerulosclerosis in diabetic kidney disease patients

APOL1 RRVs have been implicated for their susceptibility role only in non-diabetic kidney diseases [7,10, 11]. Interestingly, in a sizeable renal biopsy study, 5% of patients with diabetic nephropathy showed superimposition of collapsing glomerulosclerosis in 2-30% of glomeruli [75]. These patients showed accelerated progression to end-stage kidney disease than the rest of the patients. Unfortunately, these patients were not evaluated for the presence of *APOL1* RRVs. Therefore, it is not clear that the superimposition of the cFSGS component as a consequence of genetic underlining. However, there is a definite genetic component in patients suffering from diabetic nephropathy; it seems to be constituted by multiple genetic variants, each of little effect [76].

Incorporating APOL1 variant status into patient management

Since the *APOL1* genotype's current understanding would not change clinical management, there are currently no recommendations for genetic testing for *APOL1* risk alleles in HIV patients. Clinical guidelines have additionally been challenging to develop due to high variability in estimated glomerular filtration rate (eGFR) decline among patients with *APOL1* RRVs [77-79]. However, earlier this year, a genome-wide polygenic risk score, including 86,813 single nucleotide polymorphisms, has been identified for Swiss HIV patients to determine the likelihood of developing chronic kidney disease [80]. If a similar score could be constructed for African descent patients with an appropriate weighting of *APOL1* variants, calculated genetic risk could help physicians better screen high-risk patients.

Although there is currently a lack of consensus on how *APOL1* RRVs contribute to HIVAN, interventions using *APOL1* RRV status can improve patients' outcomes. An analogy can be drawn to the example of diabetic nephropathy, where improved knowledge of pathophysiology has led to the identification of transferrin and retinol-binding protein as diagnostic biomarkers and the clinical use of SGLT2 and DPP-4 inhibitors for treatment in addition to inhibition of the renin-angiotensin-aldosterone system [81].

Currently, FSGS is diagnosed via renal biopsy; while definitive, it is invasive and not without risk [82, 83]. Although some candidates for non-invasive biomarkers of FSGS have been identified, they have not been widely adopted clinically [83]. A non-invasive method for screening, diagnosis, or tracking of FSGS in HIV patients with *APOL1* RRVs may be urine measurement of miR193a [84]. miRNAs, including miR193a, have been identified in urinary exosomes (small extracellular vesicles derived from various parts of the nephron) [85, 86]. Urinary exosomal miR193a has been measured with increased frequency in FSGS; urinary miR193a measurement can distinguish between minimal change disease and primary FSGS in children with a sensitivity of 75% and a specificity of 80% [84]. Further study is required to determine whether similar measurements in HIV patients with APOL1 RRVs may be used to screen, diagnose, or track FSGS in HIVAN. For patients who carry two APOL1 high-risk alleles, specific therapeutic considerations can be made based on what is known thus far. Given the loss of protective effect from the G0 allele, early treatment,

and adherence to antiretroviral therapy (ART) are essential. Regardless of the effect of APOL1 on the progression of HIVAN, treating the HIV will prevent the development of HIVAN; even if HIVAN is confirmed on biopsy, ART can still delay progression to end-stage renal disease (ESRD) [2]. Before the use of ART, ACE inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs) were used to delay ESRD in HIVAN in Black patients [87]. APOL1 variants were unknown at the time, so it is unknown whether this sub-population will respond similarly. The R3 study is ongoing in Nigeria to determine the use of ACEi/ARBs and ART in APOL1 variant patients, so those results can hopefully guide future clinical practice and justify genetic testing [88].

A recent review also raised the possibility of inhibiting ApoL1 at either the transcriptional, translational, or protein levels in patients with RRVs [89]. Given that *APOL1* expression is non-essential for kidney function, and RRVs mainly have gain-of-function effects, downregulation of *APOL1* expression should prevent or slow HIVAN. VERTEX pharmaceutical company has developed a compound to inhibit the expression of *APOL1*, and it is under clinical trial as a Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis. The primary outcome is the percent change from baseline in Urine Protein to Creatinine Ratio (UPCR) at week 13. While this approach is reasonable, it may not be suitable in areas where trypanosomes are endemic, as patients without APOL1 expression be susceptible to atypical trypanosomal strains [90]. This issue could be addressed by targeting such drugs to podocytes without inhibiting the hepatic secretion of ApoL1.

Another area for future research is the use of glucocorticoids for refractory kidney disease. Given the possible importance of NF-κB signaling in upregulating APOL1, there may be a role for glucocorticoids in immunologically well-controlled patients with an undetectable viral load who still have renal disease progression despite ART. Although recent studies have not evaluated the use of glucocorticoids as adjunctive therapy in APOL1 variant patients, older studies have found a potential benefit to using glucocorticoids in reducing the inflammatory response within podocytes [87].

Conclusion

HIVAN remains a concern in HIV patients of African descent who do not receive early ART. The landmark finding of *APOL1* variants and their association with kidney disease allowed for recognizing specific genetic contributors to chronic disease development in African descent persons. While understanding the mechanism by which *APOL1* variants contribute to glomerular disease has significantly advanced, much more work remains. Translating these understandings to the clinic is incredibly essential. Nevertheless, a significant reason for optimism in this area will contribute to future therapeutic interventions for patients suffering from progressive renal disease.

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Abbreviations

APOL1	Apolipoprotein L1
APOL1G0	APOL1 non-risk allele
APOL1G1 and G2	APOL1 risk alleles/mutant
ACEi	Angiotensin I Converting Enzyme inhibitor
ARBs	Angiotensin II Receptor Blockers
ART	antiretroviral therapy
cGAS	cGMP-AMP synthase
ESRD	end-stage renal disease
eGFR	estimated glomerular filtration rate
FSGS	focal segmental glomerular sclerosis
cFSGS	collapsing variant of focal segmental glomerular sclerosis
IFN	interferons
IFI16	interferon-inducible protein 16
IRF3	interferon-regulatory factor 3
IL-1β	interleukin-1β
MAPK	Mitogen Activated Protein Kinase
NF-κB	Nuclear factor kappa B
PI3KC3	phosphatidylinositol 3-kinase class III
PI(4)	phosphatidylinositol 4
UPCR	Urine Protein to Creatinine Ratio
Rubicon	run domain beclin-1-interacting and cysteine-rich domain containing protein
RRVs	renal risk variants
RIG-I	Retinoic acid-inducible gene I
SAVI	STING-associated vasculopathy
STING	Stimulator of interferon genes
suPAR	soluble urokinase-type plasminogen activator receptor
TLR3	toll-like receptor 3

TNF-α	tumor necrosis factor-α
VDR	vitamin D receptor
WT1	Wilms tumor type 1

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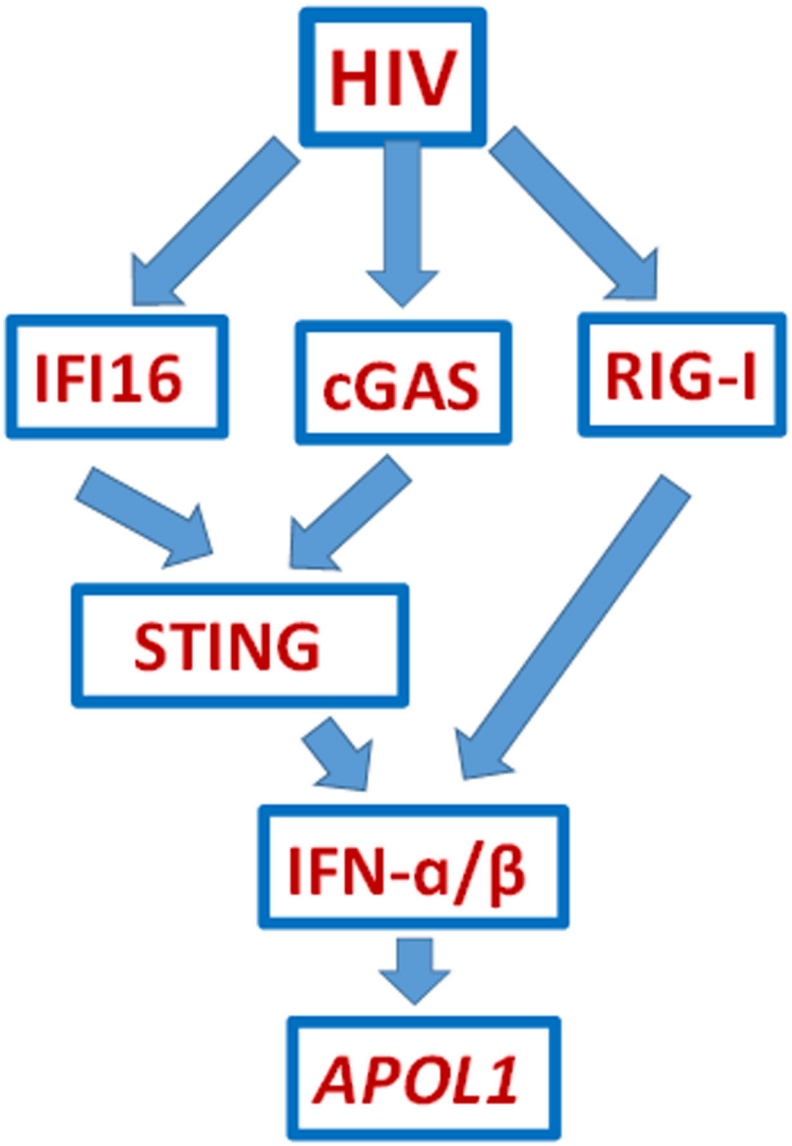

Figure 1.

cGMP-AMP synthase (cGAS), interferon-inducible protein 16 (IFI16), and RIG-I are sensors of HIV infection. cGAS and IFI16 activate STING, which upregulates interferon (IFN)-β; the latter acts in an autocrine/paracrine manner to upregulate *APOL1* and IFI16, which then further enhance STING upregulation. Retinoic acid-inducible gene (RIG)-I also mediates transcriptional activation of type 1 interferons, which upregulate *APOL1*.

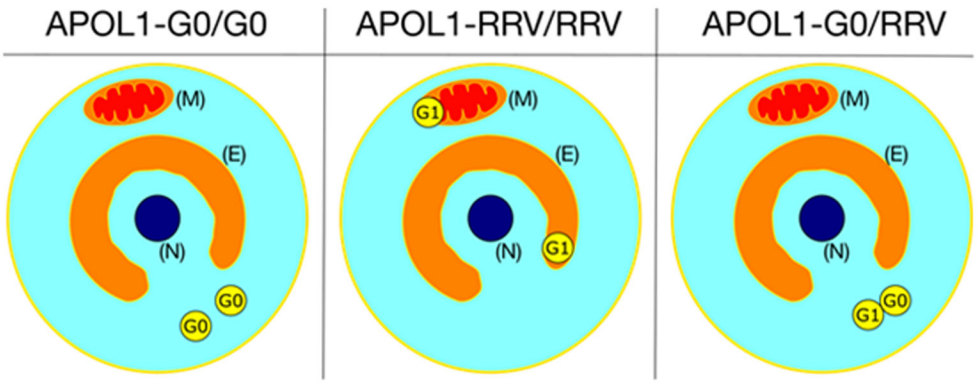

Figure 2.

The APOL1 G0 variant has been shown to preferentially localize to intracellular lipid droplets, whereas RRVs (G1 used as an example) preferentially localize to membrane-bound organelles such as the endoplasmic reticulum and mitochondrion. Interestingly, the G0 allele has been described to exert a protective effect by causing RRVs to also localize to intracellular lipid droplets. M, Mitochondria; E, endoplasmic reticulum; N, nucleus

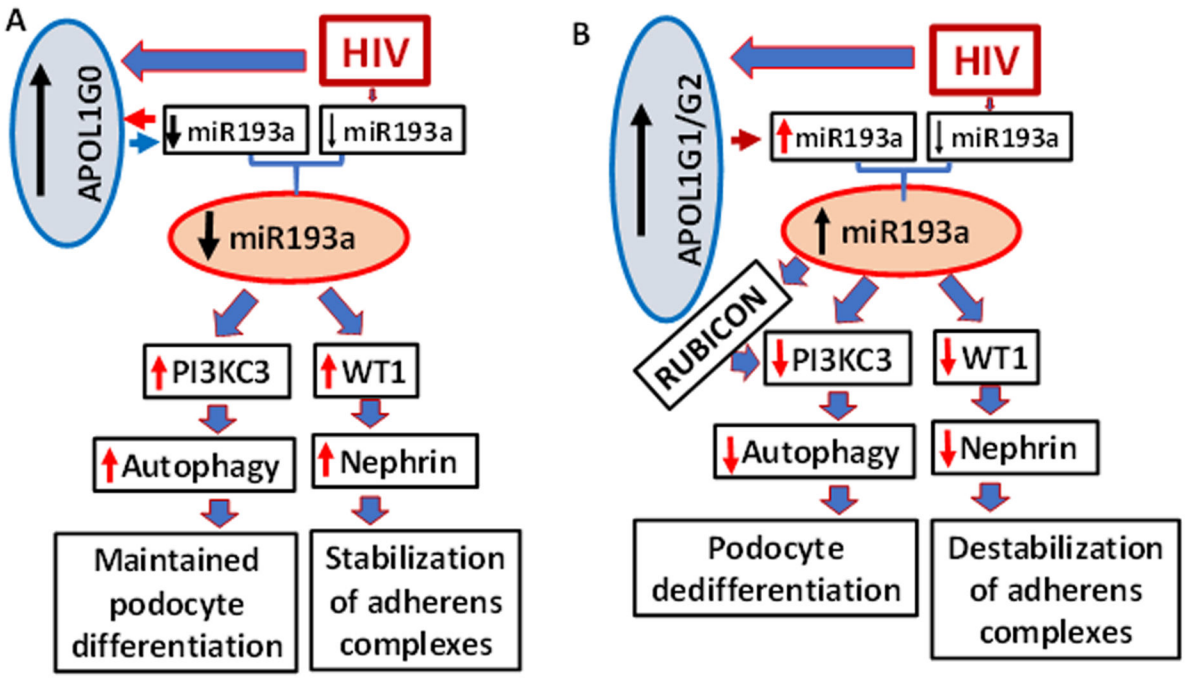

Figure 3.

A. The *APOL1*-G0 allele down-regulates miR193a, which enhances autophagy and podocyte molecular markers sustaining podocytes in differentiated state. B. *APOL1*-G1 and G2 cause increased miR193a, which induces podocyte de-differentiation via autophagy blockade and favoring adherens complex destabilization.

Table 1.

Odds Ratio (95% CI) of Collapsing Glomerulosclerosis with High Risk APOL1 Variants Under a Recessive Model [18, 19]

Idiopathic FSGS	16.9 (11, 26.5)
Systemic Lupus Erythematosus	5.4 (2.4, 12.1)
HIVAN	29.2 (13.1, 68.5)

Table 2.

APOL1 Variant Loss of Function vs Gain of Function Effects

	Organelle	Effect
Loss of G0 Function	Cytosol	G0 variant targets HIV viral proteins and inhibits viral replication [56]
		G0 variant promotes localization of G1/G2 variants to intracellular lipid droplets [51]
	Cytoskeleton	G0 variant preserves podocyte architecture by stabilizing adherens complexes and actin skeleton [50]
	Nucleus	G0 variant promotes differentiation of parietal epithelial cells to podocytes [47]
Gain of G1/G2 Function	Mitochondria	G1/G2 variants shown to reduce maximal respiration rate, reserve respiration capacity, and mitochondrial membrane potential [52, 58]
		G1/G2 variants shown to promote mitochondrial fission [59]
	Cytosol	G1/G2 variants stimulate pyroptosis via inflammasome activation [70]
	Cytoskeleton	G1/G2 variants upregulate miR193a which reduces adherens complex stability [50]
		G1/G2 variants inhibit activation of Golgi PI(4) kinase IIIB, interfering with actomyosin skeletal organization [67]
	Cell Membrane	G1/G2 variants increase cell detachment by forming membrane complexes with suPAR and avβ3-integrin [45]
		G1/G2 variants alter pore configuration to cause K^+ efflux [70-72]
	Endosomes	G1/G2 variants associated with impaired trafficking and acidification [60]
		G1/G2 variants upregulate miR193a which blocks autophagy and promotes podocyte dedifferentiation [62]