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A STUDY ON THE ADVERSE DRUG REACTIONS OF HIV-TB CO-INFECTED PATIENTS IN A TERTIARY CARE HOSPITAL OF NORTH EAST INDIA - A PROSPECTIVE COHORT STUDY

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Keywords:

Adverse drug reaction, HIV-TB co-infection, ATT, ART, Opportunistic infection

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ABSTRACT: The reporting of adverse drug reactions after taking any medicines is very much essential to establish a safe patient profile for drugs. The co-infection of HIV and TB has been a major concern for the healthcare system, and the various drugs interaction from taking ART and ATT should be highlighted to avoid unwanted reactions. The present study was conducted in a hospital set up for a period of one year in the ART center, where the ADR cases were recorded from the HIV patients suffering from tuberculosis. During the study, 135 patients co-infected with HIV and TB were analyzed from which a total 135 adverse drug reactions were collected and recorded. It is observed that rash, raised liver function, fever, peripheral neuropathy, and anaemia are the most common adverse drug reactions from the concomitant therapy of ART and ATT. From the study, 13 different types of ADRs were reported in patients on the ART and ATT therapy. It is important to do the causality assessment according to the WHO-UMC scale of the suspected drug reaction in order to determine whether drug discontinuation is needed or not, as well as to put emphasis on patient education to avoid the same adverse events in the future.

INTRODUCTION: Adverse drug reaction is a major health concern for patients across the world. No medicine is devoid of any side effects. The reporting of adverse drug reactions is highly essential as it helps in analyzing the various drug reactions by the regulatory concerns and could help in preparing an effective patient safety profile. WHO defined Pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drugs-related problems [1].

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Tuberculosis is considered a highly contagious disease since ancient times and still continuing to show its dominance worldwide. TB in humans can be traced back to 9,000 years ago in Atlit Yam, a city now under the Mediterranean Sea, off the coast of Israel. The ancient literature mentions that TB was in India about 3,300 years ago [2].

The causative organism of tuberculosis is *Mycobacterium tuberculosis*, and it mainly affects the lung, which is known as pulmonary tuberculosis (PTB). PTB generally spreads through air transmission; when a person suffering from PTB expels the bacteria by sneezing, it results in the release of a large number of bacteria to the nearby surrounding. The droplets of air may enter the other person and infect it. Tuberculosis can occur in other sites of the body, which is known as

extra-pulmonary tuberculosis. Tuberculosis (TB) continues to be a public health challenge in India, and it is estimated that 1.9 million new cases of TB occur in India annually [4].

Next to tuberculosis, HIV infection has turned to be a global pandemic. As per the National AIDS Control Organization **(**NACO) surveillance report of 2007, the prevalence of HIV infection in India is estimated to be 0.34 % of the population, which accounts to 2.31 million people living with HIV/ AIDS in India and has the third-highest number of HIV cases in the world [3, 4].

Tuberculosis is recorded as the most common opportunistic infection in HIV-infected patients and is the major cause of death. A person suffering from HIV has a weak immune system which makes them vulnerable to get infected with TB easily, which further deteriorates their health condition. It is also difficult for a physician to treat a tuberculosis patient co-infected with HIV. The sign and symptoms of TB are difficult to recognize in HIV-infected patients, as the patient may already suffer from low immunity count and also chances of less sputum production for the confirmation of TB [5]. Due to failure of proper identification and diagnosis and patients' carelessness, there may be high chances to develop drug-resistant tuberculosis, such as multi-drug resistance TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), which become difficult for treatment at a later stage. The bacteria *Mycobacterium tuberculosis* results in rapid viral replication in HIV-infected patients, which causes more death due to AIDS [6]. This two infection combined has also been coined as "the cursed duet" [7]. A lot of this co-infection has been reported from the developing nations where there are large number of HIV cases, mainly India and Africa [8].

A report published from WHO in the year 2018 estimated that 8,62,000 people living with HIV (PLHIV) worldwide fell ill with TB. TB is the leading cause of death among people with HIV, which counts around 2,51,000 people death from HIV-associated TB in 2018, and this is about one-third of AIDS deaths. PLHIV faces the threat of drug-resistant TB. If a diagnosis is delayed, there is an increased risk of mortality from multidrug-resistant and extensively drug-resistant TB [9].

It is seen that the rate of HIV-TB co-infection is higher in the sexually active age group of a male between 31-45 years as compared to female in India. The main causes of the coinfection lack of primary level of education, people living in rural areas, unemployed, truck drivers, labourer, migrants, prisoners, low income-earning capacity [10]. The heterosexual route of transmission is the most common route for infection in this population among both genders [11] along with intravenous drug abusers [12].

HIV and Opportunistic Infections: Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). AIDS is the most severe stage of HIV (Clinical Stage 3). Opportunistic infections (OIs) are infections that occur more often or are more severe in people with weakened immune systems. People with AIDS have badly damaged immune systems resulting in increasing the chances for opportunistic infections (OIs). CD4 cells are white blood cells that play an important role in the immune system. The CD4 cell count gives an indication of the health of the immune system, which is the body's natural defense system against pathogens, infections, and illnesses [13]. The normal range of CD4 cells in a healthy person is 500-1500 cells/µl of blood. A person infected with HIV shows a gradual depletion of CD4 count with the progression of HIV infection, making the patient vulnerable to various opportunistic infections. On reaching CD4 cell count near 200 cells/µl of blood, most patients get affected with a number of various OIs. A further depletion in the CD4 count (<50 cells/µl) may finally succumb the patient to death.

Tuberculosis (TB) as Opportunistic Infection in HIV: HIV weakens the immune system, increasing the risk of TB in people with HIV. TB can attack HIV patients at any CD4 cell count; however, the CD4 cell count < 200 cells/µl of blood are more vulnerable to contact with TB. Common symptoms are persistent cough with blood smeared sputum, chest pain, weakness or fatigue, loss of appetite, weight loss, chills, fever, night sweats. Infection with both HIV and TB is called HIV/TB coinfection. The untreated latent TB infection is more likely to advance to TB disease in people with HIV than in people without HIV. It is

recommended to treat patients with antiretroviral and anti-TB therapy concurrently to achieve substantial results.

Treatment for TB: Patients suffering from TB are given treatment with Directly Observed Treatment Short-course (DOTS) regimens according to the Revised National Tuberculosis Control Programme (RNTCP) in India. They are referred to the DOTS center for antituberculosis therapy (ATT) which consists of H (isoniazid), R (rifampicin), Z (pyrazinamide), E (ethambutol). The regimens used for the treatment of pulmonary and extrapulmonary tuberculosis are the same in both HIV-positive and negative individuals. The treatment regimen for pulmonary tuberculosis is six months which is categorised into two phases: Intensive Phase (IP) consisting of 56 days and Continuous Phase (CP) for 112 days. The treatment regimen for extra-pulmonary tuberculosis such as miliary TB, bone or joint TB, and tubercular meningitis also consists of around 6 months but may extend upto 9-10 months depending upon the diagnosis. A persistent positive sputum culture after 2–3 months of initiation of therapy raises the chance of developing drug-resistant TB or non-compliance with first-line therapy of TB. Those patients are required to undergo a Line probe Assay (LPA) for detecting isoniazid resistance or Cartridge based nucleic acid amplification test (CB-NAAT, GeneXpert,) to detect the rifampicin resistance [14]. The treatment of TB under DOTS can be categorized into.

Intensive Phase (IP): In a normal adult, the dose of HRZE is given daily in fixed-dose combination **Table 1** according to the bodyweight of the patient for 56 days.

TABLE 1: INTENSIVE PHASE DRUGS

Weight category	Number of tablets (in FDC) HRZE (75/150/400/275 mg)
25-39 kg	2
40-54 kg	3
55-69 kg	4
>=70 kg	5

TABLE: 2 CONTINUOUS PHASE DRUGS

Weight category	Number of tablets (in FDC) HRE (75/150/275 mg)
25-39 kg	2
40-54 kg	3
55-69 kg	4
>=70 kg	5

Continuous Phase (CP): The continuous phase dose includes HRE, which is also given daily to the adults in a fixed-dose combination **Table 2** according to the patient's body weight for a period of 112 days.

Mdr Tb: If there is a failure in the first-line treatment of ATT in the patients and it is confirmed by the LPA or CBNAAT test, then the patient may develop resistance to isoniazid or rifampicin, and his dose regimen will also vary accordingly. The MDR dose regimen includes. Intensive phase for [6-9] months with kanamycin, levofloxacin, ethambutol, pyrazinamide, ethionamide, and cycloserine and continuous phase for 18 months with levofloxacin, ethambutol, ethionamide, and cycloserine.

Treatment for the Co-infection of Tuberculosis and HIV: It is difficult to manage the treatment of HIV and TB simultaneously due to possible drug-drug interactions between ART and ATT, pill burden for the patient, adherence, and drug toxicity. The treatment regimen for TB patients diagnosed with HIV includes in **Table 3** given below.

TABLE: 3 HIV AND TB TREATMENT DRUG

First-line ART	Zidovudine or Tenofovir Disoproxil Fumarate + Lamivudine + Efavirenz
Second line ART	**Two NRTIs** (zidovudine, stavudine, lamivudine, didanosine, abacavir, tenofovir) + **PI** (lopinavir, saquinavir, ritonavir, nelfinavir, atazanavir, indinavir)

*NRTI is Nucleoside reverse transcriptase inhibitors
*PI is Protease Inhibitors

In HIV-infected TB patients, rifampicin alters the metabolism of Protease Inhibitors, including Lopinavir, Atazanavir, and Ritonavir, and reduces the effectiveness of standard doses. However, rifamycin-class drugs are highly efficacious in the treatment of tuberculosis. The monitoring of the CD4 count during active TB is vital for determining the effectiveness of the therapy and to reflect the actual level of immunosuppression [15].

MATERIALS AND METHODS:

Study Settings: The present study was a hospital-based prospective cohort study which was carried out in the Out-Patient Department of the Antiretroviral Therapy (ART) Centre of Guwahati Medical College and Hospital, Guwahati, Assam. The time period for the study was 12 months *i.e.* from 20th December 2018 to 20th December 2019.

Ethical Permission: The ethical permission for the study was obtained from the Institutional Ethical Committee of Guwahati Medical College and Hospital, Guwahati on 20th December, 2018 bearing the approval no: MC/190/2007/Pt-11/Dec-18/34, 5th January 2019. The study has also been approved by The Project Director, AIDS Control Society (Assam) and the Nodal Officer of ART Centre, Guwahati Medical College, and Hospital, Guwahati.

Patients: For the study, HIV infected patients more than 14 years of age of both sex are selected who are also suffering from tuberculosis and taking both anti tubercular and anti-retroviral therapy regularly.

Exclusion Criteria: HIV-infected patients taking only ART, patients less than 14 years of age and debilitating patients, and patients with terminal illnesses are excluded from the study. The ADR was collected and recorded in a specially designed form by visiting the outpatient Department of ART Centre, Guwahati Medical College, and Hospital, Guwahati. The consent of the patients is taken before data collection and was maintained confidential.

Statistical Analysis: The data were analyzed statistically by using an independent sample t-test and one-way ANOVA to compare the means of variables between various patient subsets. P-values less than 0.05 were considered to indicate statistical significance.

RESULT: A total of 135 patients were screened for the study (n=135), of which 77% (n=102) of the population were male **Fig. 1** and 23% (n=33) of the population were female. Out of the 135 patients **Table 7**, 108 numbers received Tenofovir + Lamivudine + Efavirenz + Isoniazid (TLEI) (n=108) *i.e.* 80% 24 numbers received Lamivudine + Nevirapine + Zidovudine + Isoniazid (LNZI) (n=24) *i.e.* 18% and 3 numbers of patients received Stavudine + Lamivudine + Nevirapine + Isoniazid (SLNI) (n=3) *i.e.* 2%. Distribution of ADRs reveals that TLEI group (n=108) showed 12 different ADRs of which raised liver function were observed in 27 patients *i.e.* 26% skin rashes in 27 patients *i.e.*, 24%, and fever in 15 patients *i.e.* 14%. The LNZI group (n=24) showed 4 different ADRs of which anaemia was observed in 9 patients *i.e.* 43%, gastritis in 6 patients *i.e.* 29%. In SLNI group (n=3) rash was observed in all the patients *i.e.* 100%. Overall rash and raised liver function covers 24% and 22% respectively, fever is reported in 11% of patients **Table 5**. Out of 135 patients (n=135), 45% of patients fall under the age group of 45-55 years and 24% of patients come under 25-30 years of age. According to the WHO-UMC causality assessment scale **Table 8** most of the ADRs were under probable/likely (n=129) *i.e.*, 96% 3 cases are under possible *i.e.* 2% and 3 cases are reported as unlikely *i.e.* 2%. According to WHO Clinical staging of HIV, **Table 4** out of 135 patients (n=135) **Fig. 4** the various percentage is described as.

TABLE 4: WHO - CLINICAL STAGES OF HIV

WHO Clinical Stage of HIV	Number of Patients (N=135)	Percentage
Stage I	63 nos	47%
Stage II	30 nos	22%
Stage II	24 nos	18%
Stage IV	18 nos	13%

TABLE 5: TYPES OF ADR

Types of ADR	N=135
Amenorrhea	3
Anaemia	9
Diarrhoea	3
Fever	15
Gastritis	9
Genital ulcer	3
Headache	6
Oral ulcer	3
Peripheral neuropathy	9
Psychosis	3
Raised LFT	33
Rash	36
Rigors	3
Total	135

TABLE 6: TOTAL SEX

Sex	n=135
Female	33
Male	102
Total	135

TABLE 7: DISTRIBUTIONS OF PATIENTS ACCORDING TO REGIMENS

Regimens of ART and ATT	Total patients n = 135	Different types of ADRs observed in patients	ADR %
T+L+E+I group	108 (80%)	12	75%
L+N+Z+I group	24 (18%)	4	24%
S+L+N+I group	3 (2)	1	1%

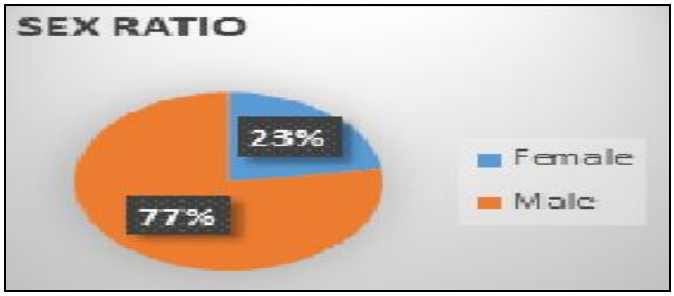

FIG. 1: SEX RATIO

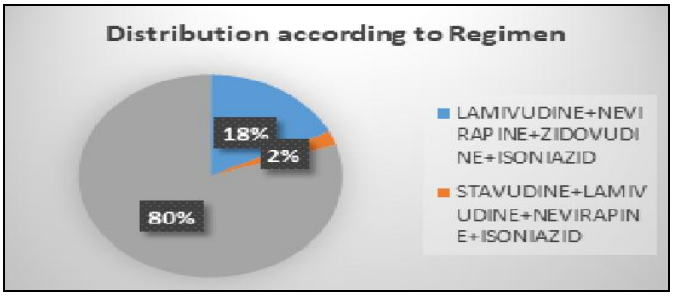

FIG. 2: DOSAGE REGIMEN

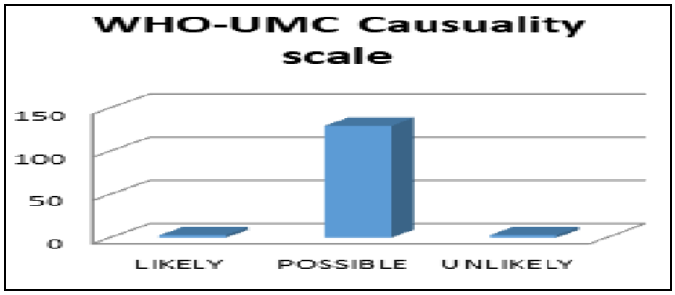

FIG. 3: CAUSALITY SCALE

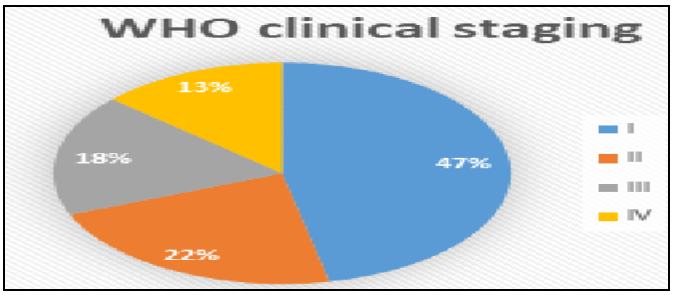

FIG. 4: WHO CLINICAL STAGES

DISCUSSION: A total 135 number of HIV and TB co-infected patients **Table 6** on treatment with various regimens of anti-retroviral and anti-tuberculosis therapy were evaluated for adverse drug reactions (ADR) over a period of one year. From the study, a total of 13 various types of ADRs **Table 5** were reported from the patients on ART and ATT therapy which accounts for a total of 135 ADR cases. It is observed that the percentages of ADR are more in males (77%), as compared to the female population (23%).

The study reports the incidence of rash, which accounts for 24% of the total ADR and can be considered as the most common ADR among the patients receiving tenofovir + lamivudine + efavirenz + isoniazid combinations *i.e.*, 80% of our total study population **Fig. 2.** A number of clinical studies have documented rash from ART therapy, mainly with nevirapine [16, 17 ,18], drug hypersensitivity in the form of a rash occur with HAART therapy, usually in first 6 weeks of therapy [19]. Nevirapine, delavirdine and efavirenz, abacavir, amprenavir have been reported to cause rashes frequently due to hypersensitivity, which usually resolves spontaneously [18]. So rash may occur due to intake of efavirenz. Hepatitis with raised liver enzymes is also a common manifestation accounting for 22% of the study population. A number of reports documented the incidence of hepatitis [16, 17, 18, 20] due to the use of nevirapine. In our study, it is observed that nevirapine is being taken by 20% of our study population. So nevirapine can cause hepatitis.

A number of gastrointestinal side effects are also observed in the study, such as gastritis (7%), and diarrhoea (2%). Identical to our observation, it is observed that similar gastritis ADR has been reported in 10% of patients who took ART [21]. Gastrointestinal side effects mainly comprise diarrhoea, vomiting, abdominal pain, which can be recovered with short-term discontinuation of ART and ATT [22].

Anaemia has been observed in 7% patients. In our study, lamivudine + nevirapine+ zidovudine + isoniazid-based combination was prescribed in the majority of the patients (18%) and zidovudine being a myelosuppressive drug is known to cause anaemia within 3 months of initiating ART. This could be the reason for the incidence of anaemia in our study which can be compared with previously reported studies [23, 24]. Peripheral neuropathy was observed in 7% of patients of our study. Peripheral neuropathy is mainly seen with stavudine, didanosine, and zalcitabine [18]. These drugs inhibit nerve growth factor resulting in (1.3-22.3%) cases of neuropathy. As per the WHO-UMC scale majority of patients in our study, **Fig. 3** were reported with possible ADRs accounting for (96%), likely (2%), and unlikely (2%). It is important to examine the causality assessment according to the WHO-UMC scale of the suspected drug reaction in order to determine whether drug discontinuation is

needed or not, as well as to put emphasis on patient education to avoid adverse events in the future.

CONCLUSION: From the above study, it can be concluded that a patient who is taking ART along with ATT should be carefully monitored by the Health care professionals for any ADR and should be immediately reported to the physician if any mild or serious ADR occurs. This study may help in creating a database about the probable ADR, which may be helpful during a patient consultation**.**

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CONFLICTS OF INTEREST: All the authors declare that they have no conflict of interest.

REFERENCES:

1. Kalaiselvan V, Thota P and Singh GN: Pharmacovigilance Programme of India: Recent developments and future perspectives. Indian J of Pharmacology 2016; 48(6): 624.
2. www.cdc.gov, Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/tb/worldtbday/ history.htm
3. www.avert.org, Global information and education on HIV and AIDS. Available from: https://www.avert.org/ professionals/hiv-around-world/asia-pacific/india
4. www.tbcindia.gov.in, Central TB Division, Ministry of Health & Family Welfare, Government of India. Available from: National Framework for Joint HIV/TB Collaborative Activities October 2009.
5. Swaminathan S and Narendran G: HIV and tuberculosis in India. J Biosci 2008; 33(4): 527–37.
6. Srivastav S: Socio-Demographic Profile of TBHIV Co-Infected Patients in Bundelkhand Region, Uttar-Pradesh. Natl J Med Res 2012; 2(2): 149-51.
7. Maher D, Harries A and Getahun H: Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies. Tropical Medicine & International Health 2005; 10(8): 734-42.
8. Global tuberculosis control: Epidemiology, strategy, financing. WHO/HTM/TB/2009. 411.
9. www.who.int, World health Organisation. Tuberculosis and HIV. Available from: https://www.who.int/ hiv/topics/ tb/en/
10. Kamath R, Sharma V, Pattanshetty S, Hegde MB and Chandrasekaran V: HIV-TB coinfection: Clinico-epidemiological determinants at an antiretroviral therapy center in Southern India. Lung India: official organ of Indian Chest Society 2013; 30(4): 302.
11. Pawlowski A, Jansson M, Sköld M, Rottenberg ME and Källenius G: Tuberculosis and HIV co-infection. Plos Pathog 2012; 8(2): e1002464.
12. Bhagyabati DS, Naorem S, Singh TJ, Singh KB, Prasad L and Shantidevi T: HIV and TB Co-infection. Journal, Indian Academy of Clinical Medicine 2005; 6(3): 220-3.
13. Chavan VR, Chaudhary V, Ahir P, Mehta R, Mavani PS, Kerkar C and Pramanik JM: Current scenario of Opportunistic and co-infections in HIV-infected individuals at a tertiary care hospital in Mumbai, India. Indian Journal of Medical Microbiology 2015; 33(1): 78.
14. www.tbcindia.gov.in, Central TB Division, Ministry of Health & Family Welfare, GOI. Available from: https://www.tbcindia.gov.in/view.php?lid=3219&type=1
15. www.naco.gov.in, National AIDS Control organisation. ART guidelines for HIV-Infected Adults and Adolescents: May 2013.
16. Lartey M, Asante-Quashie A, Essel A, Kenu E, Ganu V and Neequaye A: Adverse drug reactions to antiretroviral therapy during the early art period at a tertiary hospital in Ghana. The Pan African Medical Journal 2014; 18.
17. Millogo A, Lankoande D, Yameogo I, Yameogo AA and Sawadogo AB: Polyneuropathies in patients treated with HAART in Bobo-Dioulasso hospital, Burkina Faso. Bulletin de la Societe de pathologie exotique (1990). 2008; 101(1): 11-3.
18. Patel A, Pujari S, Patel K, Patel J, Shah N, Patel B and Gupte N: Nevirapine versus efavirenz based antiretroviral treatment in naive Indian patients: comparison of effectiveness in clinical cohort. JAPI 2006; 54: 915-8.
19. Salami AK, Olatunji PO, Fawibe EA and Oluboyo PO: Influence of highly active antiretroviral therapy (HAART) on the survival of HIV-infected patients: part report of the Ilorin Trial Center. African Journal of Clinical and Experimental Microbiology 2005; 6(1): 34-9.
20. Sharma A, Vora R, Modi M, Sharma A and Marfati Y: Adverse effects of antiretroviral treatment. Indian J Dermatol Venerel Leprol 2008; 74(3): 234–7.
21. Singh H, Dulhani N, Tiwari P, Singh P and Sinha T: A prospective, observational cohort study to elicit adverse effects of antiretroviral agents in a remote resource-restricted tribal population of Chhattisgarh. Indian Journal of Pharmacology 2009; 41(5): 224.
22. Seth P: The situation of HIV/M. tuberculosis co-infection in India. The Open Infectious Diseases J 2011; 65(1).
23. Montessori V, Press N, Harris M, Akagi L and Montaner JS: Adverse effects of antiretroviral therapy for HIV infection. Cmaj 2004; 20170(2): 229-38.
24. Nadkar MY and Bajpai S: Antiretroviral therapy: toxicity and adherence. JAPI 2009; 157: 375-6.

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