

Inflammatory status hepatic enzymes and serum creatinine in HIV–, HIV+ and HIV-TB co-infected adult Central Africans

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Background and aim: Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome is a major public health issue in Africa. The objective of this study was to determine which of isolated HIV-infection, isolated naive pulmonary tuberculosis (PTB), or naive HIV-PTB coinfection was more harmful to inflammatory, hepatic, and renal functions.

Methods: This cross-sectional study was undertaken among ten patients with isolated HIV infection, ten patients with isolated naive HIV infection, ten patients with isolated PTB and 32 patients with HIV-PTB coinfection, with the aim of determining which group had the highest levels of oxidative stress and hepatic and renal dysfunction markers. Serum aminotransferase (AST), alanine transferase (ALT), gamma-glutamyl transferase (GGT), and creatinine measurements were compared across the three groups of patients, who were managed from admission in the pulmonology division of the Brazzaville Teaching Hospital, Congo.

Results: HIV patients had the highest levels of ALT, GGT, and creatinine before and after adjusting for age and sex. Adjusted levels of AST, ALT, GGT, and creatinine were higher in HIV-PTB coinfection patients than in sero-negative PTB patients.

Conclusion: There is a significant association between HIV infection and increase in concentration of ALT, GGT, and creatinine.

Keywords: Africa, tuberculosis, HIV-tuberculosis coinfection, renal function

Background

It is well-known that the HIV/AIDS pandemic is responsible for the resurgence of tuberculosis (TB), with increased morbidity and mortality worldwide.¹ Developing settings such as sub-Saharan Africa and South-East Asia are most vulnerable to this pandemic.¹

The HIV/AIDS pandemic has led to 9% of all new TB cases worldwide, 31% of which are in Africa.² TB is the top cause of morbidity and mortality in patients suffering from HIV/AIDS.^{3,4} There is a synergistic interaction between HIV and *Mycobacterium tuberculosis*, with each accentuating the progression of the other.⁵⁻⁷

In patients with TB, acute renal failure is one of the factors significantly and independently associated with mortality.⁸ Renal structure and function are often compromised in HIV/AIDS patients.⁹⁻¹¹

Mortality is higher among HIV/AIDS patients not on antiretroviral therapy and those with elevated liver enzymes.¹² A recently published prospective study from Uganda showed that cumulated mortality among HIV-infected patients diagnosed with TB at baseline or follow-up was higher than in those HIV-infected patients without TB.¹³ Moreover, markers of inflammation are present in atherosclerotic populations.¹⁴

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Alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) are now considered markers of inflammation with immune dysfunction in HIV¹⁵ and oxidative stress.¹⁶ HIV infection results from chronic immune system activation and inflammatory cytokine release.

In terms of outcome, the mortality of HIV-infected patients with TB is comparatively higher than that of HIV-negative TB patients.¹⁷ Recent developments have focused on ongoing challenges in the pathophysiology, diagnosis, and treatment of HIV-related kidney disease.¹⁸ However, no baseline data on oxidative inflammatory hepatic and renal functions according to HIV status, TB, and their concurrence are available. Thus, the present research aimed to determine which of isolated naive HIV-infection, isolated naive pulmonary TB (PTB), or naive HIV-PTB coinfection is more harmful on inflammatory, hepatic, and renal functions.

Materials and methods

This cross-sectional and comparative study, approved by the local Research Ethics Committee of the Marien Ngouabi University, Brazzaville, Republic of Congo, was conducted in March, randomly selected from 2006 to 2011.

The study was undertaken according to the Helsinki declaration after written consent was obtained from consecutive adult patients managed within the division of Infectious Diseases at Brazzaville Teaching Hospital.

Inclusion criteria included admission for naive isolated PTB, naive isolated HIV-infected, and HIV-PTB coinfection. Exclusion criteria were: age < 18 years; hepatitis; cigarette smoking; history of drug and/or alcohol abuse (defined as ≥ 4 drinks/day in men and ≥ 3 drinks/day in women), previous anti-TB therapy or antiretroviral treatment; viral hepatitis A, B, C, or E; and Epstein–Barr virus.

From 60 eligible patients, 52 were accepted into the study (response rate of 86.6%).

Diagnosis of PTB was based on the WHO criteria: a positive culture for *Mycobacterium tuberculosis* or negative culture associated with clinical and radiological features.¹⁹ Diagnosis of HIV-infection was based on clinical criteria from WHO²⁰ and the Centers for Disease Control and Prevention.²¹ The patients with AIDS had a CD4 count of <200.

Demographic characteristics (age, sex, sex ratio) and laboratory measurements were obtained from the patients. Serum liver enzymes (AST, ALT, and GGT) were measured for hepatic function, while serum creatinine was measured for renal function, using drawn venous blood at admission and after a 10-hour overnight fasting. Venous blood samples were

collected for quantitative C-reactive protein (CRP) analysis using TURBILYTE-CRPs (Tulip Diagnostics, Goa, India) according to the manufacturer's instructions, with a detection limit of 0.5 mg/L and measuring range of 0–22 mg/L.

The serum was separated after centrifugation of the blood and kept frozen at -20°C before analysis at the National Laboratory of Public Health in Brazzaville, Republic of Congo.

Serum AST was evaluated by a kinetic determination: malate dehydrogenase was used to catalyze the reaction between oxaloacetic acid and $\beta\text{-NADH}_2$, forming lactic acid and $\beta\text{-NAD}$. Serum ALT was also evaluated by a kinetic determination: lactate dehydrogenase was used to catalyze the reaction between pyruvic acid and $\beta\text{-NADH}_2$, forming lactic acid and $\beta\text{-NAD}$. Serum GGT was evaluated using an enzymatic colorimetric method. Finally, serum creatinine was measured using an alkaline picrate method developed by Jaffe two centuries ago and modified for routine practice in sub-Saharan Africa.²²

All laboratory measurements were performed using bioMérieux reagents and an automated analyzer, using the VIDAS TPSA kit (bioMérieux, Marcy l'Etoile, France). The inter-assay coefficients of variation of these laboratory measurements were as follows: AST, 0.8%; ALT, 0.5%; GGT, 0.6%; and creatinine, 1.1%. These were within the 0.87%–2.1% interval.

Statistical analysis

The data were expressed as frequency, ratio, and proportions for qualitative variables and as mean \pm standard deviation (SD) for continuous variables.

One-way analysis of variance (ANOVA) with Bonferroni post-hoc test for multiple comparisons was used to compare the means of AST, GGT, CRP, and creatinine across the study groups before and after adjusting for sex and age. A P value <0.05 was considered statistically significant. SPSS[®] software for Windows (v 19.0; SPSS Inc, Chicago, IL) was used for analysis of data.

Results

Patient characteristics

Demographic and clinical characteristics for the 52 patients included in the study are shown in Table 1. There was a predominance of females, with a female to male ratio of 3:1 in average; 4:1 in the naive HIV-PTB coinfection and 2:1 in isolated naive HIV sero-positive groups. However, there was a predominance of males, with a male to female ratio of 2:1, in the isolated naive PTB group. Two-thirds of the participants had naive HIV-PTB coinfection.

Table 1 Demographic and clinical characteristics of the study population

Variables	Nor mean \pm SD	%
Gender		
Male	13	25
Female	39	75
Age (years)	37 \pm 10.8	
Groups		
HIV and PTB coinfection	32	61.5
HIV+ and PTB-	10	19.2
PTB+ and HIV-	10	19.2

Abbreviations: HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis; SD, standard deviation.

Comparisons

Table 2 compares the mean values of age, AST, ALT, GGT, CRP, and creatinine, which varied significantly (ANOVA: $P < 0.05$) across the groups. The highest age and levels of ALT, GGT, creatinine, and CRP were observed in HIV+ and PTB+ patients. However, the highest mean AST was in HIV- and PTB+ patients.

After adjusting for age and sex (Table 3), the means of AST, ALT, GGT, CRP, and creatinine varied highly significantly ($P < 0.01$) across the study groups. The highest concentrations of ALT, GGT, creatinine, and CRP were reported among naive HIV+ patients, while the highest level of AST was in patients with HIV-PTB coinfection.

Discussion

The present study demonstrated that isolated naive infection was associated with higher levels of ALT, GGT, and creatinine before and after adjusting for age and sex.

However, isolated naive HIV-PTB coinfection patients had higher levels of AST, ALT, GGT, and creatinine than naive PTB patients without HIV infection.

In sub-Saharan Africa, females are more likely to use medical facilities than males. On this continent, however, males have

Table 2 Comparisons of characteristics across the groups without adjusting for age and sex

Variables	HIV+ and PTB+, n = 32 naive	HIV+ and PTB-, n = 10	HIV- and PTB+, n = 10
Age (years)	37 \pm 10.8	38 \pm 10.5	32 \pm 8.5
AST (U/L)	7.7 \pm 4.9	8.7 \pm 4.5	15.7 \pm 10.8
ALT (U/L)	11.2 \pm 6.2	27.5 \pm 5.5	9.1 \pm 8.1
GGT (U/L)	42.5 \pm 10	55.6 \pm 10.2	32.3 \pm 5.1
Creatinine (mg/dL)	0.6 \pm 0.3	1.5 \pm 0.5	1.3 \pm 0.4
CRP (mg/L)	7.6 \pm 2.6	22.4 \pm 3.4	17.6 \pm 2.9

Abbreviations: ALT, alanine transferase; AST, aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis.

Table 3 Comparisons of characteristics across the study groups after adjusting for age and sex

Variables	Naive HIV-PTB coinfection	Naive HIV+	Naive PTB
AST (U/L)	15 \pm 5	9 \pm 4.8	13.2 \pm 9
ALT (U/L)	13.2 \pm 5	29.4 \pm 7.2	8.3 \pm 6.4
GGT (U/L)	44.5 \pm 11	59.7 \pm 9.5	30 \pm 4.9
Creatinine (mg/dL)	1.4 \pm 0.4	2.1 \pm 0.6	1.2 \pm 0.3
CRP (mg/L)	13.8 \pm 5.3	45.7 \pm 6.9	34.6 \pm 4.8

Abbreviations: ALT, alanine transferase; AST, aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis.

a higher prevalence of TB infection than females,²³ a tendency reflected in this study.

HIV infection and laboratory data

Patients with isolated naive HIV infection were older than the rest of the participants. This may explain the positive and significant association between higher levels of ALT, GGT, and HIV infection itself. Aging is related to oxidative stress²⁴ and decline in renal function.

Coupled with the aging process, the extended exposure of these adults to HIV, the persistent activation of immune cells by the virus, inflammation, and oxidative stress related to HIV-infection,¹⁵ will probably mean that they have increased risk of impaired kidney function compared with their non-HIV-infected counterparts.^{9-11,25,26}

Antiretroviral treatment might suppress HIV replication, with a reduction in HIV-related mortality, opportunistic disease, malignancy, cardiovascular disease, and metabolic, bone, renal and liver diseases, not unlike that in aging patients.²⁵ CRP is not known as a biomarker of inflammation in HIV-related morbidity.¹⁵

Clinical implications

The present study emphasizes the need for a resource-appropriate screening algorithm for inflammatory hepatic and renal disease biomarkers, both as part of anti-TB and antiretroviral therapy eligibility and pretreatment assessment.

HIV/AIDS is associated with both direct (HIV-associated nephropathy) and indirect (opportunistic infections such as TB and HIV-hepatitis C coinfection as well as medication-related) renal complications.

HIV and HIV-PTB coinfection pose a risk to older individuals, with potential complex treatment challenges. Therefore, older adult at risk need to get tested for the virus and take steps to protect themselves and their loved

ones from becoming infected. Research is needed to help health professionals tackle the often-complicated treatment of HIV infection, PTB, and related illnesses in older patients.

In case of diagnosis of renal failure of unknown etiology, provision of antiretroviral therapy may improve renal function.^{27–30}

HIV-infected patients do respond well to the standard 6-month anti-TB therapy.⁵ Guidelines for the management of HIV-TB coinfection are still evolving. Timely anti-TB and antiretroviral treatment may improve the outcomes of HIV-PTB coinfection.⁵ However, pharmacokinetic interactions occur between rifampicin and protease inhibitors, and non-nucleoside reverse transcriptase.^{31–35} Our findings recommend that all PTB patients should be tested for HIV.³⁶

Study limitations

It should be acknowledged that these findings apply only to this small group of selected patients and generalization to other series might be premature in the absence of additional data to confirm the results of this study. In addition, the cross-sectional design limits the conclusion with regard to the causal association of HIV itself or HIV-PTB coinfection with oxidative stress and hepatic and renal function markers.

Diet, ethnicity and lean mass may impact on the values of renal function in HIV and PTB coinfection.³⁷

These limitations notwithstanding, the findings of the present study have practical implications for managing HIV-infected patients and patients with HIV-PTB coinfection in Brazzaville, Republic of Congo.

In the future, there is a need to adjust for right inflammation markers, hepatic and creatinine concentrations.

Conclusion

This study found a significant association between HIV infection and an increase in serum levels of ALT, CRP, GGT, and creatinine.

Disclosure

The authors declare no conflicts of interest in this work.

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