LONG-ACTING FORMULATIONS FOR THE TREAMENT OF LATENT TUBERCULOSIS INFECTION: OPPORTUNITIES AND CHALLENGES

Susan Swindells[1], **Marco Siccardi**[2], **Stephanie E. Barrett**[3], **David B. Olsen**[4], **Jay A. Grobler**[4], **Anthony Podany**[1], **Eric Nuermberger**[5], **Peter Kim**[6], **Clif Barry**[7], **Andrew Owen**[2], **Daria Hazuda**[4], and **Charles Flexner**[5]

[1]University of Nebraska Medical Center, Omaha NE, USA

[2]University of Liverpool, UK

[3]Sterile Formulation Sciences, Merck Sharp & Dohme, West Point PA, USA

[4]Infectious Disease, Merck Sharp & Dohme, West Point PA, USA

[5]Johns Hopkins University, Baltimore MD, USA

[6]Office of AIDS Research, National Institutes of Health, Bethesda MD, USA

[7]National Institute of Allergy & Infectious Diseases, NIH, Bethesda, MD, USA

SUMMARY

Long-acting/extended release drug formulations have proved very successful in diverse areas of medicine including contraception, psychiatry, and most recently, HIV disease. While challenging, application of this technology to TB treatment could have substantial impact. The length of treatment required for all forms of TB put existing regimens at risk for failure because of early discontinuations and treatment default. Long-acting injections, for example administered monthly, could improve patient adherence and treatment outcomes. We review the state of the science for potential long-acting formulations of existing TB drugs, and propose a Target Product Profile for new formulations to treat latent TB infection. The physicochemical properties of some TB drugs make them unsuitable for long-acting formulation, but there are promising candidates that have been identified through modeling and simulation, and other novel agents and formulations in preclinical testing. An efficacious long-acting treatment for latent TB infection, particularly for those co-infected with HIV, and if coupled with a biomarker to target those at highest risk for disease progression, would be an important tool to accelerate progress towards TB elimination.

Corresponding author: Susan Swindells MBBS, Professor and Medical Director, HIV Clinic, Department of Internal Medicine, Mailing address:, University of Nebraska Medical Center, 988106 Nebraska Medical Center, Omaha, NE 68198-8106, Voice: +14025595392, Fax: +14025535527, sswindells@unmc.edu.

Authorship contributions:

Conception and design : Swindells, Siccardi, Olsen, Owen, Flexner

Drafting and revising: Swindells, Siccardi, Barrett, Olsen, Podany, Nuermberger, Barry, Owen, Flexner

Final approval: All authors

Keywords

Tuberculosis; latent infection; long-acting; extended release

INTRODUCTION

The World Health Organization (WHO) strategy to end the global tuberculosis (TB) epidemic can only be accomplished by dramatic acceleration of early diagnosis of TB, preventive treatment of those at risk for disease progression, and treatment of all patients with TB.[1] Of the 23% of the world's population allegedly infected with latent tuberculosis infection (LTBI), less than 5% are diagnosed and treated, therefore diagnosis and management of LTBI is a crucial intervention for TB elimination.[2,3] Reasons for poor uptake of isoniazid preventive therapy (IPT) include the length of treatment, risk of side effects, perceived risk of development of drug-resistant TB, lack of acceptance by persons at risk, and suboptimal completion rates.[4] Because of the poor positive predictive value of the current screening tests, the large number of people needed to treat prevent a case of TB is also an obstacle.[5]

Of all the risk factors for TB disease progression, human immunodeficiency virus (HIV) co-infection is the most powerful predictor. TB is the leading cause of death in HIV-infected persons worldwide, and this has persisted despite the fact that provision of antiretroviral therapy (ART) is increasing - three quarters of co-infected patients with HIV and TB received ART in 2014.[6] Globally, HIV-infected persons account for 12% of people who develop TB annually, and 25% of deaths from TB.[7]

People infected with TB but not HIV have an average 10% lifetime risk of developing TB disease, and there is a growing research portfolio investigating biomarkers to identify those at highest risk.[8] Transcriptional biomarkers and T-cell activation markers are showing promise, as are sophisticated imaging techniques such as positron emission tomography.[9–11] Better diagnostic and prognostic tools will enable targeted preventive therapy for those at high risk of disease progression.

Preventive therapy is effective. In a Cochrane Database review of 12 randomized clinical trials of LTBI treatment in 8578 randomized HIV-infected persons, preventive therapy with any anti-TB drugs administered for 6–12 months versus placebo resulted in an overall 32% reduction in the incidence of active TB (relative risk [RR] 0.68; 95% confidence interval [CI] 0.54, 0.85).[12] The effect was greater for those with a positive TB skin test (TST) (62% reduction; RR 0.38; [95% CI 0.25, 0.57]) than for those with a negative TST (11% reduction; RR 0.89; [95% CI 0.64, 1.24]). Three months of weekly rifapentine and isoniazid (3HP) is as effective as 9 months of isoniazid, and had higher completion rates (82% versus 69%, p<0.001).[13] This regimen is also safe and effective in HIV-infected persons, although not on antiretroviral therapy, and was better tolerated with higher completion rates than 9 months of isoniazid.[14]

Drug-drug interactions are important considerations, especially for HIV-infected persons on antiretroviral therapy but co-treatment is possible.[15] For orally administered drugs,

bioavailability is limited by drug transporter proteins (E.g. ABC transporters such a P-glycoprotein) and metabolic enzymes (E.g. cytochrome P450 isoforms) within the intestinal epithelium and during first-pass through the liver via the hepatic portal vein. Moreover, the expression and activity of many of these proteins is governed by variants in genes coding for them or their transcriptional regulators, and these same proteins are important mediators of many pharmacokinetic drug-drug interactions seen clinically. Since parenteral delivery avoids the gastrointestinal tract and first pass metabolism, it is conceivable that the magnitude of some transporter or enzyme-mediated drug-drug interactions or pharmacogenetic variability may be less with long-acting formulations, but this remains to be seen and will require careful evaluation.[16]

Background on LA therapy

The term long-acting (LA) has been employed in drug delivery to cover applications in oral and parenteral administration, and has historically not been defined by an explicit duration of pharmacokinetic exposure. Notably, the term was previously employed for once-daily oral formats for insulin[17] which is clearly not the ambition for the recent developments, where the goal is to achieve therapeutic exposure for periods ranging from weeks to months. Recently, it was proposed that a candidate should achieve at least once weekly, once monthly, or once 6-monthly dosing to qualify as LA when considering oral, injection, or implant, respectively, in the context of HIV.[16] Thus, the application of the term should be strongly considered in the context of the specific indication for which a new medicine is being developed, and for TB this has informed the target product profile (TPP) discussed below.

The convenience and durability of LA drug formulations has provided substantial benefit to diverse areas of human health. The extended duration of drug delivery conferred by these formulations leads to improved adherence and, as a consequence, to improved outcomes. Broadly, LA injectable medicines have been explored utilizing either intramuscular or subcutaneous administration of oil-based solutions, drug-encapsulated in polymer microparticles, in-situ formation of gels or solid/semi-solid structures, or drug particle suspensions.[16] The recent paradigm for LA injectables has emerged from the delivery of antipsychotic drugs such as paliperidone palmitate,[18] which involve intramuscular administration of solid drug nanoparticle (SDN) suspensions. Indeed, the exciting new developments for HIV prevention and therapy have involved the formation of SDNs of rilpivirine and cabotegravir, by the process of wet-bead milling.[19,20] These formulations are spearheading the advent of LA injectables for infectious diseases, and provide between 1 month and 3 months of therapeutic exposure from a single intramuscular depot. The two-drug combination of injectable long-acting cabotegravir with rilpivirine every 4 weeks or every 8 weeks was recently shown to be as effective as daily three-drug oral therapy at maintaining HIV-1 viral suppression through 96 weeks and was well accepted and tolerated.[21] Work in HIV disease has been encouraged by the early accreditation of patient acceptability, which indicated that of 400 adult patients with HIV infection surveyed in the US, 84% indicated they would or probably try an injectable nanoformulated antiretroviral therapy that provided monthly administration.[22] This early indication of patient acceptability has also been born out through attitudes surveys imbedded within subsequent clinical trials,

and is likely to be driven by the well-recognized issues of treatment-fatigue, which subsequently drive patient non-adherence and its associated consequences.

Suitability of TB drugs for LA formulation

Clearly the development of LA injectable formulations is highly dependent on the specific clinical needs, and so far, the approach has focused predominantly on indications that require chronic dosing. There are clear paradigms shared between HIV and TB therapy, such as the need for delivery of drug combinations, concerns regarding emergence of resistance, and issues with adherence to medication. Moreover, the potential for a single administration providing a "one shot cure" is an almost irresistible ambition for future TB treatment, which should also prove extremely compatible with directly observed therapy (DOT). In addition, it is tempting to speculate that avoiding oral delivery and associated first pass metabolism through the liver may bring additional benefits in terms of drug-drug interactions, which have complicated TB therapy for decades. Importantly, all the existing LA injectable formulations (across indications) have been developed using drugs first approved for oral administration. While this has inevitably precluded the robust evaluation of the critical physicochemical properties required for the approach, it is encouraging that existing drugs may be LA-enabled by reformulation, and this may also simplify the regulatory pathway. However, the development of LA injectables for TB requires that either the existing drugs be compatible with the advanced formulation technologies, or that new drugs be developed specifically for such applications.

Existing LA injectable drugs are characterized by specific pharmacokinetic and pharmacodynamic properties which support their compatibility with the approach. In addition to the obvious need for favorable safety profiles, formation of drug nanoparticle suspensions requires low aqueous solubility (water-soluble nanoparticles rapidly dissolve and release drug), high potency (to minimize the requirement for high plasma concentrations), and long pharmacokinetic half-lives (to minimize rapid clearance). For existing TB drugs, these properties are summarized in Table 1, using therapeutic plasma concentrations as a surrogate for potency. The drugs were selected based on their common usage for LTBI and in first and second therapy, with potential suitability for LA formulation. The three key properties (half-life, water solubility and therapeutic concentrations) of existing LA injectable drugs are represented in Figure 1, and overlaid with existing anti-TB agents. Accordingly, rifapentine, delamanid, bedaquiline and rifabutin have pharmacological and physicochemical characteristics that make them potential candidates for LA administration using the drug nanoparticle suspension approach (half-life > 12 hours, therapeutic concentrations < 1000 ng/mL and water solubility < 50 mg/mL).

TB LEAP activities

A Working Group on LA/ER Formulations for the Prevention and Treatment of TB was established in 2015 under the auspices of the Long-Acting/Extended Release Antiretroviral Resource Program (LEAP). LEAP was established in 2015 with a 5-year R24 grant from the National Institute of Allergy and Infectious Diseases to support established investigators, and encourage new investigators working on LA/ER formulations by: 1) encouraging scientific innovation through access to a centralized group of subject matter experts in the

chemistry, pharmacology, regulation, clinical development, and commercialization of LA/ER ARV's; 2) establishing a communications and data hub for dissemination of important data and results from ongoing laboratory and clinical studies as well as facilitation of communication amongst investigators and stakeholders; and 3) developing and offering a modeling and simulation core of actual and predicted drug concentrations for LA formulations to aid investigators in assigning priority to drugs and formulations in development (described in full detail at www.longactinghiv.org). The LEAP TB Working Group supports development of LA/ER drugs for TB, especially in TB/HIV co-infection. This group has led the effort to develop a Target Product Profile (TPP) for anti-TB formulations for use in TB prevention, use of the Modelling and Simulation Core to screen existing molecules for suitability for LA/ER formulation for the treatment or prevention of TB, and hosts an annual meeting to support these activities.

Target product Profile for long-acting drugs for the treatment of latent TB infection

A TPP for LA latent TB treatment was drafted that describes the attributes of the treatment that would be ideal as well as the minimally acceptable attributes that would be required in a viable regimen (Table 2). These attributes fall under categories that include the anticipated efficacy, the number of agents, the presentation of the regimen (volume, number, and frequency of administrations), as well as cost and contraindications. While the TPP was drafted by the TB LEAP with input from appropriate subject matter experts that weighed in on the drug discovery, formulation, clinical, and public policy aspects, it is important to note that it is a living document that should evolve with the understanding of the field.

Preliminary Data

Multiple approaches have been investigated for prolonging the dosing interval of both orally and parenterally administered anti-TB drugs, although the vast majority of reported data in the literature consists of *in vitro* work, with minimal preclinical data and no clinical pharmacology data either in healthy volunteers or in individuals with TB.[23] The primary focus of sustained release approaches has been the use of novel drug delivery systems and reformulations of current available anti-TB drugs. Several explore pulmonary delivery of TB drugs as a means to increase drug concentrations at the anatomic site of TB disease.[24] Pulmonary delivery methods have been shown to sustain therapeutic drug levels for extended periods of time; for example, a study of rifampin microspheres maintained rifampin concentrations above the MIC for 26 days.[25] Early parenteral approaches to sustained drug delivery involved microsphere and liposomal formulations of anti-TB drugs.[26,27] Poly lactic-co-glycolic acid (PLGA) and poly (D-L-lactic acid) micro particles have been shown to be suitable carriers for both rifampicin and isoniazid, with preclinical data suggesting once weekly dosing as a possibility.[28,29] Many natural occurring proteins and polymers such as the plant protein zein, the collagen degradation product gelatin, as well as plant derived alginate and chitosan have been explored as biodegradable, biocompatible slow release mechanisms for anti-TB drug delivery.[30,31] Oral nanoparticle formulations consisting of carriers derived from these agents have demonstrated sustained therapeutic plasma drug concentrations of INH/RIF/PZA/EMB for up to 5–7 days in single dose animal models.[32] More recently, the field of TB drug delivery has migrated toward nano-particle formulations, summarized by Pandey et al.[33]

Using the LEAP modelling core, computational simulations were utilized to simulate potential LA administration strategies for four anti-TB agents. Drugs used for latent TB and/or having favorable physicochemical/pharmacological properties were selected. The modelling approach predicted that 1500 mg of delamanid and 250 mg of rifapentine could be sufficient doses for monthly IM administration while bedaquiline and isoniazid would require more frequent IM dosing compared to the other two agents. Clearly, these data do not provide direct evidence that the drugs can be formulated as an LA injectable, but they do provide a potential pharmacological rationale for their assessment.

DISCUSSION

As imperfect adherence and poor completion rates for preventive treatment of latent TB infection are major obstacles to the effectiveness of this strategy, an important and novel solution to this problem could be the development of long-acting/extended-release injectable anti-TB drugs that can be administered periodically in a clinic setting, eliminating the problems of suboptimal adherence and treatment completion.[34] This strategy may be especially important for vulnerable populations, including children, adolescents, and pregnant women. Bypassing oral dosing may improve bioavailability, and possibly improve tissue penetration although this remains to be established. In addition, incidence of certain adverse effects and drug-drug interactions may be decreased. Opportunities and challenges presented by LA treatment for TB are summarized in Table 3.

The development of LA products is complex and challenging. Treatment of infectious diseases presents unique challenges in particular due the potential for the development of drug resistance. To mitigate this risk, drugs used to treat infectious disease are often administered at high multiples above their minimally efficacious doses, often at maximally tolerated doses, and are frequently used in regimens containing multiple agents. This can be at odds with the development of LA formulations where the ideal is a minimal number of drugs that can be administered at low doses that minimizes the size (and therefore invasiveness) of the parenterally administered regimen and that provides the maximal duration of drug delivery. Thus far, all successful LA agents are administered separately. LA cabotegravir and rilpivirine have proved very successful in clinical trials for HIV treatment, but the drugs are still given as two separate intramuscular injections.[35] To date, most LA injectables have been developed from existing oral formulations although the physicochemical properties of many compounds render them unsuitable for this approach. This is especially true for existing oral anti-TB drugs, many of which lack the right balance of water solubilty, lipophilicity, half-life and potency.[16] Management of adverse effects may be more challenging with LA injectable formulations as they cannot be immediately discontinued, and the physicochemical properties that make them suitable for LA injectables also negate the option of dialysis or other strategies to remove the drug. New drug delivery technologies, such as removable solid or semi-solid implants, may alleviate many of these problems by providing options that are readily removable.[36]

Robust *in vitro* and *in silico* methods are being developed to investigate the potential of LA TB treatment, and animal models are also needed. Preclinical research on the therapeutic potential of new TB drugs and regimens relies heavily on mouse infection models. While

these models provide useful information about efficacy, data about important pharmacokinetic/pharmacodynamic relationships may be lacking and can only be established from large and costly trials in humans.[37,38]

The TB LEAP group is first focusing on development of LA anti-TB treatment for latent infection, which presents an attractive target since there is a reasonably high likelihood that its treatment with a single agent would be efficacious in due to the relatively low mycobacterial burden. However, successful LA TB drugs could also have important applications for treatment of both drug sensitive and drug resistant TB disease. For example, the development of LA isoniazid and rifampin formulations that could be administered monthly would result in the continuation phase of TB treatment being accomplished with 4 monthly injections. This could have substantial impact on treatment completion rates.

CONCLUSION

LA/ER TB treatment has theoretical potential to dramatically improve adherence to and completion of treatment for latent infection. New LA/ER formulations are likely to have their most immediate impact on the treatment of LTBI.[39] Coupled with a field-friendly diagnostic test to identify those at highest risk for progression to disease, an LA/ER TB formulation could enable a test-and-treat strategy that would greatly increase the possibility of TB eradication.

Acknowledgments

References

1. WHO. The END TB Strategy. 2015.

2. Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016; 13(10):e1002152. [PubMed: 27780211]

3. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016; 16(11):1269–1278. [PubMed: 27522233]

4. Fiske CT, Yan FX, Hirsch-Moverman Y, Sterling TR, Reichler MR. Tuberculosis Epidemiologic Studies Consortium Task Order T. Risk factors for treatment default in close contacts with latent tuberculous infection. Int J Tuberc Lung Dis. 2014; 18(4):421–427. [PubMed: 24670696]

5. Sester M, van Crevel R, Leth F, Lange C. Numbers needed to treat to prevent tuberculosis. Eur Respir J. 2015; 46(6):1836–1838. [PubMed: 26621887]

6. Raviglione M, Sulis G. Tuberculosis 2015: Burden, Challenges and Strategy for Control and Elimination. Infect Dis Rep. 2016; 8(2):6570. [PubMed: 27403269]

7. World Health Organization. Global tuberculosis report. 2015. Available from: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1

8. Barry CE, Boshoff H, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the goals of prophylaxis. Nature reviews Microbiology. 2009; 7(12):845–855. [PubMed: 19855401]

9. Esmail H, Lai RP, Lesosky M, et al. Characterization of progressive HIV-associated tuberculosis using 2-deoxy-2-[(18)F]fluoro-D-glucose positron emission and computed tomography. Nature medicine. 2016; 22(10):1090–1093.

10. Petruccioli E, Scriba TJ, Petrone L, et al. Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis. European Respiratory Journal. 2016; 48(6):1751–1763. [PubMed: 27836953]

11. Berry MPR, Graham CM, McNab FW, et al. An Interferon-Inducible Neutrophil-Driven Blood Transcriptional Signature in Human Tuberculosis. Nature. 2010; 466(7309):973–977. [PubMed: 20725040]

12. Akolo C, Adetifa I, Shepperd S, Volmink J. Cochrane Database of Systematic Reviews. 2010. Treatment of latent tuberculosis infection in HIV infected persons.

13. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011; 365(23):2155–2166. [PubMed: 22150035]

14. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS. 2016; 30(10):1607–1615. [PubMed: 27243774]

15. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

16. Owen A, Rannard S. Strengths, weaknesses, opportunities and challenges for long acting injectable therapies: Insights for applications in HIV therapy. Adv Drug Deliv Rev. 2016; 103:144–156. [PubMed: 26916628]

17. Owens DR, Bolli GB. Beyond the era of NPH insulin--long-acting insulin analogs: chemistry, comparative pharmacology, and clinical application. Diabetes Technol Ther. 2008; 10(5):333–349. [PubMed: 18715209]

18. Fleischhacker WW, Gopal S, Lane R, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. Int J Neuropsychopharmacol. 2012; 15(1):107–118. [PubMed: 21777507]

19. Williams PE, Crauwels HM, Basstanie ED. Formulation and pharmacology of long-acting rilpivirine. Curr Opin HIV AIDS. 2015; 10(4):233–238. [PubMed: 26049947]

20. Trezza C, Ford SL, Spreen W, Pan R, Piscitelli S. Formulation and pharmacology of long-acting cabotegravir. Curr Opin HIV AIDS. 2015; 10(4):239–245. [PubMed: 26049948]

21. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet. 2017

22. Williams J, Sayles HR, Meza JL, et al. Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients. Nanomedicine (Lond). 2013; 8(11):1807–1813. [PubMed: 23611617]

23. Bullo Saifullah MZBH, Al Ali SHH. Controlled-release approaches towards the chemotherapy of tuberculosis. International journal of nanomedicine. 2012; 7:5451. [PubMed: 23091386]

24. Suarez S, O'hara P, Kazantseva M, et al. Airways delivery of rifampicin microparticles for the treatment of tuberculosis. Journal of Antimicrobial Chemotherapy. 2001; 48(3):431–434. [PubMed: 11533012]

25. Zahoor A, Sharma S, Khuller G. Inhalable alginate nanoparticles as antitubercular drug carriers against experimental tuberculosis. International journal of antimicrobial agents. 2005; 26(4):298–303. [PubMed: 16154726]

26. Quenelle DC, Winchester GA, Staas JK, Barrow EL, Barrow WW. Treatment of tuberculosis using a combination of sustained-release rifampin-loaded microspheres and oral dosing with isoniazid. Antimicrobial agents and chemotherapy. 2001; 45(6):1637–1644. [PubMed: 11353605]

27. Deol P, Khuller G. Lung specific stealth liposomes: stability, biodistribution and toxicity of liposomal antitubercular drugs in mice. Biochimica et Biophysica Acta (BBA)-General Subjects. 1997; 1334(2):161–172. [PubMed: 9101710]

28. Dutt M, Khuller G. Sustained release of isoniazid from a single injectable dose of poly (DL-lactide-co-glycolide) microparticles as a therapeutic approach towards tuberculosis. International journal of antimicrobial agents. 2001; 17(2):115–122. [PubMed: 11165115]

29. Dutt M, Khuller G. Chemotherapy of Mycobacterium tuberculosis infections in mice with a combination of isoniazid and rifampicin entrapped in Poly (DL-lactide-co-glycolide)

microparticles. Journal of Antimicrobial Chemotherapy. 2001; 47(6):829–835. [PubMed: 11389115]

30. Sharma S, Khuller G, Garg S. Alginate-based oral drug delivery system for tuberculosis: pharmacokinetics and therapeutic effects. Journal of antimicrobial chemotherapy. 2003; 51(4): 931–938. [PubMed: 12654730]

31. Pandey R, Khuller G. Chemotherapeutic potential of alginate–chitosan microspheres as anti-tubercular drug carriers. Journal of Antimicrobial Chemotherapy. 2004; 53(4):635–640. [PubMed: 14998985]

32. Ahmad Z, Pandey R, Sharma S, Khuller GK. Pharmacokinetic and pharmacodynamic behaviour of antitubercular drugs encapsulated in alginate nanoparticles at two doses. International journal of antimicrobial agents. 2006; 27(5):409–416. [PubMed: 16624533]

33. Pandey R, Ahmad Z. Nanomedicine and experimental tuberculosis: facts, flaws, and future. Nanomedicine: Nanotechnology, Biology and Medicine. 2011; 7(3):259–272.

34. Horsburgh CR Jr, Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. Chest. 2010; 137(2):401–409. [PubMed: 19793865]

35. Margolis DA. LONG-TERM SAFETY AND EFFICACY OF CAB AND RPV AS 2-DRUG ORAL MAINTENANCE THERAPY.

36. Kleiner LW, Wright JC, Wang Y. Evolution of implantable and insertable drug delivery systems. Journal of controlled release : official journal of the Controlled Release Society. 2014; 181:1–10. [PubMed: 24548479]

37. Nuermberger E, Sizemore C, Romero K, Hanna D. Toward an Evidence-Based Nonclinical Road Map for Evaluating the Efficacy of New Tuberculosis (TB) Drug Regimens: Proceedings of a Critical Path to TB Drug Regimens-National Institute of Allergy and Infectious Diseases In Vivo Pharmacology Workshop for TB Drug Development. Antimicrob Agents Chemother. 2016; 60(3): 1177–1182. [PubMed: 26824941]

38. Nuermberger EL. Preclinical Efficacy Testing of New Drug Candidates. Microbiol Spectr. 2017; 5(3)

39. Abu-Raddad LJ, Sabatelli L, Achterberg JT, et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(33):13980–13985. [PubMed: 19666590]

40. Nitti V, Delli Veneri F, Ninni A, Meola G. Rifampicin blood serum levels and half-life during prolonged administration in tuberculous patients. Chemotherapy. 1972; 17(2):121–129. [PubMed: 4558400]

41. Ruslami R, Nijland HM, Alisjahbana B, Parwati I, van Crevel R, Aarnoutse RE. Pharmacokinetics and tolerability of a higher rifampin dose versus the standard dose in pulmonary tuberculosis patients. Antimicrob Agents Chemother. 2007; 51(7):2546–2551. [PubMed: 17452486]

42. DrugBank. [Accessed 7th June, 2017] Rifampicin - DB01045 (APRD00207, EXPT02777). 2017. https://www.drugbank.ca/drugs/DB01045

43. Drugbank. Isoniazid - DB00951 (APRD01055, EXPT01940). 2017. [Accessed 7th June, 2017]

44. Zhu M, Starke JR, Burman WJ, et al. Population pharmacokinetic modeling of pyrazinamide in children and adults with tuberculosis. Pharmacotherapy. 2002; 22(6):686–695. [PubMed: 12066959]

45. Alsultan A, Savic R, Dooley KE, et al. Population Pharmacokinetics of Pyrazinamide in Patients with Tuberculosis. Antimicrob Agents Chemother. 2017; 61(6)

46. DrugBank. [Accessed 7th June, 2017] Pyrazinamide (DB00339, APRD01206). 2017. https://www.drugbank.ca/drugs/DB00339

47. Lee CS, Gambertoglio JG, Brater DC, Benet LZ. Kinetics of oral ethambutol in the normal subject. Clin Pharmacol Ther. 1977; 22(5 Pt 1):615–621. [PubMed: 410579]

48. Denti P, Jeremiah K, Chigutsa E, et al. Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Newly Diagnosed Pulmonary TB Patients in Tanzania. PloS one. 2015; 10(10):e0141002. [PubMed: 26501782]

49. DrugBank. [Accessed 7th June, 2017] Ethambutol (DB00330, APRD00957). 2017. https://www.drugbank.ca/drugs/DB00330

50. Vourvahis M, Davis J, Wang R, et al. Effect of rifampin and rifabutin on the pharmacokinetics of lersivirine and effect of lersivirine on the pharmacokinetics of rifabutin and 25-O-desacetyl-rifabutin in healthy subjects. Antimicrob Agents Chemother. 2012; 56(8):4303–4309. [PubMed: 22644026]

51. Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. Antimicrob Agents Chemother. 1998; 42(3):631–639. [PubMed: 9517944]

52. DrugBank. [Accessed 7th June, 2017] Rifabutin (DB00615, APRD00094). 2017. https://www.drugbank.ca/drugs/DB00615

53. Weiner M, Bock N, Peloquin CA, et al. Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. Am J Respir Crit Care Med. 2004; 169(11):1191–1197. [PubMed: 14962821]

54. Weiner M, Bock N, Peloquin CA, et al. Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. Am J Resp Crit Care. 2004; 169(11):1191–1197.

55. DrugBank. [Accessed 7th June, 2017] Rifapentine (DB01201, APRD01217). 2017. https://www.drugbank.ca/drugs/DB01201

56. Xavier AS, Lakshmanan M. Delamanid: A new armor in combating drug-resistant tuberculosis. J Pharmacol Pharmacother. 2014; 5(3):222–224. [PubMed: 25210407]

57. Diacon AH, Dawson R, Hanekom M, et al. Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. Int J Tuberc Lung D. 2011; 15(7):949–954.

58. ChemSpider. [Accessed 7th June, 2017] Delamanid. 2017. http://www.chemspider.com/Chemical-Structure.4981055.html

59. Deoghare S. Bedaquiline: a new drug approved for treatment of multidrug-resistant tuberculosis. Indian J Pharmacol. 2013; 45(5):536–537. [PubMed: 24130398]

60. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Ch. 2008; 52(8):2831–2835.

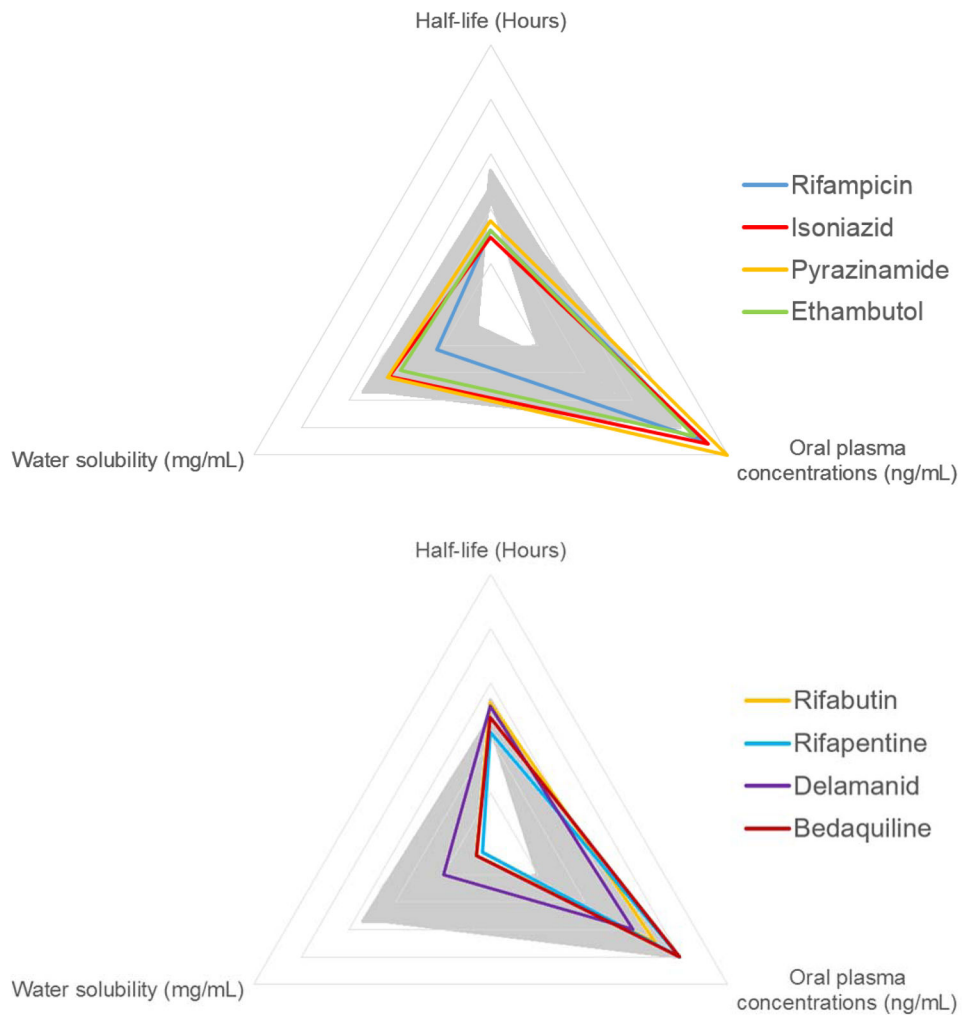61. DrugBank. [Accessed 7th of June, 2017] Bedaquiline (DB08903). 2017. https://www.drugbank.ca/drugs/DB08903

Figure 1.
Schematic representation of the three drug-specific properties influencing physicochemical and pharmacological compatibility with LA administration, as described in the main text. The grey area represents the range for existing LA formulations for multiple disease areas (paliperidone palmitate, olanzapine pamoate, risperidone, medroxyprogesterone acetate, rilpivirine and cabotegravir; half-life > 12 hours, therapeutic concentrations < 1000 ng/ml and water solubility < 50 mg/ml). Axis span across 0.1 to 10000 (log_{10} scale). It can be seen that rifabutin, rifapentine, delamanid and bedaquiline have properties in the range of other LA medicines, whereas other drugs currently used in TB therapy do not.

Table 1

Physicochemical and pharmacological properties of select anti-TB agents

	Half-life (Hours)	Average concentration at steady state (μg/mL) [*]	Daily oral dose (mg)	LogP	Water solubility (mg/mL)
Rifampicin	4 [40]	3.3 [40,41]	600	2.7 [42]	1.4 [42]
Isoniazid	1–5 [43]	1.3–3	300	−0.7 [43]	14 [43]
Pyrazinamide	6 [44]	12.8 [45]	1500	−0.6 [46]	15 [46]
Ethambutol	4 [47]	0.98 [47,48]	1200	−0.3 [49]	8 [49]
Rifabutin	30–50 [50]	0.29 [48,51]	300	4.1 [52]	0.017 [52]
Rifapentine	13 [53]	4.1 [54]	129–600	4.8 [55]	0.02 [55]
Delamanid	38 [56]	0.15 [57]	200	4.75 [58]	<1 [56]
Bedaquiline	24 [59]	0.67–2.7 [60]	100–400	7.5 [61]	0.0177 [61]

[*] Calculated as AUC/time

Table 2

Target Product Profile for a LA/ER formulation for treatment of latent TB.

	Minimal Parenteral Regimen	Ideal Parenteral Regimen
Mechanism of Action	Activity against drug susceptible TB	Activity against drug susceptible and drug resistant TB
# of Compounds in the Regimen	Monotherapy	Monotherapy
Indication	Treatment of presumed drug susceptible latent TB infection	Treatment of latent TB infection, including for contacts of MDRTB
Availability of Drug Susceptibility Testing (DST) for the Index Case, if known	Rapid, low cost DST method that can be implemented at district level or below	No requirement for DST
Target Populations	Adults & other age groups with regulatory approval; irrespective of HIV or immune status	All age groups, irrespective of HIV status (pediatric formulation likely to come after adult indication)
Route of Administration	IV infusion; IM/SC injection; or implantation	IM/SC; or implantation
Product Presentation	2 x 2 ml injections; or an implant	Single injection (2 ml; 25-gauge or smaller); or an implant
Dosage Form and Schedule	Suspension administered: 1x per week or less frequently for up to 3-months; or 1x per month for 6 months; or implant lasting for up to 3 months	Suspension administered less frequently than 1x per month for up to 3-months; or implant lasting for up to 1 year
Expected Efficacy	Non-inferior to SOC (e.g. RPT/INH - 3mo)	Superior to SOC (less incident TB, shorter duration of treatment)
Contraindications, Warnings, Precautions, Interactions, and Use During Pregnancy and Lactation	No additional monitoring required compared with current therapy; DDIs no worse than current therapy; mild injection site reaction	No contraindications or warnings; no significant side effects; no significant DDIs; safe for use in pregnant and lactating women; no injection site reaction
Shelf-life and Storage	2 yr at 4°C	3 yr at 40°C and 75% humidity
Product Registration and WHO Prequalification	Approved by FDA, EMA, WHO PQ, and national regulatory authorities of high-burden countries	
Cost of Treatment	Total health system cost no greater than current	Total health system cost less than current

Table 3

Potential advantages and disadvantages of monthly injectable anti-TB treatment as compared to oral therapy.

Potential Advantage	Potential Disadvantage
Reduced inter-individual variability in drug exposures	Large injection volume
Dose reduction	Difficulty of combing more than one agent
Avoidance of gastrointestinal adverse effects	Requirement for oral lead-in
Decreased drug-drug interactions	Management of adverse effects
Improved adherence	Resistance consequences of missed doses
Compatibility with DOT	
Decreased cost	