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Viewpoint Article

Effect of concomitant HIV infection on adverse drug reactions by first line antitubercular drugs - a case series analysis

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Abstract

The pattern and severity of adverse drug reactions (ADRs) due to first-line anti-tubercular drugs in solely tubercular and TB-HIV co-infected patients could be different due to drug-disease and drug-drug interactions in TB-HIV co-infected patients. Nevertheless, the studies regarding this aspect are very meager. Hence a retrospective appraisal of individual case safety reports (ICSR) due to first-line antitubercular drugs spontaneously submitted to the ADR monitoring center was done for solely tubercular and TB-HIV coinfected patients. Out of eight ICSRs, four had concomitant HIV infection, and two of them were on antiretroviral (ARV) drugs. Co-infected patients showed rare and severe ADRs like optic neuritis, acute renal failure, and drug-induced liver injury (DILI). In contrast, four non-HIV co-infected tubercular patients suffered from comparatively less severe cutaneous reactions and vertigo. A high negative (-0.774) correlation coefficient between HIV co-infection and recovery status found that HIV co-infected patients had low chances of fully recovering. In conclusion, HIV co-infection and ARV drugs can affect the pattern, severity, and recovery status of adverse drug reactions due to first-line antitubercular drugs.

Keywords: Adverse Drug Reactions (ADR), TB-HIV Co-infection, First Line Antitubercular Drugs (FLD), Pharmacovigilance Programme, India

Background

Tuberculosis (TB) and human immunodeficiency virus (HIV) are highly infectious diseases commonly encountered in the Asian-Pacific region. According to the WHO global tuberculosis report 2014, HIV prevalence was 6.3 % in new TB cases in this region and was on an increasing trend [1]. As multiple drugs are used for a longer duration in both of them, so the possibility of drug-drug and drug-disease interactions are high in TB-HIV coinfected patients. Isoniazid, rifampicin, pyrazinamide, and ethambutol, abbreviated as HRZE, are used as first line antitubercular drugs (FLD) in tuberculosis treatment as per guidelines. For HIV, the national AIDS control organization approves multiple regimens, but in practice, tenofovir, lamivudine, and efavirenz, abbreviated as TLE_f or zidovudine, lamivudine, efavirenz (Z_dLE_f), are preferred. Common adverse drug reactions (ADRs) encountered due to FLD are nausea, vomiting, jaundice, arthralgia, pruritus, abdominal pain, paresthesia, numbness, mental disturbances, rash, fever, lethargy, and diarrhea.

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In contrast, shock, renal failure, loss of diabetes control, and optic neuritis are rare but serious adverse effects. Antiretroviral drugs mainly show hematologic and skin reactions as adverse effects [2,3]. The purpose of this case series analysis is to compare and analyze the pattern and severity of adverse drug reactions due to anti-tubercular drugs in solely tubercular and TB-HIV co-infected patients. For this, we analyzed the individual case safety reports (ICSR) submitted to ADR Monitoring Center (AMC) at Sawai Man Singh (SMS) Hospital, Jaipur from Chest and TB department in 2019.

SMS Hospital AMC was set up in 2011 as a part of the Pharmacovigilance Programme of India (PvPI). PvPI was initiated on 14th July 2010 under the aegis of the Ministry of Health and family welfare with headquarter in Ghaziabad to safeguard public health by validating the safety of medicinal products [4]. As of 2020, there are 311 AMCs in India which collect spontaneously submitted 4000-5000 individual case safety reports (ICSRs) every month. These collected ICSRs are analyzed and subjected to provisional causality assessment before directing them towards the national coordinating centre (NCC) in Ghaziabad for further proceedings and finally submitted to the Uppsala monitoring centre, Sweden through VigiFlow. SMS Hospital AMC contributes about 20-30 ICSRs every month to the NCC-PvPI. Most of the hospital ADRs are reported from cancer, HIV, skin, medicine, and TB

departments. While assessing the ICSRs from the TB department in the present study, demographic factors, associated HIV disease and its treatment, suspected antitubercular drug in combination, and the lag time between antitubercular treatment (ATT) and reporting ADR, the severity of ADR together with recovery status were noted. WHO-UMC scale and Hartwig scale were used for casualty and severity assessment, respectively [5, 6]. Individual case vignettes are as follows.

Case 1-

A male patient 40 years of age presented with complaints of progressively decreased vision six months after starting ATT therapy for extrapulmonary TB. At the time of ADR, he was receiving Isoniazid (H), rifampicin (R), ethambutol (E) in doses 5mg/kg, 10mg/kg, 15mg/kg, respectively. He was a naïve case of HIV diagnosed simultaneously with TB for which he was started the TLE_f regimen by oral route two weeks after initiating ATT. Doses used were 300, 300, 600 mg for tenofovir, lamivudine, and efavirenz, respectively. The patient did not recover from vision loss even after stopping the ethambutol.

Case 2-

A male patient of 55 years was a known HIV case for 12 years on Z_d LE_f (600, 300, and 600 mg respectively every day). He had a previous history of pulmonary TB as an opportunistic infection eight years back, for which he had received ATT for nine months and was declared cured. Now he again developed TB on November 18 and started ATT. He presented with a history of feeling a continuous decrease in the vision on January 19. Ethambutol was stopped immediately and replaced by pyrazinamide. However, he did not improve even after two months. In both the above cases, rechallenge was not done with ethambutol, and patients did not improve either after stopping the suspected drug.

Case 3-

A 43 years old naïve TB-HIV co-infected male patient on ATT presented with complaints of severe diarrhea, vomiting, and decreased urine. His serum creatinine levels, and blood urea nitrogen levels were increased to 544µmol/l and 49 mmol/l, respectively, within two weeks of starting ATT in contrast to 124µmol/l and 10 mmol/l before initiation of ATT. Liver function tests were normal. Temporal association and effect of ethambutol withdrawal to stop clinical condition worsening identified ethambutol as the suspected drug. However, biopsy reports were not available, and the reintroduction of ethambutol was not attempted. The patient did not recover fully.

Case 4-

A female patient of 63 years of age was on a TLE_f regimen for three months. Then she developed tuberculosis, for which she was started a quadrupled ATT regimen. She was hospitalized with clinically evident jaundice after two months of initiating therapy. Total bilirubin was 53µmol/l, and ALT/AST levels were 358/92 units per liter (U/L), respectively. It fulfilled the criteria of drug-induced liver injury (DILI), which states either liver enzymes more than five times of upper limit of normal or more than three times of upper limit of normal with symptoms of hepatitis or jaundice (bilirubin>51 µmol/l) [7]. All ATT drugs were stopped, and after 12 days of stopping, ATT baseline value of bilirubin and ALT/AST returned to 27µmol/l and 55/32 per liter, respectively. Isoniazid (H) and rifampicin (R) were resumed without any further side effects, but the pyrazinamide (Z), which was the main suspected drug, does not reintroduced.

Cases 5-8-

Amongst the solely tubercular patients, one male smoker patient developed severe nausea and vertigo with pyrazinamide's first dose. Symptoms subsided with a reduction of dose from 1250 to 750 mg, and again increase in dose after two days was well tolerated. No lab tests were done. Rest three tubercular patients presented with equally distributed, itchy, macular rashes all over the chest and abdomen with or without skin excoriation after seven to ten days of initiating ATT. Isoniazid (H) was the suspected drug, and on discontinuing it, they all recovered. Demographic characteristics reported ADRs, and other findings are given in table 1.

Statistical analysis

The mean age of the tubercular patients with ADR was 44 years. For calculating the correlation coefficient between HIV and recovery status, firstly, number “0” was assigned to those who did not recover, and number "1" was assigned to those who recovered. Similarly, for the presence of HIV, number “1” was assigned and “0” for the absence of HIV in the study patients, as shown below:

Recovery	HIV
0	1
0	1
0	1
1	1
1	0
1	0
1	0
1	0

Then the following formula for Correlation Coefficient was applied in Minitab 14 software, Pennsylvania (PA)

$$r = \frac{Cov\,(x,y)}{\sigma_x * \sigma_y} = \frac{\sum\sum xy - \bar{x}\bar{y}}{\sqrt{\sum x^2 - (\bar{x}^2)}\sqrt{\sum y^2 - (\bar{y}^2)}}$$

Where $\bar{x}$ and $\bar{y}$ are the mean values for the series x(recovery) and y (HIV). The correlation coefficient value came out to be -0.774, which shows a negative and high correlation between HIV and recovery. So, it was concluded that as the patient is HIV positive, there is a very low chance to recover fully.

Discussion

Ethambutol is a bacteriostatic drug that acts by inhibiting arabinosyltransferase required for mycobacterial cell wall synthesis. It is also a metal chelator that chelates iron and copper-containing complexes richly present in mitochondria. As a result, oxidative phosphorylation has interfered with the increased production of reactive oxygen species. Since the papillomacular bundle is rich in mitochondria, more damage to the optic pathway [8].

Hence, optic neuritis is a rare but significant adverse effect of ethambutol, which requires the drug's withdrawal. Human immunodeficiency virus produces cytokine and TNF-mediated secondary inflammatory changes in optic nerves predisposing them to develop optic nerve toxicity. After the priming by HIV infection, when ethambutol in concomitant TB co-infection is given, the potential for toxicity is further increased [9,10].

Table 1 Demographic characteristics reported ADRs, and other findings (n=8)

S. No	Age	Sex	Wt.	HIV Y/N	HIV Duration	ADR reported	Suspected antitubercular drug	ADR Onset Lag time	WHO-UMC casualty scale	Severity of reaction	Fully Recovered
1	40	M	49	Yes	0 months*	Optic neuritis	Ethambutol (E)	185 days	Possible	Yes	No
2	55	M	48	Yes	12 years	Optic neuritis	Ethambutol(E)	115 days	Possible	Yes	No
3	43	M	49	Yes	0 months*	Renal failure	Ethambutol(E)	14 days	Possible	Yes	No
4	63	F	43	Yes	6 months	DILI	Pyrazinamide (Z)	58 days	Possible	Yes	Yes
5	21	F	28	No	-	Skin reaction	Isoniazid(H)	7 days	Possible	No	Yes
6	52	M	40	No	-	Skin reaction	Isoniazid (H)	10 days	Certain	No	Yes
7	26	F	28	No		Skin reaction	Isoniazid (H)	7 days	Possible	No	Yes
8	52	M	43	No	-	Severe nausea, vertigo	Pyrazinamide (Z)	O days	Possible	No	Yes

0 months*=simultaneously diagnosed, ADRs= Adverse Drug Reaction, S. No= case serial number

It is usually reversible and dose-dependent, but it was irreversible in our study and occurred at an optimum dose of 15mg/kg/day as approved in guidelines. To add more, Mustak et al. [11] have found that Nucleoside analog reverse transcriptase inhibitors (NRTIs) used in HIV therapy may be a risk factor for developing toxic optic neuropathy from ethambutol therapy by virtue of their additional potential mitochondrial toxic effects. They called it a multiple hit effect [11]. A number of second-line injectable drugs such as aminoglycosides used in multidrug-resistant tuberculosis cases are nephrotoxic, but very few renal toxicity cases by FLD have been reported. Hughes et al. [12] have very recently explained that HIV-infected renal epithelial cells proliferate after acquiring the virus from macrophages, and it may contribute to precipitate renal failure in susceptible patients on ATT [12]. It seems that HIV infection rather than ARV contributes to renal disease as the patient in our study was also naïve to antiretroviral drugs, as in another similar study by Narayana et al. [13]. Ramappa et al. [14] found that concomitant HIV infection increases the risk of anti-TB drug-induced hepatotoxicity significantly (4 times), and the use of highly active anti-retroviral therapy further increases hepatotoxicity. The reason could be due to interactions together with immune reconstitution. They emphasized that a sequential regimen with or without pyrazinamide would be suitable for individuals who have a higher baseline prediction of hepatotoxicity as defined by their phenotype of malnutrition, low albumin, alcoholics, and HIV-positive individuals [14]. We also stopped pyrazinamide, and the patient recovered in a few days.

Amongst the non-HIV co-infected tubercular patients, reactions were moderately severe, with three of them suffering from skin reactions all over the thorax and abdomen, and one had excessive nausea and vertigo. All were possible on the WHO-UMC scale except one certain skin reaction due to isoniazid who developed rash again on reintroduction, and isoniazid was withdrawn. All FLD and SLD in tuberculosis can cause cutaneous reactions, the commonest being isoniazid in FLD [7,15]. Second-line anti- Koch drugs like aminoglycosides used in multidrug-resistant and extremely drug-resistant TB are notorious for causing ototoxicity with vertigo as the most common vestibular symptoms followed by tinnitus and hearing loss [16]. However, the non –HIV patient in our study suffered from severe nausea and vertigo with FLD, which abated with the decrease in pyrazinamide dose.

Limitations of the study

The study focused on one time ADR collected by the pharmacovigilance centre. Secondly, being an institution based study, limited data were available for evaluation.

Conclusion

The study largely shows that HIV co-infection and ARV can affect the pattern, severity, and recovery from toxicity due to antitubercular drugs. TB-HIV co-infection is a recent evolving infectious epidemic in the Asia- Pacific region. Hence research focused on identifying possible drug-disease and drug-drug interactions, and drug modulations should be promoted, and extra vigilance is required when dealing with coinfected patients.

Abbreviations

TB: Tuberculosis; ADR: Adverse Drug Reaction; HIV: Human Immunodeficiency Virus; PV: Pharmacovigilance; ICSR: Individual Case Safety Reports; ARV: Antiretroviral; FLD: First Line antitubercular Drugs; WHO: World Health Organization; AIDS: Acute Immune Deficiency Syndrome; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; Z_d: zidovudine; L: lamivudine; E_f: efavirenz; ATT: Antitubercular Treatment; AST: Aspartate Transaminase; ALT: Alanine Transaminase; DILI: Drug-Induced Liver Injury; TNF: Tumor Necrosis Factor; NRTI: Nucleoside Reverse Transcriptase Inhibitors; SLD: Second Line Antitubercular Drugs; mmol/l: millimole per liter; µmol/l: micromole/liter

Declarations

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Availability of data and materials

Data will be available by emailing alkabansal04@gmail.com

Authors' contributions

AB is the principal investigator in this manuscript. She observed the findings, conceived the concept, designed, and developed the study, including its writing, editing, and approved the manuscript in its present form. LS participated in data procurement, its analysis, revision, and approved the manuscript. Authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in duly compliance with the established international publishing and reporting recommendations by the EQUATOR network for enhancing quality and transparency in health research. We followed the principles of the declaration of Helsinki. The approval of the Institutional Ethics committee, SMS Hospital, Jaipur, was obtained via letter No. 4123/ MC/EC/2018 dated 9/10/18.

Consent for publication

Not applicable

Competing interest

The author declares that he has no competing interests.

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