*REVIEW*

# Water, electrolytes, and acid-base alterations in human immunodeficiency virus infected patients

Carlos G Musso, Waldo H Belloso, Richard J Glassock

Carlos G Musso, Division of Nephrology, Department of Medicine, Hospital Italiano de Buenos Aires, Buenos Aires C1199ABB, Argentina

Waldo H Belloso, Infectology Section, Division of Internal Medicine, Department of Medine, Hospital Italiano de Buenos Aires, Buenos Aires C1199ABB, Argentina

Richard J Glassock, Department of Medicine, Geffen School of Medicine, UCLA, Los Angeles, CA 90095, United States

Correspondence to: Carlos G Musso, MD, PhD, Division of Nephrology, Department of Medicine, Hospital Italiano de Buenos Aires, Gascón 450, Buenos Aires C1199ABB, Argentina. carlos.musso@hospitalitaliano.org.ar
Telephone: +54-9-1149590200-8724
Fax: +54-9-1149590200-8664

## Abstract

The clinical spectrum of human immunodeficiency virus (HIV) infection associated disease has changed significantly over the past decade, mainly due to the wide availability and improvement of combination antiretroviral therapy regiments. Serious complications associated with profound immunodeficiency are nowadays fortunately rare in patients with adequate access to care and treatment. However, HIV infected patients, and particularly those with acquired immune deficiency syndrome, are predisposed to a host of different water, electrolyte, and acid-base disorders (sometimes with opposite characteristics), since they have a modified renal physiology (reduced free water clearance, and relatively increased fractional excretion of calcium and magnesium) and they are also exposed to infectious, inflammatory, endocrinological, oncological variables which promote clinical conditions (such as fever, tachypnea, vomiting, diarrhea, polyuria, and delirium), and may require a variety of medical interventions (antiviral medication, antibiotics, antineoplastic agents), whose combination predispose them to undermine their homeostatic capability. As many of these disturbances may remain clinically silent until reaching an advanced condition, high awareness is advisable, particularly in patients with late diagnosis, concomitant inflammatory conditions and opportunistic diseases. These disorders contribute to both morbidity and mortality in HIV infected patients.

Key words: Human immunodeficiency virus; Acquired immune deficiency syndrome; Salt; Water; Potassium; Acid-base

Core tip: Human immunodeficiency virus infected patients, and particularly those with acquired immune

deficiency syndrome, are predisposed to different water, electrolyte, and acid-base disorders since they have a modified renal physiology and they also are exposed to infectious, inflammatory, endocrinological, oncological, and pharmacological variables whose combination undermine their homeostatic capability. We herein discuss each of these internal milieu alterations usually observed in this group.

## INTRODUCTION

The clinical spectrum of human immunodeficiency virus (HIV) infection associated disease has changed significantly over the past decade, mainly due to the wide availability and improvement of combination antiretroviral therapy regiments. Serious complications associated with profound immunodeficiency are nowadays fortunately rare in patients with adequate access to care and treatment. Currently, most complications observed in patients with HIV infection are derived from serious but non-acquired immune deficiency syndrome (AIDS) defining clinical events, which are more frequent due to the chronic inflammatory status promoted by the virus itself and are further aggravated by the use of some antiretroviral agents[1,2].

Renal disorders have been increasingly reported in the context of human retroviral infection, particularly the decrease over time of estimated glomerular filtration rate (eGFR), nephrotic syndrome, and proximal tubular deficiency associated with the use of tenofovir disoproxil-fumarate (TDF) and some protease inhibitors such as lopinavir/ritonavir and atazanavir[3]. Although periodic evaluation of renal function (*e.g.,* serum creatinine, eGFR) and proteinuria are routinely recommended in the care of these patients, much less is known or published about specific renal water handling abnormalities, electrolyte disturbances and alterations of acid-base balance in patients with HIV infection[3-5].

HIV infected patients, in particular those with advanced disease may be affected by infectious, autoimmune and oncologic diseases that promote clinical conditions (such as fever, tachypnea, vomiting, diarrhea, polyuria, and delirium), and may require a variety of medical interventions (antiviral medication, antibiotics, antineoplastic agents), whose combination predispose them to develop different sort of electrolytes disorders[6,7].

In the present report, renal water, electrolyte, and acid-base disorders in the HIV infected patients are analyzed.

## RENAL WATER AND ELECTROLYTES HANDLING IN HIV PATIENTS

Renal water and electrolytes handling in HIV patients on different therapeutic regimens including with tenofovir, with non-tenofovir, and without antiretroviral drugs (naïve). These exploratory renal physiology studies (urine concentration and dilution tests) found no significant differences in sodium, potassium, chloride, phosphorus, calcium, magnesium, glucose, urea, and uric acid renal handling between healthy volunteers and stable HIV patients with normal renal function, independently whether or not they were receiving anti-retroviral therapy. However, a significant reduction in maximal urine concentration - dilution capability in stable HIV patients compared to healthy volunteers was consistently documented. In this study maximum free water clearance showed values three times lower in HIV patients than in the healthy volunteers despite normal osmolar clearance[8,9]. This finding may explain the reason why HIV patients were slightly hyponatremic during the dilution test. The urine concentration-dilution defect was attributed to a dysfunction in the thick ascending limb of the loop of Henle (TAHL). Since, HIV has been detected in renal tubular cells, this suggests that either the infection itself or the associated inflammatory process may produce direct tubular damage which appears to be independent of the presence of antiretroviral treatment. This finding also means that there may be an increased risk of developing hyponatremia in stable HIV-infected patients who undergo a water load or receive hyponatremia inducing drugs, as well as dehydration when they are exposed to settings of water loss and impaired thirst or intake of water[8-10]. A recent study has shown that in a setting of volume expansion, where tubule reabsorption is reduced because of the high urinary flux, there was a significant reduction in serum calcium and magnesium values, as well as a concomitant and significant increase in their urinary fractional excretion in stable HIV-positive patients compared to healthy volunteers[9]. Since calcium and magnesium are importantly reabsorbed in TAHL, and this segment show dysfunction in this population, a basal TAHL reabsorption defect worsened by the increased urinary flux was suggested. This finding means that there is an increased risk for developing hypocalcemia or hypomagnesemia in stable HIV-infected patients who undergo volume expansion or who receive hypocalcemia or hypomagnesemia-inducing drugs[9-11].

## SALT AND WATER BALANCE IN HIV INFECTION AND AIDS

Salt and water imbalances can induce abnormalities in extra-cellular volume status and/or serum sodium depending on the nature of this alteration (increase or decrease), its absolute magnitude (mild or severe), and

its relative magnitude (body sodium content relative to body water content)[12]. A significant salt and water depletion generates real hypovolemia, and if this depletion involves an excess of hypotonic fluid loss, it can generate hypernatremia (serum sodium > 145 mmol/L), while if the loss of salt is in excess of water it may generate hyponatremia (serum sodium < 135 mmol/L)[12].

Salt and water retention induces an increase in ECF that, depending on its pathophysiologic mechanism, it may appear either as hypervolemia and edema (e.g., renal failure) or effective arterial hypovolemia and edema (e.g., cirrhosis, cardiac failure, some of nephrotic syndromes). Another factor that can modify the sodium/water ratio is body potassium content since its intracellular depletion induces hyponatremia by at least two mechanisms: A shift of sodium to the intracellular space, and possibly by aberrant vasopressin release. Edelman summarized these concepts in the following equation[13]: Serum sodium = [body (exchangeable) sodium content + body (exchangeable) potassium content]/total body water content.

Additionally, there are two infrequent causes of hyponatremia: First, a hyponatremia secondary to an overtly excessive water intake which overcomes renal capability of free water excretion and is associated with fully suppressed vasopressin secretion, especially in states of low osmolar excretion. This type of hyponatremia has been documented in AIDS patients who suffered from dementia and primary polydipsia[14]. Second, a reset osmostat hyponatremia, usually found in malnourished chronically-ill AIDS patients[12]. Based on the above mentioned pathophysiological mechanisms, hyponatremia is currently classified depending on patient's plasma tonicity level into: Hypertonic, normotonic, or hypotonic hyponatremia. In addition, hypotonic hyponatremia is classified depending on patient's extracellular fluid (ECF) status with low, normal or high ECF[12]. Each type of hyponatremia in AIDS patients was described as follows:

# HYPONATREMIA

## Normotonic hyponatremia
Normotonic hyponatremia or pseudohyponatremia (PSH) consist of a low serum sodium value in a context of normal plasma tonicity, since it is a measurement artifact caused by an increase in the solid fraction of plasma, usually due to hyperlipidemia or hyperproteinemia[4]. A direct ion-sensitive electrode potentiometry-based estimation can avoid this error[15]. Also, the addition of a non-electrolyte osmoles (sorbitol, manitol, sucrose) to the extra-cellular space with redistribution of sodium-deficient water from the intracellular space can cause this finding[14]. PSH has been described in HIV patients who have important hypergammaglobulinemia which may be related to disease progression or its response to antiretroviral therapy. Besides, polyclonal hypergammaglobulinemia in this population it may also be secondary to a co-infection with hepatitis C. It is important to identify PSH since treating it as hypotonic hyponatremia can cause severe dehydration and even death[14,16].

## Hypertonic hyponatremia
Since in absence of renal failure, plasma osmolality (Posm) is mainly determined by serum sodium and glucose level (Calculated Posm = serum sodium × 2 + glycemia/18 + uremia/6), hypertonic hyponatremia is observed in hypertonic variety of uncontrolled diabetes mellitus with severe hyperglycemia. Hyperglycemia increases extracellular tonicity which extracts sodium-deficient water out of the intracellular space diluting the serum sodium concentration in the extracellular space, inducing hyponatremia[12]. Other solutes, like sorbitol and manitol can behave similarly.

## Hypotonic hyponatremia
Patients with cardiac, hepatic, renal, lung, intracranial, and endocrine diseases can develop hypotonic hyponatremia secondary to an excess of water consumed voluntarily or administered iatrogenically, when urine free water excretion is impaired due to a decreased circulatory delivery of fluid to diluting segments (cardiac failure), altered TALH segment function (tubulopathy), and/or (inappropriate or appropiate) vasopressin release[12].

Since impairment of the function of the afore mentioned organs is frequent in the context of AIDS and associated complications, hyponatremia is not surprisingly the most frequent electrolyte abnormality (23.5%-75%) seen both in non-hospitalized and hospitalized patients with HIV infection and AIDS[17-20]. Hyponatremic patients with AIDS are more prone to morbidity and mortality and frequently manifest complicating opportunistic infection-related illnesses (particularly Pneumocystis jiroveci and cytomegalovirus)[19]. However, this poor prognosis has not been attributed to this electrolyte disorder since most of the patients were normonatremic at death, and their higher mortality has been attributed to the severity of their immune-compromised state: For instance, severe hyponatremia (serum sodium < 125 mmol/L) was associated to a lower CD4 T cell count than in AIDS patients who did not have hyponatremia[8,17,21,22].

Dao et al[23] also reported a higher mortality rate among women who showed hyponatremia and hypochloremia (in that context it means a serum chloride value significantly lower respect to the expected one for hyponatremia) compared with women who only had one electrolyte abnormality. This observation suggests that a combination of both disorders (hyponatremia + hypochloremia) may suggest a more profound clinical disturbance in a HIV patient, such as the one secondary to subclinical tuberculosis or cryptococcal lung or cerebral infection. Each type of hypotonic hyponatremia in AIDS patients has been described as follows:

| Table 1 Causes of hypotonic hyponatremia in human immunodeficiency virus infected patients |
|---|
| Hyponatremia with normal ECF |
|   SIADH: Lungs or central nervous system infection or neoplasm |
|   Hypothyroidism: Low T3 syndrome, pituitary infections, thyroiditis and miconazole |
|   Glucocorticoid deficiency: Glucocorticoid axis damaged |
| Hyponatremia with low ECF (volume depletion) |
|   Digestive losses: vomiting, diarrhea |
|   Renal losses: CSW, interstitial nephritis, cortisol resistance and adrenal insufficiency |
| Hyponatremia with high ECF (edematous states) |
|   Non-renal causes: cirrhosis, heart failure |
|   Renal causes: acute tubular necrosis, intra-tubular obstruction, interstitial nephritis, nephrocalcinosis, hemolytic-uremic syndrome, collapsing focal and segmental glomerulosclerosis |
| Hyponatremia secondary to drugs |
|   Renal insufficiency |
|   Interstitial nephritis |
|   Impair maximal urinary dilution capability by direct tubular effect |
|   Cortisol deficiency |
|   SIADH effect |

ECF: Extracellular fluid; SIADH: Syndrome of inappropriate antidiuretic hormone release; CSW: Cerebral salt wasting.

## Hyponatremia with normal ECF (Table 1)

**Syndrome of inappropriate antidiuretic hormone release:** This is an entity induced by free water retention secondary to an inappropriate (for the level of serum osmolality) vasopressin hormone release or an excessive response of its receptor (V2 receptor) in the collecting tubules, in the context of normal GFR, normal thyroid and adrenal gland function, and in the absence of hyponatremia inducing drugs[12,24].

Syndrome of inappropriate antidiuretic hormone release (SIADH) may be present in up to 36% of patients with advanced HIV infection and it can by induced by infection (neurosyphilis, *etc.*) neoplasm of the lungs or central nervous system[8,25]. SIADH must be differentiated (not always easy) from cerebral salt wasting syndrome (CSW) since both entities can appear in AIDS patients, and may present as hyponatremia with high urinary sodium, and elevated circulating natriuretic peptide and vasopressin levels. However, CSW patients show clinical signs of hypovolemia, increased serum urea:creatinine ratio, normal or high serum uric acid, lower fractional excretion of uric acid, and very high urinary sodium levels, while SIADH patients show slight hypervolemia, low urea: Creatinine ratio, low serum uric acid, higher fractional excretion of uric acid, and high urinary sodium levels[12,26].

Central pontine myelinolysis, a severe neurological disease that may be observed in hyponatremia and its overly rapid correction, has also been documented in patients with AIDS, particularly in those with advanced HIV infection, prolonged hyponatremia, anorexia, hypoalbuminemia, chronic alcoholism, disseminated malignancy, and in those patients treated with systemic chemotherapy. The clinical presentation varies between rapidly evolving spastic paraparesis with pseudobulbar palsy, and changes in mental state such as confusion or coma[26-28].

**Hyponatremia secondary to hypothyroidism:**

Several hyponatremia-inducing mechanisms have been described in patients suffering from hypothyroidism, such as reduced function of the nephron diluting segment due to low renal perfusion secondary to decrease cardiac output, inappropriate vasopressin secretion, and increased urinary salt loss[29-36].

The most frequent cause of hypothyroidism in AIDS patients is the "low T3 syndrome" which shows a normal thyroid production of T3, but an impaired peripheral conversion of T4 to T3, since 80% of serum T3 usually comes from T4 deodination in peripheral tissues. Another cause of reduction in thyroid function in this population is centrally-induced hypothyroidism secondary to pituitary infections caused by Pneumocystis, cytomegalovirus, toxoplasmosis, neurosyphilis, and HIV itself; or decrease in hypothalamic thyrotropin releasing hormone due to the wasting syndrome induced by AIDS (non-thyroidal illness syndrome)[25,36]. Finally, hypothyroidism secondary to Hashimoto's thyroiditis (autoimmunity induced by increased B cell activation), and antifungal agents such as miconazole have been described[36,37].

**Hyponatremia secondary to glucocorticoid deficiency:** Since cortisol exerts a negative effect on neurophysiological vasopressin secretion, its deficit can promote an inappropriate vasopressin release, and consequently an increased trend to hyponatremia[37]. The isolated cortisol deficit can be generated by any infectious, immunologic, or oncologic damage in the glucocorticoid axis[38,39].

## Hyponatremia with low ECF

The most common cause of hyponatremia in the AIDS population is one caused by volume depletion secondary to vomiting, diarrhea, or tubular disorders[8]. Volume depletion can induce hyponatremia by stimulating the non-osmotic vasopressin release, an appropriate response for protecting the intravascular volume, in a setting of an adequate or excessive oral water (hypotonic

solution) intake[40]. Sodium losses lead to hypovolemia and consequently induce adequate vasopressin secretion, thus hyponatremia is promoted in this case by a double mechanism: A reduction in body sodium content (sodium loss) and an increase in body water content (water retention). Negative sodium balance is worsened in settings where sodium reabsorption is ineffective, as is the case in CSW, interstitial nephritis, adrenal insufficiency[12] (Table 1).

**Gastrointestinal losses:** This is the second most common cause of hyponatremia in patients with HIV infection and AIDS, particularly when it is represented by diarrhea (induced by HIV or other organisms) in a setting of low electrolyte content fluid replacement[8,12].

**CSW:** CSW is an uncommon disorder characterized by hyponatremia, volume depletion and clinical response to water and salt replacement[26]. The etiology of this entity has been attributed to a decrease in the sympathetic nervous system outflow leading to decrease sodium reabsorption in proximal tubules, inhibition of RAAS, and also release of natriuretic peptides (*e.g.*, atrial and brain natriuretic peptides)[26,39]. CSW occurs in patients with a central nervous system insults, and its similarity with SIADH makes crucial its recognition as water restriction, a SIADH-oriented treatment, is detrimental to patients with unrecognized CSW[21,22]. Even though, differentiation between CSW and SIADH is not so simple, CSW tends to be characterized by the presence of clinical hypovolemia, normal or increased serum urea and uric acid levels, and polyuria with much more higher sodium excretion compared to SIADH[39,40,41].

**Interstitial nephritis:** Interstitial nephritis represents another potential cause of urine loss of salt which can induce volume depletion in AIDS patients since they are exposed to polypharmacy and/or autoimmunity disorders[38].

**Adrenal insufficiency:** The prevalence of adrenal insufficiency is up to 22% in AIDS patients[42,43]. Both HIV itself as well as concomitant disseminated tuberculosis can cause suppression of hypothalamus pituitary-adrenal axis and destruction of adrenal gland; and this may lead to adrenal insufficiency and subsequent hyponatremia. Other opportunistic organisms that can induce hypoadrenalism in HIV patients are Cytomegalovirus, Cryptococcus neoformans, Mycobacterium avium-intracellulare, Pneumocystis jiroveci, Histoplasma capsulatum, and Blastomyces dermatitidis. Moreover, hypoadrenalism in this population can be induced by adrenal gland damage due to Kaposi's sarcoma, lymphoma, or adrenocortical hemorrhage secondary to a coagulopathy, as well as to pharmacological intervention, as is the case of ketoconazole (inhibition of steroids synthesis), rifampicin, and phenytoin (increased cortisol metabolism)[39-44].

**Cortisol resistance:** In this entity, patients suffering from advanced HIV infection present clinical features suggestive of hypoadrenalism, such as asthenia, muco-cutaneous melanosis, hypovolemic hyponatremia, but serum testing reveal high serum cortisol and normal/high adrenocorticotropic hormone levels. This particular clinical setting of cortisol resistance characteristically improves with high doses of glucocorticoids[45-47]. In this case the presence of hyperkalemia with low potassium excretion can help to differentiate this entity from CSW[38].

### Hyponatremia with high ECF
This sort of hyponatemia is observed in severe edematous states secondary to cardiac, hepatic or renal insufficiency, as well as uncommonly in severe nephrotic syndrome.

In clinical settings of effective hypovolemia such as severe cardiac or hepatic insufficiency, and some nephrotic syndromes, hypotonic hyponatremia appears as a consequence of an impaired circulatory delivery to diluting segments, in combination with adequate vasopressin release (effective hypovolemia)[12]. On the other hand, in clinical settings of hypervolemia such as severe renal insufficiency, hypotonic hyponatremia appears as a consequence of an impair capability of free water excretion due to a significantly decrease in GFR (lower than 5 mL/min per 1.73 m²)[12].

Renal insufficiency is a well-known complication in HIV positive patients, usually induced by a heterogeneous collection of miscellaneous mechanisms: Acute tubular necrosis (toxic, ischemic), intra-tubular obstruction from uric acid or phosphate (tumor destruction), different type of glomerular (glomerulonephritis, *etc.*), tubulointerstitial (interstitial nephritis, nephrocalcinosis, *etc.*), and vascular diseases (atypical hemolytic-uremic syndrome), and also a particular type of focal and segmental glomerulosclerosis only found in this population called HIV associated nephropathy often of a collapsing variant[8,22,26,48] (Table 1).

### Hyponatremia secondary to drugs
Drug induced hyponatremia is the third most common cause of hyponatremia in AIDS patients[8].

Medication can induce hyponatremia by different mechanisms, and therefore this type of hyponatremia described here separately. AIDS patients may frequently receive medications that can induce hyponatremia by promoting water retention and/or sodium loss[17,49,50]: (1) renal insufficiency (co-trimoxazole); (2) interstitial nephritis (trimethoprim, loop diuretics, thiazides); (3) impair maximal urinary dilution capability by direct tubular effect (thiazides); (4) cortisol deficiency (rifampin, ketoconazol, suramin); (5) SIADH effect (pyrazinamide, ethambutol, narcotics, lopinavir, ritonavir); and (6) undefined mechanism (amphotericin B, pentamidine) (Table 1).

| Table 2 Causes of hypernatremia in human immunodeficiency virus infected patients |
|---|
| **Hypernatremia** |
| Increased insensible water losses: Fever and tachypnea |
| Increased digestive water losses: Vomiting, diarrhea |
| Increased urinary water losses: Central diabetes insipidus, nephrogenic diabetes insipidus secondary to nephrocalcinosis or tubule-interstitial damage caused by infection, tumors, drugs |
| Reduced water intake: Unconsciousness, adipsia: Thirst´s center destruction by a vascular, neoplastic or infectious cause |

## HYPERNATREMIA

This disorder occurs when a large loss of free water is combined with an inadequate amount of water ingestion or insufficient iatrogenic provision of water in unconscious patients, and it was reported in up to 31% of patients with very advanced disease[49-51] Among the main causes of free water loss in AIDS patients are[26,48]: (1) fever with insensible water losses through the lung and skin; (2) digestive water losses: Vomiting, diarrhea; (3) central diabetes insipidus secondary to toxoplasmosis or cytomegalovirus encephalitis; and (4) nephrogenic diabetes insipidus secondary to nephrocalcinosis, tubule-interstitial diseases caused by infections (cytomegalovirus, Mycobacterium avium intracellulare, systemic mycoses), tumors (lymphoma), or medication, such as rifampin, foscarnet, and amphotericin B.

Regarding hypernatremia secondary to low water intake in AIDS patients, it has been described in unconscious patients affected by a neurological disorder, or in those patients suffering from adipsia. The latter is a rare hypothalamic condition in which a conscious patient develops serum hyperosmolality secondary to reduced water intake because he/she have no thirst. This disorder commonly is associated with lack of vasopressin release, which was attributed to vascular, neoplastic, or granulomatous destruction of the osmoreceptor and thirst center[52] (Table 2).

## POTASSIUM IMBALANCE IN AIDS

Potassium is the main cation in the intracellular space, its total body content in healthy adults is around 3700 mmol, and muscle tissues represent its main body reserve. Potassium has two significant balances: The external balance between the organism and the environment, and the internal balance between the intracellular compartment and the extracellular compartment within the organism[53-55]. The external balance depends on nutrition as well as colonic (20%) and renal (80%) potassium excretion, and this excretion depends both on GFR and potassium distal tubule secretion, which is mainly stimulated by aldosterone hormone. The internal balance depends on the potassium shifts between intracellular and extracellular compartments. Insulin and the adrenergic system are the main stimuli for its intracellular shift along with metabolic alkalosis, plasma hypotonicity and beta-adrenergic sympathetic tone, while the main stimuli for its extracellular shift are

glucagon, metabolic acidosis, plasma hypertonicity, and alpha-adrenergic sympathetic tone[53-56].

### Hypokalemia

Hypokalemia (serum potassium < 3.5 mmol/L) has been reported in about 19% of patients with AIDS[54]. The main causes of hypokalemia in this population are gastrointestinal potassium losses, usually induced by profuse diarrhea secondary to intestinal infection, intestinal tumor, or AIDS-associated enteropathy[8,57]. Vomiting is another important cause of hypokalemia, not only by direct potassium loss (emesis) but also increasing urinary potassium excretion by inducing hypovolemia, bicarbonaturia and consequently secondary hyperaldosteronism[55]. Urinary potassium wasting can also accompany tubule injury secondary to direct toxic effect of nephrotoxic drugs (*e.g.*, amphotericin B, aminoglycosides) or interstitial nephritis or secondary to some antibiotics (*e.g.*, sulfonamides, cephalosporins) or non-steroidal anti-inflammatory (NSAIDs) drugs[56-62]. Anorexia and low potassium intake, sarcopenia and myopathy (low potassium body reserves) observed in HIV-associated wasting syndrome exacerbate the risk of hypokalemia in this population[8,63]. In addition, acquired tubulopathies can also induce urinary electrolytes wasting, and as a consequence hypomagnesemia, hypocalcemia, and hypophosphatemia (Fanconi syndrome) can develop in this population[64-70]. Among the main tubulopathy inducing drugs in AIDS patients are: TDF, foscarnet, zidovudine and didanosine[67-72] (Table 3).

### Hyperkalemia

Hyperkalemia (serum potassium > 5.5 mmol/L) has been reported in 5%-53% of AIDS patients[55,73]. Two main mechanisms of hyperkalemia have been described in these patients. First, reduced urinary potassium excretion (external balance), such as the one observed with severe renal failure (GFR < 5 mL/min per 1.73 m²), hyperkalemia inducing drugs (ACEIs, NSAIDs, trimethoprim), adrenal insufficiency, and hyporeninemic hypoaldosteronism[21,39-43,51,74-77]. Second, increased shift of potassium from the intracellular compartment to the extracellular compartment (internal balance), such as, rhabdomyolysis, tumor lysis syndrome after chemotherapy in AIDS patients affected by malignancies, and diabetes mellitus[77-80]. In this case plasma hypertonicity induced by severe hyperglycemia, develop hyperkalemia through osmotically induced water and potassium shifts from the intracellular compartment to

**Table 3  Causes of dyskalemia in human immunodeficiency virus infected patients**

Hypokalemia
  Increased gastrointestinal $K^+$ losses: Diarrhea: Infection, tumor or AIDS-associated enteropathy
  Increased urinary $K^+$ losses: Vomits, tubule toxicity, interstitial nephritis
  Low $K^+$ body content: Low potassium intake, sarcopenia and myopathy
Hyperkalemia
  Reduced urinary $K^+$ excretion: Drugs, adrenal insufficiency, hyporeninemic hypoaldosteronism
  Increased $K^+$ shift to EC: Rhabdomyolysis, tumor lysis syndrome, hyperglucemia

$K^+$: Potassium; EC: Extracellular compartment; AIDS: Acquired immune deficiency syndrome.

**Table 4  Causes of acid-Base disorders in human immunodeficiency virus infected patients**

Acidosis
   Hyperchloremic metabolic acidosis: Diarrhea, tubular damage secondary to drugs, hypergammaglobulinaemia, acute tubular necrosis, interstitial nephritis, HIV
  High anion gap metabolic acidosis: Uremia, diabetic ketoacidosis, lactic acidosis (type A or B)
Alkalosis
  Metabolic alkalosis (volume contraction): Gastro-intestinal losses, urinary losses
  Respiratory alkalosis (hyperventilation): Central nervous system alteration, altered liver function, lung opportunistic infections and malignancies

HIV: Human immunodeficiency virus.

the extracellular (intravascular) compartment[12] (Table 3).

## ACID-BASE DISORDERS

Acid-base imbalance generates different sort of internal milieu disorders such as acidosis, alkalosis, or their combination (double or triple acid-base disorders). Acidosis is the pathophysiologic process characterized by either a primary acid gain or a primary alkali loss, while acedemia indicates an increased $H^+$ concentration in the blood (blood pH < 7.36). Conversely, alkalosis is the pathophysiologic process characterized by either a primary acid loss or primary alkali gain, and alkalemia indicates a decreased $H^+$ concentration in the blood (blood pH > 7.44). Additionally, acidosis is usually classified depending on its pathophysiologic mechanism in respiratory acidosis (carbon dioxide retention), normochloremic or high anion-gap metabolic acidosis (bicarbonate conversion), and hyperchloremic or normal anion-gap metabolic acidosis (bicarbonate loss). On the other hand, alkalosis is usually classified depending on their pathophysiologic mechanism in respiratory alkalosis (carbon dioxide high excretion) and metabolic alkalosis (bicarbonate gain)[81].

In AIDS patients the main cause of hyperchloremic (normal anion-gap) metabolic acidosis is bicarbonate loss through profuse diarrhea or renal tubule dysfunction induced by drugs (TDF, pentamidine, amphotericin, B, rifampicin, ethambutol, cidofovir, adefovir, abacavir or nelfinavir), hypergammaglobulinaemia, renal diseases (acute tubular necrosis, atopic or infectious interstitial nephritis), adrenal insufficiency (type IV distal tubule acidosis), and even HIV direct tubular cytopathic effect[11,51,56,74,75,82-91].

On the other hand, normochloremic (high anion-gap) metabolic acidosis has been documented in AIDS during severe renal failure (uremic acidosis), diabetic acidosis (ketoacidosis) secondary to pentamidine-induced pancreatic damage, and in sepsis, systemic inflammatory response syndrome, or non-Hodgkin lymphoma (hypoxic lactic acidosis: Type A)[8,22,26,82,83]. It is worth mentioning that lactic acidosis secondary to lymphoma is considered a paraneoplastic syndrome of poor prognosis, since lactate production increases as the aggressive tumor outgrows its blood supply resulting in local hypoxia in the absence of any systemic hypoxia or hypoperfusion. As pathophysiological mechanism an increased glycolytic activity causing an increase in lactic acid generation, overexpression of the glycolytic enzyme hexokinase II or increased IGF-binding protein activity, has been proposed[83].

A particular type of non-hypoxic lactic acidosis (type B) has been described with the use of antiretroviral drugs that are no longer recommended, such as zalcitabine, stavudine, didanosine or zidobudine. This entity is explained mainly by mitochondrial toxicity and reveals hyperlactataemia without lactic acidosis to overt life-threatening lactic acidosis[86-97]. These antiretroviral drugs are nucleosidic inhibitors of viral reverse transcriptase which alter mitochondrial function by inhibiting the mitochondrial DNA polymerase gamma (the enzyme responsible for the replication of mitochondrial DNA). The diminution in this DNA content provokes a diminished synthesis of respiratory chain enzymes[94]. Metabolic alkalosis is frequently induced in these patients by volume contraction secondary to gastrointestinal (vomiting, diarrhea) or urinary losses (diuretics, polyuria, *etc.*)[8,84-86,90]. Opportunistic infections (*e.g.*, histoplasmosis, *etc.*) and malignancies affecting the respiratory tract, the central nervous system, or/and liver function can stimulate hyperventilation and as a

consequence induce respiratory alkalosis[98,99] (Table 4).

## CONCLUSION

HIV infected patients, and particularly those with AIDS, are predisposed to a host of different water, electrolyte, and acid-base disorders (sometimes with opposing effects), since they are exposed to infectious, inflammatory, oncological, and pharmacological variables whose combination undermine their homeostatic capability. As many of these disturbances may remain clinically silent until reaching an advanced condition, high awareness is advisable, particularly in patients with late diagnosis, concomitant inflammatory conditions and opportunistic diseases. These disorders contribute to both morbidity and mortality in HIV infected patients.

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