

# Serum electrolytes and renal alterations in HIV-seropositive Mexican subjects

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## Abstract

To examine potential risk factors associated with biochemical alterations in renal function in a population diagnosed with HIV/AIDS undergoing antiretroviral treatment.

This is an observational, transversal, and relational design study that included 179 HIV-seropositive subjects. Glucose serum, cholesterol, triglycerides, total proteins, albumin, creatine, urea, blood urea nitrogen (BUN), and electrolytes levels were determined for each individual. Renal function was evaluated through the glomerular filtration rate (GFR), using the CKD-EPI equation. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m<sup>2</sup>. Univariate model significant variables, with a 95% confidence interval (CI), were included in a multivariate logistic regression analysis.

CKD prevalence in patients was 7.3%, with comorbidities of 7.8% for type 2 diabetes mellitus, 7.3% for arterial hypertension, and 35.2% for dyslipidemia. Additionally, both hypernatremia and hypophosphatemia were detected in 57% (n = 102) of the patients. Multivariate logistic regression suggested that CD4+ T cell count < 200 (*P* = .02; OR 0.2; CI 95% 0.08–0.8) was associated to hyponatremia; similarly, detectable viral load was associated to hypokalemia (*P* = .02; OR 5.1; CI 95% 1.2–21.3), hypocalcemia (*P* = .01; OR 4.1; CI 95% 1.3–12.3), and hypermagnesemia (OR 3.9; CI 95% 1.1–13.6). Patient age was associated to both hypophosphatemia (*P* = .01; OR 2.4; CI 95% 1.1–5.0) and hypermagnesemia (*P* = .01; OR 2.8; CI 95% 1.1–7.0), and high creatinine levels were associated to nucleoside reverse transcriptase inhibitor treatment (*P* = .001; OR 42.5; CI 95% 2.2–806.9). Lastly, high BUN levels were associated to age (*P* = .03; OR 3.8; CI 95% 1.0–14.4), while GFR 60 to 89 mL/min/1.73 m<sup>2</sup> was associated to dyslipidemia (*P* = .02; OR 2.2; CI 95% 1.1–4.5).

CD4+ T cell and viral load were the main factors associated with renal biochemical alterations.

**Abbreviations:** AIDS = acquired immune deficiency syndrome, ART = antiretroviral therapy, BMI = body mass index, BUN = blood ureic nitrogen, CKD = chronic kidney disease, CKD-EPI = chronic kidney disease epidemiology collaboration, CG = Cockcroft-Gault, eGFR = estimated glomerular filtration rate, GFR = glomerular filtration rate, HIV = human immunodeficiency virus, HIVAN = human immunodeficiency virus associated nephropathy, II = integrase inhibitors, IP = protease inhibitors, MDRD = modification of diet in renal disease, NNRTI = non-nucleosides reverse transcriptase inhibitors, NRTI = reverse transcriptase nucleosides inhibitors, .

**Keywords:** HIV, CKD, serum electrolytes, ART

Editor: Mehmet Bakir.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets generated during and/or analyzed during the current study are publicly available.

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How to cite this article: Garza Tovar OA, Pérez AA, Pérez ME, Robledo IU, Galarza FF, Márquez FC. Serum electrolytes and renal alterations in HIV-seropositive Mexican subjects. *Medicine* 2021;100:20(e26016).

Received: 10 December 2020 / Received in final form: 17 March 2021 / Accepted: 29 April 2021

<http://dx.doi.org/10.1097/MD.00000000000026016>

## 1. Introduction

The rise of life expectancy as a result of the antiretroviral therapy (ART) in subjects with human immunodeficiency virus (HIV) has increased the prevalence of chronic medical conditions, such as kidney disease.<sup>[1]</sup>

Kidney disease prevalence in subjects with HIV infection is reported between 3.5% and 48.5%.<sup>[2,3]</sup> Chronic kidney disease (CKD) is regulated by complex interactions between virus presence (both renal cell infection and viral protein effects), genotype, patient response to treatment, environmental factors, and antiretroviral treatment. Advanced age, ethnicity, coinfection by hepatitis C, and low CD4+ T cell count have been reported as independent risk factors associated with the development of CKD.<sup>[2,4]</sup> HIV-infected subjects have a greater risk of developing acute kidney injury (AKI) and CKD, which are frequent complications and the main causes of mortality.<sup>[2,4,5]</sup>

The presence of proteinuria ( $\geq 3.5$  g/dL), azotemia, hypoalbuminemia, and, occasionally, hypocalcemia characterizes kidney disease associated with HIV infection. Electrolyte anomalies and mineral metabolism alteration in HIV/AIDS subjects have contributed to, among other clinical problems, the development of bone and cardiovascular diseases.<sup>[6]</sup> A wide spectrum of disorders, such as acute kidney failure, chronic glomerular

disease, HIV-associated nephropathy, hydro electrolytic, and acid-base disorders were identified as leading to terminal phase renal disease.<sup>[7–9]</sup> Kidney injury caused by HIV infection along with antiretroviral treatment, drugs for treating concurrent infections (superimposed to the central nervous system, gastrointestinal tract, or suprarenal glands), may cause anomalies in amino acid transport, uric acid, as well as volume loss and alterations in electrolytic metabolism<sup>[10]</sup>; these are common alterations in HIV infection and can be associated to mortality.<sup>[8]</sup>

More renal disorders have currently been reported within the context of HIV infection and its treatment, such as nephrotic syndrome and proximal tubular damage, which have been associated with the administration of tenofovir disoproxil fumarate and the use of some protease inhibitors such as lopinavir/ritonavir and atazanavir. These renal disorders are caused by the reductions in estimated glomerular filtration rate (eGFR).<sup>[11]</sup>

The objective of this study was to examine possible risk factors associated with biochemical alterations in renal function in a population comprising individuals diagnosed with HIV/AIDS undergoing antiretroviral treatment. Thus, we hypothesized that renal function is altered by multiple risk factors in subjects with HIV undergoing antiretroviral therapy.

## 2. Subjects and methods

The current study corresponds to an observational, transversal, and relational design. Participants were recruited from Prevention and Care for AIDS and Sexually Transmitted Infection Care Centers (CAPASITS) in Torreon, Coahuila, Mexico, and the Integral Care System of Gomez Palacio, Durango, Mexico (SAI). All participants had a viral charge and a CD4+ T cell count. Serum was used to determine glucose, cholesterol, triglycerides, total proteins, albumin, creatinine, urea, blood ureic nitrogen (BUN), and the following electrolytes: Sodium [ $\text{Na}^+$ ], potassium [ $\text{K}^+$ ], calcium [ $\text{Ca}^{+2}$ ], magnesium [ $\text{Mg}^{+2}$ ], phosphorus [ $\text{P}^{-3}$ ] and chlorine [ $\text{Cl}^{-1}$ ]. This study was approved by the Bioethics Committee of the Department of Medicine of the Universidad Autónoma de Coahuila - Torreón Unit. (C.B/08-10-17).

### 2.1. Participants

One hundred and seventy nine HIV-seropositive subjects over 18 years old undergoing antiretroviral treatment participated in this study. All participants signed an informed consent letter and completed a questionnaire, in which individuals described their pathological and non-pathological personal history, medical record review, and treatment adherence.

Arterial hypertension was defined as systolic arterial pressure  $\geq 140$  mmHg, diastolic arterial pressure  $\geq 90$  mmHg, or with antihypertensive treatment. The presence of dyslipidemia was defined as total cholesterol  $\geq 240$  mg/dL and/or triglycerides  $\geq 200$  mg/dL,<sup>[12]</sup> while the presence of type 2 diabetes mellitus was defined like a fasting glucose  $\geq 125$  mg/dL or with hypoglycemia/insulin treatment.<sup>[13]</sup>

Bodyweight was measured with an electronic scale (Beurer, GmbH Soflinger, Str. 218 Germany) and a stadiometer was used to measure stature. Body mass index was classified based on WHO's international criteria as follows: underweight ( $< 18.5$  kg/m<sup>2</sup>), normal weight (18.5/24.9 kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>), degree I obesity (30–34.9 kg/m<sup>2</sup>), degree II obesity (35–39.9 kg/m<sup>2</sup>), and degree III obesity ( $\geq 40$  kg/m<sup>2</sup>).<sup>[14]</sup>

Creatinine, blood urea nitrogen, urea, glucose, cholesterol, triglycerides, total proteins, and albumin determinations were determined in serum by dry chemistry through colorimetric tests with the ARCHITECT c4000 chemistry system. A VITROS 250 dry chemical system was used for the following serum electrolyte determinations: sodium [ $\text{Na}^+$ ], potassium [ $\text{K}^+$ ], calcium [ $\text{Ca}^{+2}$ ], magnesium [ $\text{Mg}^{+2}$ ], phosphorus [ $\text{P}^{-3}$ ], and chloride [ $\text{Cl}^{-1}$ ].

The values of 0.5–1.5 mg/dL, 20–40 mg/dL and 7–20 mg/dL creatinine, urea, and BUN, respectively, were at levels considered within the normal range. Low (hypo-) and high (hyper-) levels for serum electrolytes were defined, respectively, as follows: hypo- and hypernatremia as sodium serum levels  $< 137$  and  $> 145$  meq/L, hypo- and hyperkalemia as potassium serum levels  $< 3.5$  and  $> 5.1$  meq/L, hypo- and hyperchloremia as chloride serum levels  $< 98$  and  $> 107$  meq/L, hypo- and hypercalcemia calcium serum levels  $< 8.4$  and  $> 10.2$  mg/dL, hypo- and hyperphosphatemia as phosphorus serum levels  $< 2.5$  and  $> 4.5$  mg/dL, and hypo- and hypermagnesium as magnesium serum levels  $< 1.6$  and  $> 2.3$  mg/dL. Hypoalbuminemia was defined as albumin  $< 3.5$  g/dL, hypoproteinemia as 6.3 g/dL, hyperglycemia as  $> 125$  mg/dL, hypercholesterolemia as  $> 200$  mg/dL, and hypertriglyceridemia as  $> 150$  mg/dL, based on the values provided by the VITROS 250 equipment.

CD4+ T cell count was determined by flow cytometry and viral load was through quantitative PCR. Both values were obtained from each patient's clinical history. The CD4+ T cell count was categorized into three classes as follows:  $< 200$  cel/mm<sup>3</sup>, 201–500 cel/mm<sup>3</sup>, and  $> 500$  cel/mm<sup>3</sup>. Similarly, viral load was categorized into detectable ( $> 50$  copies/mL) and non-detectable ( $< 50$  copies/mL), based on HIV centers for disease control and prevention (CDC) criteria.<sup>[15]</sup>

Glomerular filtration rate (GFR) was used to evaluate renal function utilizing the CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration) from creatinine serum concentration, gender, age, and ethnicity data. Glomerular filtration rates were classified based on KDIGO (The Kidney Disease: Improving Global Outcomes) 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease (CKD) international guidelines into five groups: GFR  $> 90$  mL/min/1.73 m<sup>2</sup>, GFR 60–89 mL/min/1.73 m<sup>2</sup>, GFR 59–30 mL/min/1.73 m<sup>2</sup>, GFR 29–15 mL/min/1.73 m<sup>2</sup>, and GFR  $< 15$  mL/min/1.73 m<sup>2</sup>.<sup>[16]</sup>

Patients were classified into 2 groups based on years of antiretroviral treatment:  $\geq 5$  years and  $\leq 5$  years. Antiretroviral treatments were classified by family medicine into reverse transcriptase nucleosides inhibitors (NRTIs), reverse transcriptase nucleosides-tenofovir disoproxil fumarate [NRTIs (tenofovir disoproxil fumarate)], non-nucleosides reverse transcriptase inhibitors (NNRTI), integrase inhibitors (II), and protease inhibitors (IP). All 179 subjects included in the study were under highly active antiretroviral therapy, in which 13 different schemes were identified (Table 1).

### 2.2. Statistical analysis

Clinical and sociodemographic variables were analyzed through measures of central tendency (mean and standard deviation) and percentages. Only significant (CI at 95%) variables obtained from the univariate model were included in the multivariate logistic regression model. To search for possible risk factors regarding the development of biochemical alterations, data were analyzed according to gender, age, arterial hypertension, type 2

**Table 1**  
Highly active antiretroviral therapy (HAART) schemes identified in 179 HIV-seropositive subjects.

Scheme type <sup>a</sup>	n (%)
NNRTI + NRTI + NRTI(TDF)	90 (50.3)
2 IP + NRTI + NRTI(TDF)	32 (17.9)
IP + NRTI + NRTI(TDF)	17 (9.5)
2 NRTI + NNRTI	13 (7.3)
2 IP + 2 NRTI	10 (5.6)
2 NRTI + IP	5 (2.8)
NRTI + NRTI(TDF) + II	4 (2.2)
2 NRTI + II	2 (1.1)
2 IP + NRTI(TDF) + NNRTI	2 (1.1)
NRTI + NNRTI	1 (0.6)
2 NRTI + IP	1 (0.6)
2 NRTI + NRTI(TDF) + IP	1 (0.6)
2 NRTI + NNRTI	1 (0.6)

<sup>a</sup>Values expressed in frequencies and percentages (%).

NRTI = reverse transcriptase nucleosides inhibitors, NRTI(TDF) = reverse transcriptase nucleosides (tenofovir disoproxil fumarate), NNRTI: nonnucleosides reverse transcriptase inhibitors, II = integrase inhibitors, IP = protease inhibitors.

diabetes mellitus, dyslipidemia, treatment years, body mass index, hypoalbuminemia, hypoproteinemia, CD4+ T cell count, viral load, diarrhea (>15 days), and family antiretroviral treatment. Data were analyzed using SPSS 25.0 (IBM, Chicago Illinois) statistical analysis package.

### 3. Results

#### 3.1. Sociodemographic and clinical characteristics

One hundred and seventy nine subjects diagnosed with HIV/AIDS were included in the study, 77.1% were males and 22.9% females. Ages ranged from 19 to 70 years old, with a mean of 39.3 (± 10.9) years of age. The population’s self-referred alcohol consumption was 54.2% and tobacco use was 38%. Identified comorbidities included: type 2 diabetes mellitus (7.8%), arterial hypertension (7.3%) and dyslipidemia (35.2%). Viral load range was 1.3 log<sub>10</sub> to 5.76 log<sub>10</sub> copies/mL, with a viral load mean of 4.06 log<sub>10</sub> (± 4.8 log<sub>10</sub>) copies/mL, were an undetectable viral load of 76% and a detectable viral load of 18.4%. The mean CD4 + T cell count was 455.2 (± 275.7) cel/mm<sup>3</sup>. BMI range was between 15.79 and 42.72 kg/m<sup>2</sup>, with a mean of 25.65 (± 4.98 kg/m<sup>2</sup>); with 28.5% overweight, 12.3% degree I obesity, and 5.6% degree II obesity.

Mean glomerular filtration rate (CKD-EPI) was 116.27 (± 43.42) mL/min/1.73 m<sup>2</sup> were GFR values were distributed as follows: 68% for GFR > 90 mL/min/1.73 m<sup>2</sup>, 24% for GFR 60–89 mL/min/1.73 m<sup>2</sup>, 5.6% for GFR 59–30 mL/min/1.73 m<sup>2</sup>, 1.1% for GFR 29–15 mL/min/1.73 m<sup>2</sup>, and 0.6% for GFR < 15 mL/min/1.73 m<sup>2</sup> (Table 2).

#### 3.2. Biochemical tests analysis

Serum electrolytes means and deviations were: Na<sup>+</sup> (sodium) 145.13 (±14.45) meq/L, Cl<sup>-</sup> (chloride) 108.34 (±11.28) meq/L, P<sup>-3</sup> (phosphorus) 3.51 (± 1.20) mg/dL, Ca<sup>+2</sup> (calcium) 9.75 (±1.24) mg/dL, Mg<sup>+2</sup> (magnesium) 2.13 (±0.349) mg/dL, and K<sup>+1</sup> (potassium) 4.35 (±0.58) meq/L. According to these results, electrolyte level alteration, ordered by frequency, were: hypernatremia 57% (n=102), hypophosphatemia 57% (102), hyperchloremia 56.3% (n=93), hypercalcemia 29.1% (n=52), and hypermagnesemia 23.5 (n=42).

**Table 2**  
Sociodemographic data, clinical variables, and immunological parameters.

Variable	Value (mean ± S.D./%)	n
Age	39.3 ± 10.9	179
Gender		
Male	77.1	138
Female	22.9	41
Sexual preference		
Heterosexual	39.1	70
Homosexual	38.5	69
Bisexual	8.9	16
Tobacco Use	38	68
Alcohol Consumption	54.2	97
Illicit drug use	13.9	25
Combination of drugs	4.4	8
Cocaine	3.9	7
Cannabis	3.9	7
Inhaled drugs	1.11	2
Methamphetamine	0.55	1
Concomitant medications	18.4	33
Years since HIV diagnostic	9.8 ± 6.5	174
Years undergoing ART	7.3 ± 6.2	175
Antiretroviral by type		
NRTI	97.2	174
NRTI (TDF)	79.9	143
NNRTI	58.7	105
IP	36.3	65
II	3.4	6
BMI (kg/m <sup>2</sup> )	25.65 ± 4.98	179
Underweight	2.8	5
Normal weight	50.3	90
Overweight	28.5	51
Degree I obesity	12.	22
Degree II obesity	5.6	10
Type 2 Diabetes Mellitus	7.8	14
Arterial Hypertension	7.3	13
Dyslipidemia	35.2	63
CD4+ T cell (cel/dL)	455.27 ± 275.74	175
>500	36.3	65
499-200	44.1	79
<200	17.3	31
Viral load (copies/mL)*	4.06 log <sub>10</sub> (± 4.8 log <sub>10</sub> )	169
Undetectable (<50 copies/mL)	76	136
Detectable (>50 copies/mL)	18.4	33
GFR CKD-EPI (mL/min/1.73 m <sup>2</sup> )	116.27 ± 43.42	178
>90	68.2	122
60–89	24	43
59–30	5.6	10
29–15	1.1	2
<15	0.6	1

Values are expressed as central tendency measures (means and standard deviation-S.D.) and percentages.

NRTI = reverse transcriptase nucleosides inhibitors, NRTI (TDF) = reverse transcriptase nucleosides (tenofovir disoproxil fumarate), NNRTI = nonnucleosides reverse transcriptase inhibitors, II = integrase inhibitors, IP = protease, GFR = glomerular filtration rate.

(\*)Viral load is expressed in log<sub>10</sub>.

Renal function, evaluated based on creatinine levels, was abnormal (levels ≥1.5 mg/dL) in only 2.8% (n=5) of subjects, while the plasma urea levels were higher than normal values in only 5.6% of patients (n=10). For BUN levels, 8.4% (n=15) of evaluated subjects had levels higher than the normal value.

Total protein levels and albumin were 12.3% (n=22) and 6.1% (n=11), respectively, both lower than the normal range. In addition, hyperglycemia (5.6%, n=10), hypercholesterolemia

**Table 3**  
**Frequency of biochemical alterations identified in 179 HIV-seropositive subjects.**

Variable	n	Mean ± SD	Out of range values % (n)		Reference values (Conventional units)
			Low	High	
Renal biochemical parameters					
Na <sup>+1</sup>	179	145.13 ± 14.45	15.1 (27)	57 (102)	137–145 meq/L
Cl <sup>-1</sup>	179	108.34 ± 11.28	13.4 (28)	56.3 (93)	98–107 meq/L
P <sup>-3</sup>	179	3.51 ± 1.20	57 (102)	6.7 (12)	2.5–4.5 mg/dL
Ca <sup>+2</sup>	175	9.75 ± 1.24	11.7 (21)	29.1 (52)	8.4–10.2 mg/dL
Mg <sup>+2</sup>	174	2.13 ± 0.34	6.1 (11)	23.5 (42)	1.6–2.3 mg/dL
Creatinine	179	0.95 ± 0.53	23.5 (42)	2.8 (5)	0.5–1.5 mg/dL
Urea	179	28.42 ± 9.67	17.3 (31)	8.4 (15)	20–40 mg/dL
K <sup>+1</sup>	174	4.35 ± 0.58	5 (9)	10.1 (18)	3.5–5.1 meq/L
BUN	179	13.26 ± 4.51	6.1 (11)	5.6 (10)	7–20 mg/dL
Other biochemical parameters					
Total proteins	179	8.40 ± 2.24	12.3 (22)	42.5 (76)	6.3–8.2 g/dL
Albumin	179	4.75 ± 1.10	6.1 (11)	26.8 (48)	3.5–5.0 g/dL
Glucose	179	91.59 ± 31.11	-	5.6 (10)	<125 mg/dL
Cholesterol	179	174.55 ± 38.95	-	23.5 (42)	<200 mg/dL
Triglycerides	179	220.11 ± 294.65	-	54.2 (97)	<150 mg/dL

Values are expressed as measures of central tendency (means and standard deviation) and percentages.

(23.5%, n=42), and hypertriglyceridemia (54.2%, n=97) were present in the population of evaluated subjects (Table 3).

### 3.3. Risk factors for electrolytic alterations and renal function parameters

Univariate logistic regression analysis, identified hypoalbuminemia ( $P=.04$ ) CD4+ T cell count  $<200$  cel/mm<sup>3</sup> ( $P=.01$ ) and detectable VL ( $P=.01$ ) as significant variables associated with hyponatremia (lower than 137 meq/L). Additionally, subjects with absolute CD4+ T cell count  $<200$  cel/mm<sup>3</sup> had an odds ratio (OR) of 0.27 (0.089–0.84 CI 95%) of having low sodium serum levels. The only variable significantly associated with hypernatremia (higher than 145 meq/L) was detectable viral load (VL) ( $P=.04$ ) (univariate logistic regression). For hypokalemia (lower than  $<3.5$  meq/L) significantly associated variables were hypoalbuminemia ( $P<.001$ ), hypoproteinemia ( $P=.04$ ), and detectable VL ( $P=.005$ ) (univariate logistic regression).

Hypoalbuminemia and hypoproteinemia were not significant (multivariate analysis) after adjusting for detectable VL; subjects with a detectable VL had an OR of 5.89 (1.22–22.39 CI 95%) of exhibiting low serum potassium levels. For hypochloremia (lower than 98 meq/L), detectable VL ( $P=.01$ ) and absolute CD4+ T cell count  $<200$  cel/mm<sup>3</sup> ( $P=.03$ ) were significant (univariate logistic regression), but not when included in the multivariate analysis. For hypocalcemia (lower than 8.4 mg/dL), hypoalbuminemia ( $P<.001$ ), hypoproteinemia ( $P<.001$ ), and detectable VL ( $P<.001$ ) were significant as well (univariate logistic regression). Hypoalbuminemia and hypoproteinemia were not significant when included in the multivariate analysis and showed that subjects with detectable viral load had an OR of 4.11 (1.37–12.33 CI 95%) of exhibiting low calcium serum levels. For hypophosphatemia (lower than 2.5 mg/dL), significant variables were 20 to 30 years old ( $P=.001$ ), age 50 to 60 years old ( $P=.003$ ), hypoalbuminemia ( $P=.01$ ), and hypoproteinemia ( $P=.01$ ) (univariate logistic regression). Hypoalbuminemia and hypoproteinemia were not significant in multivariate analysis and showed that both subjects with age 20 to 30 years old have an OR of 2.42 (1.16–5.04 CI 95%) and subjects with age 50 to 60 years old have an OR of 0.32 (0.11–0.92 CI 95%) of exhibiting low

phosphorus serum values. For hyperphosphatemia (higher than 4.5 mg/dL), age 20 to 30 years old ( $P=.04$ ), IP ( $P=.03$ ), II ( $P=.008$ ), and treatment  $>5$  years ( $P=.03$ ) were all significant (univariate logistic regression). Neither of these 4 variables were significant after multivariate analysis adjustment. For hypomagnesemia (lower than 1.6 mg/dL) significant effects were observed for hypoalbuminemia ( $P=.002$ ), hypoproteinemia ( $P<.001$ ), and detectable VL ( $P=.002$ ) (univariate logistic regression). The three variables were not significant after multivariate analysis. For hypermagnesemia (higher than 2.3 mg/dL), significant effects were estimated for age of 50 to 60 years old ( $P=.006$ ) and detectable VL ( $P=.01$ ) (univariate logistic regression). Both variables were significant for multivariate analysis and indicated that subjects with age 50 to 60 years old had an OR of 2.89 (1.19–7 CI 95%) and detectable VL had an OR of 3.9 (1.11–13.67 CI 95%) of exhibiting high serum magnesium levels.

The only variable associated with high levels of creatinine (higher than 1.5 mg/dL) was NRTI ( $P=.0014$ ). For BUN (higher than 20 mg/dL), age 30 to 40 years old ( $P=.03$ ) had significant effects. Finally, GFR, 60 to 89 mL/min/1.73 m<sup>2</sup> was significantly associated with dyslipidemia ( $P=.02$ ) (univariate logistic regression) (Table 4).

## 4. Discussion

Renal disease is a common complication of HIV infection and its corresponding treatment. Although the antiretroviral therapy may improve life expectancy in HIV-infected subjects, its use may also increase morbidity in terms of renal function changes in HIV-infected individuals.<sup>[4]</sup> In this study, we evaluated potential risk factors associated to renal alterations in subjects diagnosed with HIV/AIDS undergoing antiretroviral treatment. Among the main findings we observed that CKW was 7.3%, whereas the mean glomerular filtration rate (CKD-EPI) was 116.27 (+ 43.42) mL/min/1.73 m<sup>2</sup>, with comorbidities of 7.8% for type 2 diabetes mellitus, 7.3% for arterial hypertension, and 35.2% for dyslipidemia. In addition, after performing a multivariate logistic regression suggested that CD4+ T cell count  $<200$  was associated to hyponatremia; similarly, detectable viral load was associated to hypokalemia, hypocalcemia, and hypermagnesemia.

**Table 4**  
**Significant risk factors for electrolytic alterations and renal function parameters.**

	s Variable	Univariate analysis			Multivariate Analysis		
		OR	CI 95%	P	OR	CI95%	P
Hyponatremia	Hypoalbuminemia	3.60	0.97–13.28	.04	–	–	–
	CD4 + T cell < 200*	0.25	0.08–0.78	.01	0.27	0.08–0.84	.025098
	Detectable VL	3.04	1.23–7.48	.01	–	–	–
Hypernatremia	Detectable VL	2.19	1.01–4.78	.04	–	–	–
Hypokalemia	Hypoalbuminemia	10.12	2.13–48.04	< .001	–	–	–
	Hypoproteinemia	3.97	0.91–17.20	.04	–	–	–
	Detectable* VL	5.89	1.48–23.34	.005	5.11	1.22–21.39	.02
Hypochloremia	CD4 + T cell < 200	0.30	0.10–0.94	.03	–	–	–
	Detectable VL	3.02	1.18–7.70	.01	–	–	–
Hypocalcemia	Hypoalbuminemia	7.91	2.17–28.86	< .001	–	–	–
	Hypoproteinemia	6.32	2.24–17.86	< .001	–	–	–
	Detectable VL*	4.94	1.88–12.96	< .001	4.11	1.37–12.33	.01
Hypophosphatemia	20–30 years old*	3.02	1.50–6.05	.001	2.42	1.16–5.04	.01
	50–60 years old*	0.23	0.08–0.66	.003	0.32	0.11–0.92	.03
	Hypoalbuminemia	8.26	1.03–65.98	.01	–	–	–
Hyperphosphatemia	Hypoproteinemia	3.91	1.26–12.08	.01	–	–	–
	20–30 years old	3.17	0.96–10.39	.04	–	–	–
	IP	7.04	0.88–55.84	.03	–	–	–
	II	0.12	0.02–0.76	.008	–	–	–
	Treatment > 5 years	3.77	0.98–14.42	.03	–	–	–
Hypomagnesemia	Hypoalbuminemia	7.5	1.66–33.77	.002	–	–	–
	Hypoproteinemia	7.40	2.04–26.84	< .001	–	–	–
	Detectable VL	5.82	1.65–20.46	.002	–	–	–
Hypermagnesemia	50–60 years old*	3.09	1.34–7.15	< .001	2.89	1.19–7.008	.01
	Detectable VL*	4.16	1.20–14.43	.01	3.90	1.11–13.67	.03
Creatinine	NRTI	42.5	2.23–806.97	< .001	–	–	–
BUN	30–40 years old	3.89	1.05–14.41	.03	–	–	–
GFR 60–89	Dyslipidemia	2.23	1.10–4.53	.02	–	–	–

Univariate logistic regression was performed with  $\chi^2$  test. For the multivariate logistic regression model, the significant variables obtained were included taking into account CI at 95%. (–) P values not significant. (\*) significant P values. VL = viral load, IP = protease inhibitors, II = integrase inhibitors, NRTI = nucleoside reverse transcriptase inhibitors, BUN = blood ureic nitrogen.

There are different equations to estimate creatinine depuration or GFR, including Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The CG and MDRD equations have been derived from subjects with a GFR  $\leq 90$  mL/min/1.73 m<sup>2</sup>, these have not been validated in subjects with normal renal function and tend to underestimate actual higher GFR values.<sup>[17]</sup> Cristelli et al, 2017 suggest that the MDRD equation could underestimate renal function for GFR higher 60 mL/min/1.73 m<sup>2</sup>, concluding the CKD-EPI equation must be considered as the first choice method for evaluating renal function in HIV-infected populations.<sup>[3]</sup> The latest recommendations published by the European AIDS Clinical Society (EACS) Guidelines for 2019 established the CKD-EPI equation as the first choice method for evaluating renal function in HIV-infected populations.<sup>[18]</sup>

In this study, CKD prevalence was 7.3%, defined as GFR < 60 mL/min/1.73 m<sup>2</sup>, utilizing the CKD-EPI formula. This percentage was considerably higher in comparison to previous studies performed in populations with similar characteristics published between 2011 and 2014, CKD prevalence values (GFR < 60 mL/min/1.73 m<sup>2</sup>, CKD-EPI equation) of 4.9% in the United States,<sup>[19]</sup> 2.0% in the United Kingdom,<sup>[20]</sup> and 1.5%<sup>[21]</sup> and 3.8% in Brazil.<sup>[22]</sup> Prevalence variability in these studies may be attributed to differences in study design, demographic characteristics, and/or ethnicity.<sup>[23]</sup>

Among the risk factors for the development of renal biochemical alterations, the presence of illicit drug use (cannabis,

cocaine, methamphetamines and inhaled drugs) was not taken into account in this study because none of the users showed GFR < 60 mL/min/1.73 m<sup>2</sup>, as well as the use of concomitant medications. Moreover, risk factors found in the current study for the presence of high creatinine levels ( $\geq 1.5$  mg/dL) and GFR (< 90 mL/min/1.73 m<sup>2</sup>) were the ART scheme with NRTI and the presence of dyslipidemia, respectively. These results agree with previous reports by Cristelli et al, 2018 HIV-seropositive population from Barcelona, Spain<sup>[24]</sup> and by Emem et al, 2008 in an HIV-seropositive population of 400 subjects from Nigeria,<sup>[25]</sup> who describe said factors as independent risk factors for the development of the renal disease. Nevertheless, other risk factors for renal function deterioration in subjects with preserved initial GFR and CKD have been previously described, and they included age, gender (male), ethnicity, BMI, type 2 diabetes mellitus, hypertension, cardiovascular event history, hepatitis C virus co-infection, low CD4+ T cell count, high viral load, decreased serum albumin levels, proteinuria, albuminuria, antiretroviral drugs such as tenofovir, atazanavir, lopinavir, and indinavir,<sup>[26–29]</sup> for which we did not observe any relation to the renal function. This might be related to the low presence of these factors in our population. Likewise, the fact that a relationship between these factors and the presence of CKD was not obtained, it does not undermine its impact at a renal level.

Renal and electrolytic disorders are common in subjects that live with HIV infection.<sup>[10]</sup> Multiple authors have reported decreased Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup> serum electrolytes in HIV-

seropositive subjects.<sup>[30–34]</sup> These reports contrast with the main findings in our study, where we found biochemical alterations represented by hypernatremia and hyperchloremia. At the same time, these findings agree with Emejulu et al, where hypernatremia (47.5%) was reported as the most frequent alteration in a sample of 115 naive subjects and a positive association between the ion  $\text{Na}^+$  and  $\text{Cl}^-$  was also described. It is important to stress that the findings were obtained from a treatment-naive population, which can be a key point in the development of electrolytic alterations.<sup>[35]</sup>  $\text{Na}^+$  and  $\text{Cl}^-$  levels are closely regulated together and conditions prepossessing hypo/hypernatremia may also cause hypo/hyperchloremia.<sup>[8]</sup> Olaniyan et al in 2004 described that  $\text{Cl}^-$  in serum followed the same pattern as  $\text{Na}^+$  in subjects because  $\text{Na}^+$  is present (in most cases) in association with  $\text{Cl}^-$ .<sup>[36]</sup> Even though chloride serum fluctuations have few clinical consequences, they are signs of subjacent alterations in fluid and acid-base homeostasis.<sup>[35]</sup> This could explain the rather similar percentages obtained for  $\text{Na}^+$  and  $\text{Cl}^-$  levels (hypernatremia 57% and hyperchloremia 56.3%) in our study. Hypernatremia is described as a less frequent alteration. This disorder is produced when a great loss of free waterworks in combination with inadequate water ingestion in subjects that cannot replenish their volume losses due to defective access or insufficient supply by iatrogenesis in unconscious subjects; this has been reported in up to 31% of subjects with an advanced stage of the disease. Some of the main causes of free water loss in subjects with HIV are a fever with loss of insensible water through airways and skin, vomiting, diarrhea, secondary central diabetes insipidus to toxoplasmosis or encephalitis by cytomegalovirus, nephrogenic diabetes insipidus secondary to nephrocalcinosis, to tubulointerstitial diseases caused by infections (cytomegalovirus, *Mycobacterium avium*, systemic mycoses), tumors (lymphoma), or medications like rifampicin, foscarnet, and amphotericin B.<sup>[10,11]</sup>

The risk factor found in our study for the presence of hyponatremia was a  $\text{CD4}^+$  T cell count of  $<200$  cel/ $\text{mm}^3$ . Xu et al reported that  $\text{Na}^+$  levels presented a negative correlation with the clinical stage. Subjects in advanced stages had significantly lower natremia.<sup>[37]</sup>

Braconnier et al. mentioned a positive correlation between serum Na and  $\text{CD4}^+$  T cell and that this was based on the fact that the subjects with hyponatremia presented more advanced stages with lower  $\text{CD4}^+$  T cell counts, a higher number of follow-up hospitalizations, and greater AIDS prevalence in comparison with the subjects with normal serum  $\text{Na}^+$  concentration.<sup>[38]</sup> Our analysis agrees with previous reports about the positive relation between serum  $\text{Na}^+$  and  $\text{CD4}^+$  T cell count ( $P = .025$ ,  $\text{OR} = 0.27$ ). Hyponatremia is the most common alteration in adults with the HIV advanced disease.<sup>[10,39,40]</sup> and it is associated with volume losses due to diarrhea, vomiting, or adrenocortical insufficiency, which included the concomitant presence of hyperkalemia and metabolic acidosis in a subject with systemic mycobacterium disease (*Mycobacterium avium* complex, or tuberculosis), or cytomegalovirus infection.<sup>[10]</sup>

Even though we obtained a mean value of  $\text{P}^{-3}$  within normal ranges, 57% of the population manifested hypophosphatemia. This agrees with findings reported by Obum-Nnadi et al, Heimbürger et al, and Wikman et al, who described that hypophosphatemia is relatively frequent in subjects with HIV undergoing antiretroviral treatment<sup>[6,41,42]</sup> and not necessarily low  $\text{CD4}^+$  T cell counts.<sup>[43,44]</sup> This could be the result of phosphorus displacement from the extracellular space to the

intracellular space, phosphorus loss at the renal level, and a decrease in phosphorus intestinal absorption. Elsewhere, it has been reported that the reduction of phosphorus serum levels at the beginning of antiretroviral treatment in subjects with HIV is an independent prediction factor of early mortality.<sup>[43]</sup>

A detectable viral load defined as  $>50$  copies/mL was identified as a risk factor for the presence of hypokalemia, hypocalcemia, and hypermagnesemia. The association between viral load and the development of electrolytic alterations has been rarely described. Braconnier et al. described a negative correlation between serum Na levels and the rise of viral charge, stating this as an argument for the hypothesis that hyponatremia is an indicator of HIV severity.<sup>[38]</sup> Bagnis et al. tried to determine the association between viral load and reduced levels of serum phosphorus without success.<sup>[45]</sup> There is a direct relationship between viral replication and renal disease in HIV-associated nephropathy (HIVAN). There is evidence that HIV ribonucleic acid is located in the kidney's podocytes and tubular epithelial cells, which might explain why these cells manifest outstanding anomalies in nephropathy associated with HIV. HIV viral replication in renal cells is a prerequisite for the development of a renal disease, and viral load is associated with its progression. The possibility of a similar relation between viral replication and renal-level alterations in all subjects with HIV, not only in subjects with HIVAN, but also in those with a normal renal function, has been the object of several recent reports.<sup>[4,46]</sup> This could explain the relationship between viral load and metabolism alteration for some electrolytes.

Epstein et al. found a significant relationship between  $\text{CD4}^+$  T cell count and females for magnesium serum levels in an HIV-seropositive population.<sup>[47]</sup> The findings from our study did not agree with these reports, since hypermagnesemia was more frequent at 23.5% and because we did not find any association with  $\text{CD4}^+$  T cell count nor gender. In a previous study, Obum-Nnadi et al. reported that plasma magnesium concentration in the HIV/AIDS subjects was not correlated to  $\text{CD4}^+$  T cell count and that this variable could be affected by antiretroviral treatment type, diet, and health conditions of subjects.<sup>[43]</sup> Several studies have reported how critical magnesium is for efficient energy production and protein synthesis and how it is not appropriately metabolized by up to half of HIV-positive subjects.<sup>[47]</sup>

## 5. Limitations

Given that this study corresponds to a cross-sectional design, it might have some limitations including the lack of baseline values for several biochemical parameters. Likewise, hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus (anti-HCV) determination were not carried out for identifying the presence of hepatitis B and C co-infections which are described as risk factors for the development of alterations at the renal level. Also, it would have been ideal to obtain urine samples to determine the presence of proteinuria, as well as electrolytes excretory analyses to get a broader outlook of electrolyte metabolism. Finally, there was no control group that allowed us to perform comparisons between groups and obtain results regarding the effect of antiretroviral treatment.

## 6. Conclusion

Renal and electrolytic disorders are frequent, they have a multifactorial etiology in subjects infected by the HIV, including

age, gender (male), ethnicity, BMI, type 2 diabetes mellitus, hypertension, dyslipidemia, malnutrition, cardiovascular events record, the disease's complications, co-infections, low CD4+ T cell count, ribonucleic acid HIV high viral load, serum albumin, proteinuria, albuminuria, and drugs used for HIV treatment. Electrolytic equilibrium is determined and it can be modified by the anatomical composition of the body, environmental factors, physiological body status, diet factors, drugs, and CD4+ T cell count. Our study suggests that CD4+ T cell levels and viral charge are the main factors for the presence of alterations at the renal level, also stating the importance of ART to achieve established goals.

The impact of these risk factors should be established for our population. A global perspective, prevention strategies, early detection, and close follow-up is required to establish an integral treatment because most factors can be monitored and are potentially treatable; thus, resulting in a decrease of morbidity and mortality in these subjects.

### Acknowledgments

Thanks to Dra. Maria de Jesus Vaquera of Torreon's General Hospital of the Secretaria de Salud in Coahuila, Mexico, to the patients included in this study, and to the "Dr. Joaquin del Valle Sanchez" Laboratory of the Hospital General Universitario in Torreon, Coahuila, Mexico, for all the facilities provided for the fulfillment of the current study.

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