

REVIEW ARTICLE

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Mycobacterium / HIV interaction and development and emergence of unique Mycobacterium strains and the challenges they pose

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Abstract

The upsurges of tuberculous (TB) and non-tuberculous mycobacterial (NTM) epidemics are believed to be associated with the Human Immunodeficiency virus (HIV) / acquired immunodeficiency syndrome (AIDS) pandemic. Tuberculosis kills over 2 million people worldwide every year even though the disease is preventable and curable. The World Health Organization (WHO) in 2005 declared TB as a public health emergency due its high morbidity and mortality worldwide. It is feared that people in the excess of one billion will contract TB with the attendant 35 million deaths from the disease by the year 2020. The majority of these will be HIV / AIDS patients. The TB - HIV co-infection problem is further aggravated by the emergence of NTM, which cause TB-like syndromes among immunocompromised patients. The association of HIV / AIDS with phenomena such as increasing of multiple drug resistant TB and the NTM syndromes may be pointing to the possibility of HIV - Mycobacterium genomic interaction resulting into the emergence of unique Mycobacterium strains. The objective of this article was to theorize the possibility of occurrence of Mycobacterium - HIV genomic interaction and emergence of unique Mycobacterium strains, and the opportunities such occurrence may provide in the world of medicine. Literature search on internet and peer reviewed articles in journals were reviewed to deduce the possibility of Mycobacterium and HIV genomic interaction and development of new and unique strains of Mycobacterium. The intimate association of the upsurge of TB and NTM epidemics with HIV / AIDS raises the assumption of occurrence of Mycobacterium - HIV genomic interaction in Mycobacterium - HIV co-infected individuals, which may lead to development of unique Mycobacterium strains. It is essential to interrogate this assumption to generate information that may lead to improved control of TB and NTM epidemics.

Keywords: Mycobacterium, HIV genomic interaction, unique mycobacterium strains

Introduction

The advent of the HIV / AIDS in the early 1980s, has led to the emergence of many infections including opportunistic ones initially unknown. Some other infections such as TB whose prevalence were decreasing are again increasing¹. The HIV and TB co-infection has a worldwide prevalence with high morbidity and mortality². The two diseases are robbing many countries of resources slowing economic growth [2,3]. The emergence of NTM as opportunistic infections in the HIV / AIDS patients has further complicated the TB situation for they are difficult to treat [4].

The intimate relationship between TB and HIV / AIDS is a huge challenge to decipher. Tuberculosis and HIV / AIDS interaction is complicated because different strains of both HIV and Mycobacterium involved in co-infection. There is need for studies on the possibility of Mycobacterium - HIV genomic interaction (may be via T-lymphocytes) in co-infection, and whether such

interaction(s) may lead to development of unique (new) and more or less virulent strains of Mycobacterium and HIV- It would also be wise to investigate the possibility of an association between Mycobacterium strains and disease phenotypes.

Challenges of diagnosis and treatment of TB and NTM syndromes associated with HIV / AIDS: As already stated, the increasing clinical significance of NTM associated with HIV/ AIDS is a huge challenge in the detection and management of TB and NTM syndromes. Not only does it require highly skilled personnel to administer medication, but it also requires critical decision of whether to initiate anti-mycobacterial treatment first or antiretroviral therapy (ART).

The Ziehl Neelsen (ZN) stain technique originally used in the detection of TB cannot distinguish NTM syndromes from tuberculosis. It means that the NTM syndromes and TB/NTM syndrome cases may be treated as TB cases. However, multiple drug regimens are used for NTM syndromes management, particularly the newer macrolides azithromycin and clarithromycin⁵, ethambutol, and rifamycin. The use of these drugs require long period of treatment (up to 24 months) in order to facilitate complete clearance of the mycobacteria and minimize the occurrence of drug resistance [5,6]. Also, some NTM syndromes cases could

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be misdiagnosed as tuberculosis and their prevalence in high HIV prevalent settings could be underestimated [7].

However, in the case of tuberculosis and HIV co-infected cases, the WHO [8] and many national TB control programmes guidelines treatment of tuberculosis first with the six-month course and then initiate to ART. But for cases with advanced HIV / AIDS, the alternative is to give a two months treatment for tuberculosis, and then initiate ART. However, for severely immunosuppressed cases (CD4 count < 50 cells per cubic millimeter of blood) the only option is to initiate tuberculosis and HIV / AIDS treatments simultaneously [9].

The cell wall and L-forms of *Mycobacterium* in relation to TB treatment: The cell wall of *M. tuberculosis* complex and other mycobacteria is strikingly unique among the prokaryotes. The mycobacterial cell wall contains an additional layer over and above the peptidoglycan. This additional layer is rich in unusual lipids, glycolipids and polysaccharides [10]. The novel mycobacterial biosynthetic pathways generate various cell-wall components such as tuberculostearic acid, mycolic acids, mycocerosic acid, phenolthiocerol, lipoarabinomannan and arabinogalactan, some of which may contribute to host reactions and act in pathogenesis [11]. Mycolic acids are high-molecular-weight with 60-90 carbons chain of α -branched β -hydroxy fatty acids, which form a lipid layer around the mycobacterial cells. Also present are substituted groups such as cyclopropane rings or methoxy groups [12]. The rich lipids content (over 60% of the dry weight of the cell envelope) is responsible for the strong hydrophobic nature of the mycobacteria and probably for the high virulence of *M. tuberculosis* complex. The lipids also contribute to the relative impermeability to stains, acid fastness, and resistance to inactivation by substances such as acids and alkalies [13].

Equally interesting is the fact that a number of first-line anti-TB drugs (including isoniazid, ethambutol, pyrazinamide and ethionamide) inhibit enzymes that are involved in cell wall synthesis [14], and the occurrence of L-forms of mycobacteria in patients with destructive lung tuberculosis. Some of the surviving mycobacteria in TB - HIV / AIDS patients on anti-TB chemotherapy and the L-forms (deficient in the cell wall) may be less refractory to external agents like the HIV and DNA fragments, and may easily undergo transformation, transduction, or lysogeny. Lysogeny is a situation where a host bacterium incorporates a bacteriophage into its genome (DNA); "when a bacteriophage infects a bacterium it can either lyse or get integrated into the host DNA in a state referred to as lysogeny" [15]. This observation gives credence to the assumption that mycobacteria with deficient cell wall (and L-forms included) may undergo lysogeny, hence *Mycobacterium* - HIV genomic interaction.

Another interesting aspect of the tubercle bacilli is the in vivo occurrence of L-forms [16]. In their study, Chernushenko et al [16] observed L-forms of mycobacteria in 33% (40/123) of patients with destructive lung TB, of which 76% of the isolated L-forms reversed into typical tuberculous mycobacteria after 1-3 passages *in vitro*.

Correlation between *M. tuberculosis* complex genotypes and anti-mycobacterial drug resistance profiles, and their association with HIV / AIDS: The resurgence of tuberculosis and its accompaniment by alarming outbreaks of multi-drug resistance particularly among HIV / AIDS patients is a situation to worry

about. An example is the emergence a multi-drug resistant named 'M' which has been to responsible for nosocomial outbreak of tuberculosis among HIV / AIDS cases in Buenos Aires, Argentina, with the infection spreading to nearby health facilities [17].

Several outbreaks of nosocomial tuberculosis in New York, USA, have been associated with the highly drug resistant strain named 'W'. The mortality rates of these outbreaks have been as high as 80%, majority (up to 73%) being HIV / AIDS cases [18]. In this same city, multi-drug resistant tuberculosis was diagnosed among in 241 cases in 1995 through 1997, with about 90% having had no prior treatment history for TB. Majority (53.1%) of the multi-drug resistant tuberculosis cases had HIV infection compared with non-multi-drug resistant cases who constituted (31.2%) [19]. In a study by Park et al. [20] which analyzed and evaluated the outcome of 173 patients with multi-drug resistant tuberculosis hospitalized in one hospital in New York from 1983-1994, a total of 90 cases (52%) were HIV-infected. A total of 96 (55%) of the cases died in this cohort, mortality rate being higher among HIV-infected cases compared to non-infected cases (72% vs 20%, $P < 0.01$).

Multi-drug resistant tuberculosis due to the Beijing strain family (first reported in Beijing area, China, in 1995) is currently prevalent in prisons in Russia [21]. The highly drug-resistant W strain that was first identified in New York, USA, is a member of the Beijing family [18].

A study by Munsiff et al. [19] points at three possible reasons for the observed higher prevalence of HIV among multi-drug resistant tuberculosis cases compared to cases with ordinary tuberculosis cases. According to them, the initial multi-drug resistant tuberculosis outbreaks mostly involved HIV- infected persons; a large number of HIV-infected patients were most likely infected during those outbreaks; and finally, HIV-infected cases rapidly progress from infection to disease compared than non-HIV-infected cases. However, studies by Githui et al. [22] and Brindle et al. [23] indicate that microbiological response to anti-tuberculous therapy is not affected by HIV infection.

However, it may be postulated that the HIV directly or indirectly (via T-lymphocyte DNA) transfers MDR gene(s) from MDR-TB strains to sensitive TB strains, or there occurs *Mycobacterium*-HIV lysogeny giving rise to MDR-TB strains (mutants), or the HIV provirus on its own encodes for the multi-drug resistance.

The HIV / AIDS, has been associated with the emergence of extensively drug resistant tuberculosis (XDR-TB), the majority of XDR-TB cases being HIV co-infected. The XDR-TB essentially leaves patients virtually untreatable using currently available anti-mycobacterials. However, the extent and amount of XDR-TB is unknown in many countries as they lack the necessary facilities and resources for the diagnosis of the XDR-TB, limiting the availability of data in these countries. The XDR-TB is defined as MDR-TB with additional resistance to fluoroquinolones and at least one of the three second-line injectable drugs, capreomycin, kanamycin and amikacin. It has been identified in a number of countries with necessary resources for its diagnosis, including South Africa, USA and former Soviet countries. Mortality among XDR-TB cases is extremely high [24].

There is need for National TB Control Programmes to do national drug resistance surveys to identify strains with different forms of anti-TB drug resistance. This pool of resistant strains can be

subjected to Mycobacterial Interspersed Repetitive Unit Variable Number Tandem Repeat (VNTR) and spoligotyping (with the same number of control strains from susceptible cases) to determine whether the problem of resistance is associated with particular genotypes in TB and TB – HIV infected patients.

Correlation between *M. tuberculosis* complex genotypes and TB disease phenotype and their association with HIV / AIDS:

In this review, the assumption is that there is the possibility of occurrence of Mycobacterium - HIV genomic interaction in HIV / AIDS individuals which may lead to development of unique (new) Mycobacterium genotypes. It is also known that *M. tuberculosis* infection may result into PTB (smear positive or smear negative) including tuberculous lymphadenitis, tuberculous pleurisy, gastrointestinal TB, skeletal TB, TB meningitis, genitourinary TB, and tuberculous pericarditis⁴. What is not clear is whether there is any association between particular *M. tuberculosis* genotypes and these TB disease phenotypes. It would be wise to genotype (DNA sequencing, large genomic deletion analyses, VNTR, dendrogram of the fingerprints) the *M. tuberculosis* isolates from the different TB - HIV / AIDS cases establish whether particular genotypes are associated with a given disease phenotype.

New genetic typing methods such Mycobacterial Interspersed Repetitive Unit Variable Number Tandem Repeat (MIRU-VNTR) typing and spoligotyping can recognize strains that might be related to differences in severity of disease, transmissibility and mortality [25]. For instance, *M. tuberculosis* Beijing genotype has worldwide often been associated with resistance to anti-mycobacterials¹³⁻¹⁶ and the ability to circumvent the BCG-vaccine-induced immunity [26]. Even though patient management does not vary according to strain type, the ability to differentiate between genotype families might have direct clinical and epidemiological relevance that might influence vaccine and drug development for future management of tuberculosis [27].

Emergence of the NTM as opportunistic pathogens among HIV / AIDS patients: The emergence of NTM as opportunistic pathogens in HIV / AIDS patients has gained clinical significance. The NTM are Mycobacterium species different from those belonging to *M. tuberculosis* complex and *M. leprae* [28], most of them being saprophytes²⁹. However, a good number of are potential opportunistic pathogens, which may cause severe or even and fatal TB-like syndromes³⁰. Skin test data indicate that a great proportion of people have already been exposed to some NTM species. However, the predominant species may vary from country to country and even between different areas of the same country [29,31,32].

Mycobacterium avium complex (MAC), also known as *M. avium-intracellulare* (MAI) complex, is the most important cause of NTM disease. The MAC/MAI consists of some 28 serovars of two related but distinct species, namely, *M. avium*, and *M. intracellulare* [3]. The MAI/ MAC is responsible for severe and usually fatal disease if untreated, particularly in immunocompromised patients such as HIV / AIDS cases [34,3]. Second to MAC / MAI in clinical significance is *Mycobacterium kansasii* as it also causes NTM lung disease³⁴. However, the American Thoracic Society (ATS) [6] reports MAI / MAC, *M. kansasii* *M. fortuitum* and *M. chelonae* as the most common NTM causing chronic respiratory disease, with *M. kansasii* leading in the causation of chronic pulmonary disease similar to reactivation tuberculosis. *Mycobacterium kansasii* infection has a worldwide distribution, being most common in the

USA and UK [4]. In Kenya, *M. fortuitum*/*M. chelonae*, *M. szulgai*, *M. kansasii*, and *M. terrae* are among the NTM species that have been isolated from patients presenting with acute X-ray confirmed pneumonia [36].

New NTM species have also emerged as opportunistic pathogens in HIV / AIDS patients. One of them is *M. genasense* that was first isolated in 1990 from a Swiss patient. But organism is now being reported in other European countries, USA, and Australia. *Mycobacterium celatum*, that is biochemically indistinguishable from *M. avium*, but shows mycolic acid patterns closely related to that of *M. xenopi*, is also being reported to cause disease in some countries [37]. New entrants being associated with disease in HIV / AIDS patients include *M. malmoeense*, *M. xenopi* [38], *M. abscessus*, *M. chelonae*, *M. fortuitum* [39], *M. asiaticum* [40], *M. haemophilum* [41], *M. triviale*, *M. szulgai* and *M. smegmatis* [42]. Death rates from NTM syndromes are usually high even with treatment [38]. Due the wide spread of HIV in developing countries, the role of NTM causing TB-like syndromes may be underestimated particularly resource poor countries in sub-Saharan Africa [30].

Conclusions

(1) *Mycobacterium tuberculosis* DNA has been detected in the lymphocyte fraction of peripheral blood of patients with active TB; (2) *In vitro* studies have also shown DNA of *M. tuberculosis* to have considerable mutagenic potential on the chromosome of the T-lymphocytes; (3) Other studies have reported a chromosomal aberration frequency of 3.5 as much in TB patients compared to healthy individuals; (4) The HIV provirus is frequently detected in peripheral blood T-lymphocytes by PCR amplification of the env, gag and LRT gene sequences; (5) If at all mycobacteria with deficient cell wall become lysogenic, there no reason to doubt the possibility of Mycobacterium transmitting HIV through TB-HIV smear positive cases, particularly at initial stages before converting into smear negative or after defaulting.

Recommendations

There is need for studies to (1) characterize and compare Mycobacterium isolates from Mycobacterium and *Mycobacterium* - HIV co-infected patients (2) determine the frequency at which both HIV provirus and DNA fragments (IS6110) of Mycobacterium occur in DNA of T-lymphocytes of Mycobacterium - HIV co-infected patients (3) demonstrate the occurrence of HIV and Mycobacterium genomic interaction in Mycobacterium - HIV co-infected patients (4) determine the association of *M. tuberculosis* genotypes with TB disease phenotypes (5) determine the association of *M. tuberculosis* genotypes and anti-TB drug resistance profiles, (6) magnitude of NTM syndromes among HIV / AIDS patients. Results of the proposed studies are likely to facilitate the management of the diseases by clinicians.

Results of proposed studies may assist the TB and NTM syndromes control programmes to reassess or reformulate policies on how to handle various patient populations. They may also elucidate the contribution of HIV to the emergence and/or transmission of anti-mycobacterial drug resistance, and the role of the tubercle bacilli in the transmission of the HIV. The studies may assist the national TB and other mycobacterial disease control programmes to reassess or reformulate policies on how to handle various patient populations.

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Ethical approval

Before the study, permissions were obtained from local ethical committee.

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