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PROFILE OF RENAL DISEASES IN HIV PATIENTS

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CERTIFICATE

This is to certify that the dissertation titled "Profile of Renal Disease in HIV patients" submitted by Dr.S.ILANGO to the faculty of Nephrology, The Tamilnadu DR.M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of DM degree in Nephrology branch is a bonafide research work carried out by him under direct supervision and guidance for the years 2007 to 2010.

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PROFILE OF RENAL DISEASES IN HIV

INTRODUCTION

AIDS was first recognized in united states in 1981 when evaluated for Pneumocystis jiroveci infection and Kaposi sarcoma in homosexuals. In 1983 HIV virus was isolated from a patient with lymphadenopathy, and in 1984 it was demonstrated as cause of AIDS. The evolution of HIV pandemic was matched by explosive informations in areas of HIV virology, pathogenesis, treatment of HIV, opportunistic infections, prevention of infections, and toxicity of drugs used for HIV and opportunistic infections. As early as in 1984 itself physicians of New York and Miami recognized Kidney disease as a devastating complication of AIDS.

Literature of HIV and Renal Lesions is reviewed extensively and the study of this dissertation is presented.

Review of literature and background of this study

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    2) Mechanism of Renal Infection

    3) Role of HIV-1 Infection of Renal Epithelial Cells

    4) Kidney as a reservoir for HIV-1

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HIV Epidemiology

The UNAIDS statistics reports that the estimated people living with HIV/AIDS in 2008 was 33.4 million, of this adults were 31.3million, and women 15.7 million, 2.1 million were children, newly infected in 2008 were 2.7million and death in 2008 was 2 million, and more than 25million people died of AIDS since 1981. In developing and transitional countries, 9.5 million people are in immediate need of life-saving AIDS drugs, of these, only 4 million (42%) are receiving the drugs. India has a population of more than one billion, around half of whom are adults in the sexually active age group. The first case of AIDS in India was detected in 1986 and since then HIV infection has been reported from all states and union territories. Spread of HIV in India has been uneven .The highest HIV prevalence rates are found in Andhra Pradesh, Maharashtra, TamilNadu and Karnataka in the south; and Manipur and Nagaland in the north-east. In the southern states, HIV is primarily spread through heterosexual contact. Infections in the north-east are mainly found amongst injecting drug users and sex workers. Indian government AIDS control organization NACO in 2008 reported that people with HIV/AIDS living in India in 2007 was 2.31 million, 39% are females with a prevalence of 0.34% above the age of 15yrs.

HIV Etiopathogenesis

General

AIDS is caused most commonly by Human Immunodeficiency viruses HIV I, and also by HIV II viruses. They belong to human retrovirus family, and sub family of lentiviruses and they are RNA cytopathic viruses. HIV virion is isosahedral in structure contains numerous external spikes formed by two major envelope proteins gp120 and gp41.They are transmitted through sexual contacts, body fluids, during pregnancy, delivery and breast feeding .The replication of virions begin with binding of gp120 with CD4 molecule through its Vi region. CD4 present in CD4 T lymphocytes, monocytes/macrophges and dentritic/langerhans cells. Once gp120 binds with CD4, gp120 undergoes conformational changes and binds also with one of a group of co-receptors.

Two major co-receptors for HIV I are CCR5 and CXCR4, responsible for cellular tropism of viruses. Fusion with cell membrane occurs via newly exposed gp41, and preintegration complex composed of viral RNA, viral enzymes, surrounded by capsid is released into cytoplasm. In the cytoplasm viral reverse transcriptase catalyses reverse transcription of viral RNA into double stranded HIV DNA which is exported through nuclear pore into nucleus. And integrated with introns of active genes of nuclear DNA by the virally encoded integrase, and transcription of integrated proviral DNA into genomic RNA or mRNA occurs. HIV mRNA is translated into proteins that undergo glycosylation, myristalisation, phosphorylation and cleavage. The viral particle is formed by assembly of HIV proteins enzymes, and genomic RNA at the plasma membrane of cells. Budding of virions through lipid rafts in lipid bilayer of host cell membrane where core acquires the envelope.

HIV-I has genes that encode structural proteins of the virus; gag encodes proteins that form core including p24. Pol encodes for the enzyme of proteases, reverse transcriptase, and integrase. The

gene env codes for envelope glycoprotein. Six other genes tat, rev, nef, vpr, vif and vpu encode for proteins involved in modification of host cell to enhance cell growth and regulate viral gene expression. Transcription activation factor p14 bind TAR in the presence of host cyclin and CDk 9 and enhance RNA pol II elongation in the viral envelope, and rev inhibits viral RNA splicing and promote export of incompletely spliced viral RNAs nef encode for negative factor p27 which promotes down regulation of CD4 and MHC1 expression, blocks apoptosis, enhance virion infectivity, and alters state of cellular activation. The vpr gene promotes G2 cell cycle arrest and facilitates HIV infection of macrophages. The gene vif encodes for p23 which is a viral infectivity factor, which overcomes the inhibitory effects of APOBEC preventing hypermutation and viral DNA degradation. The vpu gene encodes viral protein U which promotes CD4 degradation and influence virion release. Long terminal repeat (LTR) codes for control regions that bind with host transcription factors NF-kB, NFAT.sp-1 and TBP.

The hallmark of HIV disease is profound immunodeficiency results primarily from quantitative and qualitative deficiency of CD4 T helper cells. Patients with CD4 count below 200cell/ml become susceptible to opportunistic infections, and the definition of AIDS includes all HIV patients below this level. HIV virus enters the blood stream enters spleen and other lymphoid organs where primary infection begins, followed by wider dissemination throughout other lymphoid tissue particularly in the Gut associated lymphoid tissue (GALT) where the establishment of chronic and persistent infection occurs. Sustained level of replication viral diversity via mutation, inability to contain quasi species with antibodies, down regulation of HLA I on the surface of infected cell by nef protein of HIV, and evasion of response to antibody because of hypervariablity of primary sequence of envelope, extensive glycosylation of envelope, conformational masking of neutralizing epitopes all contribute to the progression of HIV infection.

Renal Pathogenesis: Disease of kidney in HIV may be a direct consequence of HIV infection, due to opportunistic infections, neoplasm or drug related toxicity and other factors as in general population. The literature was reviewed in the following headings.

1) Genetics

2) Mechanism of Renal Infection

3) Role of HIV-1 Infection of Renal Epithelial Cells

4) Kidney as a Reservoir for HIV-1

5) HIVAN is caused by HIV Infection of Renal Epithelial Cells

6) Viral Factors: Nef, Vpr, TAT

7) Factors Promoting Apoptosis and Fibro Genesis

8) Inflammatory Mediators

9) Proliferation.

10) Mediators of Cell Adhesion, Cell Signaling, and Extra cellular Matrix

Genetics

The reason behind the increased predilection among black persons for the development of HIV-associated nephropathy is not clear. In general, black persons have a higher incidence of other renal diseases (e.g., diabetic nephropathy, lupus, abuse).Therefore they may have an underlying genetic predisposition to severe renal disease, regardless of the etiology. The type of host response to the HIV infection itself may determines whether or not nephropathy develops in a specific individual. Although HIV infection of the renal epithelium is a necessary step in HIVAN pathogenesis, only genetically susceptible persons respond to this infection by developing HIVAN. The host response to HIV infection is therefore a critical determinant in the pathobiology of HIVAN. Although genetic factors clearly contribute to the susceptibility of blacks to HIVAN, these factors remain unknown.

However, several studies have identified features of the response of renal epithelial cells to HIV gene expression that contribute to the development of progressive renal disease.

Mechanism of HIV-1 Renal Infection The mechanism by which HIV-1 enters renal epithelial cells remains unknown. The virus infects lymphocytes and macrophages via interaction of the viral envelope protein gp120 with the cellular CD4 receptor and either the CXCR4 or CCR5 co-receptor.

Conaldi et al detected CXCR4 and CD4 in a subpopulation of cultured renal epithelial cells, suggesting that HIV-1 may infect renal epithelial cells via these receptors. *Ray et al* reported infection of primary renal tubular epithelial cells (RTECs) using HIV isolated from the Periphral Blood Mononuclear Cells (PBMC) of children with HIVAN. The addition of a CD4 antibody did not inhibit infection, suggesting that RTEC infection by renal tropic HIV virus may occur via a CD4 independent mechanism. Another group found that the kidney-derived viruses were capable of infecting cells expressing CD4 and either CXCR4 or CCR5, whereas the blood-derived viruses could infect only CCR5-expressing cells. The investigators also showed that kidney-derived isolates were able to infect cell lines using the alternate HIV co-receptors BONZO/STRL33 and BOB/GPR15.

A recent study reported that the C-type lectin DEC-205 can mediate internalization and nonproductive infection of the HK-2–immortalized tubular cell line. Taken together, these studies suggest that there may be renal tropic strains of HIV and the receptor use of these HIV variants may differ from common HIV isolates. However, the question of how HIV gains entry into renal epithelial cells remains unresolved. Evidence of direct infection by HIV of mesangial or renal endothelial cells also remains inconclusive.

Role of HIV-1 Infection of Renal Epithelial Cells

In 1989 *Cohen et al* reported detection of HIV-1 in renal epithelial cells by DNA in situ hybridization. Other investigators reported detecting HIV-1 by PCR in tubules micro dissected from HIVAN biopsies specimens. Studies using an HIV-1 transgenic mouse model of HIVAN have

provided important insight into HIVAN pathogenesis. Mice transgenic for a replication-defective HIV-1 construct lacking the gag and pol genes, expressed under control of the viral promoter (long terminal repeat or LTR), develop proteinuria, renal failure, and histologic renal disease identical to HIVAN.

Bruggeman et al later demonstrated that the HIV-1 transgene is expressed in renal glomerular and tubular epithelial cells and that transgene expression in renal epithelial cells was required for the development of the HIVAN phenotype. The mechanism role of direct infection of renal parenchymal cells in HIVAN pathogenesis was provided by a macaque model of HIV-induced renal disease. Stephens et al reported that passage of a chimeric simian-human immunodeficiency virus (SHIV) containing sequence from HIV-1 and the simian immunodeficiency virus (SIV) was capable of causing severe glomerulosclerosis and tubular disease and differences in viral strains mediated renal pathogenesis..

In 2000 *Bruggeman* et al. reported a series of 20 HIV-1–seropositive patients with renal disease who underwent renal biopsies. All but one of the patients was black or Hispanic, and 15 had HIVAN. In 11 of 15 patients with HIVAN, HIV-1 was detectable in renal epithelial cells by RNA in situ hybridization. In several samples, the presence of HIV-1 was confirmed using riboprobes specific for both the nef and gag genes and by DNA in situ hybridization. HIV-1 RNA was detected in renal tubular epithelial cells, glomerular visceral and parietal epithelial cells, and interstitial leukocytes. The pattern of HIV-1 infection of renal tubules is focal and may involve epithelial cells from multiple nephron segments, including proximal tubule, thick ascending loop of Henle, and collecting duct. The distribution of HIV-infection of renal tubules is similar to the pattern of micro cystic tubular disease in HIVAN.

Kidney as a Reservoir for HIV-1

Infection of renal epithelial cells by HIV-1 has important implications for HIV-1 seropositive patients not only because it contributes to renal disease but also because the kidney may be an important reservoir for HIV-1. *Bruggeman et al d*etected HIV-1 by both RNA in situ hybridization and DNA in situ PCR in three patients who had undetectable viral loads in peripheral blood sample .He also published a study in which biopsy specimens were collected prospectively from 21 HIV-positive patients with renal disease including HIVAN (N16) and other renal diseases (N5). The investigators used several techniques, RNA in situ hybridization, and DNA in situ polymerase chain reaction to detect HIV nucleic acid in renal biopsy specimens. They detected HIV infection of renal epithelial cells, including podocytes, glomerular parietal epithelial cells, and tubular cells, in the majority of biopsy samples .HIV was detected in kidney specimens from patients with HIVAN and other forms of renal disease and further studies have shown that HIV infection and tubular microcystic dilatation occur in a focal distribution that can affect all nephron segments and renal tubular infection.

These findings were confirmed recently and extended by *Tanji et al*, who reported that in addition to renal epithelial cells, HIV-infected macrophages and T cells are present in the renal interstitium. No studies have definitely shown infection of nonepithelial renal parenchymal cells in vivo. Interestingly, in the series from *Bruggeman* et al, HIV-1 RNA was detected in each of the 4 patients who had no detectable viral RNA in the plasma, suggesting that HIV can remain transcriptionally active in renal epithelial cells even in the presence of maximal viral suppression with antiretroviral therapy (ART). Moreover, *Winston et al* reported a patient who developed HIVAN in the setting of acute HIV-1 seroconversion. Proteinuria, renal failure, and histologic abnormalities improved dramatically after treatment with HAART. Despite an undetectable viral load in the peripheral blood while on HAART, the patient continued to express HIV-1 in renal epithelial cells as determined by RNA in situ hybridization. Thus, even in the face of an optimal virologic response to

antiretroviral therapy and clinical remission of HIVAN, HIV-1 infection persisted in the renal epithelium and the virus remained transcriptionally active at a low level.

Marras et al isolated HIV-infected renal tubules from two patients with HIVAN using laser capture microdissection to characterize the *HIV-1* quasi-species present in the renal tubular epithelium. HIV-1 envelope sequences were amplified from isolated tubules by PCR and sequenced. Phylogenetic analyses were performed on envelope sequences from renal tubular epithelial cells and peripheral blood mononuclear cells (PBMC) from the same patient. In each patient, there was variation in the HIV-1 envelope sequences present in the renal epithelium.

As viral replication is required for viral evolution and sequence variation, this study provided direct evidence that the HIV-infected tubular epithelium in HIVAN is capable of supporting viral replication. Moreover, the quasi-species of HIV-1 present in renal epithelial cells clustered separately from sequences derived from the same patients' PBMC, indicating that HIV-1 infection of tubular epithelial cells represents a viral compartment that is separate from the blood.

Thus, the renal tubular epithelium is a reservoir for actively replicating HIV-1 and may support evolution of viral strains that differ significantly from virus present in a patient's blood. It is not known whether the renal epithelial compartment is more likely to harbor drug-resistant HIV-1 strains or whether the renal epithelium is susceptible to currently available antiretroviral drugs.

These studies resulted in two major findings. First, there was divergence in the gp120 sequences cloned from the renal epithelial cells, indicating that these cells are able to support full viral replication (which had not been shown previously). Second, phylogenetic analysis revealed that the gp120 sequences from kidney clustered separately within the radiation of gp120 sequences from the same patients peripheral blood mononuclear cells. These data suggest that the renal epithelium is a reservoir for HIV-1 that is not in equilibrium with the blood compartment. Whether this renal reservoir

contributes to rebound of plasma viral loads in patients who had previously been well controlled is unknown.

HIVAN is caused by HIV Infection of Renal Epithelial Cells

Studies using transgenic animal models have been invaluable for determining the viral and patient-related factors that contribute to the pathogenesis of HIVAN. In the most extensively used transgenic model, known as Tg26, mice are transgenic for an HIV provirus with deletions of the gag and pol genes that is expressed under control of the endogenous viral long terminal repeat (LTR) promoter. Tg26 mice develop a clinical and histopathologic syndrome that is identical to HIVAN.

Gharavi et al used genome-wide linkage analysis to identify genetic loci that are associated with a risk for developing the HIVAN phenotype, although the culprit genes have not yet been identified. Investigators have used the Tg26 model to determine whether the HIVAN phenotype is a result of renal expression of HIV-1 genes or, alternatively, the effect of systemic factors on the kidney. In reciprocal transplantation studies, kidneys from Tg26 mice that were transplanted into wild-type mice developed the HIVAN phenotype whereas wild-type kidneys transplanted into Tg26 mice remained normal, thereby showing that renal expression of HIV genes is necessary to produce the HIVAN phenotype. Expression of HIV-1 genes in vitro is able to recapitulate many of the cellular abnormalities associated with HIVAN in vivo.

One of the histopathologic hallmarks of HIVAN is the presence of podocyte proliferation. Normal podocytes are terminally differentiated quiescent cells and in most forms of chronic renal disease the number of podocytes decreases. In HIVAN, however, podocytes proliferate and undergo dedifferentiation with loss of expression of podocyte-specific markers including CALLA, synaptopodin, WT-1, and podocalyxin. *Schwartz et al* showed that podocytes isolated from Tg26 mice have increased levels of proliferation and express lower levels of podocyte markers than podocytes isolated from wild-type mice. Furthermore, infection of wild-type podocytes with HIV-1

induces these same changes in vitro. The availability of transgenic models and in vitro cell-based assays that reliably model the in vivo histopathologic features of HIVAN have allowed investigators to identify viral and host factors that are critical for HIVAN pathogenesis.

Viral Factors The Tg26 mouse model, which recapitulates the full HIVAN phenotype, lacks the gag and pol genes, making it unlikely that expression of either of these genes is necessary for HIVAN pathogenesis. *Zhong et al* created several murine transgenic lines that expressed all HIV genes except gag, pol, and env under control of the nephrin promoter, thereby ensuring podocyte-specific gene expression. Most of these mice developed proteinuria and the typical glomerular and tubular changes of HIVAN. The renal phenotype in these mice also was dependent on the genetic strain of the mice, with a severe phenotype noted in FVB/N mice (same strain as Tg26) and minimal disease in C57BL/6 mice. This study suggests that expression of vif, vpu, vpr, tat, rev, and/or nef in podocytes is sufficient to induce the HIVAN phenotype.

NEF

Nef is a 206-amino acid protein with many reported functions.1) reduction of CD4 trafficking to the cell surface 2) effects on cytokine expression, and 3) prevention of apoptosis**.** *Hanna et al* created transgenic mice that express nef under the control of the human CD4 promoter, developed several features of acquired immune deficiency syndrome– like illness (loss of CD4 cells, wasting, and so forth) and interstitial nephritis. nef with a mutated SH3 binding not developed the wasting disease or renal disease.

Hussein et al found that mutation of nef completely eliminated podocyte proliferation and that infection of podocytes with a vector expressing nef alone induced podocyte proliferation and dedifferentiation. He showed that nef induced proliferation, and dedifferentiation of murine podocytes is mediated via Src kinase activation, with subsequent phosphorylation and activation of signal transducer and activator of transcription (STAT3) and mitogen-activated protein kinase (MAPK) Tg26

mice. In the study by *Hussein et al* podocytes that expressed nef showed loss of expression of the podocyte differentiation markers WT1 and synaptopodin, and had increased expression of the proliferation marker Ki-67.

VPR Vpr is a 96–amino acid protein whose actions include facilitating nuclear import of the HIV preintegration complex and transactivation of the viral LTR promoter. *Dickie et al,* who created HIV transgenic mice vpr gene developed proteinuria and glomerulosclerosis, transgenic mice expressing tat and vpr under the control of the LTR promoter significant proteinuria and glomerulosclerosis, other HIV genes worsen the course of vpr-induced renal disease. The gene vpr was expressed under control of the c-fms (macrophage-specific) promoter also developed modest proteinuria and glomerulosclerosis. The mechanism of renal pathogenesis in these mice is unclear, however, because free Vpr protein can directly transduce cells, it is possible that macrophage-derived Vpr was taken up by renal epithelial cells, resulting in the renal phenotype.

Studies in nonrenal cells have shown that vpr can induce several cellular effects, including G2/M cell-cycle arrest and apoptosis. *Rosenstiel et al* showed that vpr expression in the HK-2 human proximal tubular epithelial cell line impaired cytokinesis and induced accumulation of multinucleated cells, RTEC in Tg26 mice and human HIVAN biopsies had increased levels of epithelial cell hypertrophy and multinucleation. These findings suggest that the in vitro abnormalities observed in vpr-expressing HK-2 cells also are present in HIVAN, provide insight into the mechanism of tubulointerstitial disease in HIVAN.

TAT and ENV

Tat is a 101–amino acid protein critical activator of HIV transcription and can induce cellular changes including cytokine production and apoptosis. *Conaldi et al* reported Tat protein induces dose dependent proliferation and loss of differentiation markers in vitro.HIV-1 env gene encodes the gp160 protein, which after cleavage yields the gp120 and gp41 proteins. Gp120 is present on the surface of

HIV virions and facilitates infection of target cells by interacting with CD4 and a co-receptor. Gp120 can induce aberrant proliferation and apoptosis of human mesangial cells40 and apoptosis of both tubular and glomerular epithelial cells...as mentioned above, podocytes are infected by HIV-1 in HIVAN. This infection induces several abnormalities, including increased proliferation and decreased expression of markers of differentiation, including synaptopodin, WT-1, GLEPP-1, and podocalyxin.

Similar alterations in podocyte phenotype are found in the glomeruli of HIV-1 transgenic mice. In vitro studies using podocytes from HIV-1 transgenic mice and wild-type murine podocytes infected with HIV-1 have demonstrated increased levels of proliferation and anchorage-independent growth in podocytes expressing HIV-1. Phenotypic abnormalities of the tubular epithelium are also prominent with increased proliferation and apoptosis, microcystic dilatation, flattening and atrophy of epithelial cells, and loss of expression of differentiation markers, with abnormal polarization of the sodium-potassium ATPase.

Transcriptional regulation of HIV-1 in renal epithelial cells appears to occur via similar mechanisms as in lymphocytes. Transcription in murine podocytes requires binding of inducible nuclear factor-ƒEB and Sp1 to the viral LTR. Inhibition of HIV-1 transcription in murine podocytes using an inhibitor of CDK-9 resulted in decreased proliferation and re-expression of podocyte differentiation markers in vitro. Systemic administration of these CDK-9 inhibitors to HIV-1 transgenic mice ameliorated the HIVAN phenotype. Given the markedly decreased efficiency of HIV-1 transcription in murine cells, however, it is unclear whether CDK-9 inhibition would have similar effects in podocytes from humans with HIVAN.

Factors Promoting Apoptosis and Fibrogenesis

Increased apoptosis of tubular epithelial cells and interstitial fibrosis are common findings in many nephropathies, including HIVAN. *Bodi et al* compared biopsy specimens from patients with HIVAN with HIV-seronegative patients with focal segmental glomerulosclerosis and found a

substantially higher rate of tubular epithelial apoptosis. *Conaldi et al* showed the ability of HIV-1 to infect human tubular cells and induce apoptosis in vitro. HIV infection induced extensive caspase-dependent apoptosis of proximal tubular cells and, in further experiments; the investigators found that the apoptosis-inducing receptor, Fas was up-regulated by HIV infection. The importance of Fas up-regulation in HIV-induced tubular cell apoptosis was not clear because addition of Fas-blocking antibodies to the cells did not prevent apoptosis.

Ross et al reported that the ubiquitin-like protein FAT10 is one of the most up-regulated genes after HIV infection in a RTEC line derived from a patient with HIVAN. Expression of FAT10 also was increased in kidneys from Tg26 mice and in HIVAN biopsy specimens, and prevention of FAT10 expression using RNA interference prevented HIV-induced apoptosis. Although these results suggest that FAT10 expression is necessary for HIV-induced RTEC apoptosis, the mechanism by which FAT10 facilitates apoptosis is not known

Transforming growth factor (TGF)-is a cytokine with important roles in promoting renal fibro genesis and apoptosis in several animal models of renal disease. Increased levels of TGF mRNA when compared with biopsy specimens of HIV-positive patients without signs of HIVAN and TGF-protein levels are increased in HIV positive patients with glomerular disease.

Inflammatory Mediators

Tubulointerstitial inflammation is a prominent histopathologic finding in HIVAN. Accordingly, several case series and retrospective case-control studies have reported an association between corticosteroid treatment and improved renal outcomes in patients of HIVAN. These observations suggest that renal inflammation is an important factor in the clinical course of HIVAN. *Ross et al* profiled the genes that were differentially expressed after infection of a human RTEC line derived from a patient with HIVAN. The most prominent response of the cells to HIV infection was up-regulation of proinflammatory mediators, including cytokines, chemokines, and adhesion

molecules**.** Many of these same genes were found to be up-regulated markedly in kidneys from the Tg26 HIVAN model**.** The expression of HIV genes in RTEC up-regulates proinflammatory genes that then recruit leukocytes to the kidney, resulting in the tubulointerstitial inflammation that is a characteristic finding in HIVAN.

Several cytokines, including interleukin-8, monocyte chemoattractant protein-1, and RANTES**,** were increased in HIV-infected patients. Patients with HIVAN were found to have higher renal tissue levels of major HLA class II, interferon-receptor, and interferon-alfa, although levels did not correlate with the amount of interstitial inflammatory cells. These studies suggest that HIV-infected patients have increased renal levels of inflammatory mediators, which can recruit inflammatory cells into the interstitium.

Proliferation

As discussed previously, the HIV-1 nef gene induces podocyte proliferation via activation of Src kinases and the transcription factors Stat3 and MAPK. Dysregulated expression of cyclins is also an important factor in promoting podocyte proliferation in HIVAN. HIV infection increases cyclin E expression in podocytes. The expression of the cyclin-dependent kinase (CDK) inhibitors p27 and p57 are decreased in HIVAN biopsy samples as compared with normal kidneys or those with membranous and minimal change disease, whereas p21 levels are increased. Because CDK inhibitors suppress the activity of pro-proliferative cyclin/CDK complexes, the increased levels of cyclin E, coupled with decreased p27 and p57, likely contribute to podocyte proliferation in HIVAN.

Basic fibroblast growth factor is upregulated in HIVAN and has been shown previously to increase proliferation of renal epithelial cells in vitro.HIVAN is also associated with the up regulation of tansforminrg growth factor-fÀ**,** which may in part, mediate increased renal fibrosis and apoptosis. we identified a novel small leucine-rich repeat protein, Podocan, which accumulates in sclerotic

glomeruli in HIV-1 transgenic mice. The role of Podocan in HIVAN pathogenesis is currently under study.

Mediators of Cell Adhesion, Cell Signaling, and Extracellular Matrix

Kaufman et al reported that the sidekick-1(sdk-1) gene is up-regulated in HIV-infected podocytes and levels of Sdk-1 protein are increased in vivo in podocytes in the Tg26 mouse model Sidekick proteins are members of the immunoglobulin super family and have roles in neuronal guidance during retinal development. HIV-induced expression of SDK-1 leads to aggregation of podocytes in vitro and may contribute to the formation of podocyte "pseudocrescents" that are observed commonly in HIVAN.

Altered expression of vascular endothelial growth factor (VEGF) contributes to the pathogenesis of many renal diseases. In mice, increased expression of the VEGF 164 isoform induces a collapsing glomerulopathy similar to that found in HIVAN. *Korgaonkar et al* detected increased levels of VEGF protein and its transcriptional regulator (HIF-2) in glomeruli in the murine HIVAN model and in human HIVAN biopsy specimens. Infection of murine podocytes with HIV in vitro induced expression of VEGF and HIF-2, which was mediated via nef-induced activation of Src kinase and Stat3. Moreover, addition of neutralizing antibodies against VEGFR2 reduced HIV-induced podocyte proliferation and dedifferentiation in vitro. These studies suggest an important role for VEGF in HIVAN pathogenesis.

CLINICAL PROFILE OF RENAL LESIONS IN HIV

Acute Renal Failure

I. Epidemiology and Etiology

Consensus guideline for management recommend a definition of acute renal failure in HIV patients who has increase in serum creatinine of above 1.5mg/dl or increase of greater than 1.3 times

normal at the respective laboratory, that returns to base line value within 3 months. The causes of AKI in HIV classified as pre renal, intrinsic renal and post renal acute renal injuries.

a). Pre Renal causes

The most common cause is hypovolemia: The causes of hypovolemia in HIV patients include diarrhea, nausea, vomiting, and decreased oral intake. Hypovolemia also results from decrease in effective circulatory volume in few clinical situations such as sepsis, liver disease, and hypoalbuminemia (nephrotic syndrome, proteinuria,malnutrition).

b). Intrinsic Renal Injury causes

Acute Tubular Necrosis

Ischemic: Hypovolemia, Shock, Sepsis, Cardiopulmonary compromise

Nephrotoxic: Medications, Radiocontrast, Rhabdomyolysis

Parenchymal infection (bacterial, fungal and viral)

Interstitial Nephritis

Hemolytic Uremic Syndrome

Glomerular disease

HIVAN, Acute Glomerulonephritis,

DILS (diffuse infiltrative lymphocytosis syndrome)

c). Post Renal causes

Intrarenal Tubular Obstruction:

Crystalluria   from medications, Tumor Lysis Syndrome

Ureter or Bladder Obstruction:

Nephrolithiasis,

Lymphadenopathy/Tumor, Fungus ball, Blood clots,

Neurogenic Bladder

d). Risk Factors for AKI in HIV

This include old age, Diabetes mellitus, Chronic kidney disease, Liver disease/Hepatitis C, low CD4 count, high HIV-RNA level, history of AIDS-defining illness, history of Antiretroviral exposure, Immune Reconstitution Syndrome, Drugs etc.

In the pre ART era study by *Valeri et al* 1991 reported in a study of 1983-1986 ARF with serum creatinine of >2mgin 20% of 449 hospitalised HIV patients, and found the incidence in non HIV patients of 4-5%. In this series common causes of ARF include were hypovolemia (38%) medication toxicity(32%), ATN in 26%(ischemic,toxic,rhabdomyolysis) 2%with AIN, 17%of obstruction due to drug induced, paraprotein precipitation and 35% due to HUS. In a retrospective review of all cases for AKI with Serum creatinine of >6mg/dl one third occurred in HIV, from New York between 1984 and 1993 by *Rao et al,* here 52% were caused by ischemic insult, 23% due to nephrotoxic medications (aminoglycosides, amphotericin B, pentamidine, acyclovir, AIN due to NSAIDs) and rhabdomyolysis.

AKI in HIV is more likely due to sepsis and less likely due to obstructions. In 2006 Wyatt reported AKI in 1995 in hospitalized patients of 2.9% among 52580 HIV patients compared to 1% of non HIV during the same year which include both ART and non ART HIV patients. As per the New York state planning and research cooperative system data base with decrease in infections and mortality and   increase in non HIV comorbidities, the incidence of AKI during 2003 was 6% higher than for HIV negative of 2.7%, and the increase in incidence could be due to changes in reporting in the ART era.

Franceschini (2005) reported 2yrs follow up of 754 HIV patients;   incidence of AKI was 5.9 cases per 100 patient years, with at least one episode in 10% of patients. Intrinsic renal lesions were in 46%, prerenal in 38%, and 52% were associated with infections, and medications in one third.*Rao et al* in 2005 reported nephrotoxic drugs were common cause of AKI in a cohort of 2274 patients and

nearly 6% of them experienced at least one episode of AKI during the study period. Although direct infection of kidney by HIV is a cause of AKI and HIVAN is a recognized entity, rare cases of parenchymal infection include fungal infections, Mycobacterial granulomatous infection, interstitial nephritis secondary to Ebstein Barr virus, Cytomegalo Virus, Polyoma virus and other viruses.

Another rare cause of AKI is due to immune inflammation syndrome that typically occurs after initiation of ART is a systemic inflammatory response to infections or noninfectious diseases and kidney biopsy may show granulomatous nephritis. Rhabdomyolysis occurs particularly in association with cocaine, statins and in acute in HIV infections has been reported frequently.

e). Nephropathy associated with Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

Most patients are adults who have been infected for years from both sexes, of all ethnic groups, present with bilateral parotid enlargement and sicca syndrome for months ,respiratory, liver, renal lesions are rarely associated features. The disease is due to persistant CD 8 + lymphocytic infiltration of multiple organs mainly salivary gland and occasionally lungs, muscles, peripheral nerves, gastro intestinal tract liver and kidneys. Scant literature is only available and the renal syndrome is poorly described. Renal syndrome is typically present with large kidneys, tubulointerstitial disease, mild grade proteinuria composed of tubular proteins.

On renal biopsy it is characterized by acute tubulo interstitial nephritis, with patchy to dense interstitial cellular infiltrate composed of lymphocytes, monocytes and plasma cells. Zafrani et al reported in 2007 of 111pts with DILS 9% incidence of renal lesions were described. This CD8 lymphocytosis is considered to be due to HIV infection, and the recent reports indicate there are decreased incidences of DILS due to HAART. Treatment with short course of steroid helps to overcome acute symoptoms.

f). Acute Renal Failure due to Medications

Most of the renal toxicities are type B adverse drug reactions. In contrast to the more common type A adverse drug reactions, type B adverse reactions are generally idiosyncratic, not dose dependent, and have less pharmacologic predictability because they are mostly driven by uncharacterized host factors. Established renal adverse reactions have been associated with the use of several Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Protease Inhibitors (PIs). Because renal transporter–mediated mechanisms are involved in the elimination of these agents, intracellular accumulation and potential toxicities may occur if these mechanisms are perturbed.

Organic anion transporters (OATs) and organic cation transporters are expressed on the basolateral membrane of proximal tubular cells and mediate the uptake of NRTIs and PIs. Multidrug-resistant proteins and P-glycoproteins are expressed on the apical membrane of proximal tubular cells and mediate the efflux of these agents. Disruption in basolateral uptake, apical efflux, results in accumulation of these agents in the proximal tubular cells with potential drug toxicity.

1). Nucleoside Reverse Transcriptase Inhibitor (NRTI) related Nephrotoxicity

NRTIs generally require dose adjustment in patients with kidney disease, the one exception being abacavir sulfate .Adverse effects of ART have been well recognised, including metabolic, lipid, and bone toxicities. Importantly, renal toxicity has been associated with several of these agents. NRTIs are processed and eliminated by the kidney. The OATs have been postulated to constitute the initial step in the uptake of several NRTIs.

Hyperlactatemia is a relatively frequent adverse event associated with the use of NRTIs. It can be detected in up to 20% to 30% of patients treated with NRTIs, typically after several months of therapy. Most of the time lactate increases were small in magnitude (lacticacid>2.5 mmol/L), often transient, and not associated with identifiable symptoms.Severe hyperlactatemia (lactic acid,5-10 mmol/L) can occur in up to 1.5% to 2.5% of patients and is associated with a mortality rate of more

than 50%. Stavudine is one of the implicated NRTIs, although all agents in this class have been linked with hyperlactatemia.

Among NRTIs currently approved for the treatment of HIV-1, renal toxicity has been most clearly established with tenofovir. Renal toxicity also is well-described with 2 NRTIs that are related structurally to tenofovir , they are cidofovir, which is FDA-approved for the treatment of cytomegalovirus retinitis in HIV-1–infected individuals, and adefovir. Tenofovir has been associated with renal tubular toxicity resulting in acute tubular injury, Fanconi syndrome, nephrogenic diabetes insipidus, and acute or chronic reduction in glomerular filtration rate.

Mitochondrial DNA depletion owing to inhibition of DNA polymerase, the major enzyme responsible for replication of mitochondrial DNA, has been proposed as a mechanism of systemic and renal toxicity of NRTIs retrospective analysis of a large observational cohort of patients who received either tenofovir or an alternative NRTI showed that the use of tenofovir was associated with a greater decline in renal function compared with the use of other NRTIs, although the clinical significance was unclear. Study in 2007 by *Amanda et al* published largest study that assessed GFR in HIV infected persons, patients treated with tenofovir, and in indinavir had increased odds of CRF .At the time of first serum creatinine measurement within Eurosida study in a study from US 7.2% of found to have renal disease at basal line with 14% subsequently developing renal sufficiency after a mean period of 21 months.

2). NNRTI Nephrotoxicity

Rhabdomyolysis with acute renal failure was described in a single case owing to potential interaction of delavirdine mesylate, with atorvastatin. Nevirapine has been implicated in the development of acute renal failure with rash and eosinophilia in a pregnant patient. Efavirenz has been recently linked to nephrolithiasis in 2 patients. Acute renal failure has been reported to occur in 1% of patients assigned to etravirine in clinical trials.

3). Protease Inhibitor Nephrotoxicity

The use of indinavir sulfate and atazanavir sulfate has been linked to nephrolithiasis, the former to a much greater degree. Ritonavir has been implicated as a cause of acute renal failure in several reports.The incidence of symptomatic crystalluria or nephrolithiasis has been estimated at 8% to 19% of patients on chronic therapy. The prevalence of atazanavir stones to be 0.97% among those taking the drug.

4). Entry Inhibitor -HIV-1 Fusion Inhibitor Nephrotoxicity

Enfuvirtide safety analysis of the TORO 1 and TORO 2 trials, including 663 patients reported one patient with hypersensitivity reaction with a membrano proliferative nephritis.

5). Integrase Inhibitor Induced nephrotoxicity

Placebo controlled trials in treatment-experienced HIV- 1–infected patients receiving Raltegravir 600 mg daily, and also with 400 mg twice daily in combination with optimized background therapy revealed a high incidence of vomiting and diarrhea associated prerenal azotemia..

Fluid and Electrolyte disorders

This involves important electrolyte disorders occurring either at initial presentation or during the management of patient with HIV. Most commonly reported electrolyte abnormalities are hyponatremia, hypokalemia, and hyperkalemia . Magnesium deficiency also reported in patients with chronic diarrheal illnesses.

a). Hypotrnatremia

Hyponatremia is frequent among HIV infected persons with a reported prevalence of 30 to 60% of hospitalized patients, it is a marker of severe illness and associated with increased mortality. In a study of 212 HIV patients the mortality of hyponatremic group was 36.5% compared to 19.7 of normonatremic group.

The etiology and management of hyponatremia differ according to the time of its presentation. Volume depletion caused by vomiting, diarrhea are the common cause of hyponatremia at the time of hospital admission. In contrast, syndrome of SIADH is the likely culprit among patients during hospitatisation. SIADH is associated with common pulmonary and intracranial infections such as pneumocystis jiroveci, toxoplasmosis, and tuberculosis and malignancies.

b). **Potassium disorders**

Both hypokalemia and hyperkalemia are common among HIV patients. Hypokalemia is seen commonly in patients with gastro intestinal infections which leads to vomiting and diarrhea, and in patients receiving amphotericin B commonly used to treat fungal infections, which cause tubular dysfunction and lead to severe hypokalemia. Tenofovir has also associated with proximal tubule dysfunction and life threatening hypokalemia.

Drug induced hyperkalemia include high dose trimethoprim suphamethoxazole and intravenous pentamidine, similar to amiloride. These drugs inhibit sodium transport leading to decrease in potassium secretion in the distal nephron. Also actue and chronic kidney disease may contribute to hyperkalemia. Hyperkalemia may be a manifestation of mineralocorticoid deficiency resulting from adrenal deficiency or syndrome of hyporeninemic hypoaldostrenism.

c). **Acid- base balance**

They are caused by infections and drugs. Respiratory alkalosis and respiratory acidosis may occur in opportunistic infections of the lungs or nervous system. Non anion gap metabolic acidosis occurs due to many causes which includes intestinal losses of bases caused by diarrhea and renal acidosis resulting from adrenal insuffiency, syndrome of hyporeninemic hypoaldosteronism, or drug toxicity (amphotericin B). High gap acidosis results from chronic kidney disease, Type A lactic acidosis caused by tissue hypoxia, and Type B lactic acidosis presented with markedly elevated blood lactate levels caused by drug induced mitochondrial dysfunction due to NRTI such as zidovudine,

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lamivudine, stauvudine, didanosine , zalcitabine etc. Although life threatening acidocis is rare, 5-25% of treated patients may develop mildly elevated lactate levels of 2.5-5mmol/l. Routine lactate measurement in patients with low bicarbonate, elevated anion gap and abnormal anion gap is necessary for managing these groups of patients.

Chronic kidney Disease

Anatomical, biochemical, radiological and functional abnormalities of kidney disease of more than three months are included in this group of patients. This large group of patients with chronic lesions includes HIV associated nephropathy (HIVAN), HIV related immune complex Glomerulo nephritis. Hemolytic Uremic Syndrome, Chronic Interstitial Disorders due to the HIV viral infection and drugs used to treat the virus and other related complications.

HIV Associated Nephropathy (HIVAN)

In 1984 series of patients with advanced AIDS and rapidly progressive renal failure (RPRF) were reported from New York. All of then were African Americans or Haitian immigrants. Early in HIV epidemic the clinical presentation of proteinuria and RPRF was seen in 10% of cases in US. The classical presentation of HIVAN is characterized by RPRF, non hypertensive and without significant peripheral edema moderate to nephrotic proteinuria, bland urine sediment and ultra sonogram findings of large highly echo genic kidneys and most have CD4 count below 200/cmm and progressing to end-stage renal disease within 8–16 weeks.. Progression to death or ESRD was universal and become the third leading cause of ESRD among African Americans occurring between ages of 20 to 64 yrs. Since the introduction of HAART the incidence of death due to HIV in all ethnic groups including African Americans, and the number of new cases decreased after 1996, however the rate of decline in incidence of ESRD due to AIDS nephropathy has slowed and the number of new cases actually increased in 1999 (USRDS).

Renal Pathology of HIVAN

Light Microscopy

Glomeruli

Untreated HIVAN typically manifests as collapsing pattern of FSGS. Capillary lumina are occluded by implosive wrinkling and collapse of the glomerular basement membrane that is more often global than segmental .In this acute injury there is lack of appreciable increase in intracapillary or mesangial matrix. The collapsing FSGS is accompanied by prominent hypertrophy and hyperplasia of overlying podocytes, which have enlarged open vesicular nuclei and with frequent nucleoli, occasional binuleate forms and rare mitosis features. The visceral epithelial cells may be so crowded as to obliterate the urinary space forming pseudocrescents. The podocye cytoplasm is typically vacuolated: contain prominent intracytoplasmic protein resorption hyaline droplets. As the lesions evolve tuft retracts into a solidified ball crowned by overlying enlarged vacuolated visceral epithelial cells, and the urinary space appears dilated and contains proteinaceous filtrate. However repeat biopsies and postmortem studies have shown collapsing lesions may evolve into a more typical pattern of FSGS (NOS).

Tubulo Interstitium

Invariable component of HIVAN; lesions are out of proportion to the glomerular injury .In addition to tubular atrophy, interstitial fibrosis, edema and inflammation, there are widespread tubular degenerative and regenerative changes. They include tubular epithelial simplification, and hypertrophy with enlarged hyperchromatic nuclei, prominent nucleoli, mitotic figures and focal apoptosis. Distended tubules contain loose proteinaceous casts. Tubular micro cysts are seen which may be numerous. Interstitial leucocytes, predominantly of lymphocytes are present with CD4/CD8 ratios from 0.35 to 1. Monocytes,macrophages, plasma cells and B cells form relatively small percentage of the infiltrate.

Immunofluorescence

Segmental deposits of IgM , C3, and less commonly C1 in the collapsing segments. The non collapsed glomeruli may show weaker mesangial staining for IgM and C3. podocytes resorption droplets often stain for IgG, IgA, and albumin and similar findings in tubular epithelial protein droplets.

Electron Microscopy

Collapsed lobules display wrinkling with little or no thickening of GBM, overlying podocytes are markedly hypertrophic with severe foot process effacement, focal detachment, and increased numbers of electron dense protein resorptin droplets, electron lucent transport vehicles and abundant rough endoplasmic reticulum. Actin cytoskeleton is distrupted giving the cells a relatively open appearing cytoplasm. Noncollapsed glomeruli also show severe foot process effacement, typically greater than 50% of capillary surface area and often more than 90%.

Endothelial tubulo reticular inclusions also known as interferon foot prints, identified as 24nm tubular structures located in the dilated cisternae of smooth endoplasmic reticulum: they are not specific for HIV and also seen in SLE, Hepatitis C and other viral infections.and interferon therapy but lacking in pamidronate toxicity and parvovirus B19 infections.

Tubular cells show enlarged regenerative nuclei with prominent nucleoli and the cells lining the tubular microcysts are typically flattened. And there are increased number of nuclear bodies within tubular and interstitial cells.

Podocyte Dysregulation in HIVAN

The injured podocyte in HIVAN recruits back to developmental programme. That includes down regulation of cell cycline kinase inhibitors,entry into cell cycle and loss of maturation phenotype markers. It involves loss of podocyte expression of WT1 and the podocyte is called dysregulated injured podocyte. It expresses proliferation markers Ki67, and loses maturation markers such as

CD10/CALLA,C3b receptor,GLEPP-,1 podocalyxin , synapotopodin and WT-1. Synaptopodin loss precedes collapse. There is decreased expression of P27 and P57and de novo expression of P21 and Ki-67

Differential diagnosis

Biopsy picture also may be present in few other conditions which include primary FSGS, parvo virus B19, SV 40 infection, acute CMV infection, erythrophagocytosis syndrome, interferon therapy, pamidronate toxicitry, acute veno occlusive injury, famial forms and glomerular injury in renal allograft associated with microvascular disease. Increasing prevalence of FSGS NOS in parallel with reduction of HIVAN suggests modifications of collapsing pattern of HIVAN by ART are noted in the recent literature.

Immune Complex Renal Disease and HIV Infection

HIV infection often leads to the development of polyclonal hypergammaglobulinemia, and circulating immune complexes frequently are found in HIV-infected patients. *Kimmel et al* showed that immune complex deposits, composed of HIV peptides and antibodies directed against these antigens, lead to the development of glomerulonephritis. Immune complex deposition may be related to an immunologic response to opportunistic infections that stems from the immunocompromised state and may represent a state of postinfectious glomerulonephritis. It also is possible that glomerulonephritis in the setting of HIV infection may be unrelated to the underlying viral infection, but rather shares the same pathogenic mechanisms as other glomerulonephritidesthat affect the general population.

One proposed mechanism for the development of glomerulonephritis in HIV-infected patients is passive trapping of immune complexes containing HIV antigens. In several well characterized patients, the association with HIV infection has been established with certainty by showing circulating

Or tissue immune complexes consisting of HIV antigens, such as p24, gp41, and gp120, bound to IgG or IgA antibodies to these antigens. Alternatively, in situ immune complex formation, with circulating antibodies binding to HIV antigens deposited on glomerular cells, may play a causal role similar to the mechanism underlying other idiopathic glomerulonephritides. Research in HIV infected patients to date cannot discriminate whether passive trapping of immune complexes or in situ antibody deposition leads to the development of glomerulonephritis. Cellular immune responses likely play a synergistic role in the development of glomerulonephritis in HIV-infected patients.

The immune complex renal diseases associated with HIV includes, IgA nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, membranous ephropathy, Membrano proliferative glomerulonephritis, lupus like glomerulonephritis, cryoglobulinemic glomerulonephritis, immunotactoid glomerulopathy, and fibrillary glomerulonephritis .

Hass et al reported the re view of renal biopsies from 1996 to 2003 in 77 specimens 14 had met the criteria of Lupus like features with full house immune complex staining from ≥1+,and the patients serum negative or weakly positive for ANA ≤1:80and negative for Anti Ds DNA.

Thrombotic Micro Angiopathy (TMA)

Most of the literature belongs to the pre HAART era, the first described case 1984 by *Boccia et al* in with kaposis, who died of staphylococcal sepsis. Gadallah reported a 7% incidence multicente autopsy study of 214 patients, French study of 92 patients, 60 underwent renal biopsy and the TMA incidence was in 32 patients. TMA appears to occur in with untreated advanced infection indicated by low CD4 counts, though case reports also described as a first manifestation of HIV. Peraldi reported in 1999 the largest series with with TMA, with low mean CD4 of 43cells /mm3 evidence for TMA was seen in 20 out of 26 biopsies, mean serum creatinine was 4.2mg, 12 of 26 had active CMV infection,

8% on one ART drug and 12% were on 3 drugs, the pathogenesis clearly involving endothelial cells and not different from the general population.

Non HIV related diseases in HIV patients

The life expectancy of people with HIV increased dramatically after the introduction of highly active anti retroviral treatment (HAART). The incidence of diabetes mellitus is slowly increasing in HIV patients because of the life style and drugs contributing to life expectancy. The life expectancy also increase the incidence of hypertension in HIV population along with other factors such as smoking, alcoholism, obesity, hyperlipidemias.

Hepatitis B, Hepatitis C, polyoma virus(BK), polyoma B19, and other renal diseases as in general population includes primary and secondary glomerular lesions, interstitial lesions and post renal disorders. The incidence of Hepatitis C infection is high in certain group of patients described in Middle East, Europe and United States. The incidence of Hepatitis C coinfection is varies from 10 to 30 % in few studies.

Hepatitis C and HIV

Approximately one third of HIV individuals are co infected with Hepatitis C with higher rates in patients infected parentally. A Varity of renal lesions associated with Hepatitis c include membranous, focal segmental glomerulosclerosis and membrano proliferative with or without cryoglobulinemia, these lesions observed in the co infection also. There are notable differences in co infected HIV –Hepatitis C patients. The degree of renal insufficiency was more advanced, lower prevalence of Hypocomplementemia, cryoglobulinemia compared to isolated Hepatitis C infection. Only 1% had organized deposits compared to Hepatitis c infection alone. Renal outcome is worse and the clinical course resembles more of HIVAN.

In addition PIGN, fibrillary glomerulo nephritis, and immunotactoid glomerulopathy reported in this subset of HIV patients.

BK virus and HIV 80% of population is seropositive for BK virus, it establishes latent infection in renal tubular cells, and urinary tract epithelia, results in interstitial nephritis, hemorrhagic cystitis and urethral, ureteral stenosis in transplant population. Few isolated cases were in the literature, in one series 6 cases reported with HIV and BK virus nephropathy.

End Stage Renal Disease

Though not much statistical evidence is available for the exact incidence of ESRD in HIV population, because of the high incidence of HIVAN, HIV contributes to the third leading cause of ESRD among Afro Americans. The USRDS reported 4219 ESRD cases in HIV patients from year 2000 to 2004. Almost 90% in African Americans. Early studies in 1980s reported most with ESRD die within 1-3 months of starting hemodialysis in the pre ART era, because they presented late in the disease with much advanced opportunistic infections. In year 1999 the 1 year survival rate of HIV is equivalent to the general population as per the US ESRD registry.(240 deaths vs. 236.4 per 1000 patient years) . Similar outcome was described in French dialysis and outcomes and practice pattern study II. Hemodialysis, peritoneal dialysis and renal transplantations are the accepted modes of management fore ESRD. Coinfection with HCV is common in HIV ESRD and the reported prevalence as high as 50% and the optimum therapy remains undetermined. Renal replacement therapy (RRT) in HIV- ESRD has improved the survival for the last two decades.

Hemodialysis

It is the most common form of RRT for HIV patients. Strict adherence to general principles of prevention is absolutely necessary by the health care providers. Early surgical referral for arteriovenous fistula is necessary because of increased incidence of infections and poor outcome of AV graft. Disadvantages include infections of temporary catheters and AV grafts, and risk to dialysis providers because of blood and needle stick exposures. Early referral for AV fistula preferred because of inferior outcome of AV grafts. Infection rate in synthetic grafts is 43% in AIDS, 36% with

asymptomatic HIV infection, and 15% in HIV negative patients. Thrombus free native graft survival was comparable to non HIV patients.

Peritoneal Dialysis

Outcome between Hemodialysis and Peritoneal dialysis are equivalent. Peritoneal dialysis patients have benefit of preservation of residual renal function when compared to hemodialysis patients. Disadvantages include increased protein loss, increased incidence of peritonitis especially higher incidence of pseudomonas and fungal infections. The risk to health provider is the persistence of the live virus in peritoneal fluid for over 7 days and in the tubings for over 48 hours and the spread of infection prevented by strict aseptic procedures, and use of sodium hypochlorite solution.

Kidney transplantation

Roland et al in 2007 reported 94% 3 year survival in renal recipients but 12 of 18 experienced acute rejection episodes (67%), and the 3 year cumulative rejection episodes were 73%. Despite concern of immunosuppression required to prevent graft rejection might increase HIV disease progression has not been observed in renal transplant recipients. Cyclosporine, mycophenolate mofytil and sirolimus are immunesuppressive drugs with antiretroviral activity and they may counteract the theoretical risk of HIV progression. NIH sponsoring a study in 20 centres in US for transplants in HIV-ESRD patients with the following category with preliminary results support kidney transplantation is a viable option. They include CD4 ≥200cell for adults CD4 % of ≥ 30% for children 1-2 years old, ≥ of 20% for 2-10years .and HIV RNA must be undetectable by ultrasensitive assay.

National and International studies of Renal Lesions in HIV

In 2004, HIVAN was the seventh leading cause of ESRD in the African American population. In the UK, a study from the university College London Hospitals carried out between 1992 and 1996 showed that 1% of patients with ESRD had HIV, that HIV-associated renal disease ranked 14th among the most common causes of ESRD. In Perald's study of hospitalized patients with HIV, AKI occurred

in up to 20% of cases. *Kimmel et al* in another study of hospitalized patients with HIV and AKI had a mortality rate of 18% at 2 months, with 80% of patients diagnosed with AIDS at the time of hospital admission. Prospective study by *Franceschini et al* of patients with HIV and AKI concluded that severe immunosuppression (CD4+ t-cell count<200 cells/mm3 and/or HIV rna level >10,000 copies/ml)is the predominant risk factor for AKI.

Screening studies performed across sub-Saharan Africa report widely different prevalence of kidney disease in HIV. In most of these studies kidney disease was defined as the presence of albuminuria and/or low estimated GFR (based on serum creatinine measurements). Reported prevalence ranges between 6% and 45%. this wide variation could be ascribed in part to differences in study design, populations studied (in terms of demographic characteristics and/or ethnic origin) and definitions of CKD used. Some studies measured proteinuria only by dipstick, whereas other studies quantified it and some studies might not have performed serum creatinine measurements. Very few studies described the histological pattern of kidney disease as revealed by kidney biopsy and fewer still described response to treatment.

Two screening studies have been performed in south Africa. The first study included 615 ART-naïve out patients with HIV and found that 6% had persistent proteinuria. Renal biopsy samples were collected from 30 of the 37 patients with persistent proteinuria, and histology showed HIVAN to be the predominant condition (83.3%) with other conditions observed being HIVAN combined with membranous glomerulonephritis, membranoproliferative glomerulonephritis and interstitial nephritis. The second study, which included 578 ART-naïve outpatients, reported that persistent proteinuria was observed in 5.5% of patients and that 20 renal biopsies were performed. HIV-associated immune complex disease was seen in 40% of cases, HIVAN 5%, and a combination of HIVAN and immune complex disease in 5%. Furthermore, 45% of biopsy samples displayed mesangial and/or interstitial changes that did not meet the current histological criteria for HIVAN.

In this study, initiation of ART resulted in a significant improvement in estimated GFR and a marked reduction or resolution of proteinuria, mostly within the first 6 months. Another study carried out in South Africa included 99 ART-naïve hospitalized patients and showed 27% had HIVAN, 21% had HIV-associated immune complex disease, and 13% membranous nephropathy, with the remainder of patients displaying the hallmarks of non glomerulonephritic renal disease, post infectious or mesangioproliferative glomerulo nephritis and IgA nephropathy. Evidently the histological patterns of renal disease in patients with HIV are variable, even within the same region. This observation might reflect the high degree of genetic variability among black South Africans from different ethnic groups. a study performed in Nigeria found renal disease (proteinuria or abnormal serum creatinine) in 38% of 400 patients. among the ten renal biopsy samples collected, the majority displayed the hallmarks of collapsing focal segmental glomerulosclerosis. In Cote d'ivoire, a study compared patients with HIV living in Paris, France, with patients living in Abidjan, Cote d'ivoire, and found the prevalence of albuminuria was higher in the cohort from Abidjan (26%) than from Paris (5%).37 a study in Tanzania found albuminuria to occur more frequently in patients with HIV(28.4%) than in patients without HIV (16.8%).A Kenyan study screened 216 ART-naïve patients with an average CD4+ T-cell count of 383 cells/mm3. 25% had estimated GFR <90 ml/min/1.73 m2, 2% had estimated GFR <60 ml/min/1.73 m2 and 8% had proteinuria >1 g per day.

A Ugandan study of 229 patients with WHO clinical stage 3 for HIV showed estimated GFR to be under 80 ml/min/1.73 m2 in 48.5% of patients; 20% of patients had proteinuria over 100 mg/dl.40 another Ugandan study assessed the effect of highly active art (HAART) on renal function. in this study 508 patients with HIV and creatinine clearance >0.42 ml/s (25 ml/min) were evaluated before HAART initiation: 8% of participants had serum creatinine >133 μmol/l and 20% had creatinine clearance between 0.42 ml/s (25 ml/min) and 0.84 ml/s (50 ml/min).After 2 years of HAART the median serum creatinine level decreased by 16% and the median creatinine clearance increased by

21%. the median creatinine clearance of patients with renal dysfunction at study initiation (that is, creatinine clearance 0.42–0.84 ml/s [25–50 ml/min]) increased by 53%. in multivariable analysis, baseline creatinine above 133 μmol/l, weight gain of more than 5 kg at 2 years, female gender and WHO stage 4 HIV were all associated with greater improvements in creatinine clearance. The development of antiretroviral therapy (Dart) study was carried out at centers in Uganda and Zimbabwe. Of the 3,316 participants, 45% had estimated GFR between 60 ml/min/1.73 m2 and 90 ml/min/1.73 m2 and 7% between 30 ml/min/1.73 m2 and 60 ml/min/1.73 m2 before starting ART.

In a Zambian study of 25,799 patients treated with art 33.5% had renal dysfunction. Of these participants, 3.1% had creatinine clearance <0.50 ml/s (30 ml/min), 23.4% between 0.50 ml/s (30 ml/min) and 0.99 ml/s (59 ml/min) and 73.5% between 1.0 ml/s (60 ml/min) and 1.49 ml/s (89 ml/min). Renal dysfunction was associated with increased mortality at 90 days. What is clear from these studies is that renal dysfunction is common in patients with HIV from sub-Saharan Africa, and although dysfunction seems to be a predictor of poor outcome, it responds to ART.

Results from the few studies that have reported histology data seem to indicate that there could be a wider spectrum of histological lesions with a higher number of immune-complex diseases in sub-Saharan African patients than among black patients from developed countries. Outcomes in patients with HIVAN have been correlated with the clinical stage of their disease, suggesting that survival improves with early detection of the condition. Relative risk of all-cause mortality increases 2.5–3.0-fold if Hivan is associated with proteinuria, after correcting for other risk factors. In one study, 77% of renal abnormalities consistent with HIVAN developed in patients with CD4+ t-cell counts above 200 cells/mm3.

A similar outcome was also observed in a study from South Africa, where the mean CD4+ Tcell count of patients with biopsy-proven Hivan was 232 cells/mm3.33 a CD4+ T-cell count below 200 cells/mm3 cannot, therefore, be used as a diagnostic criterion for Hivan. *Steel Duncan et al*

reported 2008 from Jamaica urinary tract infections were reported in 16.8% patients with HIV children and Ecoli was the most isolated, 4/7 developed indinavir associated nephropathy and tubulo interstitial diseases, six had HIVAN five were males, all had nephrotic proteinuria and 3 with chronic renal failure in a group of 196 children followed over, and had a high mortality 50% with a mean follow up of 3.1yrs.

Keerkirat Praditpornsilpa reported in1999 the renal pathology and HIV infection in Thailand. The existence of a human immunodeficiency virus (HIV) associated nephropathy (HIVAN) as a distinct disease entity characterized by glomerulosclerosis is well established in North America and Western Europe. Although the large number of HIV infected cases overwhelms the Asian countries biopsy studies were not many to conclude the HIVAN incidence in Asian population of HIV affected. Researchers have studied 26 cases of HIV infected Thai patients with proteinuria more than 1.5g/dl of protein during 1995 and 1996. None of the patients was treated with antiretroviral drugs at the time of renal biopsy. Intravenous drug addiction and sexual transmission were risk factors in 11 and 15 patients, respectively.

Pathological examinations were performed by light microscopic and immunoperoxidase study. Mesangial proliferative glomerulopnephritis was found in 17 cases, immunoglobulinA (IgA) nephropathy in 2 cases and diffuse proliferative glomerulonephritis and interstitial nephritis secondary to Cryptococcus infection in 2 cases each. One case each had membranous glomerulopathy, membranoproliferative glomerulonephritis and granulomatous interstitial nephritis secondary to tuberculosis. The renal pathological findings of HIVAN with the unique features described in previous literature were not evident in these patients. Although the data in this study are limited to the 26 HIV infected patients, we believed that HIVAN is uncommon in the Asian HIV infected population. Renal biopsy study reported from northern Italy in 2009 0f 73 renal biopsies, it was found HIVAN in 9

cases, immune complex glomerulonephritis in 40 cases, 13 non collapsing FSGS and various others in the remaining.

Amandi mocroft et al in 2007 reported the incidence of chronic renal failure in HIV patients. They screened 4474 patients and found the incidence of CKD in 158 (3.5%) patients by cock croft gault and 209(4.7%) with MDRD at baseline, with higher incidence in patients receving indinavir and tenofovir. Andre kabanda et al in 1996 reported the high incidence (82.6%) of low molecular weight proteinuria in HIV patients, they include albumin, beta 2 microglobulin, retinol binding protein, acetyl beta D glucosaminidase and clara cell protein (CC16). Agati et al 2009 reported the incidence of renal lesion in HIV in the era of HAART, that HIVAN and glomerulonephritis were the frequent in 89 HIV patients evaluated postmortem. Early FSGS was identified and others include parenchymal infections bacterial and fungal causing chronic pyelonephritis.

Rao et al 1984 reported nephrotic syndrome with FSGS in nine HIV infected individuals. PP varma reported in 2000 proteinuria in 17.6% of 142 patients screened, none in nephrotic range, mesangioproliferative in 8, FSGS in 4, HIVAN in 1, 2 cases of cryptococcal infiltration and one with lymphomatous deposits. one with granuloma and 3 with mononuclear infiltration. HariJanahiraman et al reported from Chennai in 2008 after studying 104 HIV patients, urine albumin by dipstick performed renal biopsy with albuminuria 2+ or more albuminuria was observed in 27% of patients, which revealed negative correlation with CD4 cell counts. Patients with CD4 count <350 cells/cmm had a 3 folr increase in proteinuria, and there was no significant correlation with development of proteinuria and albuminuria had a negative correlation with hemoglobin levels.10 patients undergone renal biopsy and 7 had HIVAN, chronic intertstitial nephritis(CIN) in 1,membranous nephropathy in 1,diffuse proliferative glomerulonephritis in 1 patient. NP Sing et al reported in 2005 the usefulness of renal biopsy in patients suspected to have HIVAN, but the predictivity in only 55 to 60% of renal biopsies.

Background of study

In India the free supply of ART drugs to all the HIV patients since 5 years has improved quality of life as well as the life expectancy of HIV population. Although the opportunistic infective complications secondary to HIV infections have come done dramatically, the evidences are not many. Few international studies gave a more or less a comprehensive picture of renal lesions in HIV-AIDS patients. There are specific renal renal lesions in HIV due to HIV infection. There are definite reports of decreased incidences of HIV related renal lesions in the ART era. The nephrotoxicity of ART drugs are important contributing factors for the development and progression of renal lesions in era of HAART. Certain non modifiable factors such as Age, Sex ,Race, Genetic factors, and modifiable factors such as diabetes hypertension, smoking, hyperlipidemias, alcohol intake, time of initiation of ART , and other factors as in general population are most important in the initiation and progression of renal lesions. The increased life expectancy contributes to the number of patients with chronic kidney disease and patients seeking treatment for end stage renal disease secondary to renal lesions in HIV-AIDS population. The benefits are as comparable to non HIV patients for dialysis requiring CKD HIV patients. Data of Renal transplantation and the additional benefits of CNI drugs in ESRD of HIV group are emerging and studies highlighted the near comparable survival in HIV population.

Overall only few studies are available for pattern of renal lesions in the Indian subcontinent and few studies based upon clinical profile and others with pathological correlations. The profile of renal lesions with renal biopsy is not extensively studied in this part India with a higher prevalence rate of HIV infection .So this study of renal lesions in HIV patients was planned to be carried out to know the profile of renal lesions in HIV population.

AIM OF THE STUDY

1. To study the Profile of Renal diseases in HIV patients.

2. To do comparative evaluation of renal lesions diagnosed in various centers.

Materials and Methods

The study protocols were approved by The Institutional Review Board of Government Hospital for Thoracic Medicine, Tambaram at Chennai, and also by the Ethical committee for research studies of Government Kilpauk Medical College Hospital Chennai.Informed consent was obtained from the proposed study group of seven thousand three hundred and sixty three (7363) patients. The study protocols include recruitment of patients diagnosed to have HIVat the HIV clinic as well as inpatients from the above institutions. All the consecutive patients excluding those aged below 15 years were screened for renal lesions and assigned separate serial number. The patients include persons newly diagnosed to have HIV those HIV patients who are not on ART because of CD4 above 200cell/cmm, as well as those on ART drugs. Initially all of them were investigated with urine analysis for protein, sugar, and deposits for Red Blood Cells, Pus cells, Casts and crystals .Urine protein was done by sulphosalisylic acid method and or dipstick. Other screening laboratory investigation was serum creatinine. Serum creatinine was done using Jaffe's method.

Patients with proteinuria of >500mg/day, hematuriua >5RBCs/HPF, pathologic casts in urine, serum creatinine of >1.2mg/dl and GFR of <60ml/mt were evaluated further. This include repeat urine analysis, spot urine protein and creatinine ratio, 24 hours urine protein, urine culture and sensitivity, complete blood count (ncluding total and differential WBC count, hemoglobin, total RBC count, ESR, platelet count , bleeding time, clotting time, fragmented RBCs, and toxic granules in WBCs,), blood sugar, blood urea, serum creatinine, serum electrolytes , serum total protein, serum albumin, CD4 count, HbsAg, AntiHCV, complements C3,and C4, and ultra sonogram of kidneys and abdomen .Ultra sonogram evaluation of kidney size, parenchymal thickness, and echogenicity were done. Patients who were identified as acute renal failure were excluded for renal biopsy. Patients with severe illness associated with respiratory, cardiac, pulmonary, neurological systems and hemodynamic instability were excluded from renal biopsy. Patients with reversible causes of renal failure, which

include prerenal, renal and post renal causes were identified, and treated . Six patients required peritoneal dialysis prior to renal biopsy. After consent for renal biopsy patients were admitted in nephrology ward. Ultra sonogram guided renal biopsies were done using biopsy gun of Bard maxcore renal biopsy instrument. The renal biopsy study included light microscopy and immunoflourescence.

Results

Total number of HIV population screened was 7363 patients. Of this 864 persons are from Government Kilpauk Medical College Hospital and the remaining major group of patients were from Government Hospital for Thoracic Medicine, Tambaram, Chennai. The analysis of this study involves both the groups together.

Of the 7363 patients, males were predominant. 4941were males ,2411 were females and 10 were Trasgenders.. In the males 126 were less than 20 yrs of age, 346 patients were of 20 to 29 yrs of age, 1863 were in the 30 to 39 yrs of age, 1972 were in 40 to 49 yrs of age, 452 were in the 50 to 50 yrs of age, and 183 patients were 60 and above yrs of age. In the females 66 were less than 20 yrs of age, 400 were in 20 to 29 yrs of age, 1109 in 30 to 39 yrs of age, 671in 40 to 49 yrs of age, 130 patients were in 5o to 59 yrs and 49 were above age of 60 yrs.

These groups were further sub classified into patients receiving drugs for retro virus (ART) and those who are not receiving retroviral drugs (non ART).The group of patients receiving ART include four thousand nine hundred and sixty persons and in this group three thousand five hundred and thirty five were males, one thousand four hundred and twenty five were females and trans genders were five. Two thousand four hundred and eight not received ART drugs of them one thousand four hundred and two were males, nine hundred and ninety were females and five Transgender.

Gender Stratification of Patients Screened
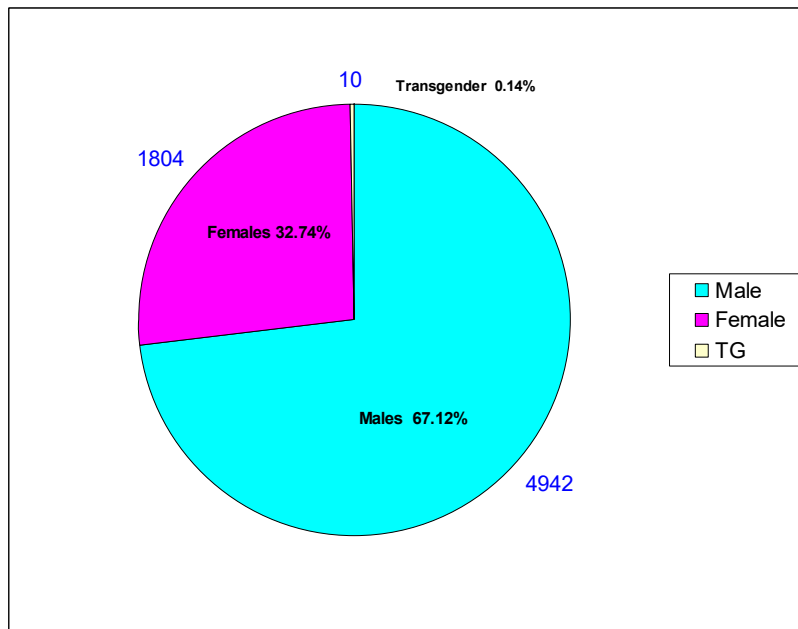
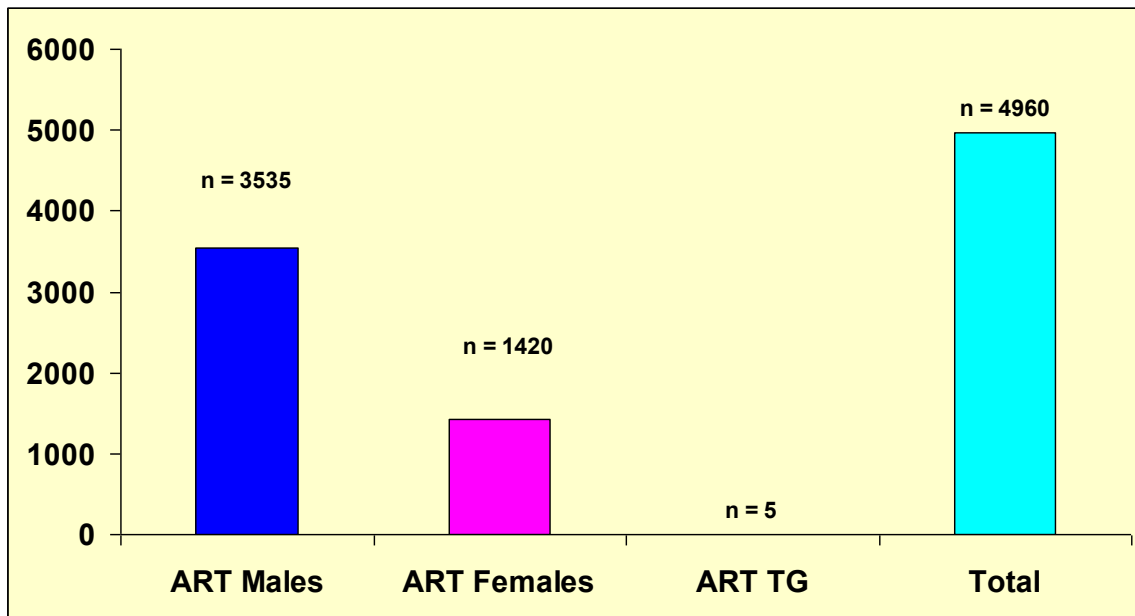## PATIENTS on ART = 4960: Gender Data

TABLE - I

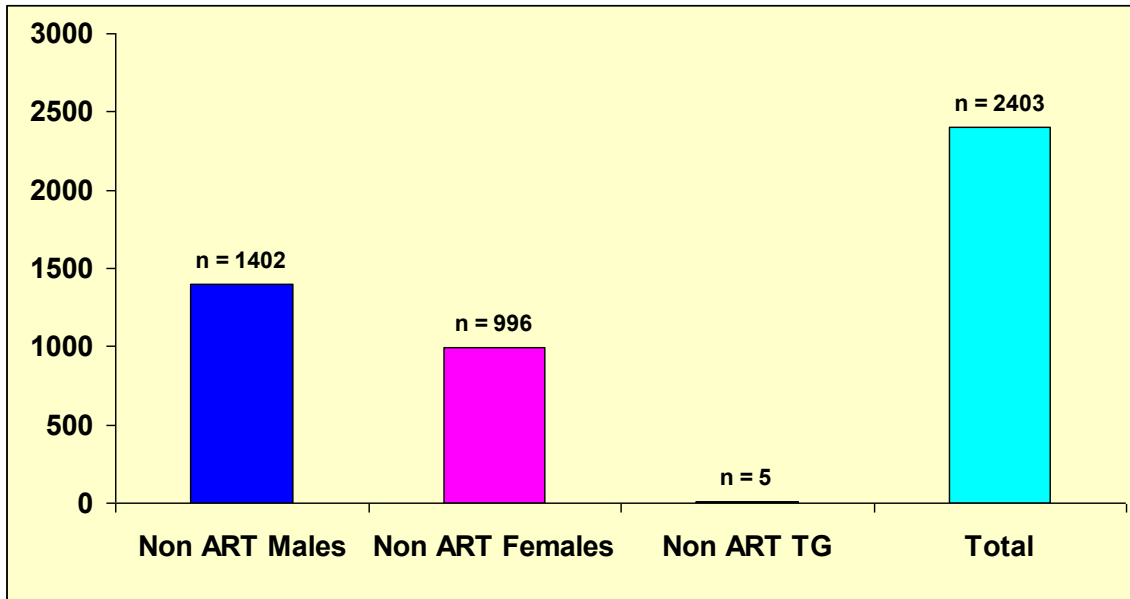## HIV PATIENTS Not on ART = 2403: Gender Data

TABLE - II

Initial group of 7363 patients proteinuria evaluation revealed 2581 patients had proteinuria from trace to 4+. Of them 1905 were males and 676 were females. In the males 829 had trace proteinuria, 661 had 1+ proteinuria, and 292 had 2+ proteinuria, 165 had 3+ proteinuria and 13 had 4+ proteinuria. In the females of the screened of 2411 patients 358 had trace proteinuria, 219 had 1+ proteinuria, 74 had 2 + proteinuria, 23 had 3 + proteinuria and only 2 had 4+ proteinuria.

In the sub group results of the proteinuria group of the 2581 males, in those who were below 20 yrs of age, 4 had 1+ proteinuria, 30 had 3+ proteinuria. In the males of the 20 to 29 age group of 346 patients, 69 had trace proteinuria, 43 had 1 + proteinuria, 8 had 2 + proteinuria, 10 had 3+ proteinuria. In the 30 to 39 age group 1863 patients, 248 had trace proteinuria, 252 had 1 + proteinuria,150 had 2 + proteinuria, 64 had 3 + proteinuria and 4 had 4 + proteinuria. In the 40 to 49 age group of 1972 patients, 430 had trace proteinuria, 182 had 1+ proteinuria, and 92 had 2 + proteinuria, 45 had 3 + proteinuria and 9 had 4 + proteinuria. In the 50 to 59 age group of 452 patients, 46 had trace

45

proteinuria, 112 had 1+ proteinuria, and 26 had 2+ proteinuria, and 16 in the 4+ proteinuria range. Of the183 patients of 60 yrs and above, 6 had trace proteinuria, 26 had 1+ proteinuria, 16 had 2+ proteinuria and none in the 3+ and 4+ groups.

Proteinuria in Males Screened n = 4942

Age	Proteinuria						
	Nil	Trace	1+	2+	3+	4+	Total
< 20	92	0	4	0	30	0	126
20 – 29	224	69	43	8	10	0	346
30-39	1165	278	294	150	64	4	1863
40-49	1114	430	182	92	45	9	1972
50-59	252	46	112	26	16	0	452
>= 60	135	6	26	16	0	0	183
Total	2982	829	661	292	165	13	4942

TABLE – III
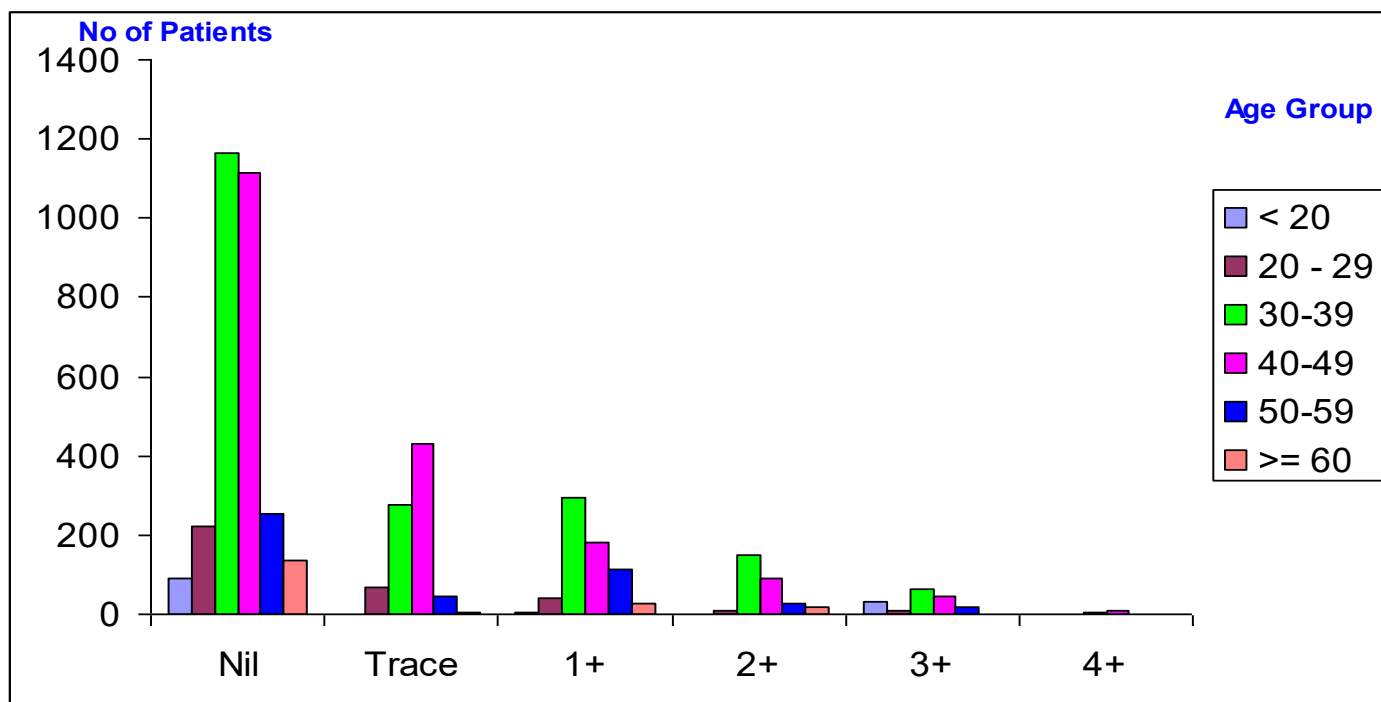
Proteinuria in Females Screened   n = 2411

Age	Proteinuria						
	Nil	Trace	1+	2+	3+	4+	Total
< 20	51	12	5	2	1	0	71
20 - 29	225	121	33	16	2	0	397
30-39	764	195	104	31	12	1	1107
40-49	531	28	69	16	6	2	652
50-59	105	12	7	9	2	0	135
>= 60	36	6	2	4	1	0	49
Total	1712	374	220	78	24	3	2411

TABLE - IV
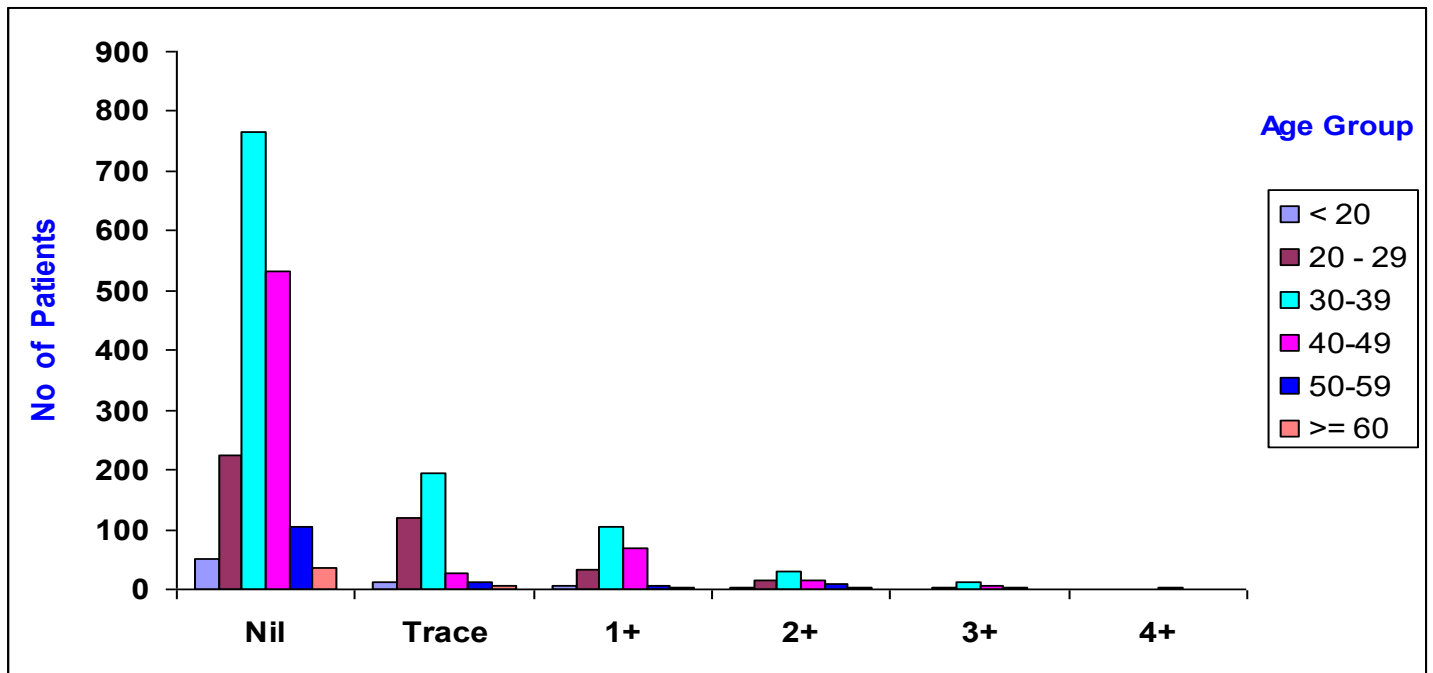
Total of 2411 female patients were screened for proteinuria. In the less than 20 yrs of age group of 66 persons, 12 had trace proteinuria, 5 had 1+ proteinuria, 2 had 2+ proteinuria, 1 had 3+ proteinuria and none in the 4 + proteinuria group. In the 20 to 29 yrs group of 400 patients, 121 had trace proteinuria, 33 had 1+proteinuria, 16 had 2+ proteinuria, and 2 had 4+ proteinuria. In the 30 to 39 yrs age group of 1109 patients, trace proteinuria in 195, 1+ proteinuria in 104, 2+ proteinuria in 31, 3+ proteinuria in 12, and 4+ proteinuria in 1. In the 40 to 49 age group of 652 patients, 28 had trace proteinuria, 69 had 1+ proteinuria, 16 had 2+ proteinuria, 6 had 3+ proteinuria, and 2 had 4+ proteinuria. In the 50 to 59 group of 135 patients 12 had trace proteinuria, 7 had 1+ proteinuria, 9 had 2+ proteinuria, 2 had 3+ proteinuria and none with 4+ proteinuria. In the age group of 60 yrs and above of 49 patients 6 had trace, 2 had 1+ , 4 had 2+, 1 had 3+ proteinuria and none in the 4+ group.

Due to logistical reasons quatitatification of proteinuria was done only in 563 patients, of these significant proteinuria in the range of 300mg to 500mg were found in 114 patients and proteinuria in the range of more than 500mg to 1000mg were found in 85 patients, subnephrotic proteinuria in the range of 1gram to 3grams was found in 72 patients, nephrotic range proteinuria was found in 27 patients.

336 patients of the 7363 screened had hematuria. Microhematuria was detected in 318 patients and macrohematuria in 18 patients. Patients with microhematuria 3 and 4 cells /HPF detected in 156 persons , 5 to 9 cells /HPF in another 156 patients and in 6 patients $\geq$ 10cells/HPF.

Of the 7363 urine for pus cells study 1203 had significant pyuria of more than 5 WBCs/HPF,urine culture was done only for in patients , Ecoli was grown in 28 patients Pseudomonas in 7 cases and klebsiella was grown in 7 cases.

Hematuria

TABLE - V

Total Screened	7363
Hematuria detected	336
Micro Hematuria detected	318
Macro Hematuria detected	18
3 to 4 RBCs / HPF	156
5 to 9 RBCS / HPF	156
≥ 10 cells / HPF	24

Total Screened n = 7363
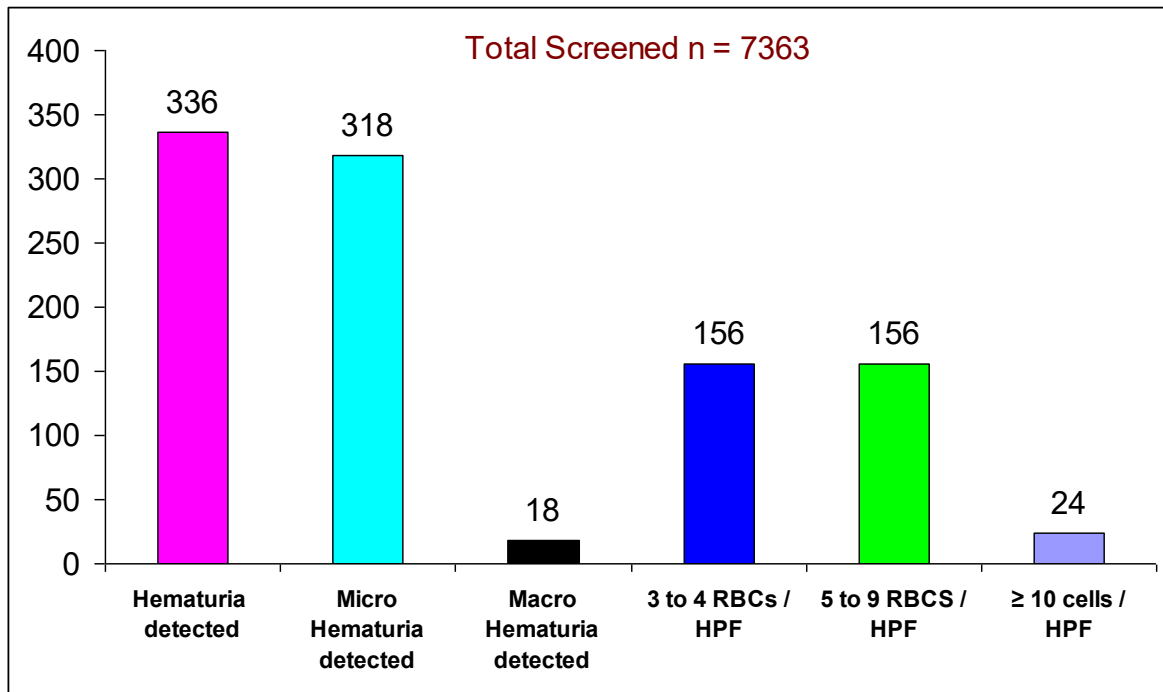
Urine Protein Creatinine Ratio

TABLE - VI

(UPCR	Total No of Patients
0.3 to ≤ 0.5	114
> 0.5 to 1.00	85
> 1.00 to < 3.00	72
≥ 3.00	27
Total Significant	298
Total Screened	563

Urine Protein Creatinine Ratio (UPCR)
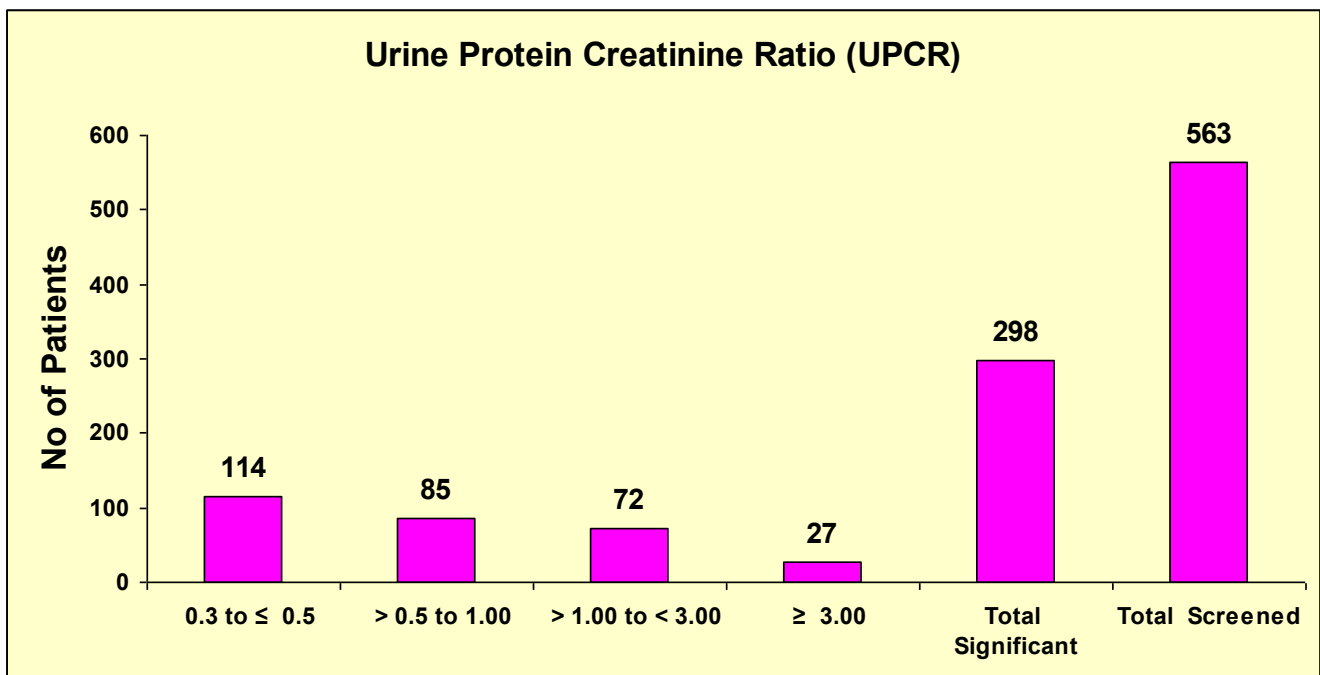
Of the 7363 patients who had undergone screening for creatinine 574 were found to have renal failure as evidenced by elevated serum creatinine of 1.3mg/dl . Of all the 574 patients who had elevated creatinine 489 were males and 85 were females and 1 was a transgender. They were subclassified by the level of serum creatinine into 3 groups – the first group with serum creatinine 1.3 to 2 mg/dl, second group from 2mg/dl to 4mg/dl and the third group above 4mg/dl. Again these groups were divided based on the age. The age wise sub classification include <20, 20 to 39, 40 to 59, ≥60. In the males group, of the 489, 330 persons had serum creatinine 1.3 to< 2mg/dl, 113 had serum creatinine 2 to 4 mg/dl and 46 had 4mg/dl and above. In the 1.3 to 2mg/dl group one patient was <20 yrs, 118 were in the 20 to 39 yrs group, 178 were in the 40 to 59 yrs age group and 33 were above 60 yrs of age. In the 2 to 4mg/dl group 39 persons belong to 20 to 39 yrs of age, 60 were in 40 to 59 age group and 14 persons are above 60 yrs. In persons with 4mg/dl and above 16 belong to 20 to 39 age group, 30 belong to 40 to 59 age group. In the females 1belongs to < 20 yrs of age, 22 belong to 20 to 39 yrs of age 20 belong to 40 to 59 yrs age group and 5 were above 60 yrs in the 1.3 to 2mg/dl group.

In the other group with 2 to 4mg/dl creatinine 1 was < 20 yrs 5 were 20 to 39 yrs of age 13 belong to 40 to 59 yrs age group and 1 was above60 yrs. In the females with serum creatinine 4mg/dl and above 6 belong to 20 to 39 age group and 11 belong to 40 to 59 age group.

Electrolyte Abnormalities

Serum sodium measurements were done in 143 patients, they had the serum sodium level range of 121meq/l to 143meq/l. 78 persons had hyponatremia below the level of 135meq/l, of them 5 had severe hyponatremia below 125meq/l. Serum potassium was done in the same 143 patients and the range was from 2meq/l to 5.2 mq/l. 20 patients had serum potassium levels below 3mq/l. 33 patients had below 3.5mq/l. Acute renal failure presented as pre renal ATN and post renal was the cause for renal impairment in 128 patients of 566 screened constituting about 15%.

TABLE - VII

RENAL FAILURE DETECTED

Total Number Screened : **7363**

Total with Renal Failure : **574**

No of Males with Renal Failure : **489**

No of Females with Renal Failure : **85**

Sr. Creatinine	Age	Males	Females	Total
1.3 to 2 mg /dl	< 20	1	1	2
	20-39	118	22	140
	40-59	178	20	198
	> 60	33	5	38
2 to 4 mg / dl	< 20	0	1	1
	20-39	39	5	44
	40-59	60	13	73
	> 60	14	1	15
>4 mg / dl	< 20	0	0	0
	20-39	16	6	22
	40-59	30	11	41
	> 60	0	0	0

Kidney Size in Patients with HIV with Renal Lesions

The 574 patients' kidney size was evaluated with ultrasound, who had either significant proteinuria or renal failure or both. Of these 29 kidneys on right side and 24 on the left side were <9cms. Bilaterally contracted kidneys in 13 patients, asymmetric kidneys in 11 patients were present. And the remaining 434 patients had kidneys of the size of more than 9cms bilaterally. The range of the kidney size varied from 9 to 15.16cms with a mean of 10.78cms and median of 10.7cms. Bilateral contacted kidneys and asymmetric kidnerys noticed in 40 patients

Renal stones were identified in 7 0f 510 USGs and in 4 four they received ART. 42 patients had evidence of UTI and urosepsis. Total patients of HIV with renal failure expired was 40 and of this 26 patients with HIV expired had renal insufficiency with multiple organ involvement and in 14 the cause of death was chronic renal failure and related complications one patient on maintenance hemodialysis, and 4 had peritoneal dialysis once.

Patients with renal failure with normal size kidneys, patients with proteinuria of 500mg and above and patients with more than 5 and above RBCs were advised to undergo evaluation in the form of renal biopsy and serological profile for hepatitis B, C and in selected cases C3 and C4. Number of patients eligible for biopsy as per our screening study was 651, which include patients with micro hematuria more than 5 RBCs /HPF proteinuria of >500mg/day , and with renal failure . Due to both medical and socioeconomic reasons biopsy could not be done to all selected patients.

The number of renal biopsies done was 72 in 71 patients.(one patient required rebiopsy) Nmber of males who underwent renal biopsy was 59, females 11,and transgender 1. Total number of patients on ART 36 and patients not on retroviral drugs was 35. Total number of males on ART was

33, and for females it was 3. Total number of males not on retro viral drugs was 26 and in females it was 8 and 1 in transgender.

TABLE - VIII

ARF DATA

ARF	128
PRE RENAL	114
RENAL ATN	10
POST RENAL	4
Total No. screened with Renal Failure	574

TABLE - IX

CKD IN HIV PATIENTS

STAGE OF CKD	MALES	FEMALES	TOTAL
CKD 3	172 (54.7%)	78 (59.09%)	250 (56.05%)
CKD 4	108 (34.48%)	40 (30.31%)	148 (31.18%)
CKD 5	34 (10.82%)	14 (10.60%)	48 (12.77%)
TOTAL	314 (100%)	132 (100%)	446 (100%)

Of the 71 patients who had undergone renal biopsy the indication for renal biopsy was renal failure with serum creatinine of ≥1.3 mg/dl was in 59, in the males it was 52, in the females it was 6 and 1 in transgender . Patients taken up for renal biopsies for proteinuria of ≥500mg/day were 12, of this 7 were males and 5 were females. Though we intended to use microhematuria of ≥ 5 RBCs /HPF as indication for renal biopsy there other indications too in these patients such as ≥1.3mg/dl of serum creatinine, and proteinuria of ≥500mg/day and the total number of patients who had hematuria was 36.

Light microscopy

Upon light microscopy, mesangial cell hypercellularity was seen in 57 of the 72 biopsies. Mesangial matrix expansion was seen in 17 biopsies which was mild in 16 and moderate in 1 patient. . Ischemic vascular changes seen in glomeruli in 28 biopsies, which was mild in 25 and moderate in 3 biopsies. Tubular atrophy was seen in 38 biopsies of which focal tubular atrophy in 22 biopsies and moderate tubular atrophy in 13 biopsies and severe tubular atrophy in 3 biopsies. Interstitial dense infiltrate of lymphocytes and other mononuclear cells were found in remarkably high number of patients of 42 renal biopsies. It was mild in 2 biopsies, dense patchy in 38 biopsies and diffuse dense in 2 biopsies.

Interstitial nephritis seen in 18 biopsies, 1 had AIN, one had ATIN, and 2 had sub acute interstitial nephritis and remaining 15 had chronic interstitial nephritis. Marked interstitial fibrosis seen in 7 biopsies. ATN features with tubular cell flattening, apoptosis, tubular dilatation seen in 5 biopsies. feature of pyelonephritis seen in 2 biopsies. Features of arterio and arteriolo sclerosis were seen in 15 biopsies.

Immunoflourescence

IgG deposits in glomeruli in the mesangial and capillary walls were seen in 16 biopsies, 2+ seen in 3 biopsies,3 + in seven biopsies, 4+ in 5biopsies.

IgM deposits was seen in glomeruli in 54 biopsies, 1+ in seven biopsies, 2+ in twenty four biopsies, 3+ in fourteen biopsies, and 4 + in seven biopsies.

IgA deposits were seen in 13 biopsies and in 11 of them it was dominant or codominant. Three had 1+ deposits in glomeruli and 4 had 2+ deposits, 3 had 3+ and 3 had 4+ deposits in glomeruli.

C3c deposits were seen in 52 biopsies, 2+ pattern in 12 biopsies, 3+ in 13 biopsies, and 4+ deposits in 27 biopsies.

C1q deposits were seen in 13 biopsies, of this one had 1+ deposit in glomeruli, seven had 2+ four had 3+, and one had 4+ deposits in glomeruli.

Fibrinogen deposits of 4+ was seen in one glomeruli.

Biopsy Diagnosis

Diffuse mesangial proliferation (**DMP**) was seen in 26 renal biopsies

HIVAN was clearly evident in 21 biopsies and in them 7 had early features of partial collapse.

Classical FSGS was seen in 6 biopsies.

IgA nephropathy was seen in 11 biopsies.

IgA with HIVAN was seen in 5 biopsies

Membranous nephropathy was seen in 2 biopsies.

Lupus nephritis with membranous, diffuse proliferative and crescents were seen in 1 patient.

Lupus like nephritis was seen in 1 biopsy.

Vasculitis with crescent in one patient, and
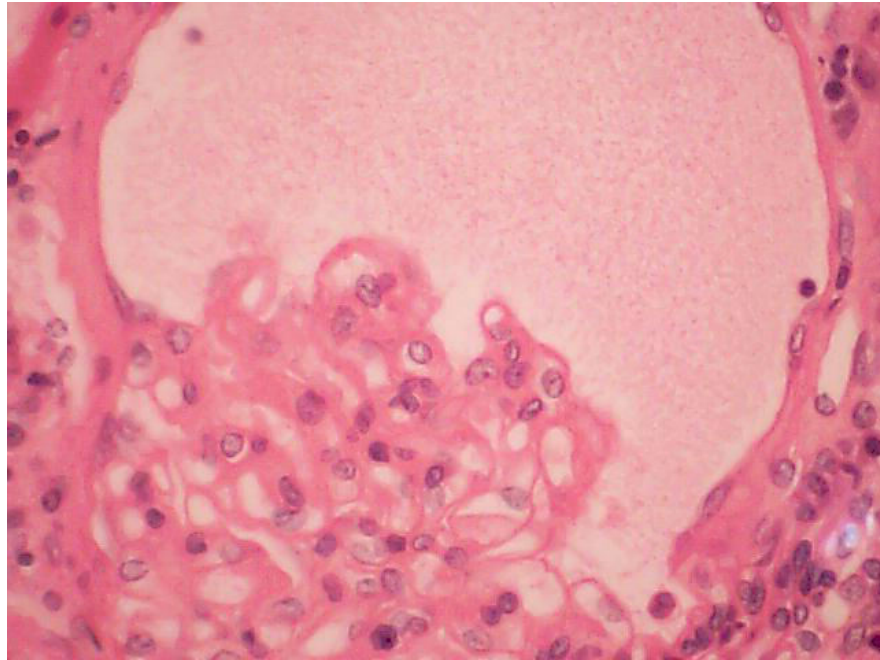
IgA with crescent was seen in one patient.

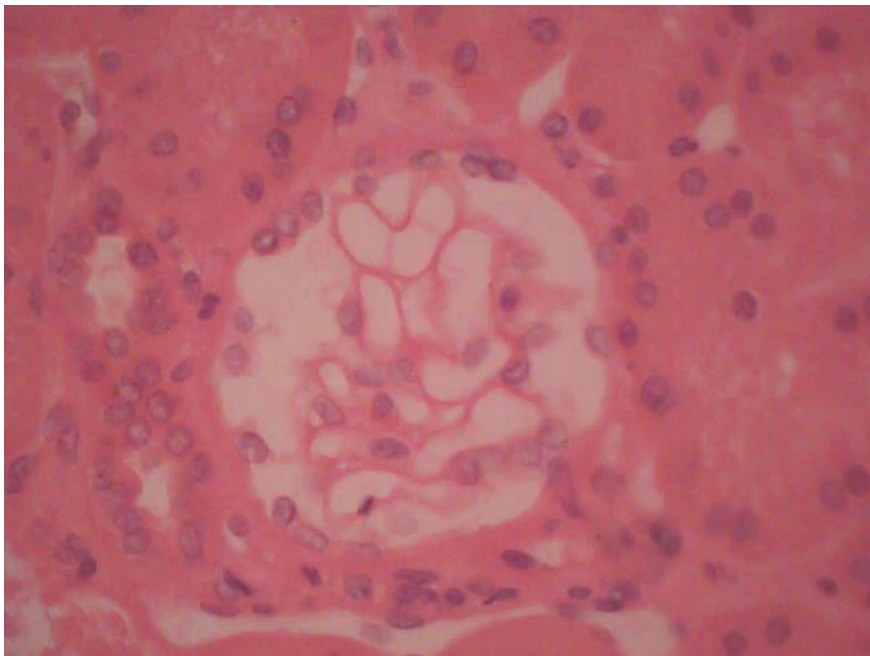**PIGN** in 3 patients

ATN in 5 patients

Interstitial nephritis seen in 18 biopsies.
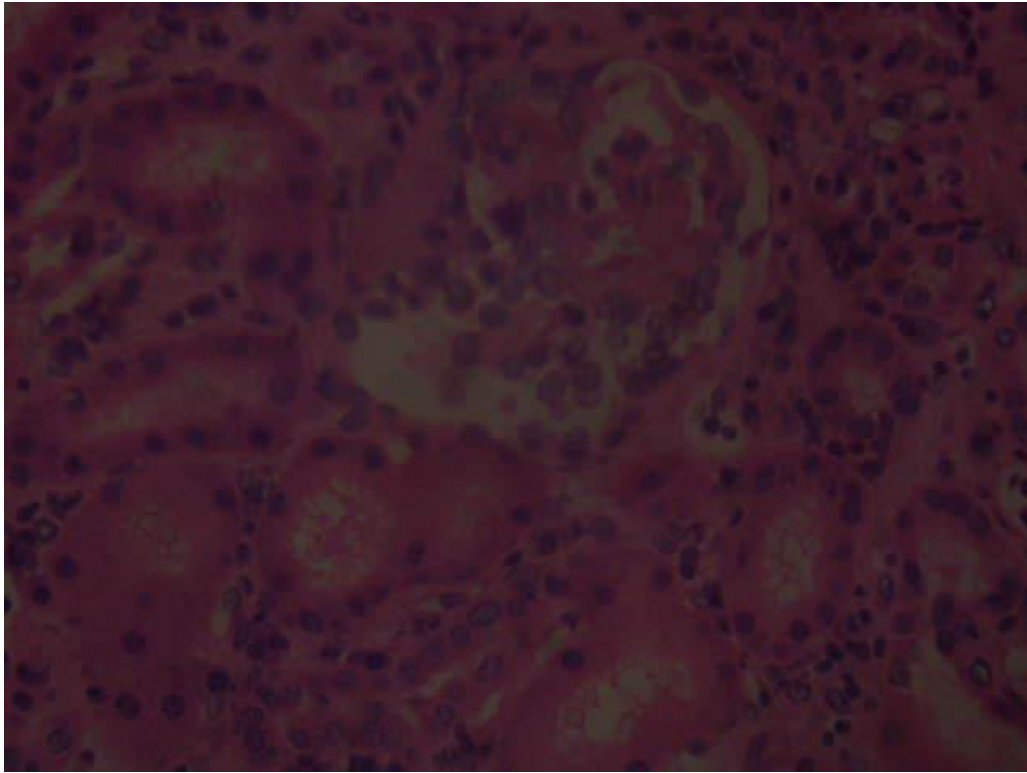
Acute pyelonephritis in 2 biopsies.
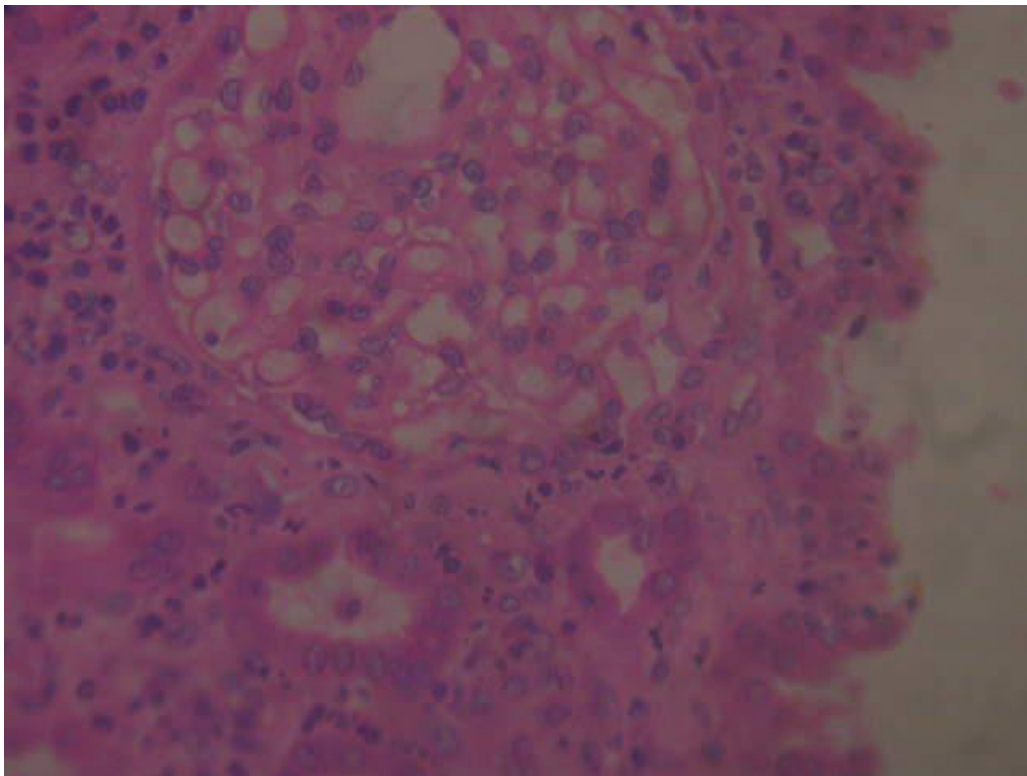
HIVAN (Collapsing FSGS)

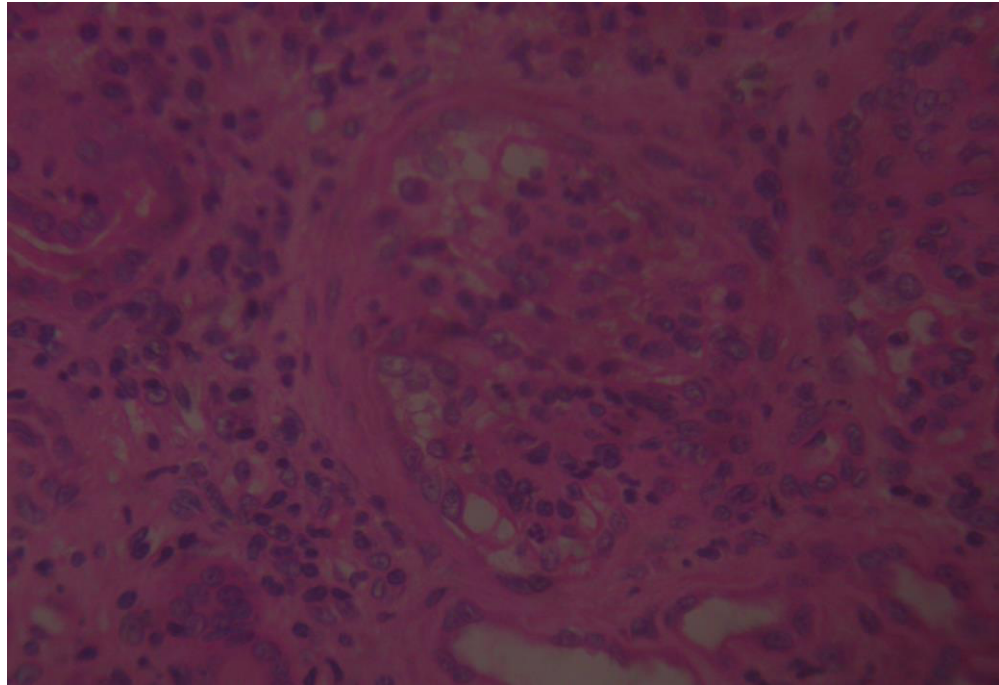# MEMBRANOUS WITH COLLAPSING FSGS

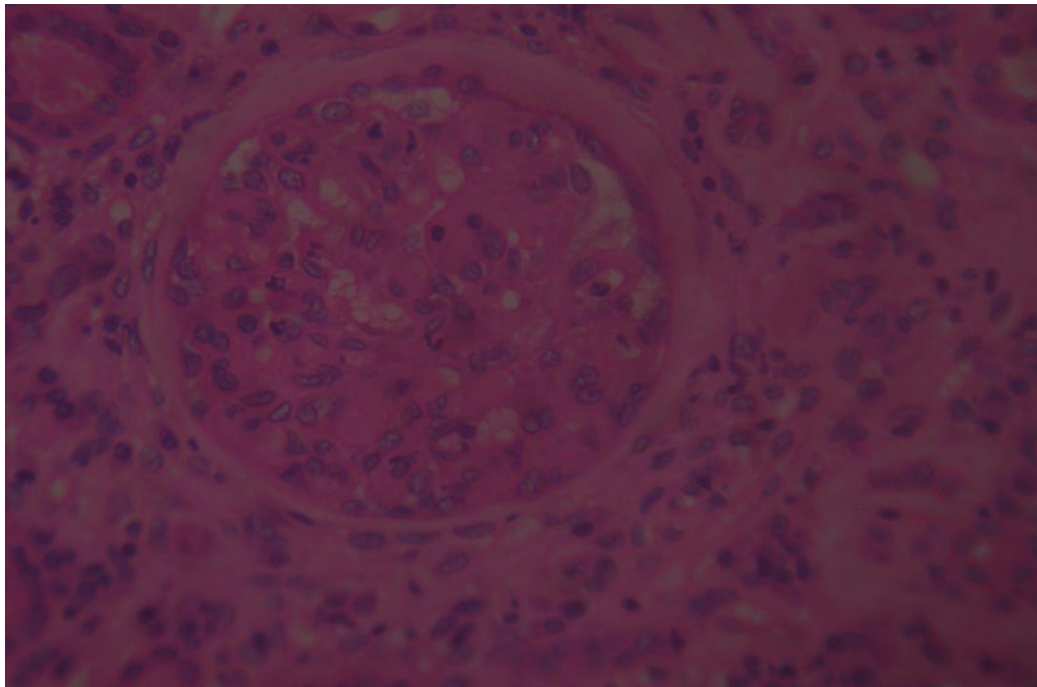**LUPUS NEPHRITIS WITH HIVAN with Tubulocystic Changes**
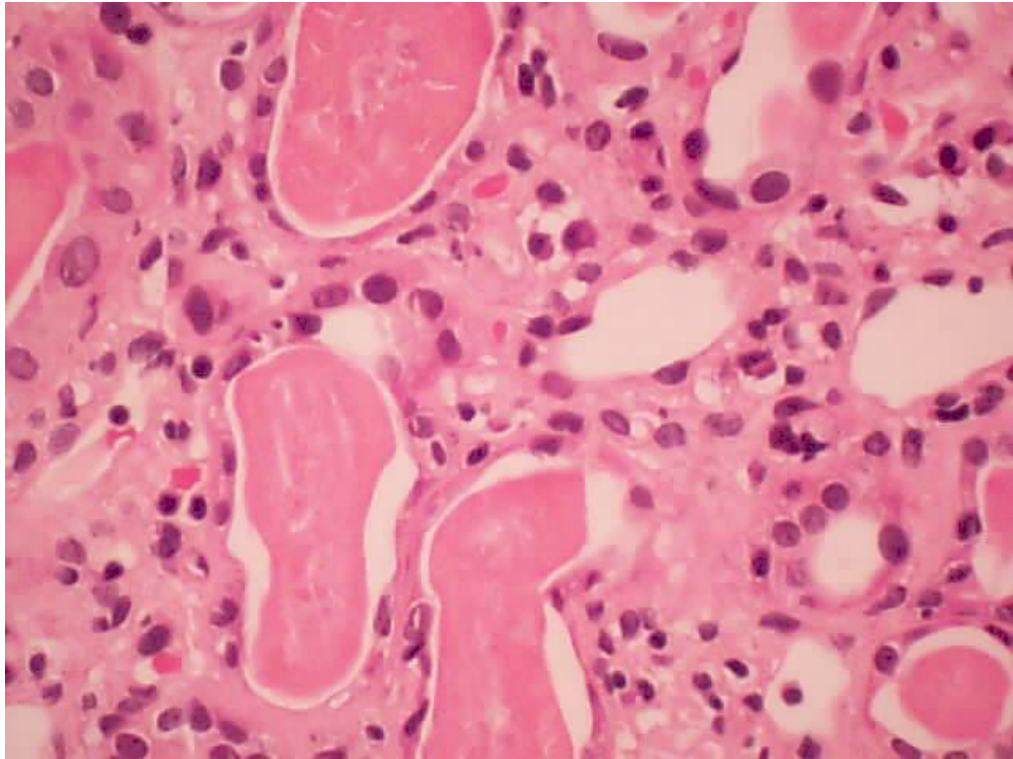

LUPUS WITH MEMBRANOUS NEPHROPATHY

LUPUS NEPHRITIS CLASS IV WITH CRESCENTS

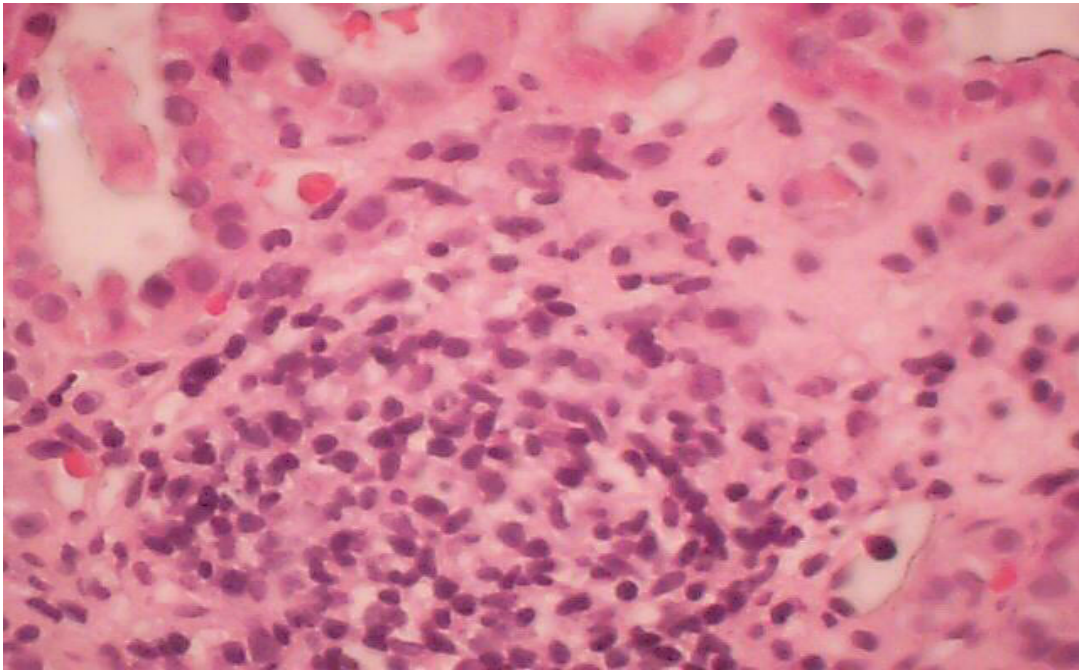**LUPUS NEPHRITIS CLASS IV WITH CRESCENTS WITH PERIGLOMERULAR FIBROS**

RENAL TUBULAR PROTEINACEOUS CASTS IN HIV

TUBULOCYSTIC LESIONS IN HIV

DIFFUSE INTERSTITIAL INFILTRATION

DISCUSSION OF THE STUDY

It is one of the largest studies involving 7363 HIV patients, with a male female ratio of approximately 2:1. Of the total of 7363 screened, 2581 had proteinuria, which corresponds to 35.5%.of the screened, this incidence was compared and found that it very well correlates with the records available from other centres which vary widely up to 30% . Quantification of proteinuria was done in 563 patients, of them 298 had proteinuria above 3oomg/day. It suggests high incidence of significant proteinuria in screened HIV patients.

Out of the 7363 screened HIV patients, 336 were found to have hematuria, constituting about 4.5%. This level of detection of hematuria is not reported in any other studies. 574 patients had renal failure which constitutes about 7.79% of the HIV patients screened and of this 128 patients had evidence of acute kidney injury ARF due to pre renal, ATN and post renal causes constituting of about 1.75%. In contrast the studies of ARF reported by *Peraldi et al* in 1999 and others during the

same period which were around 4 to 5%. The earlier studies reported incidence of ARF up to 20% in pre ART era.

Though good health care facilities are available for early detection of HIV, this high incidence of renal failure in HIV could be attributed to the psychosocial behaviour of the patient and the timing of decision for evaluation and treatment. The incidence of sepsis including due to urinary tract infection was 42 of the 574 followed up patients which constitute of about 7.4%.

Only 72 biopsies were done because of socioeconomic reasons. In this group Diffuse mesangial proliferation was present in 26 renal biopsies and is the major group. The high incidence of this group with DMP could be due to the early evaluation of patients. This is followed by HIVAN in 21 patients, IgA nephropathy in 11 patients and both concomitantly present in 5 patients. This signifies the diversity of acute and chronic glomerular lesions with immune complex deposition.

6 patients who had partial tuft collapse could be explained by 2 factors.1) the progression of HIV renal lesion due to renal tropic viruses not much affected by the ART. 2) There could be arrest of renal lesions of HIVAN at the level when patient started on ART. Further studies may explain this issue. When analyzing with lupus nephritis class 4& 5 with crescents and HIVAN not found in the literature were seen. HUS was not seen in the initially evaluated as well as biopsied group of patients.

Total number on ART in the study group of renal biopsy was 36, of this males were 33, and females were 3 in number, and in the non ART group there were 25 males, 8 females and 1 trans gender. When CD4 count was matched with the biopsied group the range of CD4 cells was 41 to 618 with a mean of 196 .6, median of 168 and with S.D of 123.22 in 36 patients. In the non ART group of 34, 31 had renal failure and the CD4 count in this group was with a range of 41 to 618 cells, mean of 197.45, and median value of 168 with S.D of 126.57. In the other group without renal failure on non ART of 3 patients the range was 78 to 275 and median of 210 and a mean of 187.

RENAL BIOPSY RESULTS

Serial No	Biopsy Result	No of Samples Present
1	Diffuse Mesangial Proliferation	26
2	HIVAN	21
3	Classical FSGS	6
4	IgA Nephropathy	11
5	IgA with HIVAN	5
6	Membranous Nephropathy	2
7	Lupus Nephritis	1
8	Lupus like Nephritis	1
9	Vasculitis	1
10	RPGN -Crescents	3
11	PIGN	3
12	ATN	5
13	Interstitial Nephritis	18
14	Acute Interstitial Nephritis	1
15	Acute Tubulo Interstitial Nephritis	1
16	Sub Acute Interstitial Nephritis	2
17	Acute Pyelo Nephritis	2
18	Chronic Interstitial Nephritis	15
19	TB Granuloma	1
20	Total NO. of Biopsies	72

HIVAN for Statistical Analysis

Null hypothesis (H$_0$): There is no significant difference between HIVAN, Non ART, HIVAN Rt Kidney, HIVAN Lt Kidney, HIVAN RF / CD4, Sr. Creatitine, PCR and Total CD4, HIVAN of the experimental group

One-Sample Test FOR HIVAN WITH KIDNEY SIZE,SE_CREATININE,URINE PCR AND CD4

HIVAN GROUPS					95% Confidence Interval of the Difference	
	t	df	p-value	Mean Difference	Lower	Upper
HIVAN Non ART	8.686	30	.000	197.45161	151.0241	243.8792
HIVAN_Rt Kidney	33.898	20	.000	10.48095	9.8360	11.1259
HIVAN Lt Kidney	46.778	20	.000	10.19190	9.7374	10.6464
HIVAN RF / CD4	6.252	18	.000	253.36842	168.2285	338.5083
Sr. Creatitine	4.670	20	.000	3.29048	1.8208	4.7602
PCR	5.287	20	.000	1.65571	1.0025	2.3090
Total CD4 HIVAN	6.886	20	.000	252.33333	175.8942	328.7725

Interpretation:

Since p-value is LESS than 0.05, we reject the null hypothesis at 5% level of significance. Hence we can conclude that There is a significant difference between HIVAN non art of the experimental group with cd4.

Since p-value is LESS than 0.05, we reject the null hypothesis at 5% level of significance. Hence we can conclude that there is a significant difference between Right kidneys of the experimental group.

Since p-value is LESS than 0.05, we reject the null hypothesis at 5% level of significance. Hence we can conclude that there is a significant difference between left kidneys of the experimental group.

Since p-value is LESS than 0.05, we reject the null hypothesis at 5% level of significance. Hence we can conclude that there is a significant difference between SE_CR, of the experimental group with cd4 count in HIVAN.

Since p-value is LESS than 0.05, we reject the null hypothesis at 5% level of significance. Hence we can conclude that there is a significant difference between, urine pcr of the experimental group in HIVAN.

Since p-value is LESS than 0.05, we reject the null hypothesis at 5% level of significance. Hence we can conclude that there is a significant difference between CD4 VALUES of the experimental group with HIVAN analysed in total.

When CD4 was matched with ART and renal lesions of 36 patients who had done renal biopsy, the CD4 range was 20 to 650 with a median of 160, mean of 200.91 and S.D of 146.44. This group divided into with or without renal failure of 27 and 9 patients respectively. When CD4 was matched without renal failure of 9 patients in ART group the results available was, the range of CD4 cells was 32 to 252, with mean of 162.4 with S.D of 70.4 and median of 160. In the other group with ART, CD4 and renal failure the range of CD4 was 20 to 63, median of 160 and mean of 213.74 with S.D of 163.20.

When these patients were analysed   21 HIVAN patients with CD4 counts, of them 18 were males and 3 were females. The range of CD4 was 41 to 650, median of 178, and mean of 252.33 with S.D of 167.92. Out of 21 HIVAN 19 had renal failure. This group was further divided based upon serum creatinine into three and analyse with CD4.The groups 1.3 to 2 mg s serum creatinine r.creatinine ,>2mg to 4 mg/dl og serum creatinine and above 4 mh/dl of serum creatinine. In the first group of 1.3 to 2 mg/dl the CD4 range was 99 to 650, median of 172, mean of 290.22 and S.D of 208.77. In the second group with serum creatinine of >2mg/dl to up to 4mg/dl the range was 41 to 394, median was 123.5,mean of 172.66 and S.D of 138.22. In the last group of serum creatinine above 4mg/dl the analyzis showed Cd4 range was 160 to 486, median of 260, mean of 291.5 and S.D of 141.78.

CONCLUSIONS

This study is one of the **largest** studies of HIV patients evaluated for Renal lesions

- **7363** HIV patients were screened over a period of two years (2008 to 2010). Of them **4942** were males, **2411** were females and 10 were transgenters and the male female ratio was 2.05 :1

- **Significant Proteinuria** was present in **2582(35.5%)** patients

- **Hematuria** was found in **336 (4.5%)** of patients, of them **18** had macroscopic hematuria.

- **Renal failure** was detected in **574** patients (**7.79%**)

- Acute Kidney Injury was detected in 128 patients **(1.75%)**

- **446** patients had **chronic kidney disease** in Stages **3 - 5** and of this 314(70.41%) were males and 132 (29.59%) were females.

  250 Patients were in Stage 3 CKD, 148 in Stage 4 CKD and 48 in Stage 5 CKD

  14 Patients died of ESRD and one patient is on maintenance hemodialysis.

- **Type 2 Diabetes** was the cause of CKD in 24 patients.

- **Hypertension** was seen in 66 of the 574 patients with renal failure.

- 4 Patients had **Hepatitis B** and 2 had **hepatitis C.**

- **Pyuria** was seen in **1203 (16.33%)** patients of the 7363 screened.

- Urinary tract infection (**UTI**) was documented in 42 of the 574 patients in whom urine culture was done. E.Coli was the commonest organism isolated in 66.66% followed by Pseudomonas and Klebsiella of 16.33% each.

- Of the 72 renal biopsies performed **DMP** was the commonest lesion encountered (35.5%)

- Other common lesions were **HIVAN** (29.1%) and **IgA** Nephropathy (15.49%)

- A rare combination of **Lupus nephritis (class 4&5 with crescents)** and **HIVAN** was seen in one patient

- Statistically significant correlation was observed between CD 4 count and HIVAN in patients who were not on ART.

Early identification of patients with renal lesions will help to prevent progression of kidney disease so it is recommended to screen HIV patients for proteinuria, hematuria and renal insufficiency once in three months. Early initiation of ART is to be considered in those with renal abnormalities.

Infrastructure is required for management of the patients of HIV who develop End Stage Renal Disease (ESRD) and who require renal replacement therapy in the form of dialysis including hemodialysis, peritoneal dialysis and renal transplantation.

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