Brief overview about Chronic Kidney Disease in Human Immunodeficiency Virus Infection

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Background: Acquired immunodeficiency syndrome (AIDS) refers to clusters of life-threatening infections, cancers, and wasting symptoms. Initially, Kaposi's sarcoma and pneumocystis pneumonia are the two disease indicators when AIDS was first reported in the spring of 1981 among groups of homosexual men living in New York City and California. Intriguingly, the immunodeficiency in AIDS is mutually associated with autoimmunity. Indeed, AIDS has characteristics of both immunodeficient disorders and autoimmune diseases. First, patients living with AIDS show the excessive humoral immune response defined by the presence of a variety of antibodies and circulating immune complexes. Despite the higher rates of acute rejection in recipients infected by HIV in relation to those not infected, kidney transplant seems to be a viable renal replacement therapy in HIV patients, but some strategies need to be improved to minimize rejection and manage drug interactions. Immunosuppressive therapies, such as corticosteroids, to dampen the inflammatory response to these complexes at the level of the kidney have been suggested as possible additional strategies for treatment. Many antiretroviral medications are partially or completely eliminated by the kidney and require dose adjustment in CKD. Certain drug classes, such as the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors (NNRTIs), are metabolized by the liver and do not require dose adjustment. Several studies have pointed to HIV infection being an independent risk factor for microalbuminuria. A study done in the United States showed that 11% of HIV-positive patients had microalbuminuria. It was found that the odds were 5 times higher for those with HIV to have microalbuminuria than control patients. Predictors for albuminuria in HIV patients included lower CD4 count, higher viral load, and African-American race

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Introduction

Acquired immunodeficiency syndrome (AIDS) refers to clusters of life-threatening infections, cancers, and wasting symptoms. Initially, Kaposi's sarcoma and pneumocystis pneumonia are the two disease indicators when AIDS was first reported in the spring of 1981 among groups of homosexual men living in New York City and California **(1).** In the same year, persistent defects of cell-mediated immune function characterized by decreased absolute lymphocyte counts, T cell counts, and lymphocyte proliferation were found in community-acquired pneumocystis carinii pneumonia occurred between 1979 and 1981 among 11 young men who were drug abusers

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and homosexuals. In 1983, an American research group led by Gallo and a French research group led by Luc Montagnier independently declared that a novel retrovirus, later renamed human immunodeficiency virus (HIV), might have been infecting people with AIDS. Thirty-five years later, the relationship between HIV and AIDS remains controversial: (1) HIV is the cause of AIDS, a theory proposed by Gallo and Montagnier (. (2) HIV is just a passenger virus and not the cause of AIDS, a hypothesis claimed by Duesberg. And (3) all the available data cannot prove the existence and role of 'HIV' in the development of AIDS, an argument made by the Perth Group **(2).**

The US Centers for Disease Control and Prevention (CDC) has published the list of AIDS-defining clinical conditions as a guideline for AIDS diagnosis. Typical clinical manifestations are opportunistic infections, severe loss of the body weight, Kaposi's sarcoma, fever, and symptoms. Most of the AIDS-defining clinical conditions result from persistent deficiency of innate immunity and cellular immune dysfunction. In fact, low CD4 cell counts and depressed CD4 cell function are predictive of an essential failure of cell-mediated immune system **(3).** Therefore, AIDS has the characteristics of cell-mediated immune defects. Intriguingly, the immunodeficiency in AIDS is mutually associated with autoimmunity. Indeed, AIDS has characteristics of both immunodeficient disorders and autoimmune diseases. First, patients living with AIDS show the excessive humoral immune response defined by the presence of a variety of antibodies and circulating immune complexes. Second, autoimmunity in AIDS is also evident by therapeutic benefits of immunosuppression following solid organ transplantation and bone marrow transplantation **(4)** in AIDS and HIV-infected patients. Third, several clinical trials have shown that HIV vaccines aiming at eliciting broadly neutralizing antibody responses to block HIV infection have yet far from success, principally due to the underestimation of the autoimmunity. Last, deficit of regulatory T cells (Treg) has implicated in the autoimmunity of AIDS patients **(5).**

Regulatory T cells

Treg are a specialized subpopulation of CD4+ T cells for controlling the activation and expansion of immune cells to suppress immune responses. In conditions, such as infection and cancer, Treg prevent excessive immune destruction by modulating host immune responses. Thus, Treg play an important role in the development of autoimmunity and maintenance of immune homeostasis. In theory, Treg may serve the interface of too little of cell-mediated immunodeficiency and too much of antibody-mediated humoral immunity in the AIDS-defining clinical conditions **(6).**

Deficit in the frequency of regulatory T cells

CD4+CD25+ are the cell-surface transmembrane proteins for the characterization and isolation of Treg. CD25, also known as interleukin-2 (IL-2) receptor-a, binds to IL-2 to facilitate the expansion of Treg population. Patients with AIDS have depressed CD4+CD25+ Treg as well as decreased IL-2 levels **(7).** All of these findings indicate that low Treg counts result in autoimmunity in AIDS.

Deficiency in the function of regulatory T cells

Foxp3 is the major transcription factor for the immunosuppressive activity of Treg. Several studies have revealed a decreased expression of Foxp3 in human autoimmune diseases. Similarly, AIDS patients have depressed CD4+CD25+Foxp3+ Treg **(5).** Furthermore, the Treg in AIDS patients show the deficiency in the production of inhibitory cytokines and chemokines such as IL-10 and transforming growth factor-b **(5).** Taken together, AIDS patients have the compromised function of Treg to predispose to autoimmunity.

Toll-like receptors and regulatory T cells

Human toll-like receptors (TLR) are a growing family of type I transmembrane proteins for immune homeostasis. Interestingly, TLR2 and TLR4 are the two members expressed in human Treg to enhance the Treg proliferation and immunosuppression. The decreased TLR4 expression in AIDS/HIV infection is an important predisposing factor to autoimmune disorders **(8).** In summary, defects of Treg in AIDS are evident by the low cell count, low Foxp3 expression, low production of the inhibitory cytokines, and low

TLR expression. All these defects predispose to the occurrence and persistence of autoimmune disorders manifested in AIDS-defining clinical conditions.

Autoimmunity in AIDS patients

Autoimmunity in AIDS patients is generally underestimated and is sometimes even neglected. In contrast, too much attention and too many efforts have focused on the cell-mediated immunodeficiency in AIDS patients. We have spent billions and billions of dollars on HIV vaccines without acknowledging the pivotal role of autoimmune in the development of HIV infection and AIDS. AIDS represents a syndrome of autoimmune disorders rather than immunodeficiency per se. Autoimmune mechanism has long been recognized in the development of AIDS and HIV infection **(9).**

Excess of humoral immune response

B lymphocyte hyperactivation, elevated levels of immunoglobulins and immune complexes, and the presence of autoantibodies **(10)** are three lines of compelling evidence for overreaction of humoral immune response. Autoantibodies in the sera of AIDS patients include antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-erythropoietin antibodies, anti-glomerular basement membrane antibodies, anti-phospholipid antibodies, anti-b2 GPI, anti-DNA, anti-small nuclear ribonucleoproteins (snRNP), anti-thyroglobulin, anti-thyroid peroxidase, anti-myosin, and anti-cardiolipin **(11).** Consequently, the excess of humoral immune responses predisposes AIDS patients to a wide range of autoimmune disorders. The AIDS-related autoimmune disorders comprise systemic lupus erythematosus (SLE), anti-phospholipid syndrome, vasculitis, primary biliary cirrhosis, polymyosits, Graves' disease, idiopathic thrombocytopenic purpura, reactive arthritis, psoriatic arthritis, acute nonspecific arthritis, Sjogren syndrome, and inflammatory myositis **(12).** The relation of B lymphocyte expansion and autoantibody overproduction in HIV-infected patients to clinical autoimmune disease to AIDS defining clinical conditions has yet to be established.

CHRONIC KIDNEY DISEASE IN HIV INFECTION

The prevalence of HIV-associated chronic kidney disease varies geographically and depends on the definition used. In addition to having a higher risk of kidney disease, individuals infected by the virus also present greater speed of progression of renal dysfunction compared to non-infected individuals **(13).**

The introduction of antiretroviral therapy has increased the survival of individuals infected by HIV. However, this decrease in mortality rates has been accompanied by an increase in other related diseases, such as chronic kidney disease, which has become increasingly common in HIV-infected patients and can occur at any stage of HIV infection, even before seroconversion **(15).**These patients have a combination of traditional risk factors, such as advanced age, black ethnicity, diabetes and arterial hypertension, in addition to the factors related to HIV, such as low CD4 lymphocyte count, high viral load, co-infection by the hepatitis C virus, use of injectable drugs, and exposure to antiretroviral therapy **(14).**

Since the treatment for HIV nephropathy may postpone the decline of renal function, it is recommended to screen for the disease regularly by measuring the arterial pressure, evaluating the renal function (creatinine and estimated glomerular filtration rate) and through urine examination to investigate the proteinuria, which is a common manifestation of the disease **(15).**

As a general rule, it is recommended to use antiretroviral drugs with caution in patients with chronic renal disease, avoiding nephrotoxic drugs, and adjusting the dose, with a reduction or extension of the administration period. Some antiretroviral drugs, such as tenofovir, are associated with an increased risk of both the development and progression of chronic kidney disease **(16).** The guidelines recommend avoiding the use of tenofovir if the glomerular filtration rate is less than 60 ml/min/1.73m^2. For patients in use of tenofovir who evolve with a decline greater than 25% in glomerular filtration rate in relation to the baseline renal function, it is recommended to replace the antiretroviral treatment by another one **(16).** There is no

evidence that demonstrates the best dialysis modality for HIV-positive patients. Survival in dialysis patients is similar to that of non-infected patients. There is no recommendation for isolation, nor for the exclusive use of machines in hemodialysis sessions **(16).**

Based on data from retrospective studies, it is known that renal transplantation is highly viable in recipients infected by HIV. One of the major challenges is to achieve therapeutic and non-toxic levels immunosuppressants due to their interaction with antiretroviral drugs. It is recommended to avoid antiretroviral agents that act on the cytochrome P450 pathway so that it is possible to achieve a better therapeutic level of calcineurin inhibitors and decrease the incidence of renal graft rejection; integrase inhibitors are some options in this context. Induction therapy with antithymocyte immunoglobulin should be restricted to patients at a high immune risk of rejection **(17).**

Despite the higher rates of acute rejection in recipients infected by HIV in relation to those not infected, kidney transplant seems to be a viable renal replacement therapy in HIV patients, but some strategies need to be improved to minimize rejection and manage drug interactions **(17).**

EVALUATION OF KIDNEY FUNCTION

An accurate assessment of the kidney function in patients infected by HIV is essential since antiretroviral drugs are eliminated by the kidney and require dose adjustments according to the renal function, in addition to their associated effects, such as nephrotoxicity Therefore, it is recommended to screen for renal disease at the time of diagnosis and start or modification of the antiretroviral therapy **(18).**

Serum creatinine is the biomarker of choice for estimating the glomerular filtration rate in clinical practice, and cystatin C should be considered in cases of patients who received medications that alter the tubular secretion of creatinine, such as ritonavir or sulfamethoxazole-trimethoprim, in addition to providing a better prediction of long-term mortality **(18).**

Several equations have been used to estimate the glomerular filtration rate; CKD-EPI is currently the most noteworthy of them, having been evaluated and considered the most accurate for various populations and recommended as the first method of choice to evaluate renal function by the Guidelines of the European AIDS Clinical Society (EACS). Urine analysis should be performed in all HIV-infected patients to detect the onset or worsening of proteinuria or hematuria, and, if possible, it is recommended to measure the proteinuria (albumin/creatinine or protein/creatinine ratio) **(19).**

Pathogenesis of CKD in HIV infection

CKD is mediated by factors related to the virus host, genetic predisposition, and environmental factors. The question of whether HIV directly infects renal cells is an issue central to pathogenesis. Due to the lack of CD4 and chemokine receptors needed for entry into cells, viral replication is likely restricted. Evidence from transgenic mouse models suggest that expression of single HIV genes can replicate the clinical features (proteinuria, progessive kidney disease) and pathologic features (collapsing glomerulopathy, tubular cell injury) of HIVAN as seen in human patients. Transfection of viral constructs allows renal epithelial cells to produce viral products. Cells transfected with CD4 and CXCR4 chemokine receptors support viral replication. It is still unclear how HIV-1 enters renal cells **(19).** Genetic variability of gp120 seems to influence renal infectivity. Lymphocytes may allow cell infection in a monolayer via transcytosis. Another possible mechanism is transfer of CCR5 between cells (these contain cell surface and cytoplasmic components of the original cell), thus allowing entry of the HIV virus into renal cells without endogenous expression of the co-receptor. Dendritic cells have been found to be involved in binding, dissemination and transfer of HIV in a variety of tissues and may also play a role in infection of renal cells. The dendritic cell C-type lectin receptor DEC-205 has been shown to mediate internalization of HIV into human renal tubular cells. There is increasing evidence to suggest that renal cells may support viral replication **(18).**

Impact of antiretroviral therapy on CKD

Prior to the availability of cART, HIVAN almost uniformly progressed rapidly to ESRD. With the introduction of cART, there has been a decline in the incidence of HIVAN in the USA**.** HIVAN risk was reduced by 60% with the use of cART. A recent study from France described the change in the pattern of renal disease in HIV patients over 15 years since the introduction of ART; HIVAN decreased over the 15 years and classic FSGS emerged as the commonest cause of glomerular disease during 2004 – 2007, occurring in 46.9%. HIVAN occurred more frequently in Black patients with severe immunodeficiency and severe renal failure in this study, while FSGS patients were older, more likely to have received ART and more frequently had cardiovascular risk factors and histologically, had more severe interstitial fibrosis **(20).**

Older guidelines recommend HIVAN as an indication for the initiation of cART, irrespective of the CD4 lymphocyte count. Current HIV guidelines recommend use of cART in all patients with HIV; resource constraints in some regions of the world, for example South Africa recommend cART initiation with CD4 < 350 cells/mL. Epidemiologic data showing the decline in HIVAN and HIV-associated ESKD in the United States after the introduction of ART in 1995 suggest that effective control of viral replication with ART can prevent the appearance of HIVAN. While the evidence for initiating cART in HIV-ICD is inconclusive, this seems to be a feasible approach **(20).**

There have been conflicting reports on the benefit of cART in patients with HIV- ICD. A study done by Szczech et al. found that renal function in patients with lesions other than HIVAN, including immune complex kidney disease did not benefit from ARTs. Two studies in South Africa showed improvement in renal function with cART irrespective of renal histology **(21).**

Immunosuppressive therapies, such as corticosteroids, to dampen the inflammatory response to these complexes at the level of the kidney have been suggested as possible additional strategies for treatment **(21).**

Several studies have demonstrated the overall improvement in kidney function when initiating cART for HIV CKD. The DART study conducted in Uganda and Zimbabwe, showed improvement of GFR by 1.9 – 6 mL/min/ 1.73 m2 after 4 – 5 years of ART, with 2.8% of the 3,316 patients at an eGFR < 30 mL/min/ 1.73 m2 . An improvement in median eGFR by 21% after 2 years on cART was reported in Ugandan patients with HIV CKD. A recent study from Tanzania showed improvement in renal function on ART over a median period of 2 years, with the numbers of patients with eGFR < 90 mL/min/1.73 m2 decreasing from 76% to 29.2% and those with eGFR < 60 mL/min decreasing from 21.1% to 1.1% **(15).**

Many antiretroviral medications are partially or completely eliminated by the kidney and require dose adjustment in CKD. Certain drug classes, such as the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors (NNRTIs), are metabolized by the liver and do not require dose adjustment **(21).** Most of the nucleoside reverse transcriptase inhibitors (NRTIs) are excreted unchanged in the urine and require dose adjustment. The NRTI dose may have to be supplemented following dialysis. Fixed drug combinations should not be used in patients with eGFR below 30 to 50 mL/min/1.73 m2.

Risk factors for developing CKD and ESRD

Several studies have pointed to HIV infection being an independent risk factor for microalbuminuria. A study done in the United States showed that 11% of HIV-positive patients had microalbuminuria. It was found that the odds were 5 times higher for those with HIV to have microalbuminuria than control patients. Predictors for albuminuria in HIV patients included lower CD4 count, higher viral load, and African-American race**.** In another study, older age, black race, hepatitis C infection, and lower CD4 count were independently associated with CKD. Of note, virological suppression was also more common with renal impairment, most likely due to higher blood levels of renal eliminated ARTs **(22).** More recently, a study involving multiple urine collections found the period prevalence of HIV microalbuminuria to be 14%,

with single collection giving a positive predictive value of 74% (suggesting that microalbuminuria is sometimes transient) and a negative predictive value of 98% (suggesting that annual screening is **sufficient to detect persistent albuminuria) (22).** Progression to ESRD has been reported to be more likely when the following parameters are present: high-grade proteinuria, severely reduced eGFR, hepatis B and/C coinfection, diabetes mellitus, extensive glomerulosclerosis, and chronic interstitial fibrosis. Improved renal survival was associated with use of renin angiotensin system blockers and viral suppression. HIVAN patients with two APOL1 high renal variants progressed more rapidly to ESRD in spite of effective viral suppression **(23).**

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