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Drug-Resistant Tuberculosis and HIV Co-Infection: Urgent Need to Encounter this Deadly Syndemic

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COLUMN ARTICLE

Drug-resistant tuberculosis (DR-TB) is defined as a case of tuberculosis (TB) excreting bacilli resistant to one or more anti-tubercular drugs. DR-TB exists in various forms among which multi-drug resistant tuberculosis (MDR-TB) and extensively-drug resistant tuberculosis (XDR-TB) are of particular concern. MDR-TB is defined as case of TB showing either exclusive resistance to both Isoniazid (H) and Rifampicin (R) or accompanied with resistance to other first line anti-tubercular drugs [1]. XDR-TB refers to resistance to atleast one of three fluoroquinolones (FQ's)- [Ofloxacin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx)] and at least one of three second line injectable drugs (SLID's)- [Capreomycin (Cm), Kanamycin (Km), Amikacin (Am)], in addition to multi-drug resistance. Multi-drug and extensively-drug resistant tuberculosis (M/XDR-TB) are considered to be a global health problem with notoriously difficult and challenging treatment [2]. A dynamic interaction is quite evident between TB and human immunodeficiency virus (HIV) infection. TB accelerates the progression of disease in people living with HIV (PLHIV) whereas PLHIV have increased susceptibility to TB infection. TB is a major cause of mortality among PLHIV whereas HIV is responsible for failure of TB control programmes in achieving targets particularly in high burden countries. TB and HIV co-infection enhances risk of harbouring and acquiring M/XDR-TB strains [3]. HIV co-infection with M/XDR-TB further complicates the situation and considered to be a potential threat with challenging management.

It has been estimated that PLHIV especially with lower CD4 count have 20 (17- 23) times increased risk of developing active TB as compared to people who are HIV negative [4]. According to World Health Organization (WHO), 9% of 10 million people with active TB were also living with HIV globally in 2017 whereas one-third of 36.9 million PLHIV were also infected with TB. It is well known that these PLHIV are also vulnerable to get DR-TB infection. There are several epidemiological reasons why M/XDR-TB may be associated with HIV [5]. The reasons proposed are rapid progression of TB caused due to harbouring of drug resistant strains particularly in immunocompromised as compared to immunocompetent state, drug malabsorption of anti-TB drugs leading to drug resistance and treatment failure, early reactivation of an infection due to increased vulnerability in immunocompromised state acquired from community or institutional transmission, direct contact with DR-TB cases suggesting primary or transmitted resistance, sharing of common risk factors like intravenous drug abuse, imprisonment, low socioeconomic status, alcoholism and frequent hospitalization getting repeated exposures to drug resistant isolates and poor adherence to treatment. The magnitude of global burden of DR-TB and HIV co-infection has not been exactly defined. The paucity

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of data is due to lack of infrastructure, equipment including HIV and anti-tubercular drug susceptibility testing as well as genotypic tests for joint surveillance, manpower and absence of efficient health information system. Epidemiological studies from different regions of world have shown discordant association. There was heterogeneity in setting, demographic profile, methodology and analysis of data as observed among these studies. In the Fourth WHO/IUATLD global drug surveillance report, only 11 out of 24 countries with majority from Eastern European, Sub-Saharan African and Central Asian regions, reported strong association between HIV infection and drug resistance [6]. There was heterogeneous geographic distribution with most of them confined to high risk groups such as drug abusers and prisoners in various countries showing high prevalence of MDR-TB along with emerging HIV epidemic. A systematic review and meta-analysis has recently reported that HIV positive cases have higher risk of MDR-TB by 24% as compared to HIV negative ones [7]. Institution based studies have shown stronger association as compared to community or population based studies. HIV infection is also responsible for all forms of M/XDR-TB epidemic or outbreaks. The epidemics have affected different regions of world but have converged in a deadly syndemic particularly in Sub-Saharan African and Eastern European regions. The epidemic of HIV infection in European region is concentrated in high risk groups whereas epidemic in Sub-Saharan African region has affected general population. Development of acquired drug resistance was responsible particularly due to poor adherence to treatment, deficiencies or gaps in existing knowledge regarding management of diseases and lack of uniform standards of care or guidelines causing faulty practices. However, primary or transmitted resistance is also responsible for epidemic or outbreaks. The largest global outbreak of M/XDR-TB is certainly the one that occurred in the Tugela Ferry of Kwa Zulu-Natal region in South Africa in an HIV positive population, characterized by a high mortality rate of 99%. The main driver responsible for this deadly convergence was not only evolution of the drug resistance mutations but also transmitted resistance amongst the surrounding population as unveiled by genotyping analysis or molecular fingerprinting [8,9]. Another study from Mumbai, India reported alarmingly high burden of M/XDR-TB among HIV-infected patients likely representing ongoing transmission in the community and health facilities [10]. Despite existing weakness in collection of data, the association between HIV infection and M/XDR-TB is of important concern particularly given the implications for the clinical management of these patients.

The accurate diagnosis of DR-TB in HIV-infected people is more difficult and may be confused with other pulmonary or systemic infections. The clinical and radiological features remains similar in HIV infected with CD4 count > 350/cmm^3 and uninfected patients. The presentation is more likely to be extra-pulmonary or atypical such as middle or lower lobe infiltrates, pleural effusion, mediastinal lymphadenopathy or interstitial nodular opacities especially as immunosuppression advances (CD4 < 200/cmm^3) [11]. Solid and liquid culture media based phenotypic tests and drug susceptibility test (DST) remains the gold standard for diagnosis. However, results are delayed with solid media whereas liquid media are expensive and more prone to contamination. This can result in misdiagnosis or delays in diagnosis leading to higher morbidity and mortality. The WHO recently announced new recommendation to speed up the diagnosis through the novel diagnostic test like GeneXpert MTB/RIF which can rapidly diagnose rifampicin resistance for the diagnosis of MDR-TB with HIV co-infection and also second line probe assays (LPA) to identify genetic mutation in multi-drug resistance strains to detect resistance to FQs' and SLIDs' [12,13]. Utility of genotypic tests in programmatic conditions especially in resource limited settings, need to be determined as these tests are costly and requires technical expertise. Spoligotyping and whole genome sequencing (WGS) have also been considered to be a potential diagnostic modality but requires further validation [14]. Extensive research is required to unveil this issue by generating global database in near future.

The treatment of M/XDR-TB in PLHIV is similar to that without HIV. Treatment should be initiated immediately with anti-TB as well as ART whenever this co-infection is diagnosed. Life-long uninterrupted ART remains the cornerstone treatment in PLHIV as mortality without the use of ART is extremely high. ART should be initiated in all TB patients including DR-TB, irrespective of any level of CD4

count [15]. ATT should be started first, followed by ART as soon as possible within the first eight weeks of treatment. ART should be immediately introduced within the first two weeks of initiating TB treatment when there is advanced disease with CD4 cells count < 50/cmm^3. Better outcome with reduction in mortality has been reported with concomitant treatment containing anti-retroviral drugs for HIV component and anti-tubercular drugs for DR-TB component. A systematic review and meta-analysis revealed pooled treatment success rate of 56.9% (95% confidence interval [CI] 46.2 - 67.6), 49.9% (95% CI 38.5 - 61.2) among adults and 83.4% (95%CI 74.7 - 92) among children [16]. This rate is almost similar to that reported among MDR-TB patients in general, regardless of HIV status. The pooled proportion cured among MDR-TB and HIV co-infected patients in Sub-Sahara African region was 34.9% which was higher as compared to that of European region (16%) [17]. This could be due to regional variation in quality of MDR-TB and HIV treatment services within different parts of Europe and small sample size for analysis. Proper adherence to treatment remains a critical issue in such patients due to higher pill burden, use of injectable drugs, overlapping or additive adverse drug reactions and drug-drug interactions. The M/XDR-TB component is usually treated with conventional or longer regimens at programmatic conditions but the outcome remains sub-optimal [13]. The possible reasons for poor treatment outcomes of M/XDR-TB cases are lengthy course (24 - 27 months), expensive and toxicity leading to poor compliance. WHO has recommended a shorter and economical 9 - 12 months treatment regimen for MDR-TB cases containing combination of second line anti-tubercular drugs in order to improve treatment outcome of MDR-TB [1,13]. The currently recommended shorter MDR-TB regimen consists of intensive phase of 4 months (extended upto 6 months in case of non-conversion of sputum smear) with Km, Moxifloxacin, prothionamide/ethionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol followed by a continuation phase of 5 months with gatifloxacin or moxifloxacin, clofazimine, ethambutol, and pyrazinamide. These are indicated only if previous treatment history does not contain exposure to second line anti-tubercular drugs for more than one month and also no documented resistance to SLIDs' and FQs' confirmed by second line LPAs' complemented by second line phenotypic DST. These are not recommended for extra-pulmonary M/XDR-TB (except lymph node and pleura) in PLHIV as evidence regarding efficacy is still lacking. Other situations where shorter regimens are avoided include preference by clinician as well as patient for longer regimens, confirmed resistance or suspected ineffectiveness or intolerance to drug(s), unavailability at the centre and conditions such as pregnancy, disseminated, meningeal or central nervous system TB. An important issue is whether the shorter MDR-TB regimen will work in all settings and especially outside trial conditions needs further research. Other shorter regimens are under trial that avoid injectable drugs having potential toxicity and also include newer drugs - Bedaquiline (Bdq) and Delamanid (Dlm) and repurposed drugs- linezolid and clofazimine [1,13]. These trials are conducted by Research Excellence to Stop Tuberculosis resistance (RESIST-TB) which is an initiative adopted under END-TB strategy by WHO in order to promote and conduct research on therapy for rapid control of DR-TB [18]. These shorter regimens might have promising outcome particularly in patients of M/XDR-TB and HIV co-infection as there is reduction of number of effective drugs leading to reduced pill burden, exclusion of injectable drugs and completion in less than half the time required by the conventional longer treatment of the MDR-TB. All these potential benefits can improve adherence favouring better outcome.

WHO has endorsed certain collaborative activities to reduce the joint burden of TB and HIV co-infection [19-21]. The TB-HIV collaborative activities adopted by WHO are specifically applicable to M/XDR-TB as well. This includes voluntary HIV testing and counselling, standard protocols for diagnosis, prompt introduction of ART in M/XDR-TB/HIV patients as soon as anti-TB tolerated, empirical therapy with second-line anti-tubercular drugs, cotrimoxazole prevention therapy, monitoring of therapy by specialized team, provision of nutritional and socioeconomic support, effective infection control and promotion of activities at administrative level. These activities constitute backbone of the TB/HIV collaborative adopted under STOP-TB strategy that, along with the implementation of effective DOTS programs, will strengthen and increase the success of M/XDR-TB/HIV

control and treatment activities. The END-TB strategy has been further introduced by WHO with objective of eliminating TB as a public health problem [22]. UNAID has set a goal to end HIV/AIDS as public health threat by 2030 [21]. Principle of "hit hard hit early" has been implemented in order to reduce burden of HIV infection. United Nation aims to end AIDS epidemic by 2020 with adoption of 90-90-90 strategy (90% of estimated PLHIV should know their status of which 90% should be initiated on ART of which 90% should demonstrate viral suppression) [23]. The burden of DR-TB including co-infection with HIV poses a great hurdle in elimination of disease by 2030. These DR-TB patients should be targeted separately due to emergence of primary resistance apart from management of DS-TB in order to break the chain of transmission. Various measures have been emphasized in order to drastically reduce burden of DR-TB such as improving case detection, universal DST for first line drugs as well as second line anti-tubercular drugs in order to prescribe appropriate regimen by using rapid genotypic tests, innovation of shorter or conventional regimens fortified with newer drugs, de-centralized or patient centric approach, infection control and preventive treatment for DR-TB contacts [24]. Engagement of private sector for notification and management of drug-resistant cases is also essential to reduce burden of co-infection. All these measures are difficult to implement at programmatic level particularly in resource limited settings where allocating sufficient resources for funding still remains a challenge.

M/XDR-TB in HIV-infected patients is highly lethal and a growing problem in many parts of the world. Early diagnosis with rapid genotypic tests, prompt treatment with appropriate regimens including shorter regimens with newer drugs, close clinical monitoring, management of adverse events, sound patient support and strong infection control measures are all essential components in the management of M/XDR-TB in PLHIV. TB and HIV control programs will contain the epidemic of HIV-associated M/XDR-TB.

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