Introduction

Chronic kidney disease has become epidemic in HIV/AIDS patients worldwide, especially being common in Black population. Kidney pathology is broadly divided into glomerular disease, tubulointerstitial, and vascular diseases. Glomerular disease directly related to HIV infection, HIV-associated nephropathy (HIVAN), is well established in North America, Europe and African countries. However, studies from Asian countries are very sparse and differ strikingly in histological spectrum of renal disease, particularly in absence of HIVAN. Objectives: The study was carried out to delineate the histological spectrum of renal disease and detect presence HIVAN in those with significant proteinuria (≥1 gm/day). Patients and Methods: Urine analysis was done in 510 consecutive hospitalised HIV/AIDS patients after screening 640 such patients with age >18years. Patients with dipstick proteinuria ≥1+ were subjected to 24-hour urinary protein estimation. Renal biopsy was done in 10 patients with proteinuria ≥1gm/day. Results: Dipstick proteinuria ≥1+ was present in 29% patients. In patients undergoing kidney biopsy, the most frequent glomerular lesion was mesangial proliferative glomerulonephritis (30%) followed by HIVAN (20%). Tubulo-interstitial lesions were seen in 60% of biopsies. Pooled analysis of all the available kidney biopsy series from India revealed prevalence of HIVAN to be 16.5%. Conclusion: Contrary to the popular belief, HIVAN appears to be a common entity in this part of world too. High degree of clinical suspicion is required as diagnosis of HIVAN carries higher morbidity and mortality. Moreover, an early diagnosis and timely management can improve prognosis in such patients.

Keywords: Glomerular lesion, histopathology, HIVAN, kidney biopsy, renal biopsy
earlier identification of potential kidney disease. Renal biopsy is advocated wherever feasible, because the treatment options and prognosis are influenced by the actual histological diagnosis. While HIVAN has been reported consistently in Western studies, the prevalence in studies from Asia has been found to low/absent.[7,8] The available studies from India differ strikingly, with some studies showing presence of HIVAN,[9‑11] whereas others reporting complete absence of this entity.[8,12,13] With this perspective, the present study was carried out to elucidate the histological spectrum of renal disease in HIV patients from a tertiary care center from India. Kidney biopsies were performed in HIV patients with proteinuria ≥1 g/day, to delineate the glomerular lesions including presence of possible HIVAN.

Materials and Methods

Study population and protocol
This was a single center observational study done at the Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi, India. All consecutive HIV positive patients of ≥18 years of age, admitted in general medicine or nephrology departments, were included in the study. The participants were subjected to detailed history, physical examination, and laboratory investigation. The urine was tested using standard dipstick method for screening of proteinuria. The patients having a dipstick proteinuria of 1+ or more were subjected to quantitative 24‑hour urinary protein estimation. Percutaneous ultrasound‑guided kidney biopsy was done in patients with proteinuria of ≥1 g/day. The study was conducted according to the Helsinki Declaration and the Good Clinical Practice Guidelines. Written informed consent was obtained from all patients. Ethical approval for the study protocol was obtained from Ethics Committee of IMS, BHU.

Kidney biopsy and histopathology
Kidney biopsy was done in HIV positive patients with proteinuria of ≥1 g/day, after proper counseling and taking written informed consent. Biopsy was contraindicated in patients with small/contracted kidneys, single kidney, polycystic kidney disease, hydronephrosis, and presence of urinary tract infection. Blood pressure was adequately controlled in hypertensive patients before biopsy. Biopsy was performed under ultrasound guidance with a biopsy gun (BARD 16/18 G, 22 mm, cutting edge) with the use of local anesthesia. The patients were discharged after observation for 6 hours, if the urine was clear. Two cores were taken by biopsy and the tissue was placed in 10% formalin for light microscopic (LM) examination. The tissue was studied using H and E (hematoxylin and eosin), PAS (periodic acid Schiff), and AFOG (acid fuschin orange green) stains. Immunofluorescence (IF) and electron microscopy (EM) was not done as per the institute’s policy.

Definitions
Diagnosis of HIV and AIDS were based on 1993 revised classification system by CDC (Centers for Disease Control).[14] CKD was defined as kidney damage (structural or functional abnormalities of the kidney) or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² for 3 months or more, irrespective of cause.[15] Significant proteinuria for the purpose of kidney biopsy was defined as ≥1 g/day. Nephrotic range proteinuria was defined as a 24-hour urine protein ≥3.5 g/day.

Results

Study population
A total of 510 consecutive hospitalized HIV/AIDS patients were included in the study after screening 640 such patients [Figure 1]. Dipstick proteinuria of grade ≥1+ was seen in 147 patients (29% of total), 24‑hour urinary protein estimation was done in all these patients. Only 15 patients (10.2%) had proteinuria >1 g/day, and they were eligible for kidney biopsy. However, renal biopsy could not be done in five patients, as two patients didn’t consent and urinary tract infection, contracted kidney, and single kidney was observed in one each patient.

Renal histopathology
Renal biopsy was studied by light microscopy in 10 patients [Table 1]. The classical HIV associated nephropathy (HIVAN) was seen in two patients (20%). Figure 2 shows a classic case of HIVAN, with features of collapsing FSGS (focal segmental glomerulosclerosis), microcystic tubular dilatation, tubules filled with cast and interstitial infiltrates. Most common glomerular lesion was mesangial proliferative glomerulonephritis (MesPGN), found in 3 cases (30%). Diffuse proliferative glomerulonephritis (DPGN), membranoproliferative glomerulonephritis (MPGN) and diabetic nephropathy were seen in one patient each. Figure 3 shows the histopathological features in the patient with MPGN, also known as

![Figure 1: Flow chart showing the study plan. *defined as dipstick proteinuria ≥1 + and/or serum creatinine ≥1.5 mg/dl](image-url)
Verma and Singh: Renal histopathology in HIV/AIDS patients

Table 1: Renal histopathology in HIV patients with proteinuria ≥1 gm/day (10 patients)

| Age/sex | Proteinuria | Creatinine | CD4 count | c-ART | Histopathology (predominant lesions) |
|---------|-------------|------------|-----------|-------|-------------------------------------|
| 34/M    | 3.8         | 2.3        | 108       | no    | HIVAN with CIN                       |
| 28/M    | 4.2         | 1.8        | 38        | no    | HIVAN                               |
| 36/M    | 2.5         | 1.6        | 230       | yes   | Diabetic nephropathy with IN         |
| 26/F    | 1.4         | 0.9        | 178       | yes   | Focal MesPGN with IN                 |
| 41/M    | 3.9         | 1.2        | 310       | no    | Focal MesPGN                         |
| 32/F    | 2.1         | 2.5        | 325       | yes   | Diffuse MesPGN                       |
| 27/F    | 1.1         | 0.8        | 140       | yes   | MPGN with CIN                        |
| 33/M    | 2.3         | 1.3        | 258       | no    | DPGN                                 |
| 22/M    | 1.7         | 3.4        | 48        | no    | CIN                                  |
| 29/F    | 2.3         | 2.6        | 122       | yes   | CIN                                  |

cART: Combination anti-retroviral therapy; Mes PGN: Mesangiocapillary glomerulonephritis; MPGN: Membranoproliferative glomerulonephritis; DPGN: Diffuse proliferative glomerulonephritis; MN: Membranous nephropathy; IN: Interstitial nephritis; CIN: Chronic interstitial nephritis; HIVAN: Human immunodeficiency virus associated nephropathy

Discussion

We have presented a single center, observational study on histological spectrum of renal disease in HIV/AIDS patients. Renal histopathology in 10 patients with proteinuria ≥1 g/day has been described with particular attention towards presence of HIVAN.

HIVAN is associated with characteristic glomerular, tubulointerstitial, and ultrastructural lesions. The most consistent findings include collapsing FSGS, cystic tubular dilatation, interstitial infiltrates, and dilated tubules filled with proteinaceous casts. Immunofluorescence is nonspecific and ultrastructural changes on electron microscopy are not unique to HIVAN.\(^1\) The pathogenesis of HIVAN involves local infection of the kidney, systemic HIV infection and systemic immune dysfunction.\(^1\) Patients with HIVAN typically present with nephrotic range proteinuria and rapidly progressive renal insufficiency, accompanied by varying degrees of azotemia.\(^1\) Most patients with HIVAN are young men (mean age 33 years; male to female ratio of 10:1) and >90% of patients are Blacks.\(^1\) HIVAN is associated with large echogenic kidneys, but this relation is non-specific.\(^1\) Both of our patients with HIVAN were young males presenting with nephrotic range proteinuria, CD4 count <200 cells/mm\(^3\) and large echogenic kidneys on ultrasound. The absence of both nephrotic range proteinuria and CD4 count <200 cells/mm\(^3\), are useful to exclude diagnosis of HIVAN, with a negative predictive value of 90%.\(^2\) However, HIVAN can be definitively diagnosed only by kidney biopsy.\(^3\)

The distribution of HIVAN is not uniform and the true prevalence is not known, mainly due to relatively infrequent kidney biopsies. In an autopsy study of HIV-infected persons the overall prevalence of HIVAN was 6.9%.\(^4\) Screening study for HIVAN in HIV patients with proteinuria >1.5 g/day found an overall prevalence of 3.5%.\(^5\) Prevalence of HIVAN in kidney biopsy series outside India have reported prevalence of HIVAN ranging from 0% to 83% [Table 2].\(^6\) HIVAN has been consistently and frequently reported in studies from North America, Western Europe and African countries. However, studies from Italy and Thailand have shown complete absence of this entity.\(^6\) The prevalence of HIVAN in our study was 20%, with the most common glomerular lesion being mesangiocapillary glomerulonephritis (30%) [Table 1]. MesPGN is an inconsistent finding American, African and European studies, but represents a substantial proportion in Asia accounting for 1/3\(^2\) to 2/3\(^2\) of all renal lesions.\(^7\) The probable cause of this discrepancy may lie in racial predisposition, viral genotype, environmental factors, and host susceptibility factors. On the contrary, tubulointerstitial lesions are consistently seen in all kidney biopsy series across world, and may be present in up to 70% cases.\(^1\)
Kidney biopsy series in HIV patients from India, have reported wide variability in prevalence of HIVAN, ranging from 0% to 85% [Table 3]. These widely variable results emphasize limitations on drawing conclusions from single-center studies with small sample sizes. Therefore, we did a systemic review of literature on kidney biopsy in adult HIV patients from India. Search was made on Pubmed, Scopus, and Google Scholar, excluding case reports. We pooled biopsy data from all the 10 available biopsy series (including the current study).

Among 194 patients, the most frequent glomerular lesion was HIVAN (16.5%) followed by MesPGN (13.9%) and FSGS in 7.7%. Pooling of studies though has obvious limitations, gives a fair degree of insight into the histological spectrum. The current study and pooled analysis show that HIVAN, though less common than Western countries, still has an appreciable prevalence in HIV patients from India. This is in contrast to popular belief that HIVAN is rare in Asian countries. Urinalysis should therefore be done in all HIV/AIDS patients and quantification of proteinuria should be performed wherever feasible. Kidney biopsy, being the only definite way to diagnose HIVAN, must be done in all patients with significant proteinuria. Diagnosis of HIVAN is very essential as it carries both prognostic and therapeutic implications. Several studies have reported significant improvements in renal function and proteinuria for patients with HIVAN receiving cART, corticosteroids, and ACE inhibition.

**Table 2: Prevalence of HIVAN in kidney biopsies of HIV/AIDS patients in major studies across world**

| Study | Region | Year | No. of cases | Prevalence of HIVAN |
|-------|--------|------|--------------|---------------------|
| D’agati et al. (63) | USA | 1997 | 112 | 64.7% |
| Szczecz et al. (26) | USA | 2002 | 89 | 47.2% |
| Berliner et al. (64) | USA | 2008 | 152 | 35% |
| Gerntholtz et al. (65) | S Africa | 2006 | 104 | 27% |
| Han et al. (66) | S Africa | 2006 | 30 | 83% |
| Nochy et al. (67) | France | 1993 | 60 | 43% |
| Gutiérrez et al. (68) | Spain | 2007 | 27 | 14.8% |
| Williams et al. (69) | London | 1998 | 17 | 40% |
| Casanova et al. (66) | Italy | 1995 | 26 | None |
| Cavalcante et al. (29) | Brazil | 2007 | 6 | 50% |
| Pradipornsilpa et al. (17) | Thailand | 1999 | 26 | None |
| Present Study | India | | 10 | 20% |

HIVAN: Human immunodeficiency virus associated nephropathy

**Table 3: Renal histopathology in HIV/AIDS patients in Indian studies**

| Study | Year | No. of cases | Renal Histopathology |
|-------|------|--------------|----------------------|
| Madiwale (72) | 1999 | 20 | HIVAN 85%, MPGN 5%, MCD 5%, Lupus Nephritis 5% |
| Varma et al.(20) | 2000 | 25 | Mes PGN (32%), FSGS (16%), HIVAN (4%) |
| Janakiraman et al. (21) | 2008 | 10 | HIVAN 70%, DPGN 10%, MN 10%, CIN 10% |
| Vali et al. (19) | 2012 | 27 | HIVAN (Collapsing FSGS) 11.1%, FSGS 7.4%, DPGN 7.4%, IN 30% |
| Gupta et al. (18) | 2013 | 26 | MesPGN 38%, Collapsing FSGS 7%, MPGN 7%, IN 19% |
| Sunil et al. (71) | 2016 | 32 | HIVAN (6%), MPGN (6%), DN (6%), MesPGN (6%), FSGS (3%), IN (19%) |
| Prakash et al. (23) | 2017 | 14 | MesPGN 31.2%, FSGS 12.5%, MPGN 12.5%, DPGN 12.5%, IN 71% |
| Satish et al. (22) | 2018 | 30 | DN 23.3%, FSGS 13.3%, IgAN 10%, DPGN 6.6%, IN 26.6% |
| Present Study | | 10 | MesPGN 30%, HIVAN 20%, MPGN 10%, DPGN 10%, DN 10%, IN 60% |
| Pooled analysis* (10 studies) | | 194 | HIVAN 16.8%, MesPGN 13.9%, FSGS 7.7%, DPGN 4.1%, IgAN 4.1% |

Mes PGN: Memangio proliferative glomerulonephritis; MPGN: Membranoproliferative glomerulonephritis; FSGS: Focal segmental glomerulosclerosis; AIN: Acute interstitial nephritis; DPGN: Diffuse proliferative glomerulonephritis; MN: Membranous nephropathy; CIN: Chronic interstitial nephritis; HIVAN: Human immunodeficiency virus associated nephropathy; MCD: Minimal change disease; Diabetic N: Diabetic nephropathy; IgAN: IgA nephropathy. *Pooled kidney biopsy data including all observational studies from India

**Conclusions**

With improvement in survival due to availability of cART, renal involvement has become quite common in HIV/AIDS patients. Proteinuria as detected by dipstick was present in 29% patients and of this proteinuria ≥1 g/day was seen in 10.2%. We have reported a prevalence of HIVAN in 20% of kidney biopsies. HIVAN is associated with rapid deterioration in renal function and carries a high mortality, but has good response to cART, steroids, and ACE inhibition. Moreover, unlike popular belief, HIVAN appears to be a common entity...
in this part of world too, and thereby requires a high degree of clinical suspicion. Kidney biopsy, being the only definite way to diagnose HIVAN, must be done in all patients with significant proteinuria.

Authors’ contribution
BV; concept, study design, experiments, data acquisition, analysis of information, and draft of the manuscript. AS; data analysis, information analysis, design, and approval of final manuscript.

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Conflicts of interest
There are no conflicts of interest.

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