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# The Treatment of HIV-Associated Nephropathy

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## Abstract

Antiretroviral therapy (ART) preserves kidney function in patients with human immunodeficiency virus (HIV)-associated nephropathy (HIVAN). Emerging data also document substantial renal benefits of ART in the general HIV-infected population, which is associated in part with suppression of HIV-1 viral replication. The extent to which the response to ART differs in persons with HIVAN, compared to those with other HIV-associated kidney disorders, is unknown. Beneficial effects of corticosteroids and angiotensin-converting enzyme (ACE) inhibitors on kidney function also are suggested by retrospective cohort studies and uncontrolled trials of patients with HIVAN. Underexposure to ART, or inadequate ART dosing in HIV-infected patients with CKD, may curtail the optimal benefits that may be derived from this therapy.

### Keywords

antiretroviral therapy; HIVAN; angiotensin-converting enzyme inhibitors; prednisone; chronic kidney disease

## Introduction

Recent ART treatment guidelines include HIVAN among the indications to initiate therapy, on the basis of preserved kidney function in association with ART as suggested by observational studies.(1-5) Beneficial effects of corticosteroids and ACE inhibitors also are suggested by uncontrolled trials and retrospective studies in patients with HIVAN,(2,3,6-9) while emerging data from randomized clinical trials and prospective cohort studies in the U.S. and Africa describe substantial renal benefit in association with ART among the general HIV-infected population.(10-16)

The extent to which beneficial effects of ART on kidney function may differ between persons with HIVAN and those with other kidney disorders that are associated with HIV is unknown. Contributions to kidney disease by other co-morbidities that are prevalent among HIV-infected patients, including diabetes, hypertension, and chronic hepatitis C, combined with medication-associated renal toxicity that is specific to, or more common in, HIV renders such a distinction difficult in the absence of biopsy confirmation or a valid case definition of HIVAN. What follows is a review of therapeutic interventions that have been studied in patients with HIVAN,

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including a summary of recent studies from the general HIV-infected population, which help to delineate the effects of ART on kidney function in HIV disease.

In this review, ART refers to combination therapy with three or more drugs, also called highly active antiretroviral therapy (HAART), which first became available in 1995 and includes nucleoside or nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and more recently integrase and cell entry (fusion and CCR5) inhibitors. In earlier studies, kidney function was assessed by changes in serum creatinine. Recent studies have assessed kidney function using creatinine clearance (CrCl) by the Cockcroft-Gault equation, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease equation (MDRD), or by plasma cystatin C concentrations. Weight gain often accompanies successful ART, and large differences between CrCl and eGFR have been demonstrated when actual body weight was used to calculate the former.(17,18) Although none of these renal estimates has been validated in large numbers of HIV-infected patients, consistent renal benefits of ART have been evident across several studies that used different estimates of kidney function.

## Case Definitions and Clinical Correlates of HIVAN

Studies examining treatments for HIVAN have relied on biopsy or case definitions to identify such cases.(4,6,19) Common criteria among these definitions often include: African ancestry; proteinuria and renal function impairment using various thresholds; the absence of acute or obstructive renal disease; and the exclusion of other co-morbidities that might impair renal function, including diabetes, hypertension, and collagen vascular disease.

Biopsy-confirmed HIVAN, as defined by collapsing focal glomerulosclerosis, was present in 83% of patients in a series of 30 HIV-infected South Africans with microalbuminuria identified by screening,(20) and was present in 53 to 79% of HIV-infected patients of African-descent in series from the U.S. and Europe in biopsies performed for various clinical indications.(5, 21-23) HIV-immune complex kidney disease (HIVICK) describes the other large group of HIV-associated glomerulopathies, encompassing IgA nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, and a lupus-like glomerulonephritis.(24) HIVICK is more common among Caucasians, and comprised 6 to 36% of all cases in these series.

In a clinical-pathologic correlation among 152 HIV-infected patients who underwent kidney biopsies at Johns Hopkins University from 1995 to 2004, of whom 91% were African-American, HIVAN was associated with younger age and lower eGFR.(25) The sensitivity and specificity of nephrotic-range proteinuria for HIVAN was 69% and 67%, respectively with positive and negative predictive values of 52% and 80%. The sensitivity and specificity of CD4 counts <200 cells/μL for HIVAN was 74% and 67%, respectively, with positive and negative predictive values of 58% and 82%. Although this study may support the validity of case definitions for HIVAN that include nephrotic-range proteinuria among persons of African descent with advanced HIV disease, it outlines the uncertainty that is associated with this diagnosis in the absence of biopsy.

African-Americans were at increased risk of CKD, and progressed to ESRD at a markedly faster rate compared to whites (hazard ratio 1.9 and 17.7 for progression to CKD and ESRD, respectively, for African-Americans compared to whites) in an analysis of 4259 HIV-infected subjects in the Johns Hopkins Clinical Cohort, who were followed for a mean of 4.5 years since 1990.(26) Among the 284 individuals in this cohort who had stage 3 CKD, the rate of progressive kidney disease did not differ between those who did or did not have a kidney biopsy, or among the 27 African-American subjects who underwent a kidney biopsy, regardless of whether HIVAN was present. Hence, the possibility of confounding by factors associated

with race may complicate attempts to distinguish the natural history of HIVAN from that of other kidney diseases in HIV-infected patients.

## Corticosteroids for the Treatment of HIVAN

Beneficial effects of corticosteroids on kidney function in patients with HIVAN are suggested by retrospective observational studies and uncontrolled trials that were completed before, or soon after, the earliest availability of HAART. In a single-arm, prospective trial of prednisone (60 mg/d for 2 to 11 weeks) among 20 consecutive patients with HIVAN (17 biopsy-confirmed, 3 by case definition) from a single center between 1992 and 1996, substantial reductions in serum creatinine and proteinuria were observed.(6) Retreatment for progressive azotemia that developed in 5 patients after prednisone withdrawal was again associated with substantial reductions in serum creatinine in these patients.

Corticosteroids also were examined in four retrospective cohorts of patients with HIVAN.(3, 7,8,27) In 102 biopsy-confirmed cases from 18 hospitals in France between 1984 and 1996, prednisone use (1 mg/kg for 2 to 6 weeks) was associated with longer renal survival before hemodialysis (0.29 relative risk (RR) for progression to dialysis with prednisone).(7) In a single-center study of 21 patients with biopsy-confirmed HIVAN between 1994 and 1997, prednisone (60 mg/d for one month) was associated with a lower rate of progressive kidney disease (0.2 RR for progressive azotemia with prednisone), so that none of the 13 prednisone-treated patients progressed to dialysis, compared to 3 of the 8 patients who did not receive prednisone who did progress.(8) A substantial reduction in interstitial inflammation was evident in one of these prednisone- treated patients when pre- and post-treatment biopsies were compared.(28) In a third study of 19 biopsy-confirmed cases of HIVAN between 1993 and 1998, prednisone and protease inhibitor use was each associated with a slower rate of CrCl decline (−3.32 vs −5.57 mL/min/month, with and without prednisone, respectively; −0.08 vs −4.3 mL/min/month, with and without a protease inhibitor, respectively).(3) Finally, among 31 patients with HIVAN who were followed for at least 12 months between 1996 and 1999, significantly longer renal survival before ESRD was evident in those patients who received both prednisone and ART, compared to ART alone, or those who received neither prednisone nor ART (median renal survival 26, 6, and 3 months, respectively).(27)

Where reported, prednisone was tapered over 2 to 26 weeks in these studies, for a total duration of 2 to 9 months.(6-8) Prednisone was not associated with a higher incidence of infection in the one study in which infection risk was assessed,(8) but prednisone was associated with a higher risk of avascular necrosis, involving mainly the femoral head, in other studies among HIV-infected patients.(29,30)

## ACE Inhibitors for the Treatment of HIVAN

Fosinopril was associated with longer renal survival before ESRD (479.5 vs.146.5 days) when examined in a prospective, non-randomized, single-center trial of 44 consecutive patients with biopsy-confirmed HIVAN and proteinuria who enrolled between 1993 and 1995.(9) In this study, 4 of 28 patients who received fosinopril progressed to ESRD over 5 years, compared to all of the 17 patients who progressed and did not receive fosinopril.

In a retrospective analysis of 18 patients with biopsy-proven HIVAN before 1996, the use of captopril and reverse transcriptase inhibitors each was independently associated with a longer mean renal survival before ESRD (156 vs 37 days for captopril use vs non-use, respectively) in multivariable models adjusted for age, CD4 cell counts, serum creatinine, and urine protein-to-creatinine (UPC) ratio at the time of biopsy.(2)

## Antiretroviral Therapy for the Treatment of HIVAN

Case reports and case series describe dramatic improvements in renal function in association with ART.(31-34) In addition to the aforementioned renal benefits of ART in studies that also examined prednisone and ACE inhibitors, ART was associated with a longer time to renal replacement therapy among 42 patients with biopsy-confirmed HIVAN, but not among 47 patients with biopsy changes other than HIVAN, in a multi-center series of subjects who underwent kidney biopsy.(5)

ART was associated with a 60% risk reduction for HIVAN in the Johns Hopkins Clinic Cohort. In this analysis, in which 30 of the 135 (22%) HIVAN cases were biopsy-confirmed, an increased risk of HIVAN also was associated with low CD4 cell counts (RR 3.5 with <200 cells/μL) and high HIV RNA levels (RR 3.0 with HIV RNA >100,000 copies/mL).(4) ART was not associated with any apparent renal benefits in patients with HIVAN, however, among 5147 black patients who received care in eight HIV treatment centers in the United Kingdom between 1998 and 2004, in which 29 of the 58 (50%) HIVAN cases were biopsy-confirmed. (19)

## ART and Kidney Function in the General HIV-infected Population

Evidence of both kidney function preservation and improvement in association with ART is accumulating from large prospective cohort studies and randomized clinical trials. Although the assessment of renal function was not a primary objective in any of these studies, many of them included pre-specified renal outcomes as secondary objectives.

In a case-control study of the multicenter, observational HIV Outpatient Study, ART use for at least 56 days was associated with a lower risk of CKD, and this protective effect was more pronounced among patients with nadir CD4 counts <200 cells/μL.(10) In this study, 39 of the 80 CKD cases were African-American patients, and 15 of these were attributed to HIVAN. Clinically significant kidney disease developed in 9 of 2720 subjects (0.2 events/100 person-years) who were randomized to interrupt ART in the drug conservation arm of the multicenter Strategies for Management of Antiretroviral Therapy (SMART) Study, compared to 2 cases in 2752 subjects (0.1 events/100 person-years) who were randomized to continue, or initiate, ART in the viral suppression arm.(11) African-Americans comprised 29% of the participants in this study. In a subset of these subjects, a sustained increase in cystatin C (≥0.15 mg/dL) was evident within the first month of randomization in the drug conservation compared to the viral suppression arm.(35) Similarly, a significant decline in kidney function was observed among HIV-infected Ugandans who were randomized to weekly intermittent ART (7 days on/ 7 days off ART), compared to stable function in subjects who were randomized to a shorter treatment interruption (5 days on/2 days off ART), or to continuous ART (average CrCl change of −12.4, +4.6, and +1.0 mL/min/year for each respective arm).(16) Participants in this study had achieved viral suppression in response to at least 3 months of ART before randomization, and were followed for 72 weeks. These studies provide consistent evidence of kidney function preservation in association with ART.

Evidence of kidney function improvement in association with ART in patients with renal insufficiency also is accumulating. ART was associated with improved kidney function in subjects with stage 2 or greater CKD at baseline (eGFR change of 2.8 mL/min/1.73 $m^2$ per year) in participants of the Longitudinal Linked Randomized Trials (ALLRT), a multi-center, prospective cohort of HIV-infected subjects who were also enrolled in randomized clinical trials or treatment strategies of ART in the AIDS Clinical Trials Group (ACTG), of whom 30% were African-American.(12) In this cohort, improved kidney function was associated with HIV-1 viral suppression in subjects with <200 CD4+ cells/μL (+9.2 mL/min/1.73 $m^2$ over 160

weeks), and was more pronounced in subjects with greater baseline renal impairment (+21.6 mL/min/1.73 $m^2$ with stage 3 CKD), but these improvements did not differ according to race.

The median CrCl rose from 63 to 76 mL/min in the Ugandan Home-Based AIDS Care trial of 508 subjects with symptomatic or advanced HIV disease who survived for at least 24 months after initiating ART, and greater improvement was also associated with greater baseline renal impairment (+23 mL/min in subjects with baseline CrCl <50 compared to >50 mL/min).(13) In the Development of Antiretroviral Therapy Trial (DART), a randomized trial that compared clinical and laboratory monitoring of ART versus clinical monitoring alone in 3316 HIV-infected, ART-naïve, sub-Saharan Africans, kidney function improvement was also associated with greater baseline renal impairment.(14) Despite these strong and consistent renal benefits, a small number of subjects with normal kidney function at baseline progressed to CKD stage 3 or greater in these studies (1.9% and 1.6% of subjects in ALLRT and DART, respectively).(12,14)

In keeping with these observations, HIV-infected patients on ART were more likely to exhibit either rapid kidney function improvements or declines, compared to HIV-uninfected individuals, in the prospective, multi-center Fat Redistribution and Metabolic Change in HIV Infection Cohort of 554 HIV-infected subjects on ART, and 230 HIV-uninfected controls.(15) In this study, 26% and 18% of HIV-infected subjects exhibited either a change in eGFR greater than, or less than, 3 mL/min/1.73 $m^2$ per year, respectively, compared to 6% and 13% of controls, where eGFR was estimated by plasma cystatin C over approximately five years. Kidney function improvement in this study was associated with HIV-1 viral suppression, while declining kidney function was associated with higher baseline HIV RNA plasma concentrations and increases in HIV RNA over time.

Less is known about the effects of ART on proteinuria. UPC was measured annually among 2857 ART-treated subjects in the ALLRT cohort, wherein 16% and 3% of subjects had an initial UPC ≥0.2 and ≥1, respectively.(36) Older age, female sex, lower eGFR, lower CD4 cell counts, higher plasma HIV RNA concentrations, diabetes, hypertension, and hepatitis C co-infection were each independently associated with UPC ≥0.2; African ancestry was associated with UPC ≥1, but not with lower levels of proteinuria. Although UPC did not change over a median of three years among the entire cohort, a significant decline in proteinuria (UPC change of −0.27/year) was evident among subjects with an initial UPC ≥1. Substantial declines in albuminuria also were observed in 5 of 7 subjects with macroalbuminuria (≥3.4 mg albumin/mmol creatinine) at baseline, in a substudy of a multi-center, randomized clinical trial of ART (ACTG protocol 384/5007s).(37)

These data suggest a general, detrimental effect of HIV viral replication on kidney function that may not be limited to HIVAN. Reductions in proteinuria with ART may be limited to persons with heavy proteinuria or macroalbuminuria.

## ART Exposure and Dosing Adjustments in Patients with CKD

Despite substantial improvements in survival in association with ART among patients with ESRD on chronic dialysis, ART underexposure or inadequate ART dose adjustments in patients with CKD may diminish the benefits that would otherwise have been derived from this therapy. Low rates of ART use have been documented in cross-sectional studies of patients with CKD and among chronic dialysis patients.(38-41) In one such analysis of 1041 HIV-infected U.S. veterans with CKD stage 3 or greater, ART exposure was inversely associated with eGFR (14%, 24%, and 64% less ART exposure with eGFR 30 to 59, 15 to 29, and <15 mL/min/1.73 $m^2$, respectively, compared to ≥60 ml/min/1.73 $m^2$) despite adjusting for sociodemographic and clinical characteristics.(41) In this study, more ART dosing errors were

also observed among patients with CKD (3.4% vs 0.2% with and without CKD, respectively). ART underexposure or dosing errors contributed to 22.2% to 35.5% of the excess mortality that was observed among patients with different levels of CKD. Incorrect ART dosing also was independently associated with a lower two-year survival in a multi-center analysis of 129 HIV-infected, hemodialysis patients from France.(42)

On the basis of many of the above cited studies, the HIV Medicine Association and the Infectious Diseases Society of America recommended that all patients with HIVAN should receive ART. If renal function does not improve,(43) the addition of ACE inhibitors or angiotensin receptor blockers and/or prednisone (at a dose of 1mg/kg/day up to a maximum dose of 80 mg/day for 2 months, followed by a 2- to 4-month taper) should be considered. Because most studies of ACE inhibitors and prednisone for HIVAN were completed prior to the availability of HAART, much less is known about their effects on kidney function in the context of ART.

Dose adjustments for current ART medications were recently summarized.(43-45) With the exception of abacavir, dose reductions are generally indicated for nucleoside antagonists but not for other antiretroviral agents; some experts recommend against the use of tenofovir in patients with CrCl <60 mL/min.(44)

## Conclusions

Just as ART has substantially altered the natural history of HIV disease, it also has modified the course of kidney disease in HIVAN. The beneficial effects of ART on kidney function are probably not limited to HIVAN, however, and may be mediated in part by HIV-1 viral suppression. Improved survival has resulted in an increased prevalence of CKD among HIV-infected patients, who remain at a higher risk for progression to ESRD despite ART. Future studies will be necessary to delineate any differences in the natural history or the response to therapy with ART in patients with HIVAN, compared to other prevalent or HIV-associated kidney disorders. A better understanding of the role of other therapies, including corticosteroids and ACE inhibitors, is also necessary. Current evidence justifies aggressive and vigilant use of ART in patients with HIVAN. The benefits of ART on kidney disease may not be limited to persons with HIVAN.

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**Table 1**

A summary of trials examining prednisone, ACEI, and HAART therapy in patients with HIVAN and in the general HIV-infected population. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ART, antiretroviral therapy; ART-STI, antiretroviral therapy with staggered treatment interruption; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HIVAN, HIV-associated nephropathy; HIVICK, HIV-associated immune-complex disease; pVL, plasma viral load; RCT, randomized clinical trial; UPC, urine protein-to-creatinine ratio.

| Ref | Study Design | Study Subjects | Intervention | Number of Subjects | Main Results | Comment |
|---|---|---|---|---|---|---|
| 6 | Prospective, Single-arm trial | HIVAN by biopsy or case definition | Prednisone | 20 | Prednisone use was associated with average reductions in serum creatinine (from 8.1 to 3.0 mg/dL) and proteinuria (from 9.1 to 3.2 g/d). | Large effects of prednisone were suggested by this uncontrolled study. |
| 7 | Retrospective, multi-center cohort study | HIVAN by biopsy | Prednisone | 102 | Prednisone use was associated with a 71% risk reduction in progression to renal replacement therapy in multivariable analysis. | Although selection or ascertainment bias may limit the results of these studies, consistent effects of prednisone were suggested across several studies. |
| 9 | Retrospective cohort study | HIVAN by biopsy | Prednisone | 21 | Prednisone use was associated with an 80% risk reduction for progressive azotemia, and an average 5.5 g/d reduction in proteinuria. | |
| 3 | Retrospective cohort study | HIVAN by biopsy or case definition | Prednisone & ART | 19 | Prednisone and ART use each was associated with slower rates of CrCl decline. | |
| 26 | Retrospective cohort study | HIVAN by biopsy | Prednisone & ART | 31 | Prednisone and ART use were associated with prolonged renal survival (median renal survival 26, 6, and 3 mo in association with prednisone plus ART, ART alone, and neither treatment, respectively). | Published in abstract form. |
| 9 | Prospective, non-randomized trial | HIVAN by biopsy | ACEI | 44 | ACEI use was associated with prolonged renal survival (median renal survival 479.5 vs 147.5 days in fosinopril-treated subjects vs controls, respectively). | As with studies of prednisone, similar limitations apply to studies of ACEI for HIVAN. |
| 2 | Retrospective, case-control study | HIVAN by biopsy; cases/controls: with/without ACEI use, respectively | ACEI | 9 cases<br>9 controls | ACEI use was associated with prolonged renal survival (average renal survival 156 vs 37 days in captopril-treated subjects vs controls, respectively). | |
| 5 | Retrospective, multi-center cohort study | HIVAN by biopsy | ACEI & ART | 42 HIVAN<br>47 non-HIVAN lesions | ACEI use was associated with prolonged renal survival among all | Non-HIVAN lesions included 32 cases of |

| Ref | Study Design | Study Subjects | Intervention | Number of Subjects | Main Results | Comment |
|---|---|---|---|---|---|---|
| | | | | | patients. ART use was associated with a 76% risk reduction for progression to renal replacement therapy among patients with HIVAN, but not among patients with biopsy lesions other than HIVAN. | HIVICK; in the remaining cases the observed pathology was due to other comorbidities, medication toxicities, or processes unrelated to HIV. |
| 4 | Retrospective cohort study | HIV-infected patients; HIVAN defined by biopsy or case definition | ART | 3882 HIV-infected<br>135 HIVAN | ART use was associated with a 60% risk reduction in incident HIVAN in multivariable analysis. | The first large cohort study to demonstrate renal benefits of ART. |
| 19 | Retrospective, multi-center cohort study | HIVAN by biopsy or case definition | ART | 58 | No benefit of ART use on renal survival among patients with HIVAN. | |
| 10 | Retrospective case-control study from multi-center cohort | Cases/controls: HIV-infected patients with/ without CKD, respectively | ART | 108 cases<br>314 controls | ART use reduced the risk of CKD by 50%. | |
| 11,34 | Prospective, multi-center RCT | HIV-infected patients with >350 CD4+ cells/μL | ART-STI | 5472 | ART-STI was associated with a greater risk of CKD (hazard ratio 4.5) and sustained increases in cystatin C. | In this landmark study, ART was associated with significant benefits in clinical events that were not thought to be a direct consequence of HIV infection. |
| 16 | Prospective RCT | HIV-infected patients with >3 mo ART and pVL <50 copies/mL | ART-STI | 151 | Intermittent weekly ART (7 days on/7days off) was associated with a greater rate of CrCl decline than continuous ART or intermittent ART (5 days on/2 days off). | Published in abstract form. |
| 12 | Prospective, multi-center cohort study | ART-naïve or -experienced HIV-infected subjects receiving ART through one of several RCTs | ART | 1776 | ART use was associated with improved eGFR over time among subjects with CKD, and greater eGFR improvement was associated with lower baseline eGFR. Increased eGFR was associated with pVL suppression among subjects with CKD stage 2 or greater who had <200 CD4 cells/ μL at baseline. | Greater improvement in kidney function was associated with greater baseline renal dysfunction, as observed in this and the subsequent 2 studies. Suppression of pVL was associated with renal function improvement, but only among subjects with low baseline CD4 cell counts. |
| 13 | Prospective, multi-center, non-randomized trial | ART-naïve, symptomatic, HIV-infected subjects initiating ART | ART | 508 | Improved CrCl from baseline among patients who survived at least 24 months; greater CrCl | |

| Ref | Study Design | Study Subjects | Intervention | Number of Subjects | Main Results | Comment |
|---|---|---|---|---|---|---|
| | | | | | improvement was associated with lower baseline CrCl. | |
| 14 | Prospective, multi-center, non-randomized trial | ART-naïve HIV-infected patients initiating ART | ART | 3316 | Greater eGFR improvement was associated with lower baseline eGFR. | |
| 15 | Prospective, multi-center cohort | HIV-infected patients on ART and HIV-uninfected controls | ART | 554 HIV-infected 230 controls | HIV-infected patients were at infected higher risk of either a significant increase or decline in eGFR (defined as -3 or +3 mL/min/ year, respectively) compared to controls. Decline in eGFR was associated with higher pVL, and increased eGFR was associated with suppression of pVL. | Unlike above study, suppression of pVL was associated with renal function improvement, but this change did not depend on CD4 cell count. |
| 35 | Prospective, multi-center cohort study | ART-naïve or -experienced HIV-infected subjects receiving ART through one of several RCTs | ART | 2857 | Proteinuria declined over time in ART-treated subjects with initial UPC ≥1, but not among subjects with UPC ≥0.2 but <1. | Beneficial effects of ART on proteinuria may be limited to persons with heavy proteinuria or macroalbuminuria. |
| 36 | Prospective multi-center RCT | HIV-infected, ART-naïve patients without renal insufficiency initiating ART | ART | 68 | Reductions in albuminuria in association with ART were observed in 5 of 7 subjects with macroalbuminuria (≥3.4 mg albumin/mmol creatinine) at baseline. | |

## Table 2
### Antiretroviral dosing guidelines with renal insufficiency

Dose adjustments for renal insufficiency are not necessary for non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, etravirine, nevirapine); protease inhibitors (atazanivir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saqinavir, tipranavir); CCR5 antagonists (maraviroc); fusion inhibitors (enfuvirtide); or integrase inhibitors (raltegravir). Table adapted from U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents for HIV-1-Infected Adults and Adolescents. (46) Abbreviations: CAPD, chronic ambulatory peritoneal dialysis; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HD*, dose after hemodialysis.

| Antiretroviral Agent | Daily Dose | CrCl (mL/min) | Dose |
|---|---|---|---|
| **Abacavir** (ZIAGEN) | 300 mg twice daily | No dosage adjustment necessary | |
| **Didanosine** (VIDEX EC) | >60 kg: 400 mg daily | 30-59<br>10-29<br><10<br>CAPD or HD | 200 mg<br>125 mg<br>125 mg<br>125 mg |
| | <60 kg: 250 mg daily | 30-59<br>10-29<br><10<br>CAPD or HD | 125 mg<br>125 mg<br>Not recommended<br>Not recommended |
| **Didanosine** oral solution (VIDEX) | >60 kg: 200 mg twice daily or 400 mg daily | 30-59<br>10-29<br><10<br>CAPD or HD | 200 mg<br>150 mg<br>100 mg<br>100 mg |
| | <60 kg: 250 mg twice daily or 125 mg daily | 30-59<br>10-29<br><10<br>CAPD or HD | 150 mg<br>100 mg<br>75 mg<br>75 mg |
| **Emtricidabine** (EMTRIVA) | 200 mg oral capsule daily | 30-49<br>15-29<br><15<br>or HD* | 200 mg q 48h<br>200 mg q 72h<br>200 mg q 96h<br>200 mg q 96h |
| | 240 mg (24 mL) oral solution daily | 30-49<br>15-29<br><15<br>or HD* | 120 mg q 24h<br>80 mg q 24h<br>60 mg q 24h<br>60 mg q 24h |
| **Lamivudine** (EPIVIR) | 300 mg daily or 150 mg twice daily | 30-49<br>15-29<br>5-14<br><5<br>or HD* | 150 mg q 24h<br>150 mg ×1 then 100 mg q 24h<br>150 mg ×1 then 50 mg q 24h<br>150 mg ×1 then 25 mg q 24h<br>150 mg ×1 then 25 mg q 24h |
| **Stavudine** (ZERIT) | >60 kg: 40 mg twice daily | 26-50<br>10-25<br>or HD* | 20 mg q 12h<br>20 mg q 24h<br>20 mg q 24h |
| | <60 kg: 30 mg twice daily | 26-50<br>10-25<br>or HD* | 15 mg q 12h<br>15 mg q 24h<br>15 mg q 24h |

| Antiretroviral Agent | Daily Dose | CrCl (mL/min) | Dose |
|---|---|---|---|
| **Tenofovir** (VIREAD)¶ | 300 mg daily | 30-49<br>10-29<br>ESRD<br>or HD* | 300 mg q 48h<br>300 mg twice weekly<br>300 mg weekly<br>300 mg weekly |
| **Zidovudine** (RETROVIR) | 300 mg twice daily | < 15<br>or HD* | 300 mg q 24h<br>300 mg q 24h |
| **Combination Medications** | **Daily Dose** | **CrCl (mL/min)** | **Dose** |
| **Abacavir + Lamivudine** (EPZICOM) | 1 tablet daily | Not recommended for CrCl <50 | |
| **Tenofovir + Emtricitabine** (TRUVADA)¶ | 1 tablet daily | 30-49<br><30 | 1 tablet q 48h<br>Not recommended |
| **Efavirenz + Tenovovir + Emtricidabine** (ATRIPLA)¶ | 1 tablet daily | Not recommended for CrCl <50 | |
| **Zidovudine + Lamivudine** (COMBIVIR) | 1 tablet twice daily | Not recommended for CrCl <50 | |
| **Zidovudine + Lamivudine + Abacavir** (TRIZIVIR) | 1 tablet daily | Not recommended for CrCl <50 | |

¶Some experts recommend against prescribing for eGFR <60 mL/min/1.73 $m^2$.