IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
May 2015 Vol.:1, Issue:1

A Review on Prevalence of TB and HIV Co-infection

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
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Jyoti P. Waghmode*,
Pranita C. Sontakke [2], Amitkumar A. Khade[1]

Department of Pharmacology,
Government College of Pharmacy, Karad, India.

Submission: 19 April 2015
Accepted: 28 April 2015
Published: 10 May 2015

www.ijsrm.humanjournals.com

Keywords: tuberculosis, HIV, co-infection, prevalence

ABSTRACT

Tuberculosis (TB) and HIV have been closely linked since the emergence of AIDS. There is a complex relationship between infection with human immunodeficiency virus (HIV) and tuberculosis (TB) infection that results in a synergistic increase in their prevalence, morbidity and mortality. HIV-associated TB contributes substantially to the burden of TB-associated morbidity and mortality. Of the estimated 33.4 million people living with HIV in 2008, nearly 30% were estimated to have latent or active TB infection conversely. So with an estimated 1.42 million people having active TB when they died, of these 30% also had HIV infection. In the same year there were an estimated 8.7 million new cases of active TB worldwide, of which 1.1 (13%) million are estimated to have been among people living with HIV.

INTRODUCTION

Tuberculosis (TB) and HIV have been closely linked since the emergence of AIDS. Worldwide, TB is the most common opportunistic infection affecting HIV- individuals, and it remains the most common cause of death in patients with AIDS. HIV infection has contributed to a significant increase in the worldwide incidence of TB. By producing a progressive decline in cell-mediated immunity, HIV alters the pathogenesis of TB, greatly increasing the risk of disease from TB in HIV-co infected individuals and leading to more frequent extra pulmonary involvement, atypical radiographic manifestations, and paucibacillary disease, which can impede timely diagnosis. Although HIV-related TB is both treatable and preventable, incidence continues to climb in developing nations wherein HIV infection and TB are endemic and resources are limited. Interactions between HIV and TB medications, overlapping medication toxicities, and immune reconstitution inflammatory syndrome (IRIS) complicate the co treatment of HIV and TB. This chapter will review the epidemiology, pathogenesis, management, and prevention of TB in the setting of HIV infection [1].

Interaction between HIV and TB and the Implications [2]

There is a complex relationship between infection with human immunodeficiency virus (HIV) and tuberculosis (TB) infection that results in a synergistic increase in their prevalence, morbidity and mortality. The occurrence of both infections is a great public health problem looming as a potential pandemic, in Ghana, as is in other African countries. This should be of great concern and spur immediate action to reduce and control these infections. The interaction between HIV and TB is summarized in the following:

In HIV:

- TB is a most important opportunistic disease;
- TB is infectious not only to HIV-infected persons but also to non-infected persons;
- TB causes severe illness and increases progression to AIDS; and
- TB kills – it is the number one killer in HIV.

In TB:

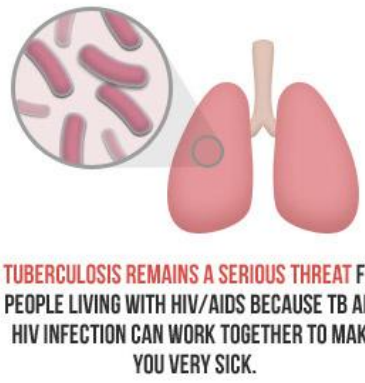
- HIV is the main risk factor for progression from latent TB infection to active disease;

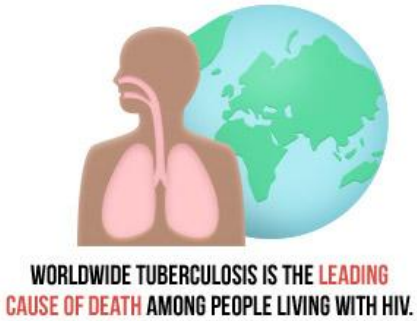
- HIV increases TB incidence;
- HIV leads to hot spots of TB transmission;
- HIV increases morbidity in TB patients because of HIV related diseases;
- HIV increases adverse drug reactions to TB treatment;
- HIV increases TB case fatality rates; and
- HIV increases risk of recurrent TB.

How HIV leads to TB? [3]

- As many as 14 million people in the United States have been exposed to the bacteria that cause tuberculosis (TB). That doesn't mean that all of them will get sick, however- fewer than 10 percent will develop active tuberculosis disease.
- The odds change, however, for someone with HIV. HIV attacks and weakens the immune system, leaving the body vulnerable to infection. So once the bacteria that cause TB enters the body of someone with HIV, usually through the lungs, the bacteria are able to multiply, invade, and cause full-blown tuberculosis, rather than being contained by a healthy immune system. For people with HIV, the body just can't fight the tuberculosis infection.

Images of TB with HIV [4]





Epidemiology [5]

A Syndemic is defined as the convergence of two or more diseases that act synergistically to magnify the burden of disease. The Syndemic interaction between the human immunodeficiency virus (HIV) and tuberculosis (TB) epidemics has deadly consequences around the world. This review examines current knowledge of the state and impact of the HIV-TB Syndemic and reviews epidemiological, clinical, cellular, and molecular interactions between HIV and TB.

Scale of the Problem: Millions Affected and Millions of Lives Lost

HIV-associated TB contributes substantially to the burden of TB-associated morbidity and mortality. Of the estimated 33.4 million people living with HIV in 2008, nearly 30% were estimated to have latent or active TB infection conversely, of the 9.4 million cases of incident TB worldwide, an estimated 1.4 million (15%) were coinfected with HIV in 2008. HIV infection is the strongest known risk factor for TB. High HIV prevalence rates are significantly correlated with high TB incidence rates. The confluence of the two epidemics has hit hardest in sub-Saharan Africa, which constituted 79% of all cases of incident TB in persons with HIV infection in 2007. South Africa alone accounted for 24% of all incidents HIV-associated TB cases worldwide in 2008, even though its estimated population is less than 1% of the global population. Of the 15 countries with the highest estimated TB incidence rates in 2007, over half were sub-Saharan African countries with HIV prevalence rates of over 10% in the general population.

HIV-associated TB accounts for a disproportionate share of TB-associated mortality. In 2008, HIV-associated TB accounted for 29% of deaths among incident TB cases, even though it contributed to 15% of all incident TB cases. The estimated case-fatality rate of incident TB was more than 2-fold higher for people infected with HIV (37%) than for those without HIV (16%). The higher case-fatality rate of TB in HIV-infected individuals is likely due to a combination of factors associated with HIV co infection:

The rapid progression of disease is due to the failure of immune responses to restrict the growth of *Mycobacterium tuberculosis.*

(i) delayed diagnosis and treatment of TB infection due to atypical presentation and lower rates of sputum smear positivity,

(ii) delayed diagnosis of HIV infection due to stigma or insufficient uptake of HIV testing in TB clinics

(iii) delayed start or lack of access to combination antiretroviral therapy (ART), and

(iv) Higher rates of multidrug-resistant TB (MDR-TB) leading to a delayed initiation of effective therapy.

Deaths due to TB accounted for one-quarter of the estimated 2 million HIV-related deaths worldwide in 2008, and TB is the leading cause of death for people living with HIV in low- and middle-income countries. In 2007, the burden of deaths from HIV-associated TB was highest in South Africa, Nigeria, India, Zimbabwe, Ethiopia, the United Republic of Tanzania, Mozambique, Uganda, and Kenya and accounted for the majority of TB-associated mortality in most of these countries.

Urban Population Growth May Escalate the HIV and TB Syndemic:

In 2008, the composition of the world's population tipped such that the majority lived in urban areas instead of rural areas for the first time in history. Urban population growth in Africa and Asia is expected to drive the majority of future global population growth, with concomitant increases in slum areas and levels of urban poverty. In developing countries, the majority of urban populations live in slums: 72% of the urban population in sub-Saharan Africa and 56% in South Asia. Key features of slum life, such as crowded housing, working conditions with poor ventilation, poor nutrition, and lack of access to quality health care, continue to drive TB transmission. The association between poverty, urbanization, housing density, and TB incidence is well documented. The level of poverty, as measured by the gross domestic product per capita, is directly related to the incidence of TB. Many socioeconomic determinants of TB are also drivers of risk behaviors for HIV transmission, such as injection drug use and commercial sex work. A prospective study from New York City found significantly higher rates of TB, AIDS, and death for substance users on welfare than for the general population of New York City (risk ratios of 15, 10, and 5, respectively). In addition, HIV-infected persons living in resource-constrained settings face socioeconomic and behavioral barriers to HIV testing and access to

antiretroviral treatment. Without adequate urban planning and investment in equitable urban health care systems, including integrated TB and HIV programs, the rise in slum areas and urban poverty will continue to propel the transmission of HIV-associated TB and its associated morbidity and mortality.

TB and HIV: Interactions at the Population Level

Individuals with a new diagnosis of TB are nearly 19 times more likely to be co infected with HIV than those without TB (0.8% HIV prevalence in adults aged 15 to 49 years and 15% HIV prevalence in incident TB cases). Conversely, people living with HIV are 20 to 30 times more likely to develop TB than those without HIV. The TB incidence rate ratio (IRR), the relative risk of TB developing in HIV-infected persons compared to that in HIV-uninfected persons, varies according to HIV prevalence. Countries with a generalized HIV epidemic have a TB IRR of 20.6. Countries with concentrated HIV epidemics (HIV prevalence, 0.1% to 1%) have a TB IRR of 26.7, and countries with a low prevalence of HIV infection (HIV prevalence less than 0.1%) have a TB IRR of 36.7. This apparently paradoxical inverse relationship between TB IRR and HIV prevalence likely depends on the interplay between local TB incidence and prevalence rates in the general population, the rate of detection of new TB cases, and other associations between HIV and TB transmission that increase the likelihood of co infection. For example, countries with a generalized HIV epidemic may have high rates of malnutrition and poverty, barriers to basic health care, and high rates of TB exposure, leading to a high cumulative lifetime risk for incident TB regardless of HIV status. Therefore, these countries may have less divergence in the incidence rates of TB in HIV-infected individuals compared with the general population. On the other hand, in countries with concentrated or low-prevalence HIV epidemics, the drivers of TB transmission may be more closely linked with specific risk factors for HIV infection (for example, living in grouped housing such as jails, shelters, and psychiatric wards and injection drug use), and thus, the incidence rate of TB infection in HIV-infected individuals is much higher than that in the general.

HIV is a Driver of the TB Epidemic:

Evidence that HIV serves as a driver of TB at the population level has been noted by multiple epidemiological studies. In the United States, numbers of observed TB cases had been declining

from 1980 to 1985 but increased by 20% from 1985 to 1992, with an estimated 51,700 excess TB cases attributed to the growing HIV epidemic. The largest increases in rates of TB occurred in areas and populations heavily affected by the HIV epidemic at the time: New York (84%), California (54%), urban areas (29%), and the 25- to 44-year age group (55%). In San Francisco, the HIV epidemic contributed an additional 14% of TB cases from 1991 to 2002. Most of these cases were due to a reactivation of latent TB, although 41% were attributed to recent transmission. In England and Wales, nearly one-third of the increase in number of cases of TB from 1999 to 2003 occurred in HIV-infected patients. In South Africa, the burgeoning HIV epidemic was associated temporally with a worsening of the TB epidemic in a per urban community. As the HIV prevalence rate increased from 6.3% in 1996 to 22% in 2004, annual TB notification rates increased 2.5 fold, culminating in a staggering 1,468 TB cases per 100,000 persons in 2004. For each 1% increase in HIV prevalence, TB notification rates increased by 55 cases per 100,000 persons in 1998 to 1999 and increased by 81 cases per 100,000 persons in 2004. Biologically, this association makes sense: increasing number of individuals immune compromised by HIV infection lead to a larger reservoir of individuals susceptible to reactivation TB and result in more TB cases.

Does HIV alter the Transmission Dynamics of TB?

At the community level, the relationship between HIV and the transmission of TB as measured by the annual risk of TB infection (ARTI) is unclear. Traditionally, TB surveillance programs use the ARTI as an indicator to monitor TB transmission in the community. The ARTI is calculated as the prevalence of positive tuberculin skin tests (TSTs) in school-children divided by their average age. One early study in Kenya found that the ARTI increased from 1986 to 1996 in a setting of high HIV prevalence, which suggested an increased rate of transmission of TB. However, another study in Tanzania found a decrease in the ARTI in the context of a rising HIV prevalence from 1983 to 2003. A third study from South Africa found that the ARTI was unchanged from 1999 to 2005, while the HIV prevalence increased from 14% to 23% during that period.

In light of other studies showing HIV to be a driver of TB incidence, these conflicting findings may be due to the failure of the ARTI to accurately reflect ongoing TB transmission in the adult

population. The use of the ARTI to monitor TB transmission in the community assumes that the TST positivity rate in children is proportional to the incidence rate of primary TB infection in children and that the TB incidence in children is reflective of TB transmission in the general population. The first assumption may be problematic in areas with widespread *Mycobacterium bovis* BCG vaccination or where *M. bovis* is endemic. The second assumption assumes generalizability despite a no representative sample selection, which may be problematic due to variable levels of social mixing between TB-HIV- confected adults and the young children used to determine the ARTI. In support of this, a South African study investigated the change in TB notification rates by age group from 1996 to 2004, a period in which adult HIV prevalence increased from 6% in 1996 to 22% in 2004. The burden of excess TB cases was greatest in adults; adolescents also experienced a significant rise in notified TB cases. However, children did not have a significant increase in TB notification rates despite the rise in HIV prevalence and excess TB cases in adults. Due to the limited generalizability, the ARTI may not be an accurate measure of TB transmission in the general population.

A more direct method to investigate the transmission of TB in HIV-infected patients is to evaluate close contacts of index cases. Although initial studies of close contacts of TB patients with HIV infection had conflicting results, more recent studies suggested that TB patients confected with HIV may be less infectious than TB patients without HIV infection. A prospective cohort study in the Dominican Republic of over 800 household contacts of 58 HIV-infected and 116 matched HIV-uninfected index cases with newly diagnosed smear-positive or culture-positive pulmonary TB found that HIV-infected index cases were half as likely as HIV-uninfected index cases to transmit TB to their close contacts, even after controlling for the degree of smear positivity. Similarly, in Brazil, a prospective cohort study of 360 contacts of 86 patients with smear-positive pulmonary TB found a significantly decreased risk of TST conversion in contacts of HIV-infected index cases, with an odds ratio (OR) of 0.24 (95% confidence interval [CI], 0.09 to 0.65). A meta-analysis of eight studies comparing the prevalence's of TST positivity among household contacts of TB index cases found a lower rate of TST positivity among contacts of HIV-infected than among contacts of HIV-uninfected index TB cases. A cross-sectional study evaluating the prevalence of positive TSTs in pediatric contacts of adults with TB and HIV infection in Botswana found a lower proportion of TST

positivity in children exposed to adult index cases with CD4 counts of <200 cells/µl.than in those exposed to index cases with CD4 counts of ≥200 cells/µ1. In summary, HIV-infected patients with pulmonary TB are less likely than HIV-uninfected patients to transmit TB to their household contacts, and patients with advanced AIDS may be less infectious than patients with earlier stages of HIV infection. Possible explanations for the decreased transmission of TB by HIV-infected patients include less frequent cavitary TB, lower sputum bacillary burden, weakened cough with more severe disease, and greater social isolation.

TB and HIV Co-infection [6]

TB and HIV co-infection is when people have both HIV infection, and also either latent or active TB disease.

In 2011, 430,000 people are estimated to have died of TB and HIV co-infection, in addition to the 990,000 people who died from TB alone[1].

Those people, who have HIV infection as well as TB when they die, are internationally reported as having died of HIV infection. In total an estimated 1.7 million people died of HIV infection in 2011.[3] So this means that the deaths from TB and HIV are:

Deaths from HIV and TB co-infection: 430,000

Deaths from TB alone: 990,000

Deaths from HIV alone: 1,270,000

So with an estimated 1.42 million people having active TB when they died, of these 30% also had HIV infection. In the same year there were an estimated 8.7 million new cases of active TB worldwide, of which 1.1 (13%) million are estimated to have been among people living with HIV.

Table 1. Demographic and Clinical Characteristics of TB patients by HIV status in New York City, 2000–2005[1]

Variable	HIV-infected patients (n=1,113)		HIV-uninfected patients (n=3,580)		OR	P value
	N	%	N	%		
Age						
0 –18	8	0.7	264	7.4	0.09	<.0001
19–44	671	60.3	2,085	58.2	1.09	.226
45–65	412	37.0	881	24.6	1.80	<.0001
65 and over	22	2.0	350	9.8	0.19	<.0001
US-born	707	63.5	962	26.9	4.74	<.0001
Homeless	203	18.2	167	4.7	4.56	<.0001
History of Substance Abuse	593	53.3	640	17.9	5.24	<.0001
Race/ Ethnicity						
Non-Hispanic White	62	5.6	264	7.4	0.74	.039
Non-Hispanic Black	708	63.6	1,046	29.2	4.23	<.0001
Hispanic	308	27.7	1,226	34.2	0.73	<.0001
Asian	34	3.1	1,030	28.8	0.08	<.0001
Culture Positive	879	79.0	2,769	77.4	1.10	.254
Respiratory Smear Positive	522	47.0	1,549	43.3	1.16	.033
Tuberculin Skin Test Positive[2]	313	52.8	1,929	80.0	0.28	<.0001
Site of Disease						
Pulmonary Only	632	56.8	2,482	69.3	0.58	<.0001

Extra pulmonary Only	202	18.2	808	22.6	0.76	.002
Both	279	25.1	290	8.1	3.80	<.0001
Chest Radiograph Status						
Normal	261	23.5	587	16.4	1.56	<.0001
Abnormal/Cavitary[3]	74	11.7	635	25.6	0.39	<.0001
Abnormal/Non-cavitary[2]	476	75.3	1,776	71.6	1.21	.059
Multidrug-resistant TB	33	3.0	83	2.3	1.29	.225
Other Drug Resistance	99	8.9	363	10.1	0.87	.223

[1] HIV-status was unknown in 2,079 patients. [2] Among those that were TST -tested. [3] Among pulmonary TB patients only.

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