

Electrolyte imbalance and sleep problems during anti-retroviral therapy: An under-recognized problem

Md Dilshad Manzar ¹
Peter Sony ¹
Mohammed Salahuddin ¹
Abera Kumalo ¹
Mathewos Geneto ¹
Seithikurippu R Pandi-Perumal ²
Adam Moscovitch ⁵
Ahmed S BaHammam ^{3,4*}

¹ Department of Biomedical Sciences, College of Health Sciences, Mizan-Tepi University (Mizan Campus), ETHIOPIA Mizan-Aman - Etiópia.

² Somnogen Canada Inc, College Street, ON, Canada - Toronto - Ontario - Canadá.

³ College of Medicine, King Saud University, The University Sleep Disorders Center - Riyadh - Riyadh - Arábia Saudita.

⁴ King Saud Univeristy, National Plan for Science and Technology - Riyadh - Riyadh - Arábia Saudita.

⁵ The University of Calgary, Sleep and Fatigue Institute - Calgary - Alberta - Canadá.

ABSTRACT

Human immunodeficiency virus (HIV) infection, and the anti-retroviral therapy (ART) associated complications necessitate that the medical care system keeps evolving for proper management of this group of patients. Electrolyte imbalance and sleep problems are common in patients on ART. Both of these conditions are associated with increased morbidity (such as acute kidney injury, chronic kidney disease, low CD4 count, non-adherence and depression) and mortality. Therefore, screening for both sleep problems and electrolytes imbalance may help to decrease the risk of complications in patients on ART.

Keywords: Mortality; Water-Electrolyte Imbalance; Anti-Retroviral Agents; AIDS Serodiagnosis.

Corresponding author:

Ahmed S BaHammam.
E-mail: ashammam2@gmail.com
Received: March 30, 2017;
Accepted: May 12, 2017.

INTRODUCTION

Human immunodeficiency virus (HIV) infection and the ensuing acquired immune deficiency syndrome (AIDS) is a global pandemic, and 78 million people have become infected with HIV since the start of the epidemic. Although HIV-related mortality has seen decline of approximately 45% since 2005, mortality is still staggering with 1.1 million deaths in 2015¹. Expansion of accessibility to antiretroviral treatment (ART) has considerably reduced the incidence of new HIV infections, AIDS mortality and its related co-morbidities². However, ART related complications, associated mortality and non-adherence to therapy are major challenges that necessitate a steadfast and evolving healthcare management²⁻⁷. Therefore, persistent systematic exploration for factors, which may be prospective clinical markers for management of ART related major complications and that minimize associated mortality and non-adherence are needed.

ART is the cornerstone of the ever-evolving clinical management scheme of patients with HIV infection and/or AIDS^{8,9}. ART regimens include different combinations of drugs from various classes of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors and integrase inhibitors⁸. The use of ART has presented new challenges to both patients and health care providers. Proper management of adverse effects and identification of predictors of non-adherence and mortality need continuous evolution.

The innovative clinical use of mortality predictors may help reduce mortality and manage morbidity. Both HIV infection and ART lead to adverse physiological changes, which are predisposing factors for sleep problems and electrolyte complications¹⁰. This brief review summarizes the evidence of ART-related electrolyte imbalance and sleep problems. Further, previous evidence of supporting a relationship between these two conditions and mortality or predictors of mortality in patients on ART is streamlined in a model (Figure 1). Additionally, it is proposed that screening for sleep problems and electrolyte imbalance may help to reduce mortality and morbidity in patients on ART.

ELECTROLYTE IMBALANCE AND ANTI-RETROVIRAL THERAPY

Renal complication such as acute kidney injury (AKI) and chronic kidney disease (CKD) have been reported to occur in patients on ART. Moreover, patients on ART may develop a variety of electrolyte disturbances including, hyponatremia, hypokalemia, hypocalcemia and others^{3-5,11}. These electrolyte disturbances are related to the type of drug used. Table 1 shows a list of drugs used in ART and the electrolyte disturbances usually associated with them. Electrolyte imbalance represents a major problem in patients receiving ART.

African women on ART regimens including nevirapine or efavirenz plus lamivudine with either stavudine or zidovudine have been reported to develop electrolyte imbalances namely

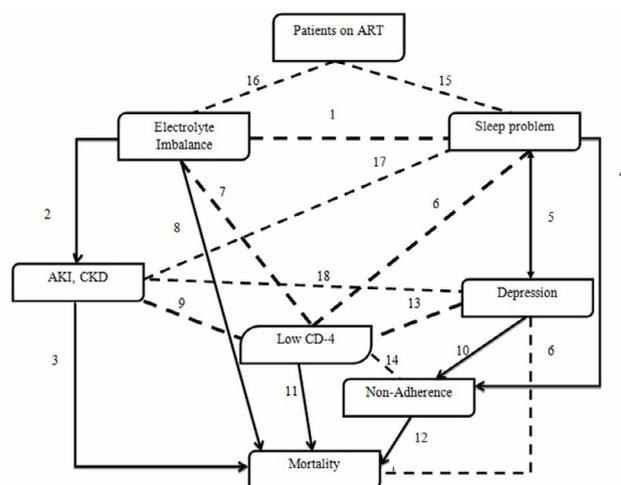


Figure 1. Schematic representation of relationship between sleep problems, electrolyte imbalance, and major predictors of mortality i.e. depression, non-adherence of ART, low CD-4 count, AKI and CKD in patients on Anti-retroviral therapy (ART). AKI: acute kidney injury; CKD: chronic kidney disease. Single arrows (bent and straight) as well as arabic numerals 1-18 on them represent relationship between the two connected items^{2-7,9,10,12,13,17-21}. Dotted line: association evidences in the literature, one way arrow: associated conditions with possibility of first leading to the second, two way: diabolic associations between two connected conditions.

Table 1. Electrolyte imbalance reported for some common drugs used in antiretroviral therapy.

Electrolyte imbalance	Drugs used in anti-retroviral therapy
Hypermagnesemia	Didanosine
Hyperuricemia	Didanosine, Stavudine
Hypokalemia	Didanosine, Tenofovir
Hypophosphatemia	Tenofovir
Hyponatremia	Didanosine
Hypomagnesemia	Zidovudine
Hypocalcemia	Didanosine

hyponatremia and hypochloremia⁵. Didanosine is associated with several electrolyte imbalances including hypomagnesemia, and hypocalcemia (Table 1)^{11,12}. Tenofovir use have been reported to be associated with AKI, severe hypokalemia and hypophosphatemia^{12,13}. The combination of protease inhibitors (i.e. ritonavir with tenofovir) has been shown to increase susceptibility to renal toxicity¹³. Hypophosphatemia was found in Zambian adults on ART regimens of efavirenz or nevirapine in combination with lamivudine with either zidovudine or stavudine³.

Sleep problems and anti-retroviral therapy

HIV infected patients have a high prevalence of insomnia and complaints of daytime sleepiness. Sleep-disordered breathing was high in patients using ART¹⁰. Increased neck circumference, and obesity are potential risk factors for Obstructive sleep apnea among HIV patients on ART¹⁴. The investigations into potential physiologic causes of insomnia in ART are marred by inconsistencies¹⁵. Of the psychosocial factors, stress associated with HIV infection may be implicated in onset of insomnia¹⁶. Moreover, depression shares a direct relationship with insomnia¹⁷, which may further explain stabilization of insomnia in these patients with treatment.

Some of the drugs used in ART regimen are found to be related to the development of insomnia, sleep abnormalities and changes in sleep quality. HIV positive women on ART therapy had greater sleep disturbances as well as poor overall sleep quality⁷. Efavirenz, and Raltegravir at higher plasma levels have been linked to the development of insomnia¹⁷. Efavirenz was reportedly implicated in sleep disturbance among Nigerian children on ART.

It was used in two regimens with zidovudine plus lamivudine and stavudine plus lamivudine¹⁸. In patients on long-term ART (i.e. 8.8 (5.7-9.5) years), polysomnographic studies revealed relatively higher stage N1 (light sleep) and lower rapid eye movement (REM) sleep suggesting poor sleep compared to ART naive HIV patients¹⁰. Table 2 shows a list of some drugs used in ART and sleep problems usually associated with them.

Sleep disorders associated with electrolyte imbalance

Sleep problems such as insomnia, restless sleep, daytime sleepiness, sleep apnea syndrome, periodic limb movement disorder, and restless legs syndrome are prevalent among dialysis patients having electrolyte complications. In dialysis patients, poor sleep quality is associated with depression and poor quality of life¹⁹. History of depression was the only independent predictor of poor sleep quality in chronic renal disease²⁰. Therefore, the commonality of depression as a predictor of poor sleep in both ART related kidney diseases (with most likely involvement of electrolyte imbalance) as well as non-HIV kidney diseases suggestively implicate common physiological mechanisms.

Some of the drugs used in ART are associated with both electrolyte imbalance and sleep problem. Zidovudine is implicated in hypomagnesemia as well as insomnia⁴. While, Tenofovir one of the drugs used in ART have been implicated in electrolyte imbalance and sleep problem as well as a major predictor of mortality in ART patients i.e. depression^{7,12,13,21}. Thus, involvements of a single drug in both sleep disturbances, and electrolyte imbalance may suggest common and/or intricately related biochemical mechanism. Future investigations are needed to understand the underlying biochemical pathways.

Sleep problems, electrolyte imbalance and predictors of mortality.

Figure 1 presents a schematic representation of the proposed relationship between sleep problems, electrolyte

Table 2. Sleep and associated problems reported for some common drugs used in antiretroviral therapy.

Sleep and associated problems	Drugs used in anti-retroviral therapy
Sleep disturbances	Efavirenz, Tenofovir, Lamivudine
Insomnia	Lamivudine, Zidovudine, Rilpivirine, Atazanavir, Cobicistat, Dolutegravir, Raltegravir
Abnormal dreams	Efavirenz, Cobicistat, Dolutegravir
Drowsiness	Cobicistat
Depression	Efavirenz, Rilpivirine, Tenofovir, Cobicistat

imbalance, and major predictors of mortality i.e. depression, non-adherence of ART, low CD-4 count, AKI and CKD in patients on Anti-retroviral therapy (ART).

The relationship model is based on the epidemiological studies in different demographics across the world. Hyponatremia and hypochloremia in patients on ART regimens including nevirapine or efavirenz plus lamivudine with either stavudine or zidovudine increased the risk of mortality by 7.8 times in African women⁵. Baseline serum phosphate was found to be an independent predictor of mortality in Africans on ART³. Hypomagnesemia is very common in AIDS patients. It is a major risk factor for AKI, sepsis, non-recovery of renal function and consequent mortality⁴.

Sleep disturbances as well as poor overall sleep quality in women on ART therapy are associated with low CD4 count, which is a strong predictor of AIDS related mortality⁷. Insomniac HIV-infected persons have a decreased daily activity. Insomnia is associated with an increased waist circumference and depression¹⁷. Women with greater sleep disturbance were associated with depression symptoms and poor adherence to their ART regimen.

This suggests that screening for sleep disturbance may help to identify prospective non-adherents²¹. Poor sleep quality was associated with non-adherence and depression, which is again a predictor of non-adherence in American patients on ART. Moreover, it has been shown that individuals with insomnia and bad dream complaints are poor adherents of ART⁶. Adherence to ART was associated with CD4 count in the sub-Saharan African country of Togo². Screening for both sleep problem and electrolyte imbalance especially hyponatremia, hypochloremia, hypomagnesemia and hypophosphatemia may help decrease risks of complications-associated death in anti-retroviral therapy. The model linking sleep problem/electrolyte imbalance and mortality and non-adherence in patients on ART should be studied further to help in the management of HIV/AIDS patients.

Compliance with Ethical Standards

Funding Statement

No funding has been reported for this study.

Disclosure of potential conflicts of interest

The authors have read the journal's policy and have the following potential conflicts: S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. He declares that he has no competing interests that might be perceived to influence the content of this article. This does not alter the authors' adherence to all the journal policies.

All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable for this study.

REFERENCES

1. The Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDS Update 2016 [cited 2017 Jun 5]. Available from: http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf
2. Yaya I, Landoh DE, Saka B, Patchali PM, Wasswa P, Aboubakari AS, et al. Predictors of adherence to antiretroviral therapy among people living with HIV and AIDS at the regional hospital of Sokodé, Togo. *BMC Public Health*. 2014;14:1308.
3. Heimbürger DC, Koethe JR, Nyirenda C, Bosire C, Chiasera JM, Blevins M, et al. Serum phosphate predicts early mortality in adults starting antiretroviral therapy in Lusaka, Zambia: a prospective cohort study. *PLoS One*. 2010;5(5):e10687.
4. Santos MS, Seguro AC, Andrade L. Hypomagnesemia is a risk factor for nonrecovery of renal function and mortality in AIDS patients with acute kidney injury. *Braz J Med Biol Res*. 2010;43(3):316-23.
5. Dao CN, Peters PJ, Kiarie JN, Zulu I, Muiruri P, Ong'ech J, et al. Hyponatremia, hypochloremia, and hypoalbuminemia predict an increased risk of mortality during the first year of antiretroviral therapy among HIV-infected Zambian and Kenyan women. *AIDS Res Hum Retroviruses*. 2011;27(11):1149-55.
6. Saberi P, Neilands TB, Johnson MO. Quality of sleep: associations with antiretroviral nonadherence. *AIDS Patient Care STDS*. 2011;25(9):517-24.
7. Seay JS, McIntosh R, Fekete EM, Fletcher MA, Kumar M, Schneiderman N, et al. Self-reported sleep disturbance is associated with lower CD4 count and 24-h urinary dopamine levels in ethnic minority women living with HIV. *Psychoneuroendocrinology*. 2013;38(11):2647-53.
8. Dybul M, Fauci AS, Bartlett JG, Kaplan JE, Pau AK; Panel on Clinical Practices for the Treatment of HIV. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. Recommendations of the Panel on Clinical Practices for Treatment of HIV. *MMWR Recomm Rep*. 2002;51(RR-7):1-55.
9. Rai S, Mahapatra B, Sircar S, Raj PY, Venkatesh S, Shaikat M, et al. Adherence to Antiretroviral Therapy and Its Effect on Survival of HIV-Infected Individuals in Jharkhand, India. *PLoS One*. 2013;8(6):e66860.
10. Patil SP, Brown TT, Jacobson LP, Margolick JB, Laffan A, Johnson-Hill L, et al. Sleep disordered breathing, fatigue, and sleepiness in HIV-infected and -uninfected men. *PLoS One*. 2014;9(7):e99258.
11. Ortiz-Interian CJ, de Medina MD, Perez GO, Bourgoignie JJ, Watkins F, Velez-Robinson E, et al. Recurrence and clearance of hepatitis B surface antigenemia in a dialysis patient infected with the human immunodeficiency virus. *Am J Kidney Dis*. 1990;16(2):154-6.
12. Salifu MO, Misra N. HIV-Associated Nephropathy. *MedScape*; 2015. p. [cited 2017 Jun 2]. Available from: <http://emedicine.medscape.com/article/246031-overview#showall>
13. Kalyesubula R, Perazella M. HIV-related drug nephrotoxicity In sub-Saharan Africa. *Internet J Nephrol*. 2009;6(1):1-10.
14. Lo Re V 3rd, Schutte-Rodin S, Kostman JR. Obstructive sleep apnoea among HIV patients. *Int J STD AIDS*. 2006;17(9):614-20.
15. Taibi DM. Sleep disturbances in persons living with HIV. *J Assoc Nurses AIDS Care*. 2013;24(1 Suppl):S72-85.
16. Cruess DG, Antoni MH, Gonzalez J, Fletcher MA, Klimas N, Duran R, et al. Sleep disturbance mediates the association between psychological distress and immune status among HIV-positive men and women on combination antiretroviral therapy. *J Psychosom Res*. 2003;54(3):185-9.
17. Crum-Cianflone NF, Roediger MP, Moore DJ, Hale B, Weintrob A, Ganesan A, et al. Prevalence and factors associated with sleep disturbances among early-treated HIV-infected persons. *Clin Infect Dis*. 2012;54(10):1485-94.
18. Ejeliogu EU, Ebonyi AO, Okpe SE, Yiltok ES, Ige OO, Ochoga MO, et al. Pattern of Adverse Drug Reaction in HIV-infected Children on Anti-Retroviral Therapy in Jos, Nigeria. *Open Sci J Clin Med*. 2014;2(4):89-93.
19. Elder SJ, Pisoni RL, Akizawa T, Fissell R, Andreucci VE, Fukuhara S, et al. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2008;23(3):998-1004.
20. Iliescu EA, Yeates KE, Holland DC. Quality of sleep in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2004;19(1):95-9.
21. Phillips KD, Moneyham L, Murdaugh C, Boyd MR, Tavakoli A, Jackson K, et al. Sleep disturbance and depression as barriers to adherence. *Clin Nurs Res*. 2005;14(3):273-93.