



A CASE CONTROL STUDY OF RISK OF PULMONARY TUBERCULOSIS AMONG CIGARETTE SMOKERS IN HIV INFECTED PATIENTS.

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ABSTRACT

Introduction: Recognized as an emerging disease only in early 1980s, AIDS has rapidly established itself throughout the world, and is likely to endure and persist well into 21st century. AIDS has evolved from mysterious illness to a global pandemic which has infected tens of millions in less than 20 years. Promising development is seen in recent years in global efforts to address the AIDS epidemic, including increased access to effective treatment and preventive programs. However, the number of people living with HIV continues to grow, as does the number of deaths due to AIDS. **Results:** The present study was undertaken to study the risk of pulmonary tuberculosis among cigarette smokers in HIV infected patients. The study included 35 patients as cases with history of cigarette smoking with pulmonary tuberculosis in HIV infected patients and 35 patients as controls with no history of cigarette smoking with pulmonary tuberculosis in HIV infected patients. There was male predominance in both the groups. Majority of the patients (57.1%) in Controls group and 88.6% of the patients in Cases group were males in the age group of 50-59 years. Significant number of patients in Cases group were educated upto primary schooling or lesser as compared to Controls group (45.7% vs. 14.3%) and 60% patients in Cases group were unemployed. The median duration of HIV infection was significantly shorter among Cases group as compared to Controls group (44 days vs. 80 days). Median CD4 count was lower (60 vs. 81 cells/mm³, P = 0.03) and median viral load was higher (173 vs. 67 copies/ul per thousand, among Cases versus Controls group. 16 patients in Cases group were current smokers whereas 19 patients were former smokers. 3 patients in Current Smokers smoked 1-5 cigarettes per day while 6 and 7 patients respectively smoked 6-10 and >10 cigarettes respectively. 2 patients in Current Smokers smoked for 1-5 years while 4 and 10 patients respectively smoked 6-10 and >10 years respectively. 8 patients in Former Smokers smoked for 1-5 years while 7 and 4 patients respectively smoked 6-10 and >10 years respectively. There was significant association between the groups as per Chi-Square test (p<0.05). **Conclusion:** There are approximately 2.5 million people living with HIV/AIDS (PLWHA) in India - the young being particularly vulnerable. The prevalence of smoking has increased in India especially among rural, lower socio-economic and illiterate men. Studies have shown that HIV-infected smokers may be at additional risk for several infectious and non-infectious complications, including malignancies and cardiovascular events. As the epidemiology of TB, HIV and tobacco merge, it is important to address tobacco use as the leading cause of preventable death to ensure that patients with TB and HIV can realize the benefits of life-saving TB treatment. Future research is needed to assess the impact of

extensive programs to encourage adults with HIV to stop smoking to reduce the odds of TB and promote general health for patients with HIV.

INTRODUCTION

Recognized as an emerging disease only in early 1980s, AIDS has rapidly established itself throughout the world, and is likely to endure and persist well into 21st century. AIDS has evolved from mysterious illness to a global pandemic which has infected tens of millions in less than 20 years.

Promising development has been seen in recent years in global efforts to address the AIDS epidemic, including increased access to effective treatment and preventive programmes. However, the number of people living with HIV continues to grow, as does the number of deaths due to AIDS.

According to Fact sheet 2022 estimates of UNAIDS-Global HIV & AIDS statistics 39.0 million [33.1 million-45.7 million] people globally were living with HIV in 2022. 1.3 million [1 million-1.7 million] people became newly infected with HIV in 2022. 630 000 [480 000-880 000] people died from AIDS-related illnesses in 2022. 29.8 million people were accessing antiretroviral therapy in 2022. 85.6 million [64.8 million-113.0 million] people have become infected with HIV since the start of the epidemic. 40.4 million [32.9 million-51.3 million] people have died from AIDS-related illnesses since the start of the epidemic. 86% [73- >98%] of all people living with HIV knew their HIV status. Among people who knew their status, 89% [75- >98%] were accessing treatment. And among people accessing treatment, 93% [79- >98%] were virally suppressed. Every week, 4000 adolescent girls and young women aged 15-24 years became infected with HIV globally in 2022. 3100 of these infections occurred in sub-Saharan Africa.¹

HIV continues to be a major public health problem in the SEAR countries. With an estimated 3.6 million people living with HIV/AIDS, South East Asia Region is the second most affected region in the world.²

Demographically the second largest country in the world, India has also the third largest number of people living with HIV/AIDS. As per the provisional HIV estimate of 2008-09, there are an estimated 22.7 lakh people living with HIV/AIDS in India.³

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS-related morbidity and mortality.⁴⁻⁵ However, prolonged treatment with combination regimens can be difficult to sustain because of problems with adherence and toxic effects. All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient.

Tobacco consumption is currently the single leading preventable cause of death;⁶ over 500 million people may die due to tobacco by 2030.⁷ Cigarette smoking is associated with a ten-fold increase in the risk of dying from chronic obstructive lung disease.⁸ Smoking cessation has received little attention in HIV-infected persons. Yet smoking contributes significantly to the pulmonary complications of HIV (COPD, pneumonia).⁹⁻¹⁰

There are approximately 2.5 million people living with HIV/AIDS (PLWHA) in India - the young being particularly vulnerable. The prevalence of smoking has increased in India especially among rural, lower socio-economic and illiterate men. Studies have shown that HIV-infected smokers may be at

additional risk for several infectious and non-infectious complications, including malignancies and cardiovascular events. Smoking alters immunological mechanisms and suppresses host defenses in the alveolar environment. HIV-infected smokers have also been found to have a poorer response to antiretroviral therapy and a higher risk of death. HIV-infected individuals who smoke could be at a greater risk for developing TB and subsequently suffer higher morbidity and mortality than those who do not smoke. Currently available smoking cessation interventions like physician's advice, nicotine replacement therapy and pharmacological agents like bupropion and varenicline have had varying degrees of success. Smoking cessation intervention in the HIV-infected population might be more complex because of associated psychosocial problems like drug addiction, alcoholism, depression, etc. More research including clinical trials testing the efficacy of smoking cessation interventions in HIV infected persons is required in India. In addition to public health measures like banning smoking in public places and raising tobacco tax, comprehensive guidelines for health workers can help address this problem. Counseling on smoking cessation should be one of the main components of primary care, especially in the management of HIV-infected persons.

Risk of developing TB is over 20 times greater in HIV-positive patients than among those who do not have HIV infection. If smoking increases the impact of TB in HIV-negative patients, its effect in HIV positive patients may be significantly greater, with a deleterious synergistic interaction between smoking, HIV, and TB.¹¹

This study will help physicians gain a working knowledge of these adverse effects, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment, on the risk of pulmonary tuberculosis among cigarette smokers.

MATERIALS AND METHODS

Study design: A Case control study.

Place of Study: The study setting was done in the Department of Medicine, Civil Hospital, Aizawl, Mizoram.

Selection of cases: Consecutive patients above age 18 years who have confirmed pulmonary TB in HIV infected patients and history of cigarette smoking detected in ART centre, Medicine OPD, and admitted to the Medicine wards was taken as study population i.e cases. Detailed clinical examination and relevant investigations was done.

Selection of control: Consecutive patients above age 18 years who have confirmed pulmonary tuberculosis in HIV infected patients and no history of cigarette smoking detected in ART centre, Medicine OPD, and admitted to the Medicine ward.

Sample size: 70 patients (35 each in cases and controls)

Sample size was calculated with reference to the study conducted by using following formula:

$$n = 2Z_1^2 S_2^2 / d_2 = 34.86$$

Z_1 = value associated with alpha = 1.96

σ_1 = standard deviation of Group I = 2.57
 σ_2 = standard deviation of Group II = 1.87
 S_2 = Pooled SD = $\sigma_1 + \sigma_2 / 2 = 2.57 + 1.87 / 2 = 2.22$
 d_2 = Absolute precision = 0.5

The sample size comes out to be $n = 34.86 = 35$. Hence the sample size for each group was 35.

Inclusion criteria:

- Patients above 18 years of age; irrespective of sex.
- All cases and control in this study were HIV test positive. They were on ART treatment or not on ART treatment.
- Patients with HIV positive with clinical finding and investigations suggestive of pulmonary tuberculosis.
- All extra-pulmonary tuberculosis with pulmonary tuberculosis in HIV positive patients.

Exclusion criteria:

- Patients less than 18 years of age.
- All Pulmonary TB with HIV negative.
- All Extra-pulmonary tuberculosis with no evidence of pulmonary tuberculosis with HIV positive.
- All those patients who were unwilling to give consent.

STATISTICAL ANALYSIS

Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of paired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Chi-Square and Fisher test. 'p' value less than 0.05 is taken as significant.

Pearson's chi-squared test

$$X^2 = \sum_{i=1}^n \frac{(O_i - E_i)^2}{E_i}$$

Where,

X^2 = Pearson's cumulative test statistic.

O_i = an observed frequency;

E_i = an expected frequency, asserted by the null hypothesis;

n = the number of cells in the table.

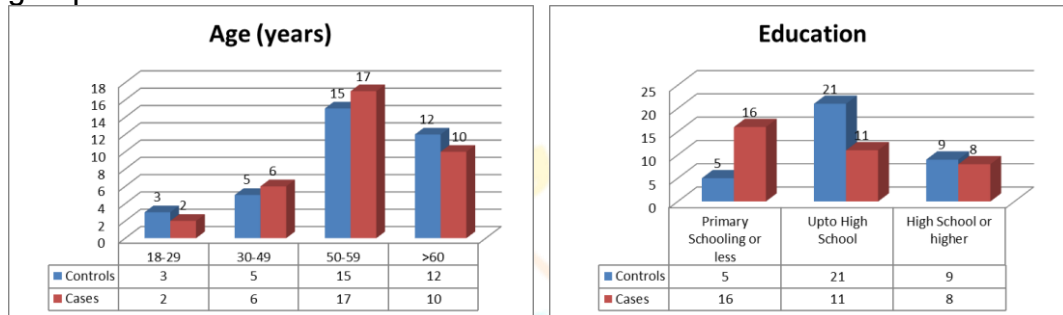
Results were graphically represented where deemed necessary. Appropriate statistical software, including but not restricted to MS Excel, SPSS ver. 20 will be used for statistical analysis. Graphical representation will be done in MS Excel 2010.

RESULTS

The present study was undertaken to study the risk of pulmonary tuberculosis among cigarette smokers in HIV infected patients. The study included 35 patients as cases with history of cigarette smoking with pulmonary

tuberculosis in HIV infected patients and 35 patients as controls with no history of cigarette smoking with pulmonary tuberculosis in HIV infected patients.

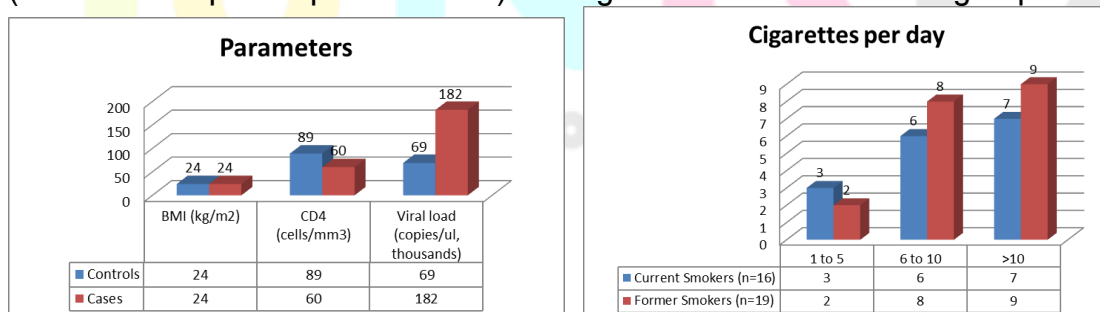
In the present study male predominance was observed in both the groups with majority of the patients were males (57.1%) in Controls group & 88.6% in Cases group. Majority of the patients 15 (42.9%) patients were in the age groups of 50-59 years followed by 12 (34.2%) patients in greater than 60 years, 5 (14.3%) the age groups of 30-49 and 3 patients (8.6%) in the age group of 18-29 years respectively and age was comparable between the two group.



It was observed that significant number of patients in Cases group were educated upto primary schooling or lesser as compared to Controls group (45.7% vs. 14.3%). 60% and 31.4% patients in Controls and Cases group respectively were educated upto High School while 25.7% and 22.9% patients in Controls and Cases group respectively were educated till High School or higher. There was significant association between groups.

31.4% patients in Controls group were unemployed while 28.6% and 40% patients were working part time and full time respectively. 60% patients in Cases group were unemployed while 11.4% and 28.6% patients were working part time and full time respectively. There was significant association between groups.

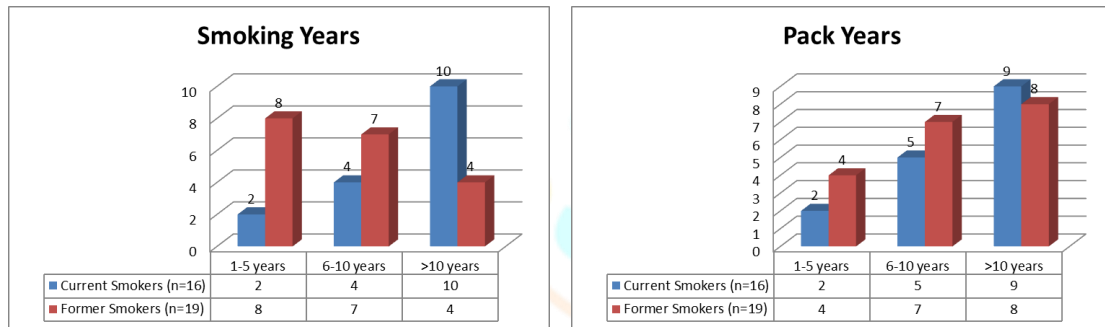
The median duration of HIV infection was significantly shorter among Cases group as compared to Controls group (44 days vs. 80 days). Median BMI was relatively high for both Controls and Cases group. Median CD4 count was lower (60 vs. 81 cells/mm³) and median viral load was higher (173 vs. 67 copies/ul per thousand) among Cases versus Controls group.



As per criteria used by the Centers for Disease Control and Prevention's Global Adult Tobacco Survey¹⁶ patients in Cases group were current smokers whereas 19 patients were former smokers.

3 patients in Current Smokers smoked 1-5 cigarettes per day while 6 and 7 patients respectively smoked 6-10 and >10 cigarettes respectively. 2 patients in Former Smokers smoked 1-5 cigarettes per day while 8 and 9 patients respectively smoked 6-10 and >10 cigarettes respectively.

2 patients in Current Smokers smoked for 1-5 years while 4 and 10 patients respectively smoked 6-10 and >10 years respectively. 8 patients in Former Smokers smoked for 1-5 years while 7 and 4 patients respectively smoked 6-10 and >10 years respectively with significant association between the groups.



2 patients in Current Smokers had pack years for 1-5 years while 5 and 9 patients respectively had pack years for 6-10 and >10 years respectively. 4 patients in Former Smokers had pack years for 1-5 years while 7 and 8 patients respectively had pack years for 6-10 and >10 years respectively.

DISCUSSION

Recognized as an emerging disease only in early 1980s, AIDS has rapidly established itself throughout the world, and is likely to endure and persist well into 21st century. AIDS has evolved from mysterious illness to a global pandemic which has infected tens of millions in less than 20 years. Promising development has been seen in recent years in global efforts to address the AIDS epidemic, including increased access to effective treatment and preventive programmes. However, the number of people living with HIV continues to grow, as does the number of deaths due to AIDS. Demographically the second largest country in the world, India has also the third largest number of people living with HIV/AIDS.³

There are approximately 2.5 million people living with HIV/AIDS (PLWHA) in India - the young being particularly vulnerable. The prevalence of smoking has increased in India especially among rural, lower socio-economic and illiterate men. Studies have shown that HIV-infected smokers may be at additional risk for several infectious and non-infectious complications, including malignancies and cardiovascular events.

The present study was undertaken to study the risk of pulmonary tuberculosis among cigarette smokers in HIV infected patients. The study included 35 patients as cases with history of cigarette smoking with pulmonary tuberculosis in HIV infected patients and 35 patients as controls with no history of cigarette smoking with pulmonary tuberculosis in HIV infected patients.

In the present study there is male predominance in both the groups. Majority of the patients (57.1%) in Controls group & 88.6% of the patients in Cases group were males. It was also observed that 42.9% and 48.6% patients in Controls and Cases Group respectively were in the age group of 50-59 years. Significant number of patients in Cases group were educated upto primary schooling or lesser as compared to Controls group (45.7% vs. 14.3%). 40% patients in Controls Group were working full time and 60% patients in Cases group were unemployed. This is similar to the study of Murrison LB et al¹² which found 33% of participants were current smokers, Tiwari J et al¹³ showed 64.7% of the tuberculosis group was males and 35.3% of the group was females and HIV infection is a risk factor for development of Pulmonary Tuberculosis and Mohamed S et al¹⁴ showed PTB was most prevalent in the age group of 35-54 years both in the urban (46.7%) and rural (49.4%) population.

Murrison LB et al¹² did a Case-control study of antiretroviral therapy in naïve men with confirmed HIV-infection evaluated the association of pulmonary tuberculosis (PTB) with current tobacco smoking among men with HIV. Overall, 33% of participants were currently smoking, defined as smoking a cigarette within 2 months (34% cases vs. 32% controls). Median CD4 count was lower (60 vs. 81 cells/mm³) and median viral load was higher (173 vs. 67 copies/ul per thousand) among cases versus controls. In adjusted analyses, current smoking tripled the odds of PTB and former smoking nearly doubled the odds of PTB compared to never smoking.

Males with HIV that smoke are at greater odds for developing PTB than non-smokers. Extensive smoking cessation programs are needed to reduce odds of TB and promote health among adults living with HIV.

The median duration of HIV infection was significantly shorter among Cases group as compared to Controls group (44 days vs. 80 days). Median BMI was relatively high for both Controls and Cases group. Median CD4 count was lower (60 vs. 81 cells/mm³) and median viral load was higher (173 vs. 67 copies/ul per thousand) among Cases versus Controls group. This is comparable to the studies of Dalbo M et al¹⁵ which observed relatively high

incident of tuberculosis cases among HIV infected patients with history of cigarette smoking; family size; hemoglobin level and base line WHO clinical stage were responsible for this high incidence and Semunigus T et al¹⁶ showed prevalence of smear positive PTB among TB suspect homeless individuals was 2.6 %. Among smear positive PTB, prevalence of HIV co-infection was very high 5 (55.5 %). Smoking cigarette regularly for greater than 5 years, BMI lower than 18.5 and HIV infection were factors associated with smear positive PTB.

Special emphasis is needed for homeless cigarette smoking individuals to exert intensive effort to identify undetected TB cases to limit the circulation of the disease into the community.

Dalbo M et al¹⁵ hospital based retrospective follow-up study assessing the magnitude and predictors of tuberculosis among cohort of HIV infected patients. Cumulative and incidence density of tuberculosis were 21.4% and 5.36 per 100 person year respectively. Cigarette smokers, household with family size of 3 - 4, baseline WHO clinical stage III and IV and hemoglobin level of <10 were important predictors (risk factors) of tuberculosis among HIV infected patients. Early initiation of HAART as per current guideline should be stressed, and the finding that smoking was important predictors for TB had obvious TB control measures should be initiated which require high attention focused on fighting against cigarette smoking among HIV infected cohort.

Saad T et al¹⁷ study identifying the role of host-related and environment-related factors in the development of tuberculosis (TB) concluded that TB was associated with male sex, family history of TB, smoking, alcohol, anaemia, HIV infection, and history and treatment of worm infection and they are independent risk factors of TB.

In the present study as per the criteria used by the Centers for Disease Control and Prevention's Global Adult Tobacco Survey¹⁸ 16 patients in Cases group were current smokers whereas 19 patients were former smokers. 3 patients in Current Smokers smoked 1-5 cigarettes per day while 6 and 7 patients respectively smoked 6-10 and >10 cigarettes respectively. 2 patients in Current Smokers smoked for 1-5 years while 4 and 10 patients respectively smoked 6-10 and >10 years respectively. 8 patients in Former Smokers smoked for 1-5 years while 7 and 4 patients respectively smoked 6-10 and >10 years respectively with significant association between the groups. In the control group 2 patients in Current Smokers had pack years for 1-5 years while 5 and 9 patients respectively had pack years for 6-10 and >10 years respectively. 4 patients in Former Smokers had pack years for 1-5 years while 7 and 8 patients respectively had pack years for 6-10 and >10 years respectively. Similar finding were noted by Miguez-Burbano MJ et al¹⁹ summarised that the increased risk of developing lung diseases in cigarette smokers has been well recognized and the association between smoking and the risk of developing pulmonary infections in HIV-1-infected patients has not been established however the present study observed the risk of developing pulmonary infections in HIV-1-infected patients, Petrosillo N et al²⁰ summarised that cigarette smoking is one of the most important causes of morbidity and mortality in the general population, and is a well-recognized risk factor for a variety of serious clinical conditions, including cardiovascular and

pulmonary diseases. Smoking-related morbidity and mortality are of particular concern in patients with HIV infection, as the prevalence of current cigarette smoking is higher among HIV-positive patients. Azizaa R et al²¹ identified the impact of smoking on clinical, radiological manifestations and evolutive pulmonary tuberculosis and found the harmful impact of smoking on the clinical and radiological presentation of tuberculosis, and late bacteriological negativity, therefore we need to integrate smoking control into the national TB control program in HIV infected patients.

Risk of developing TB is over 20 times greater in HIV-positive patients than among those who do not have HIV infection. If smoking increases the impact of TB in HIV-negative patients, its effect in HIV positive patients may be significantly greater, with a deleterious synergistic interaction between smoking, HIV and TB.¹¹

HIV-positive patients who smoke have significantly increased mortality compared to those who have never smoked, indicating that smoking confers different mortality risk in HIV-positive as compared to HIV-negative patients, and lifestyle-related factors may pose a greater hazard to long-term survival of HIV-positive patients than those related to the HIV infection per se. The high prevalence of smoking among HIV population, the many health risks that can result from this behavior, and the proven efficacy of cessation interventions in HIV-positive patients should encourage HIV care providers to make smoking cessation a high priority.

Previous studies have found that smoking increases the risk of TB approximately two-fold^{11,22-24} and that smoking adversely affects the immune system making people more susceptible to TB disease.²⁵ The physical environment where exposure to smoking occurs may increase risk of TB transmission and represent an ideal setting for TB detection and tobacco control. Cell mediated immunity and macrophage function, essential to the host defense against TB infection, are directly impaired by exposure to tobacco smoking.²²

The pulmonary compartment of people that currently and previously smoked is poorly prepared to combat TB infection by a number of mechanisms.²⁵⁻²⁶ Exposure to cigarette smoke skews the inflammatory mediator profile of macrophages in the lung, thus influencing their handling and elimination of TB favouring persistence and increasing risk of infection.²⁶ Natural killer (NK) cytotoxic activity, T cell function suppression in lungs and blood, impaired mucociliary clearance of particles, excessive alveolar macrophage driven regulatory ability, and inadequate cytokine response to infection have also been theorized as mechanisms of impaired host defense in people that smoke.²⁵⁻²⁶

CONCLUSION

There are approximately 2.5 million people living with HIV/AIDS (PLWHA) in India - the young being particularly vulnerable. The prevalence of smoking has increased in India especially among rural, lower socio-economic and illiterate men. Studies have shown that HIV-infected smokers may be at additional risk for several infectious and non-infectious complications, including malignancies and cardiovascular events.

Present study also shows that there is increase risk of pulmonary tuberculosis among cigarette smokers in HIV infected patients, because median duration of HIV infection was significantly shorter among Cases group as compared to Control group (44 days vs.80 days), and Median CD4 count was lower (60 vs. 81cells/mm³, P = 0.03),and also Median viral load was higher (173 vs.67 copies/ul per thousand, P<0.001) among Cases verses Controls group.

As the epidemiology of TB, HIV and tobacco merge, it is important to address tobacco use as the leading cause of preventable death to ensure that patients with TB and HIV can realize the benefits of life-saving TB treatment. Future research is needed to assess the impact of extensive programs to encourage adults with HIV to stop smoking to reduce the odds of TB and promote general health for patients with HIV.

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