Tuberculosis 122 (2020) 101921

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: http://www.elsevier.com/locate/tube

Review

HIV and tuberculosis: The paradox of dual illnesses and the challenges of their fighting in the history

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A B S T R A C T

Tuberculosis is an ancient infectious disease caused by the bacillus *Mycobacterium tuberculosis* that is still nowadays afflicting humans all over the world. It causes ill-health for 10 million people each year. Tuberculosis (TB) has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS. In recent years, infection with HIV represents a major risk factor predisposing for infection and TB is the most common cause of AIDS-related death. Despite the treatment of HIV-associated TB has essentially retraced that recommended in HIV-negative cases, it has disclosed some additional challenges over the years. The association of delayed and missed diagnoses, logistic accidents and some well-known complications of HIV and TB treatment co-administration has contributed to 300,000 people living with HIV died from a preventable and curable disease like TB in 2017. The evaluation of new diagnostic and therapeutic approaches with the struggle to erase stigma are essential to successfully manage HIV-TB coinfection.

1. From Mycobacterium tuberculosis discovery to the first effective TB treatment

On March 24, 1882, the discovery of the causative agent of Tuberculosis (TB), *Mycobacterium tuberculosis* (Mbt), opened the prospect both of a prevention program based on the attenuation in the laboratory of the germ and of the active search for a pharmacological treatment [1–3]. The first active drug against Mtb to be discovered was streptomycin in 1943, thanks to S. Waksman [4]. Unfortunately, since the first streptomycin trial carried out in London in 1950 (bed rest vs. bed rest plus streptomycin), which was the first registered randomized control clinical trial of all time, it was clear that antibiotic monotherapy allowed drug-resistances to emerge [5].

Accordingly, in the attempt to prevent further development and spread of drug-resistance, a multi-therapeutic approach with streptomycin, para-aminosalicylic acid (PAS), and isoniazid provided the first effective combination regimen against TB [3].

In spite of efforts, the onset of isoniazid and PAS resistance was rapid. However, thanks to the discovery of rifampicin in 1957, in the beginning of 1990s a therapeutic regimen based on a four-drug induction phase for two months (isoniazid, rifampicin, ethambutol and pyrazinamide), followed by a two-drug maintenance phase of four months (isoniazid and rifampicin), was implemented ensuring more than 90% of treatment success [3,6].

Despite therapeutic success, each year around eight million people develop TB making it responsible for the death of three million people worldwide [6,7].

2. The beginning of a new pandemic

On October 6, 1980, how Dominique Lapierre narrated in detail in his book *"Plus grands que l'amour"* [8], a previously healthy 31-year-old man was admitted to the Ronald Reagan UCLA Medical Center with an unusual oral mycosis and leukopenia, followed a few days later by a rare pneumocystosis.

This was only the first of an endless number of cases that led to the

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https://doi.org/10.1016/j.tube.2020.101921
Received 18 January 2020; Received in revised form 4 March 2020; Accepted 14 March 2020
Available online 25 March 2020

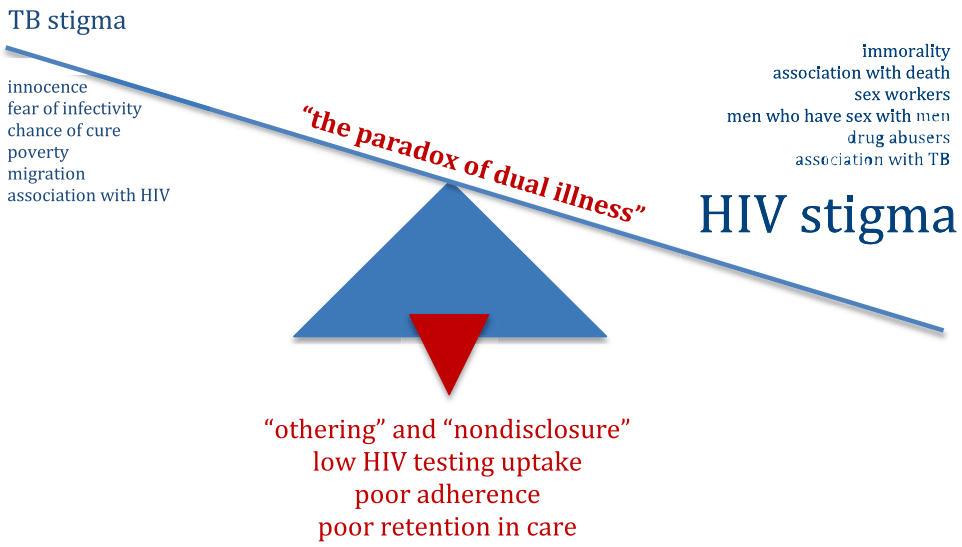

Fig. 1. Stigma and the "paradox of dual illnesses".
Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

definition of Acquired Immunodeficiency Syndrome (AIDS) on September 24, 1982 and to the identification of a retrovirus then named Human Immunodeficiency Virus (HIV) as the causative agent on May 20, 1983 [9,10]. Just while TB rates were starting to decline in the industrialised world and the disease seemed "conquered", two events cooperated to the sharp new increase of TB incidence between the end of the 1980s and the 1990s. In the first place, HIV epidemic swept across the rest of the world, making millions of persons more vulnerable to TB active infection and the reactivation of latent TB infection (LTBI) [11,12]. Secondly, the end of the Perestroika and the dissolution of the Soviet Union resulted in the collapse of Eastern Europe's health system and in an outbreak of TB, particularly multidrug-resistant TB (MDR-TB) [13].

Although TB-HIV coinfection has represented in the last decades a significant problem in Eastern Europe, Asia and the Americas, the main victim of this syndemic, according with the definition of "synergistic epidemic" of Merrill Singer, has been Africa and particularly Sub-Saharan Africa, where a recent meta-analysis reported a decrease from 33.7% before 2000 to 25.7% after 2010, thanks to the strengthening of HIV prevention and treatment programmes [14–16].

3. Stigma over stigma and ethical aspects

The concept of disease-related stigma took the cue from the definition of Erving Goffman in his "Stigma: Notes on the management of spoiled identity" published in 1963. Stigma was defined as "an attribute that is deeply discrediting" and then evolved as a social instrument which allows "normal" individuals to stigmatize individuals with "undesirable" attributes, typically already marginalized because of their gender, race, social class, or religion [16–18].

Historically, TB evoked discrimination due to the fright of infectivity. After the 1960s, progresses in chemotherapy allowed a considerable softening in stigma, until HIV epidemic favoured TB resurgence at the beginning of the 1990s [19].

Both TB and HIV infection afflicts groups already considered "undesirable": people living in impoverished and overcrowded areas and immigrants from TB-endemic low-income countries the first one; sex workers, men who have sex with men, and women the second one. Studies which estimated the stigma degree showed higher levels of stigma against individuals with HIV and HIV-TB coinfection than against TB-affected people, based on the "blameworthy" circumstances of HIV transmission (sexual practices and drug abuse), in contrast with the "innocence" of developing TB. Furthermore, TB is considered curable while HIV is considered irreversible and deadly.

However, the social drivers of TB stigma may also geographically differ: in Africa TB is closely associated with HIV infection, while in Asia it is linked to the worsening of social status and marital opportunities [20].

Daftary et al. efficaciously described "the paradox of dual illness": "While each was regarded as having distinct attributes, they were parabolic in that those who developed TB were assumed to have HIV. The greater negative social desirability, labelling and stigma reserved for people with HIV were transferred to individuals with TB. The identity associated with TB became as undesirable and stigmatized as with HIV." [18].

The implications of TB and HIV-related stigma overlap and intersection involve strategies of "nondisclosure" and separation from people with HIV ("othering"), and consequently a higher risk of low HIV testing uptake, poor adherence to treatment and low retention in HIV and TB care [21] (Fig. 1).

In light of this complex situation, a deeper comprehension of stigma dynamics might lead to improvements in both TB and HIV care delivery [18].

4. Crawling together (Africa and South Africa)

At the beginning of the 1990s, with 8 million people worldwide suffering from TB and 1–2 million deaths annually, the World Health Organization (WHO) TB Department declared TB a global emergency. A new strategy called Directly Observed Treatment Short-course (DOTS) became the recommended approach to global TB control. According to DOTS, a standardized four-drug short-course treatment (isoniazid, rifampicin, ethambutol and pyrazinamide for 6–9 months) should be provided to all smear-positive patients [22].

Globally, promising progress was observed: by 2005, the case detection rate and the treatment success rate rose from 15% to 62% and from 77% to 84%, respectively [23]. However, if DOTS proved effective in countries where the health system was working sufficiently, results were not so satisfying in Sub-Saharan Africa, which hosted the largest concentration of HIV/TB co-infected people [23].

Indeed, DOTS did not take any account of HIV, which undermined TB programme management, by increasing TB-associated morbidity and mortality, complicating the diagnosis and intensifying the stigma [24].

The Global Plan to Stop TB 2006–2015 included among its themes

Table 1
Challenges in co-treatment of tuberculosis and HIV coinfection and their management: use of new anti-TB regimens (e.g. short and individualized regimens). Abbreviations: ART, antiretroviral therapy; DDIs, drug-drug interactions; IRIS, immune reconstitution inflammatory syndrome; MDR, multidrug resistant; TB, tuberculosis; XDR, extensively drug resistant.

Challenges in co-treatment	Management
Increased mortality in MDR and XDR-TB in people living with HIV [29]	ART [30] Use of bedaquiline, delamanid, linezolid, and clofazimine [31,32]
Doubt lower drug exposure in people living with HIV	Further studies (eg. high-dose rifampicin) [33,34]
Reduced tolerability in co-treatment	Adverse drug reaction management Prospective studies on new anti-tubercular drugs
Drug-drug interactions (DDIs)	Check and management of specific DDIs [35]
Tuberculosis-associated IRIS	Prevention and treatment [36,37]

the management of TB-HIV joint activities, as specifically addressed by the three targets of the Interim TB-HIV Policy: 1) prevent TB in people living with HIV; 2) treat HIV in people with TB; 3) create cooperation between HIV and TB programmes [25,26].

In 2017, Africa was still the centre of HIV and TB epidemic convergence, with more than 75% of HIV-associated TB cases and most of the missed diagnoses and treatments [26].

5. Treatment difficulties

Despite the treatment of HIV-associated TB has essentially retraced that recommended in HIV-negative cases, it has disclosed some additional challenges over the years.

First of all, WHO guidelines recommended that antiretroviral therapy (ART) should be started within 8 weeks of TB treatment, or within 2 weeks when CD4 T lymphocyte count is less than 50 cells/μL. Unfortunately, globally in 2017, 60% of 3.8 millions of new and relapsed TB cases received documented HIV testing and 84% of notified TB patients living with HIV received ART [27].

The opportunity to start ART during TB treatment is mainly missed because of dearth of HIV tests, healthcare workers' inattention in referring patients for HIV testing or asking patients about previous testing history, and moreover because patients decline to be tested to avoid stigma.

In 2016, WHO revised treatment guidelines of rifampicin-resistant TB by recommending a 9-12-month clofazimine-based regimen for selected cases including those with HIV coinfection. Furthermore, in 2018 WHO recommended shortening MDR-TB regimen to an 18-month all-oral regimen with bedaquiline, linezolid, moxifloxacin or levofloxacin plus one of or both between clofazimine or cycloserine/terizidone [28,29].

Nevertheless, the availability of new drugs as clofazimine, bedaquiline, delamanid or linezolid are limited in countries with high-burden of HIV-TB and MDR-TB. Indeed, more evidence are emerging on the need for individualized regimens for both drug-resistant TB and sensible TB [30–32].

The association of delayed and missed diagnoses, logistic accidents and some well-known complications of HIV and TB treatment co-administration (Table 1) has contributed to 300,000 people living with HIV died from a preventable and curable disease like TB in 2017.

The evaluation of new diagnostic approaches, novel treatment strategies for drug-resistant TB [30–32], along with the struggle to erase stigma and social inequality, are essential to successfully manage HIV-TB coinfection.

References

[1] Martini M, Besozzi G, Barberis I. The never-ending story of the fight against tuberculosis: from Koch's bacillus to global control programs. J Prev Med Hyg 2018 Sep 28;59(3):E241–7.
[2] Cambau E, Drancourt M. Steps towards the discovery of Mycobacterium tuberculosis by robert koch, 1882. Clin Microbiol Infect 2014 Mar;20(3):196–201.
[3] Daniel TM. The history of tuberculosis. Respir Med 2006 Nov;100(11):1862–70.
[4] Woodruff HB. Selman A. Waksman, winner of the 1952 Nobel Prize for physiology or medicine. Appl Environ Microbiol 2014;80(1):2–8.
[5] Bhatt A. Evolution of clinical research: a history before and beyond James Lind. Perspect Clin Res 2010;1(1):6–10.
[6] Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
[7] Zumla A, Malon P, Henderson J, Grange JM. Impact of HIV infection on tuberculosis. Postgrad Med J 2000;76(895):259–68.
[8] Lapierre D. Plus grands que l'amour. 1990. Arnoldo Mondadori Editore S.p.A., Milano.
[9] Centers for Disease Control (CDC). Update on acquired immune deficiency syndrome (AIDS)–United States. MMWR Morb Mortal Wkly Rep 1982 Sep 24;31 (37):507–8. 513-4.
[10] Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vézinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 1983 May 20;220(4599): 868–71.
[11] Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. Adv Tuberc Res 1976;19:1–63.
[12] Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis 2005;191: 150–8.
[13] Pokrovsky V. Tuberculosis and HIV/AIDS: the alien and the predator. Lancet 2017 Sep 30;390(10102):1618–9. https://doi.org/10.1016/S0140-6736(17)32384-X.
[14] Singer M. A dose of drugs, a touch of violence, a case of AIDS: conceptualizing the SAVA syndemic. Free Inq Creativ Sociol 1996;24:99–110.
[15] Gelaw YA, Williams G, Soares Magalhães RJ, Gilks CF, Assefa Y. HIV prevalence among Tuberculosis patients in Sub-Saharan Africa: a systematic review and meta-analysis. AIDS Behav 2019 Jun;23(6):1561–75. https://doi.org/10.1007/s10461-018-02386-4.
[16] Riccardi N, Alagna R, Motta I, Ferrarese M, Castellotti P, Nicolini LA, Diaw MM, Ndiaye M, Cirillo D, Codecasa L, Besozzi G. Towards ending TB: civil community engagement in a rural area of Senegal: results, challenges and future proposal. Infect Dis (Lond). 2019 May;51(5):392–4.
[17] Goffman E. Stigma: Notes on the management of spoiled identity. Englewood Cliffs, NJ: Prentice-Hall; 1963.
[18] Daftary A. HIV and tuberculosis: the construction and management of double stigma. Soc Sci Med 2012 May;74(10):1512–9. https://doi.org/10.1016/j.socscimed.2012.01.027.
[19] Sontag S. Illness as metaphor. AIDS and its metaphors. London: Penguin Books; 1991.
[20] Somma D, Thomas BE, Karim F, Kemp J, Arias N, Auer C, et al. Gender and socio-cultural determinants of TB-related stigma in Bangladesh, India, Malawi and Colombia. Int J Tubercul Lung Dis 2008;12:856–66.
[21] Courtwright A, Turner AN. Tuberculosis and stigmatization: pathways and interventions. Publ Health Rep 2010;125(Suppl. 4):34–42.
[22] What is DOTS?. https://www.who.int/tb/publications/dots-who-guide/en.
[23] World Health Organization. Global tuberculosis control: surveillance, planning, financing. Geneva, Switzerland: WHO; 2007. WHO report 2007. WHO/HTM/TB/2007.376.
[24] Harries AD. Robert Koch and the discovery of the tubercle bacillus: the challenge of HIV and tuberculosis 125 years later. Int J Tubercul Lung Dis 2008 Mar;12(3): 241–9.
[25] World Health Organization Stop TB Partnership. The global plan to Stop TB 2006–2015. Geneva, Switzerland: WHO; 2006.
[26] World Health Organization. Interim policy on collaborative TB/HIV activities. Stop TB Department and Department of HIV/AIDS. Geneva, Switzerland: WHO; 2004. WHO/HTM/TB/2004.330.
[27] Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
[28] Falzon D, Schunemann HJ, Harausz E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J 2017;49: 1603208.
[29] World Health Organization. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). 2018.
[30] Riccardi N, Alagna R, Saderi L, Ferrarese M, Castellotti P, Mazzola E, De Lorenzo S, Viggiani P, Udwadia Z, Besozzi G, Cirillo D, Sotgiu G, Codecasa L, for StopTB Italia Onlus Group. Towards tailored regimens in the treatment of drug-resistant tuberculosis: a retrospective study in two Italian reference Centres. BMC Infect Dis 2019 Jun 28;19(1):564.
[31] Riccardi N, Del Puente F, Magnè F, Taramasso L, Di Biagio A. Bedaquiline: a new hope for shorter and better anti-tuberculosis regimens. Recent Pat Anti-Infect Drug Discov 2018;13(1):3–11.
[32] Conradie F, Diacon A, Howell P, et al. Sustained high rate of successful treatment outcomes: Interim results of 75 patients in the Nix-TB clinical study of pretomanid,

bedaquiline and linezolid. In: 49th union world conference on lung health; the hague, Netherlands; oct 24–27; 2018. Abstract OA03-213-25.
[33] Esmail H, Lipman MC, Nunn A, Walker TM. Individualising therapy for drug-sensitive tuberculosis. Lancet Respir Med 2019;7(10):834–5. https://doi.org/10.1016/S2213-2600(19)30247-4. pii: S2213-2600(19)30247-4.
[34] Merle CS, Floyd S, Ndiaye A, et al. High-dose rifampicin tuberculosis treatment regimen to reduce 12-month mortality of TB/HIV co-infected patients: the RAFA trial results. In: 21st international AIDS conference; durban, South Africa, july 18–22; 2016. Abstract WEAB0205LB.
[35] https://www.hivdruginteractions.org.
[36] World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. In: Recommendations for public health approach; 2016.
[37] Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the prevention of paradoxical tuberculosis-associated IRIS. N Engl J Med 2018;379:1915–25.