Irini Sereti · Gregory P. Bisson
Graeme Meintjes *Editors*

HIV and Tuberculosis

A Formidable Alliance

Springer

HIV and Tuberculosis

Irini Sereti • Gregory P. Bisson
Graeme Meintjes
Editors

HIV and Tuberculosis

A Formidable Alliance

Springer

Editors
Irini Sereti
National Institute of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, MD, USA

Graeme Meintjes
Wellcome Centre for Infectious Diseases
Research in Africa, Institute of Infectious
Disease and Molecular Medicine
Department of Medicine
University of Cape Town
Cape Town, South Africa

Division of Infectious Diseases and HIV
Medicine, Department of Medicine
University of Cape Town
Cape Town, South Africa

Gregory P. Bisson
Perelman School of Medicine
at the University of Pennsylvania
Philadelphia, PA, USA

ISBN 978-3-030-29107-5 ISBN 978-3-030-29108-2 (eBook)
https://doi.org/10.1007/978-3-030-29108-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Prior to the emergence of the HIV epidemic, the global TB burden was steadily declining over time, largely due to strengthening TB treatment programs delivering short-course TB chemotherapy, which could cure most patients in 6 months. With the emergence of HIV in the 1990s, trends in progress in controlling TB, including reductions in TB incidence and decreasing TB mortality rates, began to be tragically reversed, particularly in sub-Saharan Africa but in highly resourced countries such as the United States as well [1, 2]. Evaluating changes in TB incidence over time by global region throughout the 1990s and early 2000s revealed what has now been repeatedly demonstrated in large-scale epidemiologic analyses: HIV infection profoundly increases the risk of active TB disease, and regions with the highest HIV burden experience dramatic increases in TB case notification rates at the population level [3]. Initial metrics describing the interactions between HIV and TB were nothing short of astounding. Studies from certain populations with high rates of HIV infection and intensive exposure to TB, such as South African miners, for example, began reporting some of the highest TB case notification rates on record, approaching 7000 cases per 100,000 individuals [4]. Early analytic studies provided further grim details revealing that, in areas where TB is common, not only does the risk of TB essentially double in the initial months after HIV acquisition [5] but also TB risk continues to increase as cellular immune competence, measured by CD4+ T cell counts, declines [6]. Not surprisingly, substantial rates of TB among HIV-infected individuals have pushed TB to the top of the list of causes of death among HIV-infected individuals, despite being grossly underdiagnosed [7].

Furthermore, while hope in the fight against TB has been provided by the dual triumphs of the discovery and delivery of highly active antiretroviral therapy (ART), subsequent studies revealed that ART does not completely reverse the heightened TB risk among HIV-infected individuals [8]. Further compounding the problem, the use of ART in patients with TB is complex, often triggering toxicity, with untoward drug-drug interactions or with pathologic inflammation via the immune reconstitution inflammatory syndrome [9]. Indeed, in TB meningitis, rapid provision of ART, versus a careful delay, actually appears harmful [10].

Confronting this “formidable alliance” between HIV and TB has resulted in nearly three decades of dedicated research and public health efforts that have revealed insights

into how HIV-1 and *Mycobacterium tuberculosis* interact in cells, host tissues, and communities. While each area of HIV/TB research and care is associated with substantial challenges, these challenges are being met creatively in ways that are continually advancing our understanding of not only the interaction between the two diseases but also of each of the infections. For example, the study of progression from latent to active TB disease is facilitated by the higher rate of incident TB events among latently infected, HIV-positive individuals over time [11]. This has underscored the concept, recently illuminated by positron emission tomography (PET)-computed tomography (CT) studies, that the clinical space between latent infection and TB disease is most likely a spectrum, not a dichotomy, defined by increasing bacterial replication and inflammation [12, 13]. In addition, the role of monocytes/macrophages and inflammasomes in TB-associated inflammation has been facilitated by evaluating patients longitudinally early during immune reconstitution on ART [14, 15]. More practically, the low bacillary burden of mycobacteria in the sputum of HIV-infected individuals with pulmonary TB has driven the intensive search for a more sensitive TB diagnostic for use in resource-limited settings, which culminated in the approval and scale-up of a novel desktop PCR platform for detecting both *Mtb* and rifampin resistance in patient samples in as little as 2 hours [16]. This and other diagnostic innovations are fueling, in turn, large-scale efforts aimed at detecting and treating TB in heavily affected communities.

This volume will introduce the reader to the main clinical, pathophysiologic, and public health topics within the scope of HIV/TB. Global epidemiology contributions provide an orientation to the determinants and distribution of HIV and TB disease internationally, highlighting the characteristics of regions of intense concentrations of coinfected individuals in areas such as sub-Saharan Africa. The chapter on modeling builds on the epidemiology sections and provides details on the effects of HIV, as well as public health interventions, on TB transmission and TB burden at the population level. Chapters on immunology of HIV and TB and on the TB immune reconstitution inflammatory syndrome summarize the current understanding of how HIV affects the immune system to influence host susceptibility to and manifestations of TB and how immune restoration on ART can lead to immune pathology. Aspects related to the increased risk of progression to active TB in latently infected individuals with HIV, and new and conventional treatments for latent TB, are covered in a chapter that leads into sections covering the presentation, diagnosis, and management of both drug-sensitive and drug-resistant active TB disease, including the important issue of pharmacology and drug-drug interactions as well as the diagnosis and treatment of TB meningitis, the most life-threatening form of TB disease.

We would like to take the opportunity to thank all of the chapter authors of this book for their excellent contributions. We hope that this volume stimulates further interest in the interaction of these two globally important diseases and inspires future investigations to overcome their impact on human health.

Bethesda, MD, USA — Irini Sereti
Philadelphia, PA, USA — Gregory P. Bisson
Cape Town, South Africa — Graeme Meintjes

References

1. Floyd K, Wilkinson D (1997) Tuberculosis in the HIV/AIDS era: interactions, impacts and solutions. AIDS Anal Afr 7(5):5–7
2. Barnes RF et al. (2011) Trends in mortality of tuberculosis patients in the United States: the long-term perspective. Ann Epidemiol 21(10):791–795
3. Corbett EL et al. (2006) Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. Lancet 367(9514):926–937.
4. Anonymous (2007) Tuberculosis Strategic Plan for South Africa: 2007–2011. Department of Health, Republic of South Africa.
5. Sonnenberg P et al. (2005) 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 191(2):150–158
6. Lawn SD et al. (2009) Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. AIDS 23(13):1717–1725
7. Anonymous (2018) Global TB Report 2018. World Health Organization: Geneva
8. Badri M, Wilson D, Wood R (2002) Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. Lancet 359(9323):2059–2064
9. Schutz C et al. (2010) Clinical management of tuberculosis and HIV-1 co-infection. Eur Respir J 36(6):1460-1481
10. Torok, ME et al. (2011) Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin Infect Dis 52(11):1374–1383
11. Petruccioli E et al. (2016) Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis. Eur Respir J 48(6):1751–1763
12. Esmail, H et al. (2016) Characterization of progressive HIV-associated tuberculosis using 2-deoxy-2-[(18)F]fluoro-D-glucose positron emission and computed tomography. Nat Med 22(10):1090–1093
13. Barry CE 3rd et al. (2009) The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol **7**(12):845–855.
14. Andrade BB et al. (2014) Mycobacterial antigen driven activation of CD14++CD16- monocytes is a predictor of tuberculosis-associated immune reconstitution inflammatory syndrome. PLoS Pathog 10(10):e1004433
15. Lai RPJ et al. (2015) HIV-tuberculosis-associated immune reconstitution inflammatory syndrome is characterized by Toll-like receptor and inflammasome signalling. Nat Commun 6:8451
16. Boehme CC et al. (2010) Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 363(11):1005–1015

Contents

Overview of the HIV-Associated Tuberculosis Epidemic

Constance A. Benson

Abstract Globally, tuberculosis is the leading infectious cause of death and the most common opportunistic infection in people living with HIV (PLWH) (World Health Organization. Global Tuberculosis Report 2018). TB incidence has actually declined in the past 5 years both overall and for PLWH (World Health Organization. Global Tuberculosis Report 2018). However, efforts to achieve the target goals of the "End TB Strategy" both for people with and without HIV infection, will require more aggressive interventions aimed at each of the three pillars of TB control, including increased screening and diagnosis of TB infection and disease, rapid initiation of effective TB treatment, and more effective prevention of TB disease. The last decade has seen an explosion of new diagnostic technologies, development of new or novel antimycobacterial drugs, and the evolution of shorter course treatment for latent TB infection and drug resistant TB disease. While the next 5 years is likely to see a sea-change in our approaches to more effective treatment of TB, there are numerous barriers to the scale-up of new diagnostic tests and treatment regimens for PLWH that must be overcome to reach the rates of reduction in TB incidence that will be required to achieve the 2035 TB elimination goals.

Keywords HIV · TB · Opportunistic infection · TB diagnosis · TB treatment · TB prevention · TB elimination

Introduction

Tuberculosis is now the number one leading infectious cause of death worldwide and the most common opportunistic infection and cause of death globally in people living with HIV (PLWH) [1]. There were an estimated ten million new incident cases of TB and 1.6 million TB deaths in 2017, the most recent year for which the

C. A. Benson (✉)
Division of Infectious Diseases and Global Public Health,
University of California San Diego, San Diego, CA, USA
e-mail: cbenson@ucsd.edu

I. Sereti et al. (eds.), *HIV and Tuberculosis*,
https://doi.org/10.1007/978-3-030-29108-2_1

World Health Organization (WHO) has calculated TB case notification rates [1]. An estimated 464,633 incident TB cases occurred in PLWH and there were 300,000 TB deaths in PLWH, representing 18.8% of TB deaths in 2017. Based on a recent update of global models by Houben and Dodd an estimated one quarter of the world's population, 1.7 billion people, are latently infected with *Mycobacterium tuberculosis* (MTB), although the regional distribution varies, with Southeast Asia, the western Pacific region, and the African region having the highest rates of latent TB infection [2].

Although the notification rates for new and relapsed cases of TB continue to rise slowly, TB incidence has actually declined in the past 5 years both overall and for PLWH [1]. The number of TB deaths has declined at a faster rate, particularly among PLWH, mostly attributed to the increased access to and implementation of earlier antiretroviral therapy in areas with the highest burden of TB and HIV [1]. For the first time in modern history, a United Nations General Assembly High Level Meeting took place in 2018 aimed at engaging the world's politicians and public health leaders in the efforts to end TB [3]. New global TB elimination targets were adopted and included, among others, the goals of a 95% reduction in the number of TB deaths and a 90% reduction in TB incidence rate by 2035, accompanied by "zero TB-affected households that experience catastrophic costs resulting from TB" [1, 3]. However, with current reduction rates ranging from only 1.5–2.0% in TB incidence and TB deaths, respectively, meeting these targets would require substantially more aggressive reduction rates of 10% by 2020 and 17% by 2025 to reach these new targets [1, 4].

Efforts to achieve the target goals of the "End TB Strategy" both for people with and without HIV coinfection, will require more aggressive interventions aimed at each of the three pillars of TB control, namely (1) increased systematic screening of TB contacts and high-risk groups, using improved diagnostic tests for detecting active and latent TB infection; (2) rapid evaluation and more effective treatment for active TB, including drug resistant TB, making use of universal drug susceptibility testing and more active, better tolerated, and shorter duration antimycobacterial therapies, and; (3) more effective prevention of active TB by identifying better predictors of risk of progression, implementing shorter course, more effective regimens to prevent TB, including among those exposed to drug resistant TB, and continued development of vaccines capable of preventing active TB, whether in the context of preventing infection or preventing disease. For PLWH, additional steps needed to more effectively address the epidemic include integration of HIV and TB screening and testing of contacts and high risk groups; assuring that new drugs and regimens being tested in clinical trials or used in programmatic settings have appropriate assessment of drug-drug interactions with antiretroviral drugs as well as development of formulations that can be used in children and pregnant women with HIV, and; assuring that clinical trials evaluating new drugs and regimens and new diagnostic modalities for active and latent TB infection are appropriately tested in persons with HIV coinfection, i.e., that PLWH are enrolled in all such clinical trials.

The last decade has seen an explosion of new diagnostic technologies aimed at detecting active TB at or near the point of care. The most widely accessible of these

is the GeneXpert MTB/RIF, a rapid (less than 2-h turnaround time) polymerase chain reaction (PCR)-based assay that can detect the presence of MTB and the *rpoB* gene that confers resistance to rifamycins in sputum and other body fluids with a sensitivity and specificity in persons with acid fast smear (AFB) positive and culture positive TB of 85% and 96%, respectively [5, 6]. Recent modifications of this technology resulted in the development of the MTB/RIF Ultra assay, which has improved sensitivity, particularly in those with sputum smear negative disease, comparable to that of sputum culture [6]. The Xpert MTB/RIF has revolutionized the rapid diagnosis of active TB in many settings, and in some settings, has replaced smear microscopy. Another rapid diagnostic test used as an adjunct screening test is the urine lipoarabinomannan antigen detection test; this test is more sensitive in seriously ill PLWH with advanced immunosuppression, and when used to trigger earlier initiation of ART can improve mortality in this population [7]. Additional advances in diagnostic testing have yielded the ability to conduct rapid drug susceptibility testing using either variations on the Xpert MTB/RIF technology, line probe assays for detection of key mutations conferring resistance to first and second line anti-TB drugs, and more recently whole genome sequencing to genotypically test for signature mutations that confer resistance to anti-TB drugs [8, 9]. If the combination of novel rapid tests is successfully implemented in programmatic settings, one can efficiently diagnose active TB within hours dramatically reducing the time to initiation of effective treatment. However, there remain numerous obstacles to the use of newer technologies in resource constrained high TB burden settings, not the least of which are the cost and maintenance of the equipment and supplies, the need for training laboratory staff in their use and clinicians in the interpretation of the results, and the need for strengthening infrastructure and health care systems to use them. With the broad array of newer technology in the diagnostic development pipeline, much more work is needed to determine where and how best to implement newer diagnostic tests.

As of late 2018, there were more than 15 new or novel antimycobacterial compounds in varying stages of development, and a host of phase 1–3 clinical trials underway or planned to evaluate these together with repurposed or existing anti-TB drugs in combination [1]. This, coupled with the recent approval of bedaquiline and delamanid (in Europe) for use in the treatment of drug resistant TB, represents a dramatic change in the landscape for more effective treatment of TB. Efforts at TB treatment shortening for drug-susceptible TB have been mixed. Three phase 3 clinical trials published in 2014, each incorporating the substitution of one or two newer or repurposed drugs (with greater *in vitro* activity against MTB in mouse models) into the induction or continuation phases (or both) of TB treatment in regimens aimed at shortening treatment from 6 to 4 months all failed [10–12]. The RIFAQUIN study reported a 26.9% unfavorable outcome in the 4-month arm compared to 14.4% in the standard arm [10]. The OFLOTUB trial reported a 21% unfavorable outcome rate versus 17% for the standard of care arm, primarily owing to a higher recurrence rate in the shorter course arm [11]. The ReMOX trial reported unfavorable outcomes of 20% and 15% in the two shorter course arms versus 8% in the standard of care arm [12]. While these were disappointing outcomes, it should be

noted that in each of these studies 70–80% of participants in the 4-month treatment arms were successfully treated, leading to the further investigation of factors likely to be associated with a favorable outcome that could be used to target shorter course treatment.

More encouraging has been the rapid evolution of shorter course treatment for drug resistant TB. Data from the original Bangladesh regimen studies reported an 84.4% bacteriologically favorable outcome with an intensive 9 to 12-month intensive standardized regimen for the treatment of multidrug resistant TB (MDRTB), with 95% of participants completing the regimen within 12 months [13]. These results have been recapitulated in observational studies among persons with MDRTB in a number of countries in Sub-Saharan Africa and elsewhere, leading to a WHO recommendation in 2016 to treat MDRTB in patients who meet specific criteria with a modified Bangladesh regimen that includes kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high dose isoniazid, and ethambutol for 4–6 months followed by moxifloxacin, clofazimine, pyrazinamide and ethambutol for an additional 5 months [14]. Results of two phase 2 trials demonstrating the superiority of bedaquiline (a novel diarylquinoline drug) or delamanid (a novel nitroimidazole drug), respectively, combined with optimized background therapy in the treatment of MDRTB, ultimately led to the availability of two new drugs from novel classes of anti-TB drugs that together with repurposed drugs have substantially improved the successful treatment outcome rates for MDRTB [15–18]. Coupled with the final results of the STREAM-1 randomized controlled trial of a 9-month shorter course MDRTB regimen, the plethora of new data emerging from numerous other studies over the past 2 years reporting more favorable outcomes with shorter courses of combinations of new and existing drugs led to a new WHO rapid communication in August 2018 with key changes to the recommendations for treatment of MDR- and rifampin-resistant (RR-) TB [19, 20]. TB drugs were regrouped into three categories and prioritized based on the evidence supporting their use; Group A includes levofloxacin/moxifloxacin, bedaquiline, and linezolid; Group B includes clofazimine and cycloserine/terizidone; and Group C includes delamanid, ethambutol, pyrazinamide, and other second-line anti-TB drugs. Regimens prioritize Group A, then Group B drugs with Group C drugs reserved for those unable to use one or more of those in the other two groups. The most important changes in the recommendations are that kanamycin and capreomycin are no longer recommended, and all regimens should exclude injectable drugs unless there is a compelling need for them based on drug-susceptibility testing or toxicity management.

Lastly, perhaps the most notable development in the treatment of drug resistant TB has been the interim results reported from the NixTB trial of just three drugs, bedaquiline, pretomanid, and linezolid, used in a 6-month treatment course for extensively drug-resistant TB (XDRTB). Interim results from 75 patients completing treatment as of late 2018 demonstrated durable cure in 88%, with only six deaths and two relapses [21]. Based on final results from 109 participants the U.S. Food and Drug Administration approved pretonamid in August 2019 for persons with highly drug-resistant TB. These results have led to discussion in the field of the

possibility of a "universal regimen" for treatment of drugs-susceptible and drug-resistant TB, with clinical trials underway exploring the use of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide as a universal regimen. In addition, there are now more than 20 randomized clinical trials underway worldwide exploring different regimens for treatment shortening for drug resistant TB.

While the next 5 years is likely to see a sea-change in our approach to more effective treatment of TB, there are numerous barriers to the scale-up of new treatment regimens, not the least of which are the need for new and inexpensive rapid diagnostic tests for detecting active TB and for drug-susceptibility testing, assuring that the cost of new drugs and regimens make them accessible, overcoming country level registration and importation barriers, training clinicians in the use of newer drugs and regimens, assuring adequate pharmacovigilance to assess the safety of newer drugs and regimens as they are deployed more broadly and specifically assessing their activity in PLWH who are on antiretroviral agents that may interact with one or more of the anti-TB drugs, and strengthening health systems and infrastructure for public health programs so that the promise of these drugs can be realized.

The past decade has also seen dramatic changes in our armamentarium for the prevention of latent TB infection. Current regimens now include the standard of 9 months of isoniazid, or the alternatives of once weekly isoniazid plus rifapentine for 12 weeks, or daily rifampin for 4 months all of which are similar with regard to efficacy although treatment completion rates are higher with the shorter regimens [22–26]. The most recent trial may be transformative, demonstrating in PLWH the equal efficacy of a short course regimen comprised of 1 month of daily isoniazid and rifapentine compared with daily isoniazid for 9 months [26]. While this has not yet been incorporated into WHO or other treatment guidelines, it will likely be recommended as an alternative, particularly for PLWH. Finally, recent data suggest that a novel TB vaccine construct, M72/ASO1$_E$ might reduce the incidence of progression to active TB by 54% in adults with latent TB infection, a rate of reduction similar to that seen with chemoprevention [27]. The promise of these critically important studies has not yet been realized. Implementation of effective preventive therapy in the settings where it might have the greatest impact has been disappointingly low. Among the principle obstacles to implementation of preventive therapy have been the inability to either identify those at highest risk of TB progression or to convincingly rule out the presence of active TB with currently available diagnostic tests. For example, the positive predictive value of tuberculin skin testing and interferon gamma release assays as diagnostic tests for latent TB have positive predictive values in the range of 2–7% even in the highest risk populations [28]. The focus of research in the field more recently has been on utilizing gene sequencing or key gene signatures to more effectively predict those most likely to progress in the short term. A recent study suggested a single gene pair, *C1QC/TRAV27,* that could successfully predict progression to active TB in household contacts up to 24 months before onset of active disease [29]. Whether this approach will ultimately lead to cost-effective and widely applicable technology that can be implemented in high TB burden settings remains to be established. But without more effective methods

of diagnosing those at highest risk of disease progression, and targeting them for intervention, it may not be possible to achieve the rates of reduction in new TB infections resulting from reactivation of latent TB that are required to achieve the new goals set for TB elimination.

In summary, we now have or will have in the near future, a plethora of tools that, if effectively deployed, will allow us to achieve the rates of reduction in TB incidence that will be required to achieve the 2035 TB elimination goals set by the WHO and the United Nations High Level Meeting in 2018. The remaining chapters in this textbook highlight the many elements of TB infection, disease, diagnosis, treatment and prevention that specifically pertain to PLWH and that will challenge our ability to reach these goals in this key patient population.

References

1. World Health Organization. Global Tuberculosis Report 2018
2. Houben RM, Dodd PJ (2016) The global burden of latent tuberculosis infection: a re-estimation using mathematical modeling. PLoS Med 13:e1002152
3. United Nations General Assembly. Political declaration of the UN General Assembly high-level meeting on the fight against tuberculosis. www.un.org/pga/73/event/fight-to-end-tuberculosis/
4. Tornheim JA, Dooley KE (2019) The global landscape of tuberculosis therapeutics. Ann Rev Med 70:105–120
5. Boehme CC, Nabeta P, Hillemann D (2010) Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 363:1005–1015
6. Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B et al (2018) Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. Lancet Infect Dis 18:76–84
7. Peter JG, Zijenah LS, Chanda D, Clowes P, Lesosky M, Gina P (2016) Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomized controlled trial. Lancet 387:1187–1197
8. Maningi NE, Malinga LA, Antiabong JF, Lekalakala RM, Mbelle NM (2017) Comparison of line probe assay to BACTEC MGIT 960 system for susceptibility testing of first and second-line anti-tuberculosis drugs in a referral laboratory in South Africa. BMC Infect Dis 17:795. (1–8)
9. Gygli SM, Keller PM, Ballif M, Blochliger N, Homke R, Reinhard M et al (2019) Whole-genome sequencing for drug resistance profile prediction in *Mycobacterium tuberculosis*. Antimicrob Agents Chemother 63:e02175–e02118
10. Jindani A, Harrison TS, Nunn AJ, Phillips PP, Churchyard GJ, Charalambous S et al (2014) N Engl J Med 371:1599–1608
11. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T et al (2014) A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med 371:1588–1598
12. Gillespie SH, Grook AM, McHugh TD, Mendel CM, Meredith SK, Murray SK et al (2014) N Engl J Med 371:1577–1587
13. Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, Rieder HL (2014) Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among consecutive patients. Int J Tuberc Lung Dis 18:1180–1187
14. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. 2016 Update