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Review Article

Tuberculosis and HIV Complex: A New Health Challenge in South Asian Countries

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Introduction

Tuberculosis (TB) is a granulomatous bacteriological infection, declared as public emergency in 1993 by World Health Organization (WHO) with more than 2 billion people as carriers of TB bacterium whereas 10% of them can have active form of TB once in their life. According to rough estimates, more than 10% active TB cases likewise holds HIV infection [1]. Recent advances in diagnostics, drugs, vaccines and enhanced implementation of existing interventions are increasing the likelihoods for improved clinical care and global tuberculosis control. Despite universal efforts to counter tuberculosis, it still accounts for millions of new cases of active form and thousands of deaths worldwide. Weight loss, fever, coughing up blood, weakness, chest pain, breathing problem, fatigue, night sweating, loss of appetite, chilling and malnutrition are all common indications of TB [2-6].

Nearly one-fourth of the world's population has a latent form of TB and these patients are unable of transmitting the infection with 5-14% activation chances of this disease. Smokers, Human Immunodeficiency Virus (HIV) /Acquired Immune Deficiency Syndrome (AIDS) patients and diabetics are at risk; however this infection is responsible for about 40% deaths among HIV patients [7]. HIV based TB infection is mainly concentrated in African countries owing to predominant sexual transmission but HIV/TB co-infection is

poorly quantified in Asia because of rare implementation of universal standards of identification [8]. Difference between viral genome and bacterial infection produces an ambiguous rationale behind this complex. The underlying logic could be weak immune system that easily adopts TB and show early symptoms. Latent form of TB is not a threatening issue for persons with stronger immunity but in case of HIV, the situation is totally different [9]. Patients carrying HIV are prone to the latent form of TB especially when CD4+ cell count falls less than 50/mm^3 [10]. There is a need to take obligatory actions to prevent this correlation by adopting quick, compulsory and reliable treatment system.

TB Infection and its Increasing Correlation with HIV in Asian Countries

According to World Health Organization (WHO), Pakistan is positioned at 5th number among TB burden countries and at number four in Multiple Drug Resistant (MDR) TB cases escorting 430,000 TB victims and 70,000 deceased due to this infection, annually [11,12]. Correspondingly, India and China, altogether, carrying nearly 25% of total TB cases and 11% of world's cases of MDR-TB. HIV victims are at high risk of activation of latent form of TB. Airborne transmission of infection and frequent movement of TB patients across the continents are leading towards the evolution of new forms of tuberculosis complex [13,14]. The number of HIV/TB cases in Asia is not clear so far, because most of the people do not like to declare themselves as HIV infected but undoubtedly this figure will also be alarming. WHO has documented 35000 deaths in Asia because of HIV-TB co-infections, majorly in males (15 years of age or above). As indicated in WHO report of 2014, the highest incidents of HIV co-infected with TB has been reported in Thailand, Asia. The situation in Africa is even worst where more than forty percent TB patients have been described as co-infected with HIV [Table 1; 15]. Due to lack of policies for compulsory tests of infectious diseases, the number of HIV cases in South Asian countries is not known where TB is present in highly epidemic form. Both, identification and treatment are notable difficulties in these countries and majority of the affected individuals are living without proper medication [16].

Table 1: *HIV and TB co-infection status in Asian Countries*

Incidence and Mortality of TB, HIV and HIV/TB Complex in 2014 [15]							
Incidence	**Thailand**	**Myanmar**	**India**	**Bangladesh**	**Philippines**	**Vietnam**	**Pakistan**
TB incidence (per 100,000 population)	80	200	2100	350	292	130	500
HIV prevalence (age 15-49 years)	1.1%	0.6%	0.3%	<0.1%	<0.1%	0.4%	N/A
HIV incidence in TB cases	15%	8.8%	5.7%	0.12%	0.11%	7.2%	0.53%
Total TB Mortality (per 100,000 population)	8	26	240	80	27	17	100

Treatment of HIV/TB Complex [17]		
Treatment	**Detail of Treatment**	**Comments**
PROMPT	When CD4+ cell count reaches <50/mm^3 during initial antiretroviral therapy, then immediate therapy will be delivered in first two weeks	Still in trials. Planned to lessen the death rate in HIV patients with undiagnosed TB
REMEMBER	When CD4+ cell count reaches <50/mm^3 during initial antiretroviral therapy, then immediate therapy will be delivered in seven days	Under trial. Planned to lessen the death rate in HIV patients with undiagnosed TB

Treatment of HIV/TB Co-Infection

TB leads the replication of HIV which ultimately could accelerate infection and mortality rate in dual contaminated patients. The early identification of HIV/TB complex and start of antiretroviral therapy (ART) could improve the patient recovery status but there are some complications for patients with low CD4+ cells [18-20]. It is recommended by World Health Organization (WHO) to start the ART in early phase when CD4+ count becomes less than 50 mm^3 and Body Mass Index (BMI) below 18 but the dose of treatment varies accordingly to the patient's condition. In case of tuberculosis meningitis, the start of ART results in deleterious effects instead of improvement, [21] leading to immune reconstitution inflammatory syndrome (IRIS) in more than 8% cases in new and old forms of HIV/TB complex [22]. The rate of IRIS increases up-to 50% in HIV/TB patients in the start of TB treatment and CD4+ cells becomes less than 50/mm^3 with typical symptoms of lymphadenopathy and worse respiratory tract infection. In patients with active TB form, efavirenz and other types of reverse transcriptase inhibitors are preferred but rifampicin is used in some cases to lower protease inhibitors in serum. The impact of high doses of protease inhibitors and their substitutes are under investigation [23]. Two important studies were done to reduce the early deaths in HIV/TB complex and to evaluate the impacts of various therapeutic treatments including the Presumptive Tuberculosis Treatment (PROMPT) and the Reducing Early Mortality and Morbidity by Empiric Tuberculosis treatment (REMEMBER) [24,25] but due to limited collaboration between TB and HIV control programs in under developing countries, the reliability of reported data is a continuous obstacle to devise some comprehensive policy.

Challenges in Controlling the TB/HIV Complex in Asian Countries

Awareness About Co-Infection

Due to aerosol nature of infection, TB along with HIV develops drastic bidirectional interaction. A survey was conducted to evaluate the awareness status about TB-HIV co-infection in southern areas of Pakistan. Among 100 TB infected individuals, none of them was screened for HIV nor have any knowledge about the precautionary measures (unpublished data). It was also found that various patients stop taking medicines without completing the treatment which ultimately could develop the drug resistant form of TB. Similar condition might be present in other Asian countries. As stated by WHO guidelines, HIV test is compulsory but the progress on this guideline is very slow in Asia and Africa except Bhutan and Brunei where almost 100 percent TB patients are screened for HIV [26].

Research and Development

Another major hindrance is difference of viral and bacterial diseases. HIV infection lowers the defense system by targeting CD4 helper T-cells [8] while the situation in case of MTB is quite different, where vaccine already exists but it has no effect on HIV. The development of a broad-spectrum vaccine against HIV and MTB on urgent basis is an efficient way to counter the bacterial and viral infection. To eradicate different forms of TB in next three decades, it is extremely essential to develop the protein mediated resistance which could safely provide long-lasting protection in HIV infected and non-infected individuals [27,28].

Lack of modern diagnostic centers and treatment facilities are major issues in developing countries. The availability of Gene Xpert PCR assay has been increased under the UNITAID project of WHO throughout the Asia Pacific region [15]. The Gene Xpert PCR is more efficient as compared to smear microscopy and has ability to detect TB and MDR-TB with more sensitivity [29]. Despite all these efforts, there are other biosafety issues as well. Training of staff and students to deal with infectious pathogens and lack of expertise to develop BSL facilities are the main defies. Therefore, development of Hi-tech research facilities and proper guideline to scientists and staff is a preliminary and mandatory step before start of research in Asian countries particularly Pakistan and India, where HIV is prompting as an important health concern.

Challenges in the Treatment of HIV and TB Complex

Lower immunity level increases the susceptibility to TB as well as activation of the latent form of TB. Furthermore, when TB and HIV co-infected patients are treated with antiretroviral drugs against HIV, it is quite possible that the immune system may have some abnormality in the form of Immune Reconstitution Inflammatory Syndrome (IRIS) and start reacting with bacterial infection which ultimately results in increased rate of morbidity [30]. Features and consequences of HIV and/or MTB infection are illustrated in Figure 1.

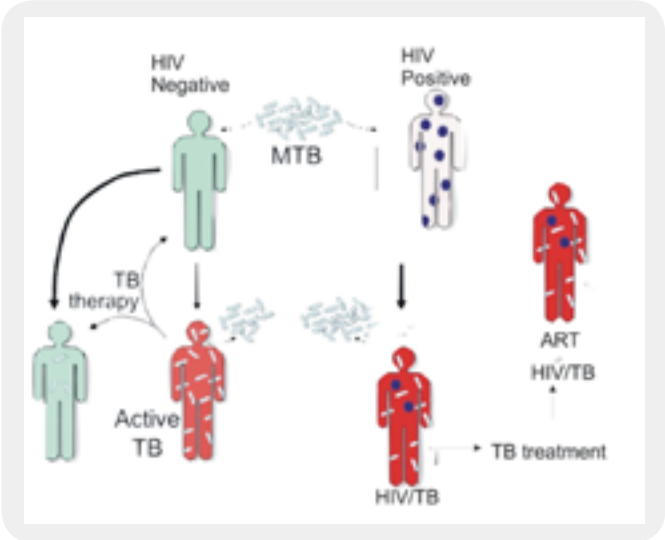

Figure 1: *The graphical description of Mycobacterium tuberculosis and HIV co-infection. (The healthy and cured TB patients are marked with light green color while active TB in red color). However, the treatment of an active patient of HIV/TB could lead to complexity due to antiretroviral therapy (ART).*

The drug resistance form is already increasing dramatically in these low-income countries and standard treatment of TB has been ineffective due to careless attitude and lack of awareness.

Pharmacokinetic study of TB drugs is essential for its safe and efficient use among infected people. Due to the poor diagnostic facilities and current drug regimes, the proportion of mortality increases [31-33], obliging a requisite to initiate the advanced treatment facilities with new and better drugs or vaccines. These new vaccines and drug therapy should be monitored by health care system and authorities and their efficacy must be evaluated [34].

It is also very important to engage some active private and effective partners in the health sector of those societies where public services are not sufficient to control tuberculosis [35]. Currently, the focused area of international organizations is to control the HIV/TB complex in Africa, but more intentions are also required in low to middle-income countries like Pakistan, India, Bangladesh, and Sri Lanka, becoming another hub of this complex due to lack of resources and research facilities.

Conclusion

The development of new synergistic relationships of TB with HIV and other viruses are posing new challenges and is a great danger towards global efforts against the epidemics. Due to poor treatment conditions, the drug resistance form of TB is intensifying. With the advancement of therapeutic techniques, it is possible to detect and quantify TB microbes in early stage but need proper management practices at all levels to make these facilities accessible to all rural areas. The experimental trials of latest anti TB drugs for treatment of resistant and latent infection are creating new hope [36]. The global scientific efforts to eradicate various TB forms is promising but further efforts are required by developing the regional TB research centers in Asian and African countries, core of various forms of TB. There is an urgent need to devise the fastest and reliable method of detection to identify all forms of TB in infants and elders with precision. So far, the most popular diagnostic method for TB in low-income countries is relying on the detection of smear-positive TB. The individuals affected with HIV in early asymptomatic stage usually have a smear-negative and extra pulmonary form of TB and these patients remain undetected in usual procedure. Therefore, the reliable diagnostic centers need to be established to provide more accurate confirmation of TB irrespective of HIV infection stage. Furthermore, the rural community of developing countries having minimal socio-economic status is highly susceptible to TB ailment. Public healthcare employees, as well as supporters, are also at higher risk, particularly respiratory therapists and pulmonologist. The international efforts to counter the TB/HIV co-infection are not sufficient. For evading disease spread and reduction in the death rate, it is extremely important to establish the state of the art diagnostic facilities and control centers to address the important health issue [37]. It is already well established that different forms of TB are one of the major cause of increase in death rate in the whole world [38]. The international platform could include the representatives from health, universities, government, public sector and community people from HIV/MTB effective areas to make joint efforts for effective and comprehensive control program of HIV/TB co-infection. Allocation of international funds for research and development in low-income countries is extremely important which is undoubtedly in favor of the whole world. This can only be achieved with strong social, financial and political commitments.

Summary

Tuberculosis (TB) is an infectious bacterial disease caused by mycobacterial complex, affecting millions of people worldwide with an average of 10 million new cases being added annually. Prevalence of joint-family system in developing countries poses a great risk of disease, as infectious agent is disseminated among individuals through aerosol droplets by coughing and sneezing. Unhygienic conditions, quirky mindsets of infected people, lack of expertise to treat the disease, subsequently leads to the emergence of new forms of TB. HIV infected individuals are even more susceptible to TB due to their immune-deficient condition. Globally, TB and Human Immunodeficiency Virus (HIV) co-infections are becoming the leading cause of mortalities regardless of their control strategies. Obstructive government policies and costly treatment give rise to severe situation in developing countries in Asia, having low living standards. Under such circumstances, the new complexes of HIV and TB might evolve into an uncontrollable epidemic that ought to be investigated comprehensively to devise a broad-spectrum strategy against viral and bacterial infections. Generally, TB causing strains are controllable with more than 70% success rate whereas disease control efficiency declines to 30% in case of drug-resistant strains. Factors concerning resistance development in mycobacterial strains and formation of new complexes are discussed in this review.

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