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RESEARCH ARTICLE

TIME TO ACT ON THE EVIL DUO: TREAT TB, MANAGE HIV AND SAVE LIVES

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ABSTRACT

TB and HIV have been closely linked since the emergence of AIDS. This review paper aims to explore the double burden of TB-HIV worldwide, social impact of the epidemic, strategies being followed to control the epidemic and the challenges associated with TB-HIV control activities. An estimated one-third of the 40 million people living with HIV/AIDS (PLHIVs) worldwide are co-infected with TB. PLHIVs are also evaluated to be 15 times more likely to develop TB than HIV negative people. These two diseases represent a lethal combination since they are more destructive together and project challenges in both diagnosis and treatment, interactions between HIV and TB medications, and overlapping medication toxicities, Immune Reconstitution Inflammatory Syndrome (IRIS) and challenges related to adherence. As the HIV and TB services seem disconnected at present, they result in an increase in the cost of care for patients, higher losses to follow-up due to depression and stigma and delays in ART initiation. To combat the fuelling epidemic of HIV and TB globally, there is a need for a Zero parallel system for HIV and TB that must create coherence and synergy between the two programs and strengthen the mechanisms that would indicate effective control, interventions to improve quality of life and significant public health gains. There is a potential need to improve TB treatment outcomes and the contribution that TB-HIV collaboration can make. It also demands additional research to reduce spread of TB, pro-actively identify TB in PLHIVs and reduce mortality.

INTRODUCTION

TB and HIV/AIDS are on the rise worldwide, posing a global public health challenge. TB may occur at any stage of HIV disease and is frequently the first recognized presentation of underlying HIV infection (Sonnenberg *et al.*, 2007; Havlir *et al.*, 2008). Of the 33.2 million people infected with HIV, one-third is estimated to be infected with *Mycobacterium tuberculosis* (MTB) as well. In 2008, about 1.4 million patients with TB were tested globally for HIV, and 81 countries tested more than half of their patients with TB for HIV, but only 4% of all persons infected with HIV were screened for TB in the same year (Getahun *et al.*, 2010). The lifetime risk of TB in immune-competent persons is 5% to 10%, but in HIV+ individuals, there is a 5% to 15% annual risk of developing active TB disease (Swaminathan and Narendran 2008). A PLHIV who is also infected with TB is 20 times more likely to become sick with active TB than someone who is HIV negative. WHO estimated 9.2 million new cases of TB globally in 2006 of which 0.7 million cases and 0.2 million deaths were in HIV-positive people (WHO 2008).An estimated 8.7 million people became ill with TB worldwide in 2011, among whom more than 1 million were living with HIV.

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In 2011, 430,000 out of 1.7 million AIDS-related deaths (25%) were caused by HIV-associated TB disease. Three-quarters of TB-HIV deaths currently occur in just ten countries; Ethiopia, India, Kenya, Mozambique, Nigeria, South Africa, the United Republic of Tanzania, Uganda, Zambia and Zimbabwe. Intensifying efforts in these 10 countries would significantly accelerate progress in achieving the 2015 goal i.e. to reduce TB deaths in PLHIV by 50% (UNAIDS 2012). TB thus is the leading cause of mortality for PLHIVs, and HIV is the most potent force driving the TB epidemic in countries with a high prevalence of HIV. This nexus of TB and HIV infection poses a major threat to the international community's effort to achieve the health-related United Nations Millennium Development Goals for TB and HIV infection.

Up to now, there is a massive failure to respond to the dual epidemic in an integrated way and despite an increasing awareness worldwide, greater commitment and increased funding, current prevention and treatment efforts as well as coordinated research initiatives need to be strengthened to address the challenge of TB-HIV co-infection (Giehl 2010). The prevention of HIV and TB, the extension of WHO DOTS programs, and a focused effort to control HIV-related TB in areas of high HIV prevalence are matters of great urgency (Corbett *et al.*, 2003). There is a need of systems for quickly tracking the numbers of people living with HIV who are

becoming ill with TB, as an important step to improving our programs. By testing for HIV and TB every five years and scaling up methods that are already available, we can reduce deaths by 50%, as targeted in the Stop TB Partnership's Global Plan to Stop TB 2011-2015 (WHO 2011). Against this background, this review paper aims to explore the global burden of TB-HIV co- infection, social impact of the epidemic, strategies being followed to control the epidemic and the challenges associated with TB-HIV control activities.

MATERIALS AND METHODS

This paper is a review of the available literature on the TB-HIV co-epidemic. Major sources of information and data collection were online journals, academic and organizational papers. Different online databases and search engines were employed to access the relevant data, using keywords and their combinations to maximize support and gain evidence for the study. Lastly, articles matching the study objectives, published in English language periodicals up to November 2013, were included in the review paper. To discover grey literature (documents published by organizations, rather than academic journal articles or books), Google Scholar was used to sought organizational websites related to TB-HIV. Citation searches and author searches were carried out on a few included articles as a final check against missing key reports. At the end, all full text articles were read, each article was analyzed critically and those considered to have met the proposed criteria were included in this review.

FINDINGS

Clinical and surveillance data show that in Asia, TB is the most important life-threatening opportunistic disease associated with HIV and the most common reported cause of hospitalization and death among AIDS patients in Thailand; 60% of AIDS patients seen in a Bangkok hospital between 1985 and 1991 had pulmonary tuberculosis. A Surveillance data from India and Nepal shows that 83% and 56% of AIDS patients had tuberculosis respectively (Narain *et al.,* 1992; Kumarasamy *et al.,* 1992). Similar studies have shown that TB accounts for one in four HIV related deaths; the rate of breakdown to clinical tuberculosis in TB-HIV infected people is in the range of 5-15% per year compared to 0.2% among those infected only with TB (Raviliogne *et al.,* 1997; WHO 2004). As the HIV epidemic is fuelling the global TB epidemic and the prevalence of TB in the spread of HIV is a sensitive cursor, a cross-sectional record analysis study covering the period from 2000 to 2011 was conducted at Central Hospital of South Eastern Railway, India. Overall, 50 (12.3%) of the consenting 406 TB patients were found to be HIV+, suggesting a prevalence of 12.3% HIV-TB co-infection among these patients (Manjareeka an Nanda 2013). In 2008, a total of 5.7 million incident TB cases were notified by national TB-control programs globally; 22% of patients with TB were tested for HIV infection (Muvunyi and Masaisa 2012; WHO 2009). In 2008 again, one of three TB related deaths (29%) were considered to be related to HIV infection, and TB contributed to 26% of the estimated deaths due to HIV infection (Global tuberculosis control 2009). A retrospective analysis conducted by the All India Institute of Medical Sciences, New Delhi, India evaluated lymphocyte profiles of subjects infected with HIV (with or without TB). At least 25% were positive for TB (HIV+TB+). A statistically significant difference (p= 0.0001) was found in the median CD4+ counts between the HIV+TB- (297.5 per microliter) and HIV+TB+ (181 per microliter) groups. TB was found to be the indicator disease for HIV infection in 34.2% and in 65.7% of HIV-infected patients. This indicated that TB, a common HIV related opportunistic infection in Indian subjects is associated with lower CD4+ counts (Vajpayee *et al.,* 2004). Based on the National policy that recommends HIV testing of all patients with TB, a cross sectional survey was conducted in West Bengal where HIV and TB records were reviewed to assess the HIV testing status of patients registered for anti-TB treatment from July-September 2010. Among 1633 patients with TB with unknown HIV status at the time of diagnosis, 435 (26%) were tested for HIV within the intensive phase of TB treatment. Patients diagnosed with and treated for TB at facilities with co-located HIV testing services were more likely to get tested for HIV than at facilities without (RR = 1.27, (95% CI 1.20-3.35)). Among 169 patients interviewed, 67 reported they were referred for HIV testing, among whom 47 were tested. During interviews, providers attributed the low proportion of patients with TB being referred and tested for HIV to inadequate knowledge among providers about the national policy, belief that patients will not test for HIV even if they are referred, shortage of HIV testing kits, and inadequate supervision by both programs. In West Bengal, poor uptake of HIV testing among patients with TB was associated with absence of HIV testing services at sites providing TB care services and to poor referral practices among providers (Bishnu *et al.,* 2013).

Using a mathematical model to capture the spatial and temporal variation in TB and HIV in India, it has been estimated that without the Revised National TB Control Program (RNTCP), HIV would increase TB prevalence by 1%, incidence by 12%, and mortality rates by 33% between a period of 1990 and 2015. With the RNTCP, on the other hand, there could be substantial reductions in prevalence (68%), incidence (41%), and mortality (39%) in the same period. Nationally, the RNTCP should be able to reverse the increases in TB burden due to HIV but, to ensure that TB mortality is reduced by 50% or more by 2015, HIV-infected TB patients should be provided with antiretroviral therapy in addition to the recommended treatment for TB (Williams *et al.,* 2005). There is an urgent need for all TB patients to be assessed for HIV risk factors and counselled to undergo HIV testing and conversely, all HIV+ cases should be screened for TB. It is observed that comprehensive policies to change providers' beliefs and practices, decentralization of HIV testing to all TB care centers, and improved HIV test kit supply chain management may scale up the proportion of patients with TB who are tested for HIV (Bishnu *et al.,* 2013).

SOCIAL IMPACT OF TB-HIV CO-INFECTION

Stigma amongst the TB-HIV co-infected patients varies from one country to another. Studies show that there is a perceived stigma among the TB-HIV co-infected patients and are more likely to be socially discriminated and isolated for the fear of infection (Dodor and Kelly 2009). In 2009, a cross sectional study conducted in Ethiopia show that the respondents who were co-infected with TB and HIV were more likely to have

perceived stigma compared to their non co- infected counterparts (OR = 1.4, (95% CI: 1.2- 2.0)) (Deribew *et al.,* 2010). These individuals are significantly stigmatised which sequentially prevents the delivery of medical care & treatment resulting in increase in number of HIV infections (Mbonu *et al.,* 2009). In countries like South Africa, stigma has been considered a primary cause of poor voluntary HIV testing and counselling. It causes delay in diagnosis, reduces the likelihood of treatment uptake after diagnosis, poor treatment adherence and manhandling of such patients by family and community members that in turn, negatively impacts TB-HIV control, increases cost to family, affects social and economic life (Suri *et al.,* 2007).

Although evidence suggests that with wider availability of antiretroviral drugs, there is an increase in testing and treatment that are subsequently used as TB-HIV stigma reduction indicators, but stigma is still quite significant, especially within the health care system (Kipp *et al.,* 2007).In a multi stage survey in Western Uganda, about 18.4% participants informed that nurses did not treat TB-HIV co-infected patients the same as non-co-infected patients (Wynne 2012). A qualitative study in Zambia explored the interconnectedness of TB and HIV for people and found that visible signs of TB sparks stigma for TB-HIV. They identified three key causes of TB-HIV stigma: judgment blame and shame; fear of contagion and public health practices, isolated waiting areas for TB patients at the hospitals (Bond and Nyblade 2006). It has been established that there exists a forked burden of stigma and discrimination associated with TB-HIV that acts as a barrier to testing, diagnosis and impedes treatment and adherence to medication. This calls for designing intervention strategies to help institutions, health workers, families and community members that could help overcome these social issues. Much research is needed to comprehend the impact of stigma by gender, age and other factors and also conclude whether reducing stigma and increasing TB-HIV knowledge could improve the treatment outcome.

STRATEGIC ACTIONS

An epidemiological model that provides a clear blueprint for saving lives has been produced through a concerted effort by the Stop TB Partnership, WHO and UNAIDS. With a primary goal of good quality and accessible TB and HIV treatment, the framework includes HIV sentinel surveillance, TB treatment for every PLHIV with active TB or to prevent TB; early commencement of ART for those who are HIV+ and patients with active TB before their immune systems deteriorates making them less vulnerable to TB infection. The model shows that by scaling up these approaches, a million lives could be saved by the end of 2015 worldwide. (WHO, Unpublished report)

HIV SENTINEL SURVEILLANCE

HIV testing and counselling for all TB patients forms the basis of surveillance in countries with a generalized epidemic state, and in countries with a concentrated epidemic state in areas where groups at high risk for HIV are localized (UNAIDS World Health Organization 2011); studies from Uganda and Zambia have recorded HIV rates of 50-70% among TB patients compared with 20-25% HIV prevalence among pregnant women (UNFPA 2009). The surveillance is carried out in order to ascertain the level of HIV prevalence and trend over time since these data reflect the association between TB and HIV. Apart from providing a standard for good quality patient care for PLHIVs, data to capture the indicators for monitoring TB-HIV activities is required as well. In this light, WHO has suggested and developed the "Three Interlinked Patient Monitoring System" (ILPMS) which links information gathered from clinical cards used in HIV care/ART services, MCH/PMTCT services and TB-HIV services. The system fulfils the dual purpose of providing indicators for monitoring TB-HIV activities and a standard for good quality patient care for PLHIVs (Narain *et al.,* 2002).

Diagnosis

Early diagnosis and effective treatment of TB among HIV-infected patients are critical to cure TB and minimize the negative effects of TB on the course of HIV. At present there are no internationally accepted evidence-based tools to screen for TB in PLHIVs. Multiple studies have been conducted to develop a simple method for ruling out TB in people with HIV infection but the methodological issues prevent the use of any of those (WHO 2013, Day *et al.,* 2006). Diagnosis of active TB in HIV infected individual is difficult because patients with HIV associated TB have fewer bacilli in their sputum (Shah *et al.,* 2009). The presence of a cough for >3 weeks is also not a sensitive symptom of TB in HIV infected person (Brindle *et al.,* 1993). The most common microscopic examination of Ziehl-Neelsen-stained sputum smears, have low sensitivity among HIV infected persons as well (Reid and Shah 2009). Due to the poor result of sputum smear microscopy in HIV infected patients, newer diagnostic tests such as liquid culture systems, nucleic acid amplification assays, and detection of mycobacterial products in various body fluids are being explored (WHO 2007).

Universal antiretroviral therapy (ART) for all HIV-infected TB patients

An increase in access of ART for TB patients has been achieved by initiating events like revision of national policies and guidelines, collaboration of HIV and TB services and decentralizing ART services to TB facilities. As a result, HIV testing of TB patients has now become a standard practice. In 2004, only 4% of the notified patients with TB in Africa were tested for HIV, and increased to 45% in 2008, with 11 countries testing >75% of all patients with TB who received a new diagnosis of HIV infection. One-third of the HIV-infected patients who received a diagnosis of TB initiated ART, representing only 7% of the estimated incident cases of HIV infection–related TB (Global tuberculosis control 2009) and 2.5% of all those who received ART in 2008 (Padmapriyadarsini *et al.,* 2011). Two meta-analyses have shown that isoniazid taken daily for six months reduces the incidence of TB by over two-thirds among HIV-infected individuals (HIV/AIDS, 2008; Wilkinson *et al.,* 1998). Studies from India and South Africa found the 6-month isoniazid regimen to be effective, well tolerated with low rates of emergence of drug resistance (Bucher *et al.*; Martinson *et al.,* 1999). It has been recommended that HIV-infected individuals with TB receive prompt treatment for both diseases, regardless

of CD4+ T cell count, but the optimal /ideal timing of ART is yet to be contended (WHO 2010). The advantages of early ART show significant reduction in early mortality, improve cure rates, cutback in relapses and a marked reduction in incidence of HIV-associated opportunistic infections other than TB. Randomized controlled trials also show that early initiation of ART during TB treatment is associated with reduced mortality rates, especially in patients with profound immunosuppression (CD4<50 cells/µl) (WHO 2007). The as a matter of emergency in TB patients with STRIDE and SAPIT trials similarly observed lower deaths and AIDS-related events with combined and earlier ART and TB treatment, especially among people with CD4 count <50 cells/µl (Havlir *et al.*, 2011; Abdool Karim *et al.*, 2010). Based on these three trials, it is believed that ART should be started CD4 less than 50 cells /µl and as early as possible in the remaining cases. Although, the guidelines for the management of patients co-infected with HIV and TB are still evolving, timely institution of anti-tuberculosis treatment using the directly observed treatment, short-course (DOTS) strategy and HAART are said to markedly improve the outcome of HIV-infected patients with TB (Sharma *et al.*, 2005).

Negating the outcomes of the above mentioned trials, findings in a study also exhibit that a low CD4 cell count increases the risk of IRIS for people that start ART within two weeks of treatment of TB whereas ART did not have an effect on the risk of IRIS for people with a CD4 count >50 cells/mm^3. The severity, frequency and complications of TB IRIS were evaluated by a randomized trial of earlier ART (within 2 weeks after TB treatment initiation) vs. later ART (8-12 weeks after TB treatment) in HIV-infected patients starting treatment for TB. Amidst 806 participants enlisted from 2006 to 2009- ART naïve and with a CD4 count below 250 cells/mm^3; TB IRIS occurred in 61 (8%) patients: 10% in earlier vs. 5% later ART, 12% with CD4 < 50 vs. 5.4% CD4 ≥ 50 cells/mm. The CD4/ART arm interaction was significant, p=0.014, with 44.3% of TB IRIS occurring with CD4 < 50 and earlier ART. TB IRIS also occurred sooner with earlier ART initiation, (29 vs. 82 days, p<0.001). Although no TB IRIS-associated deaths occurred, its management required ≥ 1 invasive procedures in 34.4%, hospitalization in 31.1% and corticosteroids in 54.1%. Overall, 31% of cases were classified as severe and required hospitalisation; 41% as moderate, requiring therapy with steroids or an invasive procedure and the remaining 28% as mild. IRIS severity did not differ according to the use of early or delayed HIV therapy. Whilst the World Health Organization (WHO) has recommended patients with HIV/TB co-infection to start ART within a few weeks of starting TB treatment to reduce AIDS related complications and mortality, both programs will require the diagnostic capabilities, clinical resources and training to manage TB IRIS (Luetkemeyer *et al.*, 2013). Although administering anti-tuberculosis and antiretroviral drugs concomitantly is an effective practice, the major challenges of this treatment include pill burden and patient compliance, drug interactions with highly active antiretroviral therapy (HAART), overlapping toxic effects, and immune reconstitution inflammatory syndrome (WHO 2007).

BARRIERS TO TB-HIV COORDINATION ACTIVITIES

Self-perception to be at risk for HIV among TB patients is one of the major barriers to effective TB-HIV control. A pilot study conducted on 4000 TB patients in two districts of Tamil Nadu, India, demonstrated that over 2/3rds were willing to undergo an HIV test and the major barrier to acceptance was patients not discerning themselves to be at risk. This suggested that if patients were counselled and explained the importance of having an HIV test, when they are diagnosed with TB, most would accept to be tested (Thomas *et al.*, 2007). Studies show that prompt and early diagnosis of HIV among TB patients has been promising as the proportion of people with TB receiving HIV testing rose from 33% to 40%, with 2.46 million people with TB being tested for HIV in 2011 (Global Report 2012). Besides the attitude of the health care staff and stigma and discrimination associated with TB, HIV and co-infection, a few obstacles to successful TB-HIV control subsume lack of political commitment and communication between the two programs at international, national and state/ district levels along with differences in the Programme structure, inequitable distribution of resources, reluctance to broaden their focus on capacity and prioritization (WHO 2007).

DISCUSSION

The HIV pandemic lays out a massive challenge to TB control. The prevention of HIV and TB, the extension of WHO DOTS programs, and a focused effort to control HIV-related TB in areas of high HIV prevalence are of prime importance. In addition to the drugs that shorten the treatment duration of TB, stepping up research and invention of a transformational tool that diagnoses TB accurately is essential for the eradication of the major plagues. A dearth of rapid and accurate TB diagnostic tools and standardized screening methods pose a challenge to accelerate implementation of intensified TB case finding and provision of IPT in resource limited settings. Increased HIV testing of TB patients must be targeted and formulation of informed strategies for control and prevention could help curb the co-infection epidemic. The increasing threat of multi-drug resistant TB among PLHIVs, and the drive towards decentralization of HIV care and ART provision to primary care and DOTS health care facilities means that it is essential that TB infection control policies should be implemented (WHO 2009). The interventions and guidelines should be aimed at all decision makers in the field of health and for managers of TB-control programs and HIV programs working at all levels in the health sector, including the private-for-profit sector, as well as donors, development agencies, nongovernmental organizations and other civil society organizations supporting such programs, and people living with, at risk of or affected by HIV and TB. Reliably ruling out active TB is likely to prove a bottleneck while implementing these strategies as a part of national program, and operational research is urgently required in this regard. Managerial directions are also needed to implement administrative, environmental and personal protective measures against TB infection in health-care facilities and congregate settings. These measures should also include surveillance of HIV and TB among health-care workers and relocation of health workers living with HIV from areas with high TB exposure, in addition to providing ART and IPT. To deliver collaborated TB & HIV services and reduce the burden of TB among PLHIVs, the services must be well strengthened to provide preventions, interventions, testing and counselling services, provide CPT for TB patients living with HIV and ART for TB

patients living with HIV. The burden of TB in PLHIVs must be reduced and an early ART should be initiated that includes the early provision of ART for PLHIV in line with WHO guidelines and scaling up the WHO 3Is strategy for TB-HIV which includes intensified TB case-finding, IPT and Infection control for TB (WHO 2012). Utilization of existing organizational structure, sharing of expertise and experience between HIV/AIDS and TB programs, a strengthened referral system, joint training of staff, sharing of resources and joint financial planning, formulation of joint health education messages, care and support, provision of TB and HIV care prevention packages, awareness of the issue of TB among HIV-infected people are some of the key factors which should be sought to boost TB – HIV co-infection control activities.

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