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[Intervention Review]

Interventions for HIV-associated nephropathy

Ismail Yahaya^{1,2}, Olalekan A Uthman³, Muhammed Mubashir B Uthman⁴

¹Save The Youth Initiative, Kaduna, Nigeria. ²Department of Public Health Sciences, Institution for Health Sciences, Mid-Sweden University, Sundsvall, Sweden. ³Centre for Evidence-Based Health Care, Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa. ⁴Epidemiology and Community Health Department, University of Ilorin Teaching Hospital, Ilorin, Nigeria

Contact address: Ismail Yahaya, Save The Youth Initiative, PO Box 3951, Kaduna North, Kaduna, Nigeria. illyahaya@yahoo.com.

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ABSTRACT

Background

Human immunodeficiency virus-associated nephropathy (HIVAN) is the most common cause of end stage kidney disease (ESKD) in human immunodeficiency virus-1 (HIV-1) serotype patients and it mostly affects patients of African descent. It rapidly progresses to ESKD if untreated. The goal of treatment is directed toward reducing HIV-1 replication and/or slowing the progression of chronic kidney disease. The following pharmacological agents have been used for the treatment of HIVAN: antiretroviral therapy, angiotensin-converting enzyme inhibitors (ACEi), steroids and recently cyclosporin. Despite this, the effect of each intervention is yet to be evaluated.

Objectives

To evaluate the benefits and harms of adjunctive therapies in the management of HIVAN and its effects on symptom severity and all-cause mortality.

Search methods

In January 2012 we searched the Cochrane Renal Group's Specialised Register, AIDS Education Global Information System (AEGIS database), ClinicalTrials.gov, the WHO International Clinical Trials Registry Portal, and reference lists of retrieved articles without language restrictions. In our original review we searched CENTRAL, MEDLINE, EMBASE, and AIDSearch, in addition to contacting individual researchers, research organisations and pharmaceutical companies.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs of any therapy used in the treatment of HIVAN.

Data collection and analysis

We independently screened the search outputs for relevant studies and to retrieve full articles when necessary. For dichotomous outcomes results were to be expressed as risk ratios with 95% confidence intervals, and for continuous scales of measurement the mean difference was to be used.

Main results

We identified four relevant ongoing studies: one is still ongoing; two have completed recruitment but are yet to be published; and the fourth study was suspended for unspecified reasons. No completed RCTs or quasi-RCTs were identified. We summarised and tabulated the data from the observational studies, however no formal analyses were performed.

Authors' conclusions

There is currently no RCT-based evidence upon which to base guidelines for the treatment of HIVAN, however three ongoing studies have been identified. Data from observational studies suggest steroids and angiotensin-converting enzyme inhibitors appear to improve kidney function in patients with HIVAN, however no formal analyses were performed in this review. This review highlights the need for good quality RCTs to address the effects of interventions for treating this group.

PLAIN LANGUAGE SUMMARY

Interventions for treating HIV-associated nephropathy

HIV-associated nephropathy (HIVAN) is a kidney disease common among HIV positive patients, especially patients of African origin. The condition rapidly deteriorates if left untreated. Various treatment options exist, but the benefit of each is unknown. These include: antiretroviral therapy, steroids, angiotensin-converting enzyme inhibitors (ACEi) and cyclosporin. The aim of this review was to determine the benefits and harms of each treatment option. No completed randomised control trials (RCT) of any interventions for HIVAN were found and so the effects of the treatment options could not be evaluated. However, the results of observational studies identified showed that steroids and ACEi were beneficial in improving the kidney functions of patients. We await the results of three ongoing studies, however more RCTs are needed.

BACKGROUND

Human immunodeficiency virus (HIV)-infected patients are at risk for developing several types of chronic kidney disease (CKD), of which HIV-associated nephropathy (HIVAN) is the most prevalent (Kopp 2003). HIVAN is a kidney syndrome in HIV-1 seropositive patients, characterized by heavy proteinuria, kidney dysfunction and rapid progression to kidney failure (Lu 2005). It was initially described in 1984 by Rao 1984 who reported a pattern of sclerosing glomerulopathy in HIV-1 seropositive patients in New York City. It is now the third leading cause of end-stage kidney disease (ESKD) in African Americans between the ages of 20 and 64 years (Lu 2005). It was initially the most common cause of ESKD in HIV-1 seropositive patients (Lu 2005), but recent studies now suggest non-HIVAN disease especially hypertensive vascular disease (Berliner 2008; Estrella 2006).

Most patients affected with HIVAN are of African descent. Blacks are 12 times more likely to develop HIVAN than non-black patients (Abbott 2001). In the United States, the current prevalence of HIVAN is probably underestimated, since the US Renal Data System (USRDS) only accounts for cases that have progressed to ESKD (Abbott 2001). Even though exact epidemiologic data are missing because of the use of different screening techniques, CKD in HIV infected patients is a common and clinically relevant finding (Roling 2006).

The prevalence of CKD in the various stages of HIV infection is difficult to assess. Proteinuria and elevated creatinine level have been found in 7% to 32% of HIV-seropositive patients and were associated with an increased rate of death in a study of 2038 female HIV-infected patients (Szczzech 2004b). The estimated prevalence of HIVAN has ranged from 3.5% in clinical studies to 12% in autopsy studies (Ahuja 1999). There is a paucity of data on the prevalence of HIVAN among population in sub-Saharan Africa. Han and colleagues found that 53% to 79% of kidney biopsies of HIV-positive black patients in South Africa demonstrated HIVAN (Han 2006).

Although the exact mechanism linking HIV-1 infection and the development of HIVAN is yet to be explained, it seems likely that host genetic variation might have an important role. It is now felt that HIVAN is caused by direct viral infection of kidney cells, particularly the visceral epithelial cells of the glomerulus and the tubular epithelial cells. HIV-1 infection of the kidney epithelium is a critical component of HIVAN pathogenesis and also represents an important reservoir in which the virus may persist despite a lack of detectable virus in plasma (Lochner 2006).

Pharmacologic agents used for the treatment of HIVAN include antiretroviral therapy, angiotensin converting enzyme inhibitors (ACEi), and steroids. Recently, cyclosporin has been used as another option in children (Ingulli 1991; Khan 2006) but clinical experience with it is limited. Highly active antiretroviral therapy (HAART) may also prevent the development of HIVAN in at-risk groups. HAART was associated with a 60% reduction in risk for developing HIVAN (Lucas 2004). However, with any of these pharmacologic strategies, the goal of treatment is directed toward reducing HIV-1 replication and/or slowing the progression of CKD.

Though HAART has dramatically reduced mortality of patients with HIV/AIDS, the incidence of ESKD due to HIVAN has remained stable and is likely to increase (Roling 2006). Since the introduction

of HAART, a variety of kidney side effects and adverse drug reactions have been recognized and vary from the development of proteinuria to acute kidney injury (Roling 2006). Recent studies based on the use of kidney biopsies for the diagnosis of HIVAN suggest that HIVAN is less common than previously thought and that HIV immune complex kidney disease had been wrongly diagnosed as HIVAN (Gerntholtz 2006).

Without adequate treatment, the prognosis of HIVAN is poor. Usually, HIVAN is diagnosed at a late stage, and untreated patients frequently have progression to ESKD within a few months (Carbone 1989). Because HIVAN typically occurs late in the course of HIV-1 infection (Winston 1999), risk factors for the development of HIVAN include a CD4 cell count < 200 cells/mm³ and a high viral burden.

Although there are general reviews on HIVAN (Atta 2008; Fine 2008; Lai 2006; Lochner 2006; Lu 2005), to the best of our knowledge there are no systematic reviews on the effects of pharmacotherapy on HIVAN. The aim of the systematic review is to assess the benefits and harms of any intervention used in treating HIVAN.

OBJECTIVES

To determine the benefits and harms of any intervention used in the management of HIVAN and its effects on symptom severity and all-cause mortality.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) determining/evaluating the effect of any intervention used in the management of patients with HIVAN. The first period of randomised cross-over studies were also to be included.

Types of participants

Inclusion criteria

All HIV infected patients (irrespective of age and sex) with HIVAN randomly assigned to the treatment group were eligible. HIVAN was defined as kidney disease in HIV infected patients characterised by severe proteinuria and progressive loss of kidney function as well as focal and segmental glomerulosclerosis with distinctive tubular and interstitial changes on histology. Any clinically useful subgroup of HIVAN was acceptable, as long as it was described in the study inclusion criteria.

Exclusion criteria

Other forms of kidney disease not associated with HIV. There was no exclusion based on the country of study.

Types of interventions

- Any intervention including antiretroviral therapy used in the treatment of HIVAN. The intervention could be one drug or a combination of therapies. Drug therapies could include HAART, antihypertensive agents (e.g. ACEi, angiotensin receptor blockers (ARB)), corticosteroids and immunosuppressive therapies (e.g. prednisolone, cyclosporin and mycophenolate

mofetil). No limits were to be placed on the frequency of use, dose, mode of administration or the duration of treatment.

- The control may be placebo, no therapy or any other therapy (single drug or a combination of therapies, complimentary medicine interventions).

Types of outcome measures

Primary outcomes

- All-cause mortality
- Progression to ESKD: requirement for renal replacement therapy (RRT).

Secondary outcomes

- Quality of life issues: ability to perform daily activities, cognitive function
- Kidney function measures: serum creatinine (SCr), creatinine clearance (CrCl), proteinuria, GFR, albuminuria, serum albumin, urinalysis
- Relapse
- Adverse effect of drugs
- Viral Load, CD4 count.

Search methods for identification of studies

We attempted to identify all relevant studies irrespective of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

For this update we searched the following resources:

1. Cochrane Renal Group's specialised register (12/01/2012)
2. AEGIS database (AIDS Education Global Information System (<http://www.aegis.com>)). AEGIS searches across AIDSLINE, a large range of HIV-AIDS related conference proceedings, newsletters and press releases (note: the AIDSearch database is no longer available)
3. ClinicalTrials.gov (12/01/2012)
4. WHO International Clinical Trials Registry Portal (12/01/2012)

See [Appendix 1](#) for search terms used in this and previous versions of the review.

Searching other resources

1. We checked the reference lists of nephrology text books, review articles and relevant studies.
2. We searched the WHO International Clinical Trials Registry Platform (<http://www.who.int/ictrp/en/>) and ClinicalTrials.gov (<http://www.clinicaltrials.gov>).

Data collection and analysis

Selection of studies

The review undertaken by three authors (IY, OU, MU). The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened independently by IY and OU, who discarded studies that were not applicable, however studies and reviews that might include relevant data or information on trials were

retained initially. The two authors (IY, OU) independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria using the designed eligibility form.

Data extraction and management

Data extraction was to be carried out independently by the same authors using standard data extraction forms. Studies reported in non-English language journals were to be translated before assessment. Where more than one publication of one study exists, the publication with the most complete data was to be included. Where relevant outcomes are only published in earlier versions these data were to be used. Any discrepancy between published versions was to be highlighted. Disagreements were to be resolved in consultation with MU.

Assessment of risk of bias in included studies

The following items were to be assessed using the risk of bias assessment tool ([Higgins 2011](#)) (see [Appendix 2](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
 - * Participants and personnel
 - * Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. death, progression to ESKD, relapse) results were to be expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. GFR, SCr), the mean difference (MD) were to be used, or the standardised mean difference (SMD) if different scales had been used.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence and any relevant information obtained in this manner will be included in the review.

Assessment of heterogeneity

Heterogeneity will be analysed using a chi squared test on N-1 degrees of freedom, with an alpha of 0.1 used for statistical significance and with the I^2 test ([Higgins 2003](#)). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be analysed to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age and kidney pathology. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy. Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

RESULTS

Description of studies

Results of the search

We prepared a QOUM statement flowchart to describe how we processed the references identified through the search results

Figure 1. Flow diagram.

Three further studies were identified from the updated search. Two were excluded due to study designs while the third study is a proposed study that dates back to 2001. The proposed study is

(Figure 1). The search strategy resulted in 891 abstracts and titles, which included two that were identified by one of the experts. We retrieved 13 papers for detailed evaluation. We identified four possibly relevant papers: three from trials registry (NCT00002397; Szczech 2004a; Kopp 2004) and one from AIDSearch (Kalayjian 1995b). NCT00002397 has been completed but is yet to be published. Letters seeking information about the studies were sent to the National Institute of Allergy and Infectious Diseases (NIAID), The AIDS Clinical Trials Group (ACTG) and the principal investigator for the Kalayjian 1995b study. The investigator's name for the NCT00002397 trial was not provided and so we could not make a direct contact. The third study (Szczech 2004a) was suspended due to unspecified reason while NCT00000819 was suspended due to poor accrual. The fourth study (Kopp 2004) is still ongoing and expected to be completed in December 2015.

a phase II clinical trial of KRX-101 (sulodexide) for the treatment of AIDS related kidney disease- HIVAN. To date this study has not been referenced elsewhere including trials registries. Letter seeking

information was sent to Keryx Biopharmaceuticals, but no data has been provided ([Keryx Biopharmaceuticals 2001](#)).

Included studies

No RCTs or quasi-RCTs were identified that satisfied the inclusion criteria. We are awaiting the results of one completed, but yet to be published study and one ongoing study. (see [Characteristics of ongoing studies](#))

Excluded studies

Eleven studies were excluded due to inappropriate study design ([Burns 1997](#); [Cosgrove 2002](#); [Eustace 2000](#); [Kalayjian 1995a](#); [Kalayjian 2008](#); [Kimmel 1996](#); [Peters 2008](#); [Smith 1994](#); [Smith 1996](#); [Szczech 2006](#); [Wei 2003](#)) (see [Characteristics of excluded studies](#)).

Risk of bias in included studies

No completed RCTs or quasi-RCTs were identified that determined/evaluated the effect of adjunctive therapy administered to patient with HIVAN.

Effects of interventions

No completed RCTs or quasi-RCTs were identified that determined/evaluated the effect of adjunctive therapy administered to patient with HIVAN.

We have summarised the results of the excluded, non-randomised studies in [Table 1](#).

DISCUSSION

No completed RCT or quasi-RCT investigating any intervention for treating HIVAN were identified. We did however identify two ongoing studies; one completed but yet to published ([NCT00002397](#)), one study currently enrolling patients ([Kopp 2004](#)), and two suspended studies ([Kalayjian 1995b](#); [Szczech 2004a](#)). [NCT00002397](#) may throw some light on the effect of Saquinavir soft gel capsules with other anti-HIV drugs when the results are available.

In the observational studies that were identified, steroids appear to improve the kidney function in patients ([Eustace 2000](#); [Kalayjian 1995a](#); [Smith 1994](#); [Smith 1996](#)). Such beneficial effects were identified in studies where ACEi were also used ([Burns 1997](#); [Wei 2003](#)). Thus, the clinical practice in HIVAN treatment is based on studies which has a weak evidence base ([Table 1](#): Summary of results from excluded studies).

Considering the continued increase in the prevalence of HIV infection around the world and especially in sub-Saharan Africa,

HIVAN is likely to become a major problem. Although the use of HAART has been shown to lead to the reduction in incidence and improvement in the prognosis of HIVAN ([Atta 2006](#); [Lucas 2004](#)), no therapy has been proven to be effective. Recommendations from the International AIDS Society USA panel however suggest that antiretroviral therapy should be started as soon as kidney disease is diagnosed in HIV patients, and that drugs of known potential nephrotoxic effects should, where possible, be avoided in persons with kidney abnormalities ([Hammer 2008](#)). Information on the benefits and risks of other pharmacological agents is also required. Thus, there is a need to conduct RCTs to provide evidence for the benefits of treatments used for HIVAN.

AUTHORS' CONCLUSIONS

Implications for practice

It is likely that clinicians will continue with their current practice, using clinical judgement and prescribing patterns to dictate treatment because there is no RCT-based evidence to help guide their choice of drug. It is difficult to know whether current practice is justified outside of a well designed, conducted and reported RCT.

Currently policy makers have no RCT-based evidence upon which to base guidelines for HIVAN. They are likely to continue to rely on opinion and habit when making their recommendations. Funders of studies may wish to make this important subgroup of people a priority for future research.

Implications for research

At present there is no convincing evidence to support the use of any intervention for HIVAN. Given the magnitude of problem associated with HIVAN, clinically meaningful RCTs are needed to help guide clinicians in their management of people with HIVAN. While ideally, RCTs evaluating the effect of interventions for treating HIVAN could be carried out, the detrimental effect of untreated HIV in the presence of effective medication (HAART) makes it unethical to conduct such a study. Thus, studies may compare different types of therapies combined with HAART as long as the intervention and control group both received HAART and the only difference between groups is a non-antiretroviral intervention. Outcomes to be included in such studies should be relevant to allow for the evaluation of the benefits and risks of the intervention.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Burns 1997	Cohort study examining the effect of ACE inhibition in HIVAN
Cosgrove 2002	Case control to determine the types of kidney lesions in patients with HIV during the era of HAART availability and the effect of HAART on kidney outcomes
Eustace 2000	Retrospective cohort study of the treatment of severe HIVAN with corticosteroids
Kalayjian 1995a	Case series of the effects of prednisolone in improving renal functions in patients with HIVAN
Kalayjian 2008	Observational, prospective, multicenter cohort study, patients with CKD and HIV but not HIVAN
Kimmel 1996	Non-RCT of effect of captopril on kidney survival in patients with HIVAN
Peters 2008	Prospective cohort study of the effects of HAART therapy on kidney functions
Smith 1994	Case series report on the effect of steroid therapy on the progression of HIVAN
Smith 1996	Case series to determine if prednisolone ameliorates the course of HIVAN
Szczecz 2006	Retrospective cohort study comparing course of HIVAN with other kidney lesions associated with HIV
Wei 2003	Non-randomised control trial to examine the long-term effects of ACE inhibition on kidney survival in HIVAN

ACE - angiotensin converting enzyme; CKD - chronic kidney disease; HAART - Highly active antiretroviral therapy; HIVAN - HIV-associated nephropathy

Characteristics of studies awaiting assessment [ordered by study ID]

Keryx Biopharmaceuticals 2001

Methods	No information available
Participants	No information available

Interventions for HIV-associated nephropathy (Review)

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Keryx Biopharmaceuticals 2001 *(Continued)*

Interventions	No information available
Outcomes	No information available
Notes	

Characteristics of ongoing studies *[ordered by study ID]*
Kalayjian 1995b

Trial name or title	A phase II randomized, double-blind, placebo-controlled trial to determine the efficacy of prednisolone therapy in HIV-associated nephropathy (HIVAN).
Methods	Randomised, double-blind, placebo-controlled
Participants	18 years and older of both sex
Interventions	Prednisolone
Outcomes	Serum creatinine, urinary protein and creatinine clearance
Starting date	02/11/1999
Contact information	Kalayjian 1995b
Notes	Study was prematurely closed because of poor accrual

Kopp 2004

Trial name or title	Retinoids for Minimal Change Disease and Focal Segmental Glomerulosclerosis
Methods	Open label, randomised trial
Participants	16 years and older of both sex
Interventions	Retinoids
Outcomes	Proteinuria, complete or partial remission at 6 months or 1 year
Starting date	November 2004
Contact information	Kopp 2004
Notes	Recruiting, last updated: June 12, 2009

NCT00002397

Trial name or title	A study of Saquinavir soft gel capsules (SGC) used in combination with two other anti-HIV drugs in patients with HIV-associated kidney disease.
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NCT00002397 (Continued)

Methods	Open-label, non-comparative, randomised
Participants	18 years and older of both sex
Interventions	Nelfinavir mesylate, saquinavir, lamivudine and stavudine
Outcomes	Progression of kidney disease, level of HIV, drug level in the body.
Starting date	02/11/1999
Contact information	NCT00002397
Notes	Completed and last updated: June 23, 2005

Szczzech 2004a

Trial name or title	A Phase III, randomized, placebo-controlled, double-blind trial of an angiotensin receptor blocker (valsartan) and highly active antiretroviral therapy (HAART) versus HAART alone for the treatment of HIV-associated nephropathy
Methods	Randomized, double-blind, active control, parallel assignment, efficacy study
Participants	18 years and older of both sex
Interventions	Valsartan
Outcomes	Physical examination, medication assessment, and blood pressure readings
Starting date	Unclear, study registered 5/8/2004
Contact information	Szczzech 2004a
Notes	Study completed. Study was suspended, reasons not stated

ADDITIONAL TABLES

Table 1. Summary of results from excluded studies

Study	Population	HIVAN de- finition	Interventions	Outcomes
Burns 1997	Hospital-based study among homosexual male patients with HIV-1 in the USA (1993 to 1995); 20 patients included. Inclusion criteria: kidney biopsy consistent with HIVAN; SCr $\leq$ 2.0 mg/dL; 24 h urinary protein excretion > 500 mg; normal BP and serum potassium.	Biopsy-proven HIVAN	Treatment group: fosinopril (10 mg orally/d) Control group: nothing. Evaluation took place on weeks 4, 8, 12, 16, 20 and 24, and involved measuring BP, SCr, serum potassium, 24 h	Non-nephritic proteinuric patients (treated versus control at 24 weeks) Average SCr: 1.5 ± 0.34 mg/dL versus 4.9 ± 2.4 mg/dL ($P = 0.006$) 24 h urinary protein excretion: 1.25 ± 0.86 g/d versus 8.5 ± 1.4 g/d ($P = 0.006$) Nephrotic range patients (treated versus control at 12 weeks)

Table 1. Summary of results from excluded studies (Continued)

	Exclusion criteria: previous kidney disease; IV drug use, or laboratory evidence of sickle cell disease.		urine protein excretion, and potential side effects of fosinopril.	Average SCr: 2.0 ± 1.0 mg/d versus 9.2 ± 2.0 mg/d ($P = 0.02$) 24 h urinary protein excretion: 2.8 ± 1.0 g/d versus 10.5 ± 3.5 g/d ($P = 0.008$)
	Treatment assignment: based on personal choice of the patients.			
Cosgrove 2002	Patients referred between July 1996 and December 2000 were retrospectively reviewed. Conducted in the USA, predominantly among African American and Hispanic patients, 23 patients were recruited into the study. Treatment assignment: based on personal choice of the patients.	Clinical and biopsy-proven HIVAN	Treatment group: HAART (13) Control group: nothing (10)	SCr: stabilised (treated) versus doubling of SCr (control) Mortality: 0 (treated) versus 2 (control) Progression to dialysis: 0 (treated) versus 8 (control)
Eustace 2000	Hospital-based cohort study (1994 and 1997), 21 patients were identified. Inclusion criteria: HIVAN confirmed by histology, without alternative cause of kidney failure; azotaemia with SCr > 2 mg/dL; no evidence of active infection; abstinent from all illicit drug use. Exclusion criteria: patients already on dialysis; no biopsy within a month of starting steroid. Treatment assignment: non-random (decision taken by physician)	Biopsy-proven HIVAN	Treatment group: 60 mg prednisolone for 1 month, followed by a planned gradual taper over approximately 2-4 months (13) Control group: nothing (8)	Three months follow-up Progressive azotaemia: treatment RR 0.20 ($P < 0.05$) Progression to dialysis: 0 (treated) versus 3 (control) Mean change in SCr: -2.22 mg/dL (-0.98 to -3.45 ; $P < 0.01$) versus 1.46 mg/dL (-0.56 to 3.47) Mean 24 hour protein excretion: decreased by -5.5 g/d (-1.6 to -9.4 ; $P = 0.01$) in treated group Six months follow-up Independent kidney function: 7 (treated) versus 1 (control) Death: 2 (treated) versus 3 (control) Twelve months follow-up Death: 4 (treated) versus 3 (control)
Kalayjian 1995a	A case series conducted in USA, 14 patients with biopsy and clinically proven HIVAN	Clinical and biopsy-proven HIVAN	Each patient received 60 mg/d prednisolone for a median of 4 weeks, tapered over 5 weeks	Mean Cr fell from 7.44 ± 3.9 mg/dL to 3.23 ± 1.36 mg/dL ($P = 0.001$) after a median of 5 weeks in 12 patients
Kalayjian 2008	Prospective multicenter cohort study. 1776 enrolled to examine the association between changes in GFR and ART mediated suppression of plasma HIV-1 viraemia	Clinical diagnosis of chronic renal failure	ART regimens in HIV-1 infected subjects (1776 ambulatory subjects)	Viral suppression (< 400 copies/mL) associated with an average increase in GFR of 9.2 mL/min/ 1.73 m ² from baseline (95% CI, 1.6 to 16.8; $P = 0.02$) over a median follow-up of 160 weeks
Kimmel 1996	Single centre study in the USA. 18 African Americans were recruited	Biopsy-proven HIVAN	Treated group: captopril 3 times/d (9)	Mean kidney survival time: 156 ± 71 days (treated) versus 37 ± 5 days (control) ($P < 0.002$, Mantel-Cox log-rank test)

Table 1. Summary of results from excluded studies (Continued)

	Inclusion criteria: biopsy-proven HIVAN		Matched controls: not treated (9)	
	Treatment assignment: physician's choice based on patient's need.			
Peters 2008	Prospective cohort study of the effect of ART on kidney function. A subset of participants (508) who were part of a RCT conducted in rural Uganda. Inclusion criteria: at least 24 months after HAART initiation and Cr results at baseline and at their 12 and 24-month follow-up visits	Clinical-proven HIVAN	Participants had HAART for at least 24 months	After 2 years Median SCr decreased by 16 µmol/L (16% decline, $P < 0.0001$) Median CrCl significantly increased by 13 mL/min (21% increase, $P < 0.0001$)
Smith 1994	Case series report on the effect of steroid on HIVAN, 4 patients included Inclusion criteria: biopsy proven HIVAN; CD4 cell count < 200 cells/µL; moderate to severe kidney insufficiency and proteinuria > 2 g/24 h. Treatment assignment: not applicable (all patients received prednisolone)	Biopsy-proven HIVAN	Prednisolone 60 mg/d for 3-6 weeks	Mean SCr decreased from 9.1 ± 5.7 mg/dL to 3.3 ± 1.8 mg/dL ($P < 0.05$) 24 h protein did not change: (5.2 ± 2.4 g pre-treatment versus 4.6 ± 4.1 g post-treatment)
Smith 1996	Hospital-based prospective study in the USA; 20 consecutive HIV-infected adult patients were recruited. Inclusion criteria: biopsy proven HIVAN or clinical characteristics of HIVAN with SCr > 2 mg/dL or proteinuria > 2.0 g/d or both Exclusion criteria: evidence of active, untreated infection. Treatment assignment: not applicable (all the patients received prednisolone)	Clinical and Biopsy-proven HIVAN	All patients received prednisolone (60 mg/d) for a median of 4 weeks (range 2-11), followed by a tapering course over 2-26 weeks.	SCr: decreased from 8.1 ± 1.2 mg/dL to 3.0 ± 0.4 mg/dL ($P < 0.001$) 24 hour urinary protein excretion (average): decreased from 9.1 ± 1.8 g/d to 3.2 ± 0.6 g/d ($p < 0.005$) Serum albumin: increased from 24.4 ± 3.6 g/L to 29.3 ± 2.6 g/L ($p = \text{NS}$)
Szczecz 2004b	Hospital based retrospective cohort study in the USA based on medical record and data of 89 patients between 1995 and 2001. Inclusion criteria: HIV infected patients who underwent kidney biopsy (HIVAN and other lesions other than HIVAN). Treatment assignment: Decision taken by physicians.	Biopsy proven HIVAN	HIVAN group: 11/42 (27 patients during the period of follow-up) patients took ART and 6/42 patients took ACEi/ARB at the time of kidney biopsy Non-HIVAN group: 16/47 (32 patients during the period of	HIVAN: ART was associated with slower progression to RRT (HR 0.24, 95% CI 0.07 to 0.84, $P = 0.03$). Use of ACEi/ARB was associated with a longer time from kidney biopsy to commencement of RRT (HR 0.41, $P = 0.04$)

Table 1. Summary of results from excluded studies (Continued)

			follow-up) patients took ART and 10/47 patients took ACEi/ARB at the time of kidney biopsy	
Wei 2003	Single-centre prospective study conducted in USA (1993 and 1997); 44 patients. Inclusion criteria: clinical and biopsy-proven HIVAN, SCr ≤ 2 mg/dL, normal BP, serum potassium and blood sugar Exclusion criteria: prior kidney disease, IV drug use and lab evidence of sickle cell disease Treatment assignment: based on personal choice of the patients	Biopsy-proven HIVAN	Treated group: fosinopril (10 mg/d) Control group: nothing	Median kidney survival: 479.5 days (treated) versus 146.5 days (control) $P < 0.0001$ Survival rate: 87.5% (treated) versus 21.4% (control) Risk of kidney failure reduced in treated group: (RR = 0.003, $P < 0.0001$) Progression to ESKD: 3.57% (treated) versus 100% (control) ($P < 0.0001$)
				Nephritic range proteinuric patients Progression to ESKD: 8.3% (treated) versus 100% (control) Mortality: 33.3% (treated) versus 87.5% (control)

ACEi - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; ART - antiretroviral therapy; BP - blood pressure; Cr - creatinine; CrCl - creatinine clearance; ESKD - end-stage kidney disease; GFR - glomerular filtration rate; HAART - highly active antiretroviral therapy; HIVAN - HIV-associated nephropathy; HR - hazard ratio; RRT - renal replacement therapy; SCr - serum creatinine

APPENDICES

Appendix 1. Search strategies

Database	Search terms
CENTRAL	1. HIV:ti,ab,kw 2. acquired immunodeficiency syndrome:ti,ab,kw 3. acquired immune deficiency syndrome:ti,ab,kw 4. AIDS:ti,ab,kw3. Acquired Immunodeficiency Syndrome/ 5. human immunodeficiency virus*:ti,ab,kw 6. (#1 OR #2 OR #3 OR #4 OR #5) 7. kidney disease*:ti,ab,kw 8. renal disease*:ti,ab,kw 9. nephropath*:ti,ab,kw 10.nephritis:ti,ab,kw 11.nephrotic:ti,ab,kw 12.glomerulosclero*:ti,ab,kw 13.proteinuri*:ti,ab,kw 14.albuminuri*:ti,ab,kw 15.(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) 16.(#6 AND #15)
MEDLINE	1. AIDS-Associated Nephropathy/

(Continued)

2. exp HIV/
3. Acquired Immunodeficiency Syndrome/
4. HIV Infections/
5. Sexually Transmitted Diseases, Viral/
6. (HIV or HIV-1 or HIV1 or HIV-2 or HIV2).tw.
7. (human immunodeficiency virus or human immuno-deficiency virus or human immunodeficiency virus or human immune-deficiency virus or (human immun\$ and deficiency virus) or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immunodeficiency syndrome or acquired immune-deficiency syndrome or (acquired immun\$ and deficiency syndrome)).tw.
8. or/2-7
9. exp Kidney Diseases/
- 10.(nephropath\$ or nephritis or nephrotic or glomerulosclero\$ or proteinuri\$ or albuminuri\$).tw.
- 11.(kidney disease\$ or renal disease\$ or kidney failure or renal failure or CRF or CKD or ESKD or ESKF or ESRD or ESRF).tw.
- 12.or/9-11
- 13.and/8,12
- 14.or/1,13

EMBASE

1. exp Kidney Disease/
2. exp Human Immunodeficiency Virus Infection/
3. exp Human Immunodeficiency Virus/
4. or/2-3
5. and/1,4
6. (HIV or AIDS or human immunodeficiency virus or acquired immune deficiency syndrome).tw.
7. (nephropath\$ or nephritis or nephrotic or glomerulosclero\$ or proteinuri\$ or kidney disease\$ or renal disease\$).tw.
8. and/6-7
9. or/5,8

AIDSEARCH

1. AIDS-Associated Nephropathy/
2. exp HIV/
3. Acquired Immunodeficiency Syndrome/
4. HIV Infections/
5. Sexually Transmitted Diseases, Viral/
6. (HIV or HIV-1 or HIV1 or HIV-2 or HIV2).tw.
7. (human immunodeficiency virus or human immuno-deficiency virus or human immunodeficiency virus or human immune-deficiency virus or (human immun\$ and deficiency virus) or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immunodeficiency syndrome or acquired immune-deficiency syndrome or (acquired immun\$ and deficiency syndrome)).tw.
8. or/2-7
9. exp Kidney Diseases/
- 10.(nephropath\$ or nephritis or nephrotic or glomerulosclero\$ or proteinuri\$ or albuminuri\$).tw.
- 11.(kidney disease\$ or renal disease\$ or kidney failure or renal failure or CRF or CKD or ESKD or ESKF or ESRD or ESRF).tw.
- 12.or/9-11
- 13.and/8,12
- 14.or/1,13

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<p><i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).</p> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.</p> <p><i>Unclear:</i> Randomisation stated but no information on method used is available.</p>
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<p><i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	<p><i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	<p><i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.</p> <p><i>High risk of bias:</i> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to</p>

(Continued)

induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Unclear: Insufficient information to permit judgement

Selective reporting

Reporting bias due to selective outcome reporting

Low risk of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: Insufficient information to permit judgement

Other bias

Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
29 October 2012	New search has been performed	New search performed, 3 potential studies excluded
29 October 2012	New citation required but conclusions have not changed	Methods brought into line with latest guidelines

CONTRIBUTIONS OF AUTHORS

- IY, OU: Development and writing of the review
- MU: Resolve disputes

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Save the Youth Initiative, Nigeria.

Interventions for HIV-associated nephropathy (Review)

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External sources

- Reviews for Africa Programme Fellowship, South Africa.
- South African Cochrane Centre, South Africa.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

New risk of bias assessment tool added to replace assessment of quality checklist.

INDEX TERMS**Medical Subject Headings (MeSH)**

AIDS-Associated Nephropathy [*drug therapy]; Angiotensin-Converting Enzyme Inhibitors [therapeutic use]; Steroids [therapeutic use]

MeSH check words

Humans