Prevalence and factors associated with renal impairment in HIV-infected patients, ANRS C03 Aquitaine Cohort, France.

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Short title: Renal impairment in HIV infection

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[†] See composition in Appendix

Abstract

Objectives

To estimate the prevalence of renal impairment (RI) among HIV-infected adult patients and to investigate the associated factors.

Methods

A cross-sectional survey was conducted in a French hospital-based cohort. Clearance of creatinin (CC) was calculated using Cockcroft-Gault formula. Four stages of RI were defined: mild (60-90 ml/min), moderate (30-60), severe (15-30), and end-stage (<15). Logistic regression models investigated factors associated with RI.

Results

The male:female ratio of the 2588 patients enrolled was 3:1 and median age 42 years. At time of assessment of CC median CD4 count was 430/mm^3 and HIV plasma viral load was <50 copies/mL in 60%. The overall prevalence of RI was 39.0%: 34.2% mild, 4.4% moderate, 0.3% severe and 0.2% end-stage.

Mild RI was associated with female gender (odds-ratio [OR] = 3.3: 95% CI 2.6-4.3), age >50 years (OR = 9.8: 7.4-13.0) and 40 to 50 years (OR=1.9: 1.5-2.4), body mass index (BMI) <22kg/m^2 (OR = 3.3: 2.7-4.3), tenofovir exposure (OR =1.4: 1.0-1.9 for < 1year and OR =1.5: 1.2-2.0 for > 1 year). Advanced RI (CC < 60 ml/mn) was associated with age >50 years (OR = 5.6: 2.9-10.9) and 40 to 50 years (OR=2.2: 1.1-1.4), BMI <22kg/m^2 (OR = 1.5: 1.0-2.4), hypertension (OR = 2.5: 1.4-2.5) and indinavir exposure >1 year (OR =2.3: 1.5-3.6).

Conclusion

This survey confirms the high prevalence of RI in HIV-infected patients and indicates the importance of the investigation of renal function especially in women, older patients, those with low BMI, or treated by tenofovir or indinavir.

Key words: Kidney, HIV infection, renal impairment

Introduction

Nowadays kidney morbidity has become common among HIV-infected patients in industrialized countries [1]. Specific renal damages characterise the HIV-associated nephropathy (HIVAN) [2-3] and several risk factors have been hypothesised and investigated individually including black ethnicity, male gender, history of injection drug use, hepatitis C virus (HCV) co-infection, low CD4+ cell count, and concurrent AIDS-defining condition. HIVAN may result in renal function impairment [4-5], although the use of antiretroviral therapy (ART) has recently contributed to lower its prevalence [6-7]. Nevertheless the overall survival improvement of HIV-infected patients receiving ART leads to the accumulation of factors that are harmful for renal function: ageing, co-morbidities such as high blood pressure, diabetes, hyperlipidemia and adverse effects of antiretroviral drugs such as indinavir and tenofovir [8]. These factors are thus likely to increase again the frequency of acute or chronic renal impairment (RI) [9].

Studies on the frequency of RI in HIV-infected patients have often been conducted in selected groups of HIV-infected patients and additional studies are needed to allow a proper estimation of its prevalence and comprehensive investigation of its determinants [10].

The objectives of our study were to estimate the prevalence of RI in a large and unselected cohort of HIV-infected patients in care and to identify associated factors that could lead to specific preventive or control measures.

Patients and Methods

We performed a cross-sectional survey within the French Agency of AIDS and Hepatitis Research (ANRS) CO3 Aquitaine Cohort of HIV-infected patients living and followed in South-western France. Patients were enrolled prospectively in this cohort through a hospital-based surveillance system, if they were aged 13 years or more and provided informed consent. Standardized epidemiological, clinical, biological and therapeutic data collection was completed by attending physicians at time of enrollment and at each hospital follow-up visit, generally every three or six months (in agreement with French recommendations for standards of care) or more frequently in case of intercurrent event, then verified and coded by research nurses with annual audit for quality control.

The main outcome of interest in our study was the renal filtration rate assessed by a single measurement of the clearance of creatinine (CC) using Cockcroft-Gault formula [11] owing to the fact that creatininemia was routinely registered in our data base from January 2004. Créatinine was measured by Jaffé methodology in the three laboratories where measurements have been carried out and calibrations have been performed to assure comparability. We did not standardize CG measurement for body surface area as there is no general consensus of whether or not this has to be performed [9]. The lack of data related to ethnicity in our systematic survey did not allow the use of the Modification of Diet in Renal Disease (MDRD) formula to assess the renal function;

nevertheless crude prevalence of RI was calculated using modified MDRD formula [12] , which does not need to know ethnicity, to allow comparisons with other studies: CC ml/mn = 175 x (serum creatinine µM/l x 0.0113)$^{-1,154}$ x age$^{-0,203}$ x 0.742 (if female).

We included in the analysis data of the cohort participants at the time of first follow-up where a simultaneous measurement of variables allowing the calculation of their CC was collected between January 2004 and September 2006. We then excluded patients with incomplete data on body weight, height and creatininemia. We also excluded patients with a body mass index (BMI) <18 kg/m^2 or >30 kg/m^2, ascites, and pregnant women in order to ensure the validity of Cockcroft-Gault formula.

According to the recommendations of the HIV Medicine Association of the Infectious Diseases Society of America [12], we assigned normal renal function to patients with a CC value >90 ml/min, and RI to those with a CC <90 ml/min. Four stages of RI were defined: mild RI for a CC between 60 and 90 ml/min; moderate RI for a CC between 30 and 60 ml/min; severe RI for a CC between 15 and 30 ml/min; and end- stage RI for a CC <15 ml/min. An advanced RI was characterized by a CC <60 ml/min (moderate, severe and end-stage combined). Explanatory variables were considered at time of assessment of the renal function : gender, age, HIV transmission group, BMI, HIV infection stage, delay since HIV infection diagnosis, HCV co-infection, history or presence of diabetes (defined by the use of antidiabetic drugs, or fasting glycaemia >11mmol/l), high blood pressure (defined by the use of antihypertensive agents, or systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg), and hyperlipidemia (prescription of lipid lowering drugs, or fasting total plasma cholesterol >6.5 mmol/l or fasting triglyceridemia >2.2 mmol/l), most recent HIV1-RNA plasma viral load (VL), CD4+ cell count, cumulated duration of use of each class of ART since inclusion in the cohort including nucleoside reverse transcriptase inhibitors (NRTI), nucleotide reverse transcriptase inhibitor (tenofovir), non-nucleoside reverse transcriptase inhibitors (NNRTI), indinavir and protease inhibitors (PI) other than indinavir. In additional models, current use of tenofovir and indinavir were added to other variables.

Statistical analysis. Prevalence of RI was computed as the number of cases of RI per 100 patients followed in the period. We calculated the crude overall RI prevalence and specific rate for each stage of RI. Patients' characteristics were selected for inclusion in the multivariate model of determinants of RI if they were significantly associated in the univariate analysis ($p<0.25$). We compared patients according to the two following thresholds: 90 ml/min (any RI) and 60 ml/min (advanced RI). In order to correct for the weaknesses due to response variable dichotomization [13], we performed a polynomial logistic regression which allowed to compare two by two, the categories of patients with normal renal function, those with mild RI and those with advanced RI. Models were fitted using the SAS software (version 9.1.3, SAS Institute Inc., Cary, NC, USA).

Interaction terms combining primary exposure and confounding measures were evaluated. A backward elimination procedure was used to determine the most parsimonious model. All statistical tests were two-sided and a *p*-value of 0.05 was considered as significant.

Results

Population characteristics

3151 patients were seen at least once in the Aquitaine Cohort between January 2004 and August 2006. Five hundred six patients were excluded of the study because of missing data allowing the calculation of their CC. Furthermore 57 additional subjects were excluded in order to ensure the validity of the use of Cockcroft-Gault formula [2 ascites, 2 pregnant women, 52 patients with either a BMI <18 kg/m^2 or >30 kg/m^2]. Thus data of 2588 patients were available for analysis (82 % of the entire cohort). There was no statistical difference between the main characteristics of the excluded population and those of the study population except for NNRTI and indinavir exposures which were more frequent among excluded patients (60.9 % vs 50.2 % and 32.4 % vs 25.5 % respectively).

At the time of evaluation of the CC, median age was 41.9 years (interquartile range [IQR]: 36.9–48.1) and male gender was predominant (74.3%). HIV transmission route was mainly sexual, with 42% of presumed homosexual transmission and 31% of heterosexual transmission followed by intravenous drug use (18.3%).The median delay since HIV infection diagnosis was 10 years (IQR: 4.3–14.6). 524 patients (22.2%) were already at the AIDS disease stage, according to the US Centers for Disease Control and Prevention (CDC) classification of HIV infection for adults and adolescents. Patients' median CD4 absolute count was 430/mL (IQR: 294–619), and 60.4% had undetectable VL (plasma HIV1 RNA< 50 copies/ml). Median BMI was 22.1 kg/m² (IQR: 20.3–24.2). This population had frequently hyperlipidemia (21.9%), more rarely high blood pressure (6.9%) or diabetes (2.6%). HCV antibodies were noticed in 322 patients (12.4%). 2 383 patients (92%) had been exposed to ART [mean cumulative exposure (CE): 4.56 years] and had already received NRTIs (77.3%) [CE: 4.52 years], tenofovir (25.4%) [CE: 3.8 months], NNRTI (50.2%) [CE: 1.21 years], or PI (49%) [indinavir (25.3%) [CE: 7.2 months] other PIs [CE: 1.40 years]. At the time of evaluation of the CC, 75.4% patients were receiving ART including NRTIs (71.9%), tenofovir (21.2%), NNRTIs (26.6%), and PIs (35.8%) including indinavir (3.3%).

Distribution of RI in the study population.

The median CC was 96.1 ml/min (IQR: 81.6–113.1) and the overall prevalence of RI was 39.0% (n=1010) (95% Confidence Interval [CI]: 38.2-40.8). RI was mild in 34.2 % (n=884) of patients (95% CI: 32.5-36.0), moderate in 4.4% (n=113) (95% CI: 3.6-5.2), severe in 0.3% (n=7) (95% CI: 0.1-0.5) and at end-stage in 0.2% (n=6) (95% CI: 0.02-0.40). Thus, renal function impairment was qualified as advanced (moderate or severe or end-stage) in 4.9% of the cohort (95% CI: 4.1-5.7).

With renal function estimated by simplified MDRD formula, results are as follows: overall prevalence of RI was 55.1% (95% CI: 53-57), with a prevalence of 49% (95% CI: 47-51) for mild RI, 5.5% (95% CI: 4.6-6.3) for moderate RI, 0.3% (95% CI: 0.1-0.5) for severe RI and 0.3 % (95% CI: 0.1-0.5) for end-stage RI**.**

Factors associated with RF

In univariate analysis, RI prevalence was significantly ($p<0.05$) associated with female gender (OR = 2.5: 2.1-3.9), age between 40 and 50 years (OR = 1.5: 1.3-1.8) or >50 years (OR = 6.3: 5.0-7.9), BMI <22 (OR = 2.3: 2.0-2.7), HIV transmission group (heterosexuals vs intravenous drug users; OR = 1.5: 1.2-2.0), AIDS stage (OR = 1.3: 1.1-1.6), undetectable VL (OR = 1.5: 1.2-1.8), NRTI exposure (OR = 1.5: 1.3-1.9 for 1 to 4 years and OR = 1.5: 1.3-2.0 for > 4 years), tenofovir exposure (OR = 1.4: 1.1-1.8 for < 1year and OR = 1.5: 1.2-1.9 for > 1 year), NNRTI exposure >1 year (OR = 1.2: 1.1-1.5), indinavir exposure >1 year (OR = 1.5: 1.2-1.8) and high blood pressure (OR = 1.4: 1.0-1.9).

A first multivariate logistic regression model (threshold of RF: 90 ml/min) showed that the overall RI (CC<90 ml/min) prevalence was significantly greater in female and older patients, those with a low BMI, an HIV transmission group other than drug abuse, undetectable VL, and tenofovir exposure (Table 1).

When RI was estimated with simplified MDRD-based calculations, undetectable viral load was no more associated while indinavir exposure (OR=1.3:1-1.6 for <1 year and OR=1.5: 1.1-2.0 for >1year) was indeed associated (global p-value=0.01).

When current use of tenofovir and indinavir were added in the model a significant association was found between RI (estimated with Cockcroft-Gault formula) and current use of both drugs: tenofovir with an OR of 1.65 [95% IC: 1.3 - 2.08] ($p< 10\text{-}4$) and indinavir with an OR of 2.17 [95%CI: 1.3 - 3.6] ($p = 3.10\text{-}3$) . In this additional model prevalence of RI remained significantly greater in female and older patients, those with a low BMI, an HIV transmission group other than drug abuse, but cumulative exposure to tenofovir and undetectable viral load were no more associated to RI.

In another multivariate model advanced RI (CC<60 ml/min) was only associated with female gender, older age, low BMI, high blood pressure and indinavir exposure >1 year (Table 2).

If current use of tenofovir and indinavir are included in the model a significant association is also found between advanced RI and current use of indinavir with an OR of 2.5 [95%IC: 1.1 - 5.9] ($p = 0.03$). In this additional model prevalence of advanced RI remained associated with female gender, older age, low BMI, high blood pressure and cumulative exposure to indinavir > 1 year (OR=1.9 [1.2 - 3.15] ; $p = 0.02$). Still no association is found for tenofovir either for cumulative exposure or current use.

Finally the polynomial regression model (Table 3) showed a significant association of mild RI (60<CC<90 ml/min), as compared with normal renal function, with female gender, older age, low BMI, HIV transmission group other than intravenous drug use, tenofovir exposure. For advanced RI (as compared with mild RI), the associated factors were older age, low BMI, high blood pressure and indinavir exposure.

It should be noted that mean exposure durations to antiretroviral-associated RI, i.e. tenofovir and indinavir, were significantly longer among patients with RI compared to those without RI : 4.7 months versus 3.3 months for tenofovir and 8.5 versus 6.1 months for indinavir ($p< 10^{-3}$ for both comparisons).

Discussion

Our study examined the prevalence of RI and its associated factors among HIV-infected persons under care in South-Western France in the most recent era of use of ART.

Our data revealed a high prevalence of RI (CC <90 ml/min) as measured by CG equation formula (39%) in this HIV-infected population. Although a lower overall prevalence of RI (28%) was recently reported in such patients followed in the US Navy [14], these frequencies are much higher than the prevalence observed in the general population of the same age, i.e. 7.7% in a representative sample of 15 625 US non–institutionalized adults aged 20 years or older [15].

The prevalence of advanced stage of RI (CC <60 ml/min) in our study (4.9% - using CG formula) is close to that reported in the EuroSIDA cohort (3.5% using CG and 4.7% using Modification of Diet in Renal Disease (MDRD) formula) [9], 5.9% in the MACS cohort [16] and 5.7 % in the King's College Hospital Cohort ([17].This figure was slightly higher in the Washington University HIV outpatient clinic (7.3%) [18], in the Johns Hopkins HIV cohort (7%) [19] and in a cross sectional survey in Barcelona (7.6%) [20].

The epidemiological differences between the studied populations can explain some of the differences between these results; indeed the traditional risk factors of renal insufficiency (high blood pressure, diabetes, dyslipidemia, age, ethnicity) and those specific to HIV disease are differentially distributed in the various studies. The different definitions of RI used in the studies (i.e.; acute versus chronic RI where confirmed value is required, additional adjustment of formulae for body surface area) could also contribute to the differences noticed between the studies. Conversely to the overall prevalence of RI, the prevalence of advanced RI is close to what has been reported in the general population: 4.7% in the US population [15], 5.7% in a Galician population

whose average age was 49.5 years [21], 5.6 % in the control group of study conducted in Catalona [20].

In our study, patients with RI were more likely to be female, older, to have a low BMI, high blood pressure or an exposure to tenofovir or indinavir >1 year.

The gender, age and BMI reflect the physiological changes of the glomerular filtration rate which are moreover taken into account in the CG formula. These factors are thus logically identified in our study as in most of the available literature [9, 10, 14, 18, 19, 22]. In one report [20], the presence of lipoatrophy was also independently associated with advanced RI; we did not study this factor but this finding is compatible with the association of a low BMI with RI.

High blood pressure, which is a well known risk factor for renal function impairment in the general population, was associated with advanced RI within our HIV-infected population, as in previous but not all reports [9, 14, 18]. The increased risk observed among patients with high blood pressure justifies sensitizing physicians to the screening and treatment of hypertension to reduce the likelihood of developing RI.

Conversely to some previous studies [9, 14, 17, 22] we did not identify any association between advanced HIV infection (AIDS stage, low CD4 count) and RI. This does not exclude the hypothesis that advanced HIV disease could be associated (through HIVAN) with severe (CC<30ml/mn) and/or end-stage (CC<15ml/mn) renal insufficiency but this has not be tested as too few patients were diagnosed at these RF stages (n=13). The absence of association with HIV-related factors in our study can also be due to the fact that most of these reports dealt specifically with acute RI which represents a minor part of the cases of RI impairment observed in our study; so in the King's college report more than half of all acute RI s occurred within three months after initiation of HIV care typically in patients with opportunistic infections or HIV-associated malignancies [17].

Despite evidence for a direct renal pathogenic role of HIV [2, 3] only one study has observed an association between high VL and RI [23], an observation we did not replicate. The association of undetectable viral load with RI, found in only one of the multivariate models, is contra intuitive and reflects very likely the potential deleterious effect of some antiretroviral drugs as further discussed.

We did not demonstrate the beneficial effect on renal function (mainly by decreasing HIVAN) of antiretroviral therapy overall, as it has been suggested in other studies [6-7], although the observation of the ORs describing the association of RI and exposure to some antiretroviral drugs is in favour of a protective (OR < 1) renal impact of NNRTIs and PIs other than indinavir (tables 1 and 2). Conversely, we identified an association of the cumulative use, even short (i.e. a few months), of other antiretroviral drugs (indinavir and tenofovir) with renal function impairment. In accordance with other reports [9, 14, 24-28], our results indicate an association of mild RI with the use of tenofovir. In an additional analysis where current use of tenofovir was added to the model,

we found a statistical association between this latter variable but no more with cumulative exposure to the drug. Our results could thus support the hypothesis that tenofovir use may result in functional renal tubular deficits, which could normalize after withdrawal of the drug, but not necessarily in structural defects [29]. A recent report showed a mild but significant difference between change from baseline of the glomerular filtration rate (CG formula) in patients treated three years with tenofovir as compared to those receiving control drug (-2 ml/mn vs + 5 ml/mn) [30]. This study population was nevertheless quite different from an unselected cohort as data came from clinical trials including patients whose median age was younger (36 years), and with few baseline renal abnormalities and risk factors such as hypertension, diabetes and hyperlipidemia. Our data showing an association of tenofovir use and mild (but not advanced) RI in routine practice are not contradictory with these clinical trial results. .We can nevertheless conclude that some factors favouring renal function impairment have to be taken into account before starting tenofovir use either to consider alternative antiretroviral drug or to lead to a closer monitoring of renal function: prexisting RI, recent or concomitant use of nephrotoxic drugs or didanosine (which increases tenofovir plasma concentration), diabetes mellitus, high blood pressure [9, 17, 29, 30, 31]. One study showed also the deleterious effect of the co-prescription of boosted PIs [32].

In our study indinavir was associated with advanced RI. This finding has been reported by other authors and is in accordance with the leading mechanism of nephrotoxicity of this drug [14, 33-35]. Nevertheless the decreasing use of this drug in current practice limits the deleterious public health impact of this molecule at least in industrialized countries.

We did not find as others any association of HCV co-infection with RI. This is probably due to the fact that, in previous reports, HCV co-infection was associated either with late–onset acute RI [17] or observed in patients with advanced chronic hepatitis or cirrhosis [31].

The susceptibility to RI of black patients, considered as especially susceptible to HIVAN, could not be evaluated as ethnicity is not registered in our data-base. We can nevertheless attest that patients enrolled in the Aquitaine cohort are very mostly of white ethnic origin.

Some limitations of our study should be noted as causal relationships, including association between RI and exposure to antiretroviral drugs, cannot be formally established from a cross-sectional survey design. We advertise for carefully designed and conducted prospective follow-up studies to undoubtedly identify the factors associated with the occurrence of RI; such cohorts should also allow distinguishing acute from chronic RI [9, 19].

Another possible limitation of the current study is the use of the CG formula to assess the renal function. This assessment is indeed an estimation and can lead to misclassification of some patients. Hence, CG and MDRD are both admitted formulas for renal function estimation [12, 36-38]. There is no general consensus in HIV-infected patients as to the most appropriate formula to use for estimating the glomerular filtration rate (GFR) although the CG formula may be more appropriate in younger and thin subjects, that is mainly the case in HIV-infected patients [39]. In our study

comparisons of data using CG formula and modified MDRD-based calculations are in favour of a slight underestimation of prevalence of RI, mainly mild, when estimated with CG formula. Recently in an HIV-infected population the CG formula was found at least equal to the MDRD one with regard to GFR-measurement with [^{125}I]-iothalamate, considered as the gold standard [40].

In conclusion, results from the current study indicate the importance of the investigation of renal function among HIV-infected patients in care, especially in women, older patients, those with low BMI, and/or treated by tenofovir or indinavir.

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Appendix

The Groupe d'Epidemiologie Clinique du Sida en Aquitaine (GECSA) steering the ANRS CO3 Aquitaine Cohort is organized as follows:

Scientific committee: F. Dabis (Chair and Principal Investigator), M. Dupon, P Mercié, P. Morlat, JL. Pellegrin, and JM. Ragnaud.
Epidemiology, Methodology: M. Bruyand, G. Chêne, F. Dabis, S. Lawson-Ayayi, R. Thiébaut.
Infectious diseases, Internal Medicine: M. Bonarek, F. Bonnal, F. Bonnet, N. Bernard, O. Caubet, L. Caunègre, C. Cazanave, J. Ceccaldi, FA Dauchy, C. De La Taille, S. De Witte, M. Dupon, P. Duffau, H. Dutronc, S. Farbos, MC Gemain, C. Greib, D. Lacoste, S. Lafarie-Castet, P. Loste, D. Malvy, P. Mercié, P. Morlat, D. Neau, A. Ochoa, JL. Pellegrin, JM. Ragnaud, S. Tchamgoué, JF. Viallard.
Immunology: I. Pellegrin, P. Blanco, JF. Moreau.
Virology: H. Fleury, ME. Lafon, B. Masquelier.
Pharmacology: D. Breilh.
Pharmacovigilance: G. Miremont-Salamé.
Data collection: MJ. Blaizeau, M. Decoin, S. Delveaux, S. Gillet, C. Hannapier, S. Labarrère, V. Lavignolle-Aurillac, B. Uwamaliya-Nziyumvira.
Data management: S. Geffard, G. Palmer, D. Touchard.