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Prevalence of tuberculosis among HIV positive patients on anti-retroviral therapy with special emphasis on pattern of adverse events of first-line anti-tubercular drug

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***Abstract*---**Background: Survival rates have been improved with concomitant use of anti-tubercular drugs in HIV subjects with tuberculosis. The use of anti-tubercular drugs combined with ART can lead to more drug interactions, non-compliance, toxicity, and adverse effects. Aim: To assess the pattern, severity, and prevalence of adverse drug reactions of first-line anti-tubercular drugs in HIV (Human Immunodeficiency Virus) positive subjects with tuberculosis. Methods: The present prospective, observational study included 391 subjects out of 19522 subjects who were diagnosed HIV Positive and scheduled for Anti-Retroviral therapy at the ART Centre. 102 subjects were enrolled as tuberculosis confirmation of HIV-TB Co-Infection disease during the study period. All the subjects were evaluated for adverse drug events including blurred vision, jaundice, neuropathy, skin infection, itching, blood urea, hepatotoxicity, tingling, numbness, pain, pancreatitis, diarrhea, skin rashes, and anemia. Results: The most prevalent side-effect noted was neuropathy reported in 26.13% (n=10) study participants followed by skin rashes reported in 21.05% (n=8) study subjects. Jaundice, vomiting, and body weakness were all reported in 15.78% (n=6) of study subjects each. Diarrhea, headache, hepatotoxicity, insomnia, mental confusion, and anorexia were all reported in 10.52% (n=4) of study participants each. Other reported side effects were pruritis/itching and anemia seen in 5,26% (n=2)

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subjects each Conclusions: Adverse drug events are reported in subjects on first-line anti-tubercular drugs with concomitant HIV infection and TB. Reporting of these events should be uplifted in health care professionals and affected subjects to get time management.

***Keywords*---**Adverse drug events, Antiretroviral therapy, acquired immunodeficiency syndrome, Human Immunodeficiency Virus, Tuberculosis.

Introduction

Tuberculosis (TB) is a chronic contagious disease posing a high burden on the healthcare sector globally, especially in developing countries. TB is caused by Mycobacterium tuberculosis which infects nearly one-fourth of the global population making it one of the deadliest diseases.[1] As per CDC (center for disease control) data of 2017, 10 million subjects were reported to have tuberculosis where 2.8 million cases alone were contributed by India. A total of 1.3 million deaths were reported globally in 2017. India shared the highest burden of TB in the World for many years with nearly 1000 mortalities every year.[2]

HIV infection incidence has been consistently increasing over the last few decades making even the smallest rise in AIDS/HIV prevalence a significant contributor to the global rise in the burden of AIDS/HIV. Also, TB is the leading cause of mortality and morbidity in subjects with (HIV) infections, especially in developing countries like India. The highest number of HIV-infected subjects in India is confined to Manipur, Nagaland, Karnataka, Maharashtra, Tamil Nadu, and Andhra Pradesh. However, anti-retroviral therapy (ART) has been shown to markedly reduce the transmission of HIV and is now adopted widely.[3]

The management of HIV and tuberculosis is difficult in subjects with concomitant infection with both the diseases along with more rapid reported disease progression. However, chemotherapy is the only effective treatment modality for tuberculosis which is highly dependent on the willingness of the subjects to be compliant with the prescribed drugs.[4] This compliance largely governs the compliance of tuberculosis subjects to the drug regimen prescribed. These anti-tubercular drugs are usually taken for prolonged periods and in combination forms. Adverse drug reactions are prominent factors in managing chronic diseases like TB. However, these adverse drug reactions are under-reported in nations like India with less follow-up, still, they form a significant factor.[5]

Previous literature data from developing countries have reported that HIV infection is an established risk factor for anti-tubercular drug reaction development.[6] Various literature studies on anti-tubercular adverse drug reactions are usually retrospective and were done with no preliminary aim to assess the adverse drug reactions warranting the need for longitudinal studies to assess the interaction of HIV and TB with the main focus on adverse drug reactions. In addition, very few of these studies were conducted in India.[7] Hence,

the present study was done to assess the pattern, severity, and prevalence of adverse drug reactions of first-line anti-tubercular drugs in HIV (Human Immunodeficiency Virus) positive subjects with tuberculosis.

Materials and Methods

The present prospective observational study was done at Chhattisgarh Institute of Medical Science Bilaspur in the Department of ART center and TB - Chest (C.G.) from January 2019 to June 2020 after Ethical committee clearance was given by the concerned Ethical committee.

The study included subjects who were newly diagnosed with HIV infections and showed seropositive results and were referred to the ART center for HAART (highly active anti-retroviral therapy) treatment. After explaining the detailed study design, informed consent was taken in both written and verbal form. The inclusion criteria for the study were subjects of age more than 18 years, in the age range of 18-60 years, HIV-positive, and subjects registered for ART. The exclusion criteria for the study were pregnant and lactating females, subjects who did not fill out the consent form, and subjects not willing to participate in the study. The study included 391 subjects out of 19522 subjects who were diagnosed HIV Positive and scheduled for Anti-Retroviral therapy at the ART Centre. 102 subjects were enrolled as tuberculosis confirmation of HIV-TB Co-Infection disease during the study period

After the final inclusion of the study subjects, detailed history was recorded for all the participants followed by an examination. After a confirmed diagnosis of being HIV-positive, all the participants were sent to the ART center to initiate anti-retroviral treatment. Counseling was done for all the participants at the ART center concerning the study protocol. Confidentiality was maintained for all the subjects. After obtaining the informed consent and counseling, my HIV-positive status was reconfirmed. ART medicines were given to all the subjects following the NACO guidelines. CB-NAAT (Cartridge Based Nucleic Acid Amplification test) was performed every six months to assess the prevalence and confirm the tuberculosis status.

To assess the adverse drug reactions a performed checklist was given to all the subjects where they marked the encountered adverse drug reactions with the first line of anti-tubercular medicine. The checklist was utilized for screening the adverse drug effects at every visit for the study duration. Along with adverse drug reactions, the death rate was also assessed in the study participants.

The collected data were analyzed statistically using SPSS software version 22 and chi-square test and t-test. Means and standard deviations were used to describe the continuous variables and the number and percentage for the categorical variables. The significance was kept at a level of $p=0.05$.

Results

The present study was done to assess the pattern, severity, and prevalence of adverse drug reactions of first-line anti-tubercular drugs in HIV (Human

Immunodeficiency Virus) positive subjects with tuberculosis. The study enrolled 391 subjects out of 19522 subjects who were diagnosed HIV Positive and scheduled for Anti-Retroviral therapy at the ART Centre. Among these subjects 64.5% (n=252) were males and 34.01% (n=133) were females and 1.53% (n=6) subjects were transgenders showing the male predilection. The demographics of 391 subjects assessed for HIV are summarized in Table 1. The majority of the study subjects were in the age range of 31-40 years with 41.4% (n=162) subjects followed by 20.20% (n=79) subjects from 51-60 years, 12.53% (n=49) subjects from 41-50 years, 10.74% 9n=42) subjects from >60 years, 7.92% (n-31) subjects in 21-30 years, and least 7.16% (n=28) subjects from <20 years. The mean duration of illness in the study subjects was 4.3±1.42 months (Table 1). On referral to the ART and reassessment, 26.08% (n=102) of subjects were found to have tuberculosis that was enrolled as tuberculosis confirmation of HIV-TB Co-Infection disease during the study period.

On the follow-up, 16.9% (n=66) subjects did not turn up making the sample size 325 subjects. Among 102 subjects with HIV and tuberculosis co-infections, all 100% (n=102) subjects were males and no female participants. The demographics of subjects with concomitant HIV infection and TB are listed in Table 2. The mean age of these subjects was 32.6±4.24 years with the majority of participants in the age of 31-40 years with 41.17% (n=42) subjects and the least subjects in >60 years age range with 2.94% (n=3) subjects.

On assessing the casualty in the study participants during the study duration, it was seen that 62.74% (n=64) of subjects died during the study period leaving only 38 subjects for final assessment where adverse drug events were only assessed in these 38 subjects as depicted in Table 3.

Concerning the adverse drug reactions with first-line anti-tubercular drugs in the 38 study participants, the most prevalent side-effect noted was neuropathy reported in 26.13% (n=10) study participants followed by skin rashes reported in 21.05% (n=8) study subjects. Jaundice, vomiting, and body weakness were all reported in 15.78% (n=6) of study subjects each. Diarrhea, headache, hepatotoxicity, insomnia, mental confusion, and anorexia were all reported in 10.52% (n=4) of study participants each. Other reported side effects were pruritis/itching and anemia seen in 5,26% (n=2) subjects each as shown in Table 4.

Discussion

Managing tuberculosis has been challenging since its inception, however, with advances in pharmacology, its management is continuously evolving based on drug resistance and co-infection of HIV-AIDS with tuberculosis. Patient compliance is a major factor governing the success of chemotherapeutic treatment for TB as the therapy is given for six to eight months. Long-term therapy and multiple drug combination are major factors predisposing these subjects to adverse drug reactions as suggested by Phillips E et al[8] in 2007. Hence, the present study was done to assess the adverse drug effects where higher adverse effects were reported compared to the previous literature studies.

As with the previous study of Ziersky M et al[9] in 1980 where authors reported lesser side-effects with anti-tubercular drugs compared to the previous studies.

Management of tuberculosis becomes a further challenge when some serious adverse effects are encountered by the subject on anti-tubercular drugs. Also, co-infection with HIV and tuberculosis has shown that disease progression for Tb is worsened in subjects with concomitant HIV with an unexpected increase in the severity and incidence of the adverse drug reactions as suggested by Erik Von Elm et al[10] in 2007. In developing countries like India, awareness about free access to HIV diagnosis, and counseling. And treatment is rather low which leads to the presentation of HIV-AIDS at the later stages compared to the early stages. This late presentation is further identified as a risk factor for more adverse reactions to different anti-microbial agents including anti-tubercular drugs as reported by Sharma SK et al[11] in 2005. HIV is also associated with high rates of hypersensitivity reactions which are more common in some spots. This was supported by the study done in 2003 in Canada by Yee D et al[12] where authors reported the correlation of HIV-positive state to major side-effects occurrence with the first line anti-tubercular drugs with an adjusted hazards ratio of 3.8.

The severe side-effects reported in the present study were neuropathy reported in 26.13% (n=10) study participants followed by skin rashes reported in 10.52% (n=4) study subjects. Jaundice, vomiting, and body weakness were all reported in 7.89% (n=3) of study subjects each. Findings of these side effects can be attributed to the aim of the study directed to assess side-effects reported by the previous study by Michael O. S et al[13] in 2016. However, in other studies with no primary aim to assess side-effects of anti-tubercular drugs, these effects remain unreported, undetected, and unnoticed, and not to the lack of knowledge about these side effects as suggested by Michael O. S et al[13] in 2016. This could also be due to difficult differentiation between drug reactions and disease processes, and uninterested physicians looking for side effects.

The study results showed that increased age was a risk factor for developing adverse drug reactions to anti-tubercular drugs. This can be an individual factor. However, this can also be considered in correlation to increase age-related changes in pharmacodynamics and pharmacokinetics, presence of multiple diseases, and intake of multiple medications which can further lead to a greater number of side effects as also reported by Corsonello A et al[14] in 2010. These factors can also be considered for the association of adverse drug events and age in other literature studies including studies by Martin RM et al[15] in 1998 supporting the present study.

Among 102 subjects with HIV and tuberculosis co-infections, all 100% (n=102) subjects were males and no female participants. This was in contrast to the previous study by Klein U et al[16] in 1976 where authors reported the high association between adverse drug reactions and the female gender. In the present study, jaundice was reported in 15.78% (n=6) of study subjects. This was similar to the previous studies by Michael OA et al[13] in 2016. However, the present study did not assess the liver enzymes as assessed by previous studies by Gulbay BE et al[17] in 2006 where authors assessed the liver enzymes which is a limitation of the present study and could provide a better picture of hepatotoxicity and jaundice.

In the present study, skin rashes were the second most common complication seen in 21.05% (n=8) subjects. This was following the previous study by Ipuge YA et al[18] in 1996 where authors reported that HIV-positive subjects have more adverse reactions to anti-tubercular drugs. The study overcame shortcomings of the previous studies where death rates were not assessed.

The study also had a few limitations including non-assessment of laboratory parameters including liver function tests, a short monitoring period, a smaller sample size, and no comparison with controls without HIV infection.

Conclusion

The present study considering its limitations concludes that adverse drug events are reported in subjects on first-line anti-tubercular drugs with concomitant HIV infection and TB. Reporting of these events should be uplifted in health care professionals and affected subjects to get time management. Early identification can be improved with adequate drug knowledge and accurate diagnoses. As HIV and TB co-infections do exist, the use of multiple drugs can lead to more adverse effects which should be carefully monitored.

Declarations

Funding: Self sources

Conflict of interest: To find adverse effects of Anti-tubercular drugs with ART drugs.
Ethical approval: Approved by IEC CIMS Bilaspur Chhattisgarh India.

References

1. CDC, 2017a. Centre for disease control and prevention. Tuberculosis (TB), Data andStatistics. Available from: https://www.cdc.gov/tb/statistics/default.htm (last accessed on10 July 2017).
2. UNAIDS. Epidemiological fact sheet on HIV and AIDS: India. 2008; available at: http://www.who.int/globalatlas/predefinedReports/EFS2008/full/EFS2008_IN.pdf, accessed on March 3, 2009.
3. Walensky RP, Ross EL, Kumarasamy N, et al. Cost-effectiveness of HIV treatment as prevention in serodiscordant couples. N Engl J Med. 2013;369:1715–25.
4. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. Clin Infect Dis. 2011; 53:84–91.
5. Ribaudo HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with an initial antiretroviral treatment containing abacavir: Short and long-term results from ACTG A5001/ALLRT. Clin Infect Dis. 2011;52:929–40.
6. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: No increased risk across 52 GlaxoSmithKline-

sponsored clinical trials in adult subjects. J Acquir Immune Defic Syndr. 2009;51:20–8.
7. Sabin CA, Worm SW, et al. D: A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D: A:D study: A multi-cohort collaboration. Lancet. 2008;371:1417-26.
8. Phillips E, Mallal S. Drug hypersensitivity in HIV. Curr Opin Allergy Clin Immunol 2007;7:324-30.
9. Zierski M, Bek E. Side-effects of drug regimens used in short-course chemotherapy for pulmonary tuberculosis. A controlled clinical study. Tubercle. 1980;61:41-9.
10. Erik von Elm**,** Douglas GA, Mattias E, *et al.* The Strengthening the reporting of Observational Studies in Epidemiology (STROBE): Guidelines for reporting observational studies. Preventive Medicine. 2007;45**:**247-51.
11. Sharma SK, Mohan A, Kadhiravan T. HIV-TB co-infection: epidemiology, diagnosis & management. Indian J Med Res 2005;121**:**550-67.
12. Yee D**,** Valiquette C, Pelletier M, *et al.* Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med. 2003;167**:**1472-7.
13. Michael OS, Sogaolu OM, Fehintola FA, et al. Adverse events to first line anti-tuberculosis drugs in patients co-infected with HIV and tuberculosis. Ann Ib Postgrad Med 2016;14:21–9.
14. Corsonello A**,** Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17**:**571-84.
15. Martin RM**,** Biswas PN, Freemantle SN, *et al.* Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. Br J Clin Pharmacol. 1998;46**:**505-11.
16. Klein U, Klein M, Sturm H, *et al.* The frequency of adverse drug reactions is dependent upon age, sex, and duration of hospitalization. Int J Clin Pharmacol Biopharm. 1976;13**:**187-95.
17. Gulbay BE**,** Gurkan OU, Yildiz OA, *et al.* Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respir Med 2006;100**:**1834-42.
18. Ipuge YA, Rieder HL, Enarson DA. Adverse cutaneous reactions to thiacetazone for tuberculosis treatment in Tanzania. Lancet 1995;346**:**657-60.
19. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. International Journal of Health Sciences, 5(1), i-v. https://doi.org/10.53730/ijhs.v5n1.2864.

Tables

Characteristics	Percentage (%)	Number (n=391)
Mean age (years)	38.4±6.23	
Age range (years)		
<20	7.16	28
21-30	7.92	31
31-40	41.4	162
41-50	12.53	49
51-60	20.20	79
>60	10.74	42
Gender		
Males	64.5	252
Females	34.01	133
Transgender	1.53	6
Duration of HIV (months)	4.3±1.42	
HIV-TB co-infection	26.08	102

Table 1: Demographic characteristics of the study subjects

Characteristics	Percentage (%)	Number (n=102)
Mean age (years)	32.6±4.24	
Age range (years)		
<20	15.68	16
21-30	12.74	13
31-40	41.17	42
41-50	18.62	19
51-60	8.82	9
>60	2.94	3
Gender		
Males	100	102
Females	0	0
Transgender	0	0

Table 2: Demographics of study participants with co-infection of HIV and TB

S. No	Casualty assessment	Percentage (%)	Number (n=102)
1.	**Deaths**	62.74%	64

Table 3: Mortality rate in the study subjects

Adverse effects	Percentage (%)	Number (n=38)
Anemia	5.26	2
Skin rashes	21.05	8
Diarrhea	10.52	4
Body weakness	15.78	6
Headache	10.52	4
Hepatotoxicity	10.52	4

Vomiting	15.78	6
Itching/pruritis	5.26	2
Insomnia	10.52	4
Neuropathy	26.13	10
Jaundice	15.78	6
Mental confusion	10.52	4
Anorexia	10.52	4

Table 4: Adverse drug reactions in the study participants with first line anti-TB and HIV co-infection