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Management of Stage-4 HIV with Cerebral Toxoplasmosis Coinfection and SIADH Complication

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Abstract

HIV/AIDS stage 4 is the stage where the HIV/AIDS patients have low immunity protection against infections, which can led to coinfections and complications. This case report presented an evaluation of the diagnosis and treatment of an HIV/AIDS stage 4 patient with cerebral toxoplasmosis coinfection and SIADH complications. A man (47 years, 35 kg), married with two children, complaining of weakness, nausea, vomiting, weight loss, and low appetite. Sodium level were measured, showing a 117 mg/dL level that continued to decrease throughout the patient's treatment. Five days later, the patient lost his consciousness with a GCS score of 224, indicating severe brain injury, and was diagnosed with cerebral toxoplasmosis based on the result of head CT-SCAN with contrast. On day 6, the patient was tested positive for HIV and diagnosed with stage 4 with an absolute CD4 count of 4 cells/µl. Therapy was provided by giving pyrimethamine-clindamycin therapy for cerebral toxoplasmosis, followed by Tenofovir, Lamivudine, and Evafirenz as antiretroviral therapy. Treatment for hyponatremia was done by administration of 3% NaCl and tolvaptan. The patient started experiencing an improvement in consciousness after the 10th day of medication, and sodium levels fluctuated throughout the treatments. Patient was discharged after 15 days with clinical improvements.

Keywords: HIV, acquired immunodeficiency syndrome, cerebral toxoplasmosis, inappropriate ADH syndrome, anti-retroviral agents, antiparasitic agents, hypertonic sodium chloride solution

Introduction

Human Immunodeficiency Virus (HIV) is a virus that infects white blood cells and causes a decrease in the human immune system, the infection causes a set of symptoms that can be known as Acquired Immune Deficiency Syndrome (AIDS).[1] There were 38.4 million cases with 650,000 deaths prevalence of HIV in the world based on WHO and the United Nations Programme on HIV/AIDS (UNAIDS) in 2021. Whereas, in Indonesia, there were 543,100 million cases of HIV/AIDS reported in 2020 with 30,137 deaths. In 2021, the number of positive HIV cases was the lowest in the last four years with 36,902 cases reported.[1,2]

HIV causes sufferers to experience decreased immunity, so that it is easier to get infected with various other infectious diseases. One of the infection that commonly occurs as a coinfection in People Living with HIV (PLHIV) at an advanced stage is cerebral toxoplasmosis which is associated with low CD4 count.[3,4] Cerebral Toxoplasmosis is an infection occurring in the brain or central nervous system (CNS) caused by the protozoa Toxoplasma gondii. Toxoplasma gondii can cause serious illness in immunocompromised patients such as in PLHIV, the most cases, involvement of CNS damage can cause encephalitis as one of the causes of death in PLHIV patients.[5,6]

Toxoplasmic encephalitis occurs in the advanced stages of HIV due to the reactivation of latent tissue cysts after a primary infection causes focal lesions in the brains of HIV/AIDS patients. Hyponatremia is a common electrolyte abnormality among AIDS patients, hyponatremia can occur in 20–80% of patients hospitalized with HIV or AIDS.[7] A common comorbidity of hyponatremia in HIV-infected patients is

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coinfection of the lungs or CNS.[8] Coinfection that attacks both organs can cause excessive induction from the release of antidiuretic hormone (ADH) or also known as vasopressin, leading to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). This case may explain why hyponatremia is inherent in this disease. In addition, hyponatremia also occurs due to adrenal insufficiency, renal impairment, and gastrointestinal sodium loss due to diarrhea and vomiting, which are observed in AIDS patients.[9,10,11] PLHIV, both with or without coinfection or complications, must receive antiretroviral therapy (ARV) aims to slow the progression of HIV that invades the patient's immune system. Especially, in conditions of coinfection with cerebral toxoplasmosis also requires pharmacological therapy and adequate sodium correction in the treatment of SIADH. It is necessary to monitor treatment closely because of the increased risk of unwanted events from polypharmacy, interactions between drugs, and even side effects of drugs that can overlap so that they interfere with or reduce the quality of treatment outcomes for PLHIV.[3,4,12]

This report will discuss a unique and rare case where stage 4 HIV disease has led to the development of cerebral toxoplasmosis co-infection accompanied by complicated SIADH. Previously, similar cases had been reported as a case series by Khosla et al., that discussed three patients who were treated with neuropsychiatric symptoms as well. These four cases were diagnosed with cerebral toxoplasmosis which later led to a diagnosis of HIV/AIDS.[13]

Comprehensive therapeutic management and collaboration between health professionals in the scope of infectious diseases and drugs are essential factors in achieving treatment success. Research by Urano et al. revealed that the role of pharmacists in HIV patient treatment programs in collaboration with doctors would improve the outcome of drug therapy. Based on the explanation above, this case report aims to report and explain in more detail the management and monitoring of drug therapy in the case of stage 4 HIV/AIDS patient with toxoplasmosis cerebral coinfection and complications of SIADH involving a collaboration of internal medicine specialists, neurologists, and pharmacists.[14]

Case

A man (35 kg, 160 cm), 47 years old, married, came to the hospital emergency room on April 2, 2021, complained of weakness since yesterday and getting worse, accompanied by nausea, vomiting, mouth ulcers, weight loss, and low appetite. Based on the anamnesis, the patient has a history of recurrent hyponatremia and taking salt capsules 3x500 g/day. The patient had no history of drug and food allergies or a family history of the disease. The results of an examination of the level of consciousness obtained a GCS score of 456 and vital signs such as blood pressure, pulse, temperature, respiratory rate, and oxygen saturation were within normal limits. On the same day, a laboratory examination was carried out in the form of a complete blood count that showed normal results, a serum electrolyte examination showed severe hyponatremia (117 mg/dL), a negative COVID-19 antigen swab, and a chest X-ray examination with readings showing no abnormalities. The patient was treated by the internist as the doctor in charge of the patient.

The next day, the correction for sodium level was done by administering an infusion of NaCl 3%/500 mL/24 hours 2 times. The patient experienced a decreased SpO2 <94%, so he mounted oxygen supplementation using an 8 liter per minute (lpm) oxygen mask. For each day, the patient experiences changes in the level of consciousness. On day 3, the patient's condition was unresponsive and decreased consciousness, accompanied by neck stiffness and hemiparesis, with a GCS score of 324. On April 6, 2021, the patient experienced diarrhea and an increase in body temperature of 37.8°C, a decrease in the GCS score of 224 with a total score of 8 indicates a severe injury to the brain. The CT-SCAN examination on the head was performed in contrast, and the results of its findings concluded that there was vasculitis and brain edema with a differential diagnosis of toxoplasmosis. The following is an overview of the imaging results:

Based on the clinical condition in the form of decreased consciousness and CT-scan results, the internist diagnosed cerebral toxoplasmosis and decided to consult this condition with neurologist. The neurologist suggested pyrimethamine 1x75 mg and clindamycin 4x600 mg as therapy for toxoplasmosis cerebral coinfection followed by the addition of 1x25 mg leucovorin oral therapy, 3x1 mg folic acid, and 1x62.5 mg methylprednisolone injection to reduce the edema in the brain. By the time of the therapy, there was an increase in patient awareness (GCS 446) on April 12, 2021.

During the hospital stay, the patient experienced a decrease in blood pressure, leading to the administration of norepinephrine

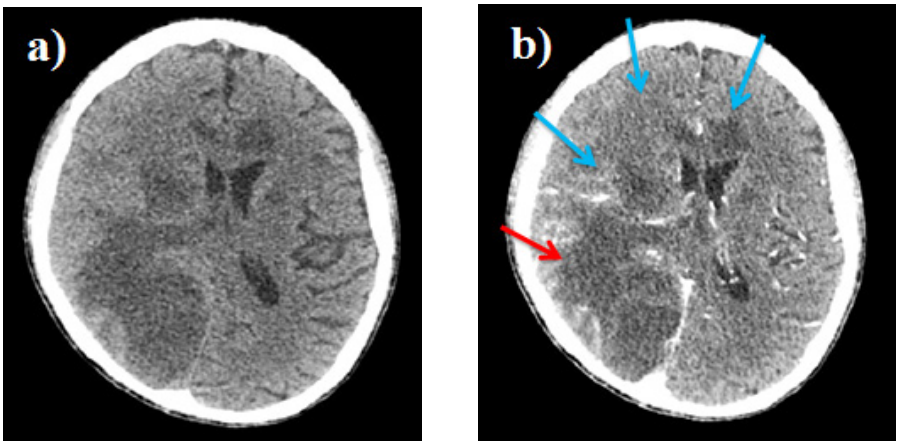

Figure 1 (a) CT-SCAN without contrast; (b) CT-SCAN with contrast

Edema Vaskulitis

as a vasopressor to target a blood pressure of 90/60 mmHg. On April 10, 2021, a follow-up laboratory examination revealed hemoglobin (Hb) levels of 8.3 g/dL and sodium at 123 mg/dL. To address these issues, the internist initiated treatment with NaCl 3% solution (500 mL over 24 hours) twice, and a transfusion of one unit of packed red cells per day to achieve a target Hb level of 10 g/dL. Additionally, the pyrimethamine dose was reduced to 25 mg once daily to mitigate

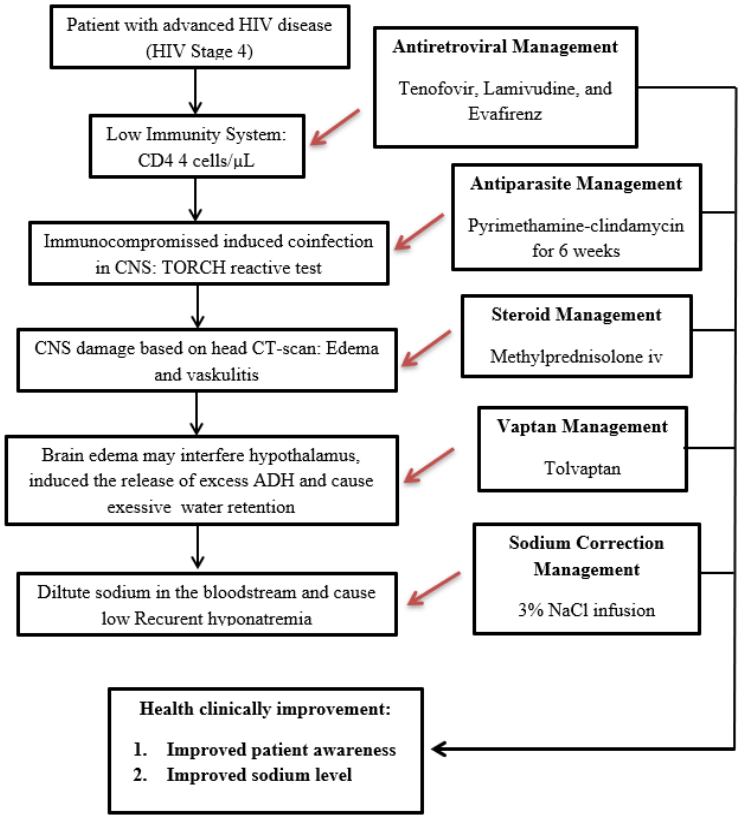

Figure 2 The Summary Flowchart of The Disease Progressivity and The Management of Each Clinical Issue

its side effects, specifically the reduction in folic acid contributing to low hemoglobin levels. By April 12, 2021, the patient's Glasgow Coma Scale (GCS) score improved to 456, indicating better communication and responsiveness.

The next day (April 13, 2021), post-transfusion laboratory examination of PRC and 3% NaCl in every 2 bottles was carried out with the result that the Hb target was reached (10.8 g/dL), while for natrium level it was still under the normal limit (121 mg/dL) by continuing 3% NaCl therapy until the 3rd unit. The neurologist recommended Tolvaptan therapy 1x15 mg to help correct sodium which has not improved. On April 16, 2021, the sodium electrolyte showed improvement (137 mg/dL), so the pharmacist suggested stopping tolvaptan therapy. On April 22, 2021, the patient's consciousness was stable and in good condition, able to communicate, answer questions, and move his hands and feet. The internist decided to start antiretroviral therapy (ARV), namely telavir with a composition of Tenofovir 300 mg, Lamivudin 300 mg, and Efavirenz 600 mg). On April 26, 2021, a liver function examination was carried out with the result of an increase of SGOT 86 U/L SGPT 205 U/L, so the patient was given a hepatoprotector Stronger Neo-Minophagen C (SNMC) injection one bottle/day). The increase in liver function was most likely caused by hepatotoxic drugs, in this case, efavirenz and cotrimoxazole, the decision to closely monitor together was given without stopping therapy which is highly suspected of being the cause of increased liver function in this case. On April 28, 2021, there was an improvement in liver function values SGOT 56 U/L SGPT 136 U/L and there were improvements in electrolytes Na 145 mg/dL. On May 2, 2021, liver function improved SGOT 44 U/L SGPT 72 U/L. The next day the patient's clinical condition improved, and the mouth ulcers and cough healed, GCS 456, as a result, the patient was allowed to be discharged with outpatient therapy. The summary of the disease progressivity and management of each clinical issue related to this case report is provided in Figure 2 in the appendix to navigate the complexities of treatment.

The study has received approval from the hospital management of Manyar Medical Centre, University of Surabaya, and adheres to Indonesian Law for the Protection of Personal Data as well as the Declaration of Helsinki. Written informed consent was obtained from the patient's family for participation in the study.

Discussion

A case of stage 4 HIV infection with coinfection with cerebral toxoplasmosis and complications of SIADH was found in a private hospital in Surabaya, Indonesia. In this case, starting from the results of the anamnesis, physical examination, and supporting examinations carried out, so that the diagnosis of opportunistic infections of HIV/AIDS could be established. This diagnosis was made based on the history of the symptoms of immunodeficiency in the form of diarrhea, yeast infection in the mouth, weight loss, nausea, vomiting, and fever. Furthermore, there was a history of same-sex sexual intercourse which could be a source of spread of HIV infection. On physical examination, the pain was found on abdominal pressure with BMI of 14.69 kg/m^2 which indicated malnutrition. Four days later, there was a decrease in the patient's level of consciousness with a total GCS score of 8 which signified a severe brain injury and followed by the results of a head CT-SCAN investigation with contrast. These results concluded that there were edema and lesions in the brain with a differential diagnosis of toxoplasmosis. The diagnosis was also supported by the results of a reactive TORCH examination with levels of 37.6 IU/mL, this confirmed the diagnosis of cerebral toxoplasmosis infection.[3,4,5,15]

According to WHO criteria, the patient in this case was diagnosed with stage 4 HIV as evidenced by a positive result on the 3-method HIV test with a CD4 count of 4 cells/μL and the presence of cerebral toxoplasmosis coinfection in the central nervous system. Cerebral toxoplasmosis is the most common cause of extensive brain lesions in PLHIV and leads to high morbidity and mortality. Especially, for PLHIV who did not receive cotrimoxazole and had a CD4 count <100 cells/mm^3, the results are illustrated as shown in this case. In immunosuppressed patients identical to this case, toxoplasmosis occurs as a result of reactivation of latent infection and causes neurological symptoms such as headache, disorientation, drowsiness, and hemiparesis (weakness on one side of the body) to loss of consciousness. The three previous cases by Khosla et al., also carried out radiological examinations in the form of CT-SCAN and/or MRI to support the diagnosis of cerebral toxoplasmosis.[3,6,13,15]

PLHIV who were on WHO stage 3 or 4 and/or CD4 count <200 cells/μL (including pregnant women) should be recommended to receive cotrimoxazole prophylaxis. On April 8, 2021,

the patient's CD4 test results were 4 cells/μL and could be categorized into the severe immunosuppression group requiring immediate ARV therapy and cotrimoxazole. Adult patients with HIV infection who are about to start ARV therapy and have a CD4 count <200 cells/μL are recommended to be given cotrimoxazole treatment two weeks before starting ARV therapy. In this case, patients had been given cotrimoxazole 1x960 mg on April 6, 2021, before initiation of ARV 2 weeks later. This delay in administration time is useful for reducing or preventing overlapping side effects between cotrimoxazole and ARV therapy, considering that many ARV combinations have the same side effects as cotrimoxazole such as nausea, vomiting, hepatotoxicity, and others. In two out of three cases reported by Khosla et al., the patient was also given ARVs as HIV therapy.[3,4,13,15]

As previously mentioned, this patient meets the WHO-defined criteria for stage 4 HIV disease or advanced HIV disease (AHD). Patients with AHD are at a high risk of death, and their mortality rate increases as their CD4 cell count decreases, even after initiating ARV treatment. Typically, patients with AHD have a life expectancy of 2 years if they are on ARV. One of the most prevalent causes of severe illness and death is coinfection-related brain damage, as reported in this case. However, the prognosis for patients who are treated with ARV agents and achieve a CD4 count greater than 500 is similar to that of someone without HIV. On the other hand, those with untreated AIDS usually have a life expectancy of about 1 to 2 years after their first opportunistic infection. The goal of initiating ARV treatment for this patient is to improve the immunity system by increasing their CD4 count and may changing their status from AIDS to HIV.[3,15]

Treatment of toxoplasmosis includes management of induction therapy followed by maintenance therapy to prevent recurrence in patients with CD4 <200 cells/mm^3. Standard therapy is an induction pyrimethamine loading dose of 100 mg, followed by 50 mg maintenance therapy plus sulfadiazine 1000 mg every 6 hours or clindamycin 600 mg every 6 hours for 6 weeks. To reduce the toxicity of pyrimethamine to the bone marrow, a folic acid supplementation of 2 to 4 mg/day can be given.[5,12,16,17]

The monitoring of liver function, creatinine serum, and blood counts was carried out in this case, for the side effects of hepatotoxicity, nephrotoxicity, and anemia are the common association the pyrimethamine and ARV treatment.[3,12,17,18]

A phase II randomized trial involving 59 patients with cerebral toxoplasmosis concluded that after 6th weeks of treatment, respectively 70% versus 65% of patients in the pyrimethamine-sulfadiazine versus pyrimethamine-clindamycin group both showed a partial or complete clinical response. Pyrimethamine and Clindamycin therapy has been given to patients since the patient was diagnosed with toxoplasmosis cerebral on April 5, 2021. The patient received Clindamycin 4x600mg and pyrimethamine at a loading dose of 1x200mg, followed by a maintenance dose of 1x75 mg. The dose of pyrimethamine is appropriate since the patient's weight is <60 kg. Folic acid has been given to reduce the toxicity of pyrimethamine to the bone marrow with the dose obtained is 3x1 mg (3 mg per day).[5,17,19]

The mechanism of pyrimethamine itself is to work synergistically by inhibiting T gondii proliferation and survival through inhibition of the folate metabolic pathway. Pyrimethamine inhibits dihydrofolate reductase and dihydropteroate synthase and consequently blocks the synthesis of tetrahydrofolate which is required by the parasite for DNA synthesis. This becomes the reason why it is necessary to add folate supplementation in patients receiving pyrimethamine therapy.[17,18,20]

Patients still received pyrimethamine and clindamycin therapy until the patient was discharged from the hospital (May 3, 2021). The patient experienced an improvement in clinical condition with improved consciousness and hemoglobin level which was initially 8.3 g/dL to 10.4 g/dL just before leaving the hospital. Cerebral toxoplasmosis was associated as a factor causing other complications in the form of serum sodium depletion as experienced by the patient, although complaints of vomiting and diarrhea could also be the reason.[9,10,21]

Hyponatremia is reported frequently in HIV/AIDS patients. In Xinjiang, China, 40% of HIV/AIDS patients experience hyponatremia, especially in the presence of opportunistic infections in the CNS called toxoplasmosis. Toxoplasmosis can cause infections in the brain, leading to brain edema or affecting its blood flow. The edema in this case occurs in the right frontal-parietal-occipital region, putting pressure on the right lateral ventricle and the third ventricle area. This can interfere with the hypothalamus, a region located in the ventral brain above the pituitary gland and below the third ventricle, which plays a vital role in coordinating the

endocrine system. The hypothalamus produces hormones by receiving signals from various parts of the brain, including ADH, which regulates fluid balance by promoting water reabsorption in the kidneys. Unfortunately, the disruption of the hypothalamus can lead to an excessive release of ADH, known as SIADH, resulting in the significant reabsorption of water in the body. This can dilute the sodium electrolytes increasingly in the bloodstream, leading to recurrent low sodium concentrations or hyponatremia.[9,21]

In this case, the management of hyponatremia was using an infusion of 3% NaCl 500 mL/24 hours for two days. In the beginning, the patient's serum sodium value was 117 mmol/L, and the dose of 3% NaCl was 0.5–1.0 mL/kg/hour. For patients with a weight of 40 kg, the 3% NaCl needed in 24 hours was 480–960 mL, the dose given to the patient was appropriate. After being given 3% NaCl for two days, there was an increase in serum sodium to 135 mmol/L. Six days later, the results of the examination of sodium levels returned to show hyponatremia values (123 mg/L). If the administration of 3% NaCl is inadequate, it is necessary to add Vaptan therapy.[21,22]

Tolvaptan is a vasopressin-2 (V2) receptor antagonist and is licensed for use in euvolemic and hypervolaemic hyponatremia, not be used in hypovolaemic hyponatremia as it works by blocking the V2 receptors at the renal collecting duct, then causes a reduction of water reabsorption which can increase the clearance of free water without sodium loss. Tolvaptan demonstrated superiority to placebo in the treatment of Chinese SIADH patients with hyponatremia by elevating serum sodium concentration with an acceptable safety profile. The patient was given Tolvaptan for two days at a dose of 15 mg/day. The dose given to the patient was appropriate as much as 10–40 g/day. After the administration of tolvaptan, the patient's serum sodium value was 137 mmol/L. It is not recommended to increase serum sodium levels in hyponatremia patients too quickly or drastically (maximum of 10 mmol/L on day 1 and 8 mmol/L on the second day) due to osmotic demyelination of the CNS.[9,21,22]

Based on the clinical and supporting examinations of the patient discussed, the diagnosis of HIV stage 4 with cerebral toxoplasmosis coinfection and complications of SIADH is established. Stage 4 HIV cases require multiple steps of treatment. Firstly, Pyrimethamine-clindamycin is used to treat cerebral toxoplasmosis while monitoring consciousness. Secondly, Tenofovir, Lamivudine, and Evafirenz are used for antiretroviral therapy for HIV while monitoring CD4 counts and clinical condition. Additionally, NaCl 3% and tolvaptan are administered for hyponatremia correction while monitoring sodium levels. The treatment of these conditions requires the collective expertise and effort of multiple specialists to oversee drug therapy, ensure effective treatment outcomes, and promptly address any side effects.

References

1. UNAIDS. Global HIV Statistics. Fact Sheet 2021. 2021;(June):1–3.
2. Kemenkes RI. Profil Kesehatan Indonesia. Jakarta: Kementrian Kesehatan Republik Indonesia; 2021. Available from: http://www.kemkes/go.id.
3. WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021. p. 594.
4. Kemenkes RI. Pedoman Nasional Pelayanan Kedokteran Tata Laksana HIV. Jakarta: Kementrian Kesehatan Republik Indonesia; 2019. Available from: https://kemkes.go.id/id/pnpk-2019---tata-laksana-hiv.
5. Vidal JE. HIV-Related cerebral toxoplasmosis revisited: current concepts and controversies of an old disease. J Int Assoc Provid AIDS Care. 2019;18:2325958219867315. doi:10.1177/2325958219867315
6. Luma HN, Tchaleu BCN, Mapoure YN, Temfack E, Doualla MS, Halle MP, et al. Toxoplasma encephalitis in HIV/AIDS patients admitted to the Douala general hospital between 2004 and 2009: A cross sectional study. BMC Res Notes. 2013;6(1):2–6.
7. Shu Z, Tian Z, Chen J, Ma J, Abudureyimu A, Qian Q. HIV/AIDS-Related hyponatremia: an old but still serious problem. Ren Fail. 2018;0(0):68–74. doi: 10.1080/0886022X.2017.1419975
8. Krajewska M, Kruczkowska A, Kusztal MA, Królicka AL. Hyponatremia in infectious diseases—a literature review. Int J Environ Res Public Health. 2020;17(15):1–16.
9. Xu L, Ye H, Huang F, Yang Z, Zhu B, Xu Y, et al. Moderate/Severe Hyponatremia Increases the Risk of Death among Hospitalized Chinese Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Patients. PLoS One. 2014;9(10):e111077.

doi:10.1371/journal.pone.0111077
10. Musso CG, Belloso WH, Glassock RJ. Water, electrolytes, and acid-base alterations in human immunodeficiency virus infected patients. World J Nephrol 2016; 5(1):33–42
11. Madariaga H, Kumar A, Khanna A. A rare mechanism of hyponatremia in HIV disease. Am J Case Rep. 2015;16:707–10.
12. Klatt EC. Pathology of HIV/AIDS Version 28, 33rd ed. J Gen Virol. 2022;91(PT 1):1–545.
13. Khosla A, Singhal S, Jotwani P, Kleyman R. Cerebral toxoplasmosis as the initial presentation of HIV: A Case Series. Cureus. 2022;14(3):1–8.
14. Urano K, Ishibashi M, Matsumoto T, Ohishi K, Muraki Y, Iwamoto T, et al. Impact of physician-pharmacist collaborative protocol-based pharmacotherapy management for HIV outpatients: A retrospective cohort study. J Pharm Health Care Sci. 2020;6:9. doi:10.1186/s40780-020-00165-9.
15. Koshy AA, Harris TH, Lodoen MB. Cerebral toxoplasmosis. Toxoplasma Gondii. Weiss LM, Kim K, editors. Chapter 24 - Cerebral toxoplasmosis. 3rd ed. United States: Academic Press; 2020. p. 1043–73.
16. Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG. Treatment of toxoplasmosis : historical perspective animal. Clin Microbiol Infect. 2018;31(4):1–33. doi:10.1128/CMR.00057-17
17. Ben-Harari RR, Goodwin E, Casoy J. Adverse event profile of pyrimethamine-based therapy in toxoplasmosis: a systematic review. Drugs R D. 2017;17(4):523–44. doi:10.1007/s40268-017-0206-8
18. Wondifraw Baynes H, Tegene B, Gebremichael M, Birhane G, Kedir W, Biadgo B. Assessment of the effect of antiretroviral therapy on renal and liver functions among HIV-infected patients: a retrospective study. HIV AIDS (Auckl). 2016;9:1–7. doi:10.2147/HIV.S120979
19. Konstantinovic N, Guegan H, Stäjner T, Belaz S, Robert-Gangneux F. Treatment of toxoplasmosis: Current options and future perspectives [published correction appears in Food Waterborne Parasitol. 2020 Dec 15;21:e00105]. Food Waterborne Parasitol. 2019;15:e00036. doi:10.1016/j.fawpar.2019.e00036
20. Elsheikha HM, Marra CM, Zhu XQ. Epidemiology, Pathophysiology, diagnosis, and management of cerebral toxoplasmosis. Clin Microbiol Rev. 2020;34(1):e00115–19. doi:10.1128/CMR.00115-19
21. H, Badireddy M. Hyponatremia. [Updated 2023 Jun 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470386/.
22. Chen S, Zhao JJ, Tong NW, Guo XH, Qiu MC, Yang GY, et al. Randomized, double blinded, placebo-controlled trial to evaluate the efficacy and safety of tolvaptan in Chinese patients with hyponatremia caused by SIADH. J Clin Pharmacol. 2014;54(12):1362–7. doi:10.1002/jcph.342