Universitat Autònoma de Barcelona

Hacia un mejor control de la tuberculosis multidrogorresistente en países en desarrollo

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que presenta el licenciado ***Ignacio Monedero Recuero***, ha sido realizada bajo su dirección, la consideran finalizada y autorizan su presentación para que sea defendida ante el tribunal que corresponda.

Dr. Joan A. Caylà i Buqueras Dr. Rafael Vidal i Pla

En Barcelona, 20 de marzo de 2013

Dedicatorias

Dedicado a mi madre Ana Maria y a tantas otras mujeres de clase trabajadora que pelearon y siguen pelando a diario y a su manera para que sus hijos tengan acceso a una educación de calidad; una educación a la que ellas no tuvieron acceso.

A Sandra por su paciencia, su buen humor, por estar y ser, por escuchar siempre, por aguantar mis ausencias y viajes, por ser dos y también uno.
Por ser tan buena madre de mi hijo.

"Um outro mundo é possível.
Mudar é difícil, mas não é impossível"

Paulo Freire, Educador

"Education is the greatest weapon that can be used to change the World"
"We can't fight AIDS unless we do much more to fight TB as well"

Nelson Mandela, Premio Nobel de la Paz y ex paciente de Tuberculosis

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RESUMEN DE LA TESIS (Castellano)

Introducción
La tuberculosis multidrogorresistente (TB-MDR) está incrementando su prevalencia a escala mundial principalmente como consecuencia del mal manejo de los casos sensibles. La transmisión primaria de TB con resistencias a la comunidad está poniendo en grave riesgo el control global de la TB. La mayoría de pacientes proceden de países en desarrollo con sistemas de salud insuficientes para diagnosticar y tratar a sus enfermos. Las herramientas diagnósticas y terapéuticas actuales están obsoletas y las herramientas futuras pueden tardar décadas en aparecer y usarse en contextos de escasos recursos.

Objetivos
El ***objetivo general*** de esta tesis doctoral es profundizar en el tema de la TB-MDR en países en desarrollo y aportar a la comunidad científica y clínica, nuevos conocimientos que colaboren en la prevención de resistencias medicamentosas o a tratar con mejores resultados a aquellos pacientes que ya tienen enfermedad con resistencias.

Hipótesis
Aún con herramientas obsoletas, los resultados en prevención y tratamiento de la TB-MDR podrían ser mejores de lo que actualmente son en países en desarrollo. El uso más eficiente de los actuales conocimientos y herramientas podría contribuir a la creación de estrategias de impacto en prevención y mayor curación de casos. Se identifican 3 posibles hipótesis:

- *Hipótesis 1.* Los medicamentos combinados en dosis fijas (MCFs) pueden tener similar eficacia que los medicamentos sueltos a un menor coste y con potenciales ventajas operativas y en prevención de resistencias.
- *Hipótesis 2.* Los tratamientos estandarizados para TB-MDR pueden aportar similares resultados que los tratamientos individualizados también con ventajas operativas y menor coste.
- *Hipótesis 3.* Es posible crear herramientas y documentos de calidad técnica para acelerar la auto-formación y actualización de clínicos en el manejo de TB-MDR. La mejor formación puede estar vinculada a la obtención de mejores resultados.

Métodos:
En función de los objetivos e hipótesis planteados, en esta tesis se ha trabajado en 3 líneas de investigación principales:

1. Revisión sistemática de la eficacia de los MCFs respecto a medicamentos sueltos.
2. Estudio de cohortes de pacientes en tratamiento para TB-MDR y evaluación de eficacia, efectividad, recaídas y efectos adversos respecto al uso de tratamientos estandarizados e individualizados.
3. Creación de documentos sencillos de alta calidad técnica para aumentar el acceso al conocimiento del manejo de la TB con resistencias orientado a los clínicos de países en desarrollo.

Resultados:
Estudio 1: Revisión sistemática de eficacia de los MCFs. El 100% de los estudios encontrados en que se comparan MCFs y medicación separada, los resultados en

eficacia de conversión de cultivo y curación son similares. Las recaídas parecen ser similares en ambos grupos. Adherencia, aceptación y capacidad para reducir resistencias están a favor de los MCFs. Otras ventajas operativas y precio también favorecen el uso de MCFs.

Estudio 2: Estudio de cohortes y evaluación de todos los pacientes con TB-MDR tratados en República Dominicana entre agosto 2006 y junio 2010. No hubo diferencias estadísticamente significativas entre regimenes estandarizados e individualizados en cuanto a conversión de cultivo. En los pacientes con tratamientos terminados, los estandarizados obtuvieron una tasa de éxito terapéutico del 74% respecto a un 66% de los individualizados ($p>0,05$). Cada enfermo presentó una mediana de 5 efectos adversos. La presencia de cavitación en radiografía de tórax y no negativizar el cultivo antes del segundo mes fue encontrado como factor de riesgo para resultado desfavorable. La tasa de recaídas fue aproximadamente de un 1% tras un año de seguimiento en la mayoría de los casos.

Estudio 3: Se llevo a cabo una revisión crítica acerca del manejo de pacientes con TB resistente. Listado y presentación de las bases bacteriológicas del tratamiento y mínimos conocimientos a tener en cuenta para un correcto manejo de casos con altas tasas de curación.

Estudio 4: Elaboración de un artículo científico abordando de forma simplificada el correcto manejo de pacientes con coinfección TB-MDR y VIH en contextos africanos de escasos recursos terapéuticos y diagnósticos.

Estudio 5: Se analizaron las diferencias en presentación y manejo de pacientes con TB-MDR procedentes de países ricos y pobres. Las soluciones de países ricos, actualmente el *gold standard* probablemente no sean extrapolables a países con escasos recursos.

Conclusión:
Los artículos científicos incluidos en la presente tesis doctoral representan un conjunto de medidas básicas de bajo coste que suponen un respaldo científico fundamental para:

- Políticas sanitarias de uso masivo de MCFs en el tratamiento para la TB presentando similares tasas de curación y recaídas, numerosas ventajas logísticas y operativas y probablemente menor adquisición de resistencias a menor precio y mayor simplicidad de manejo.
- Uso de estrategias de tratamientos estandarizados para TB-MDR ya que son capaces de obtener altas tasas de éxito terapéutico aún en países de escasos recursos con mayor simplicidad de manejo y menor coste.
- La formación de clínicos en países en vías de desarrollo se puede mejorar mediante la elaboración de artículos científicos de calidad que de forma breve y simplificada aborden el difícil manejo de la TB-MDR.

Los artículos resultantes de esta tesis doctoral aportan información científica relevante para un mejor control de la tuberculosis multidrogoresistente en países en desarrollo, objetivo principal de esta tesis.

Palabras clave:
Tuberculosis, TB, Tuberculosis multidrogorresistente, TB-MDR, Combinaciones de medicamentos fijos, Países en vías de desarrollo

RESUM DE LA TESIS (Català)

Introducció
La Tuberculosi Multidrogoresistent (TB- MDR) està incrementant la seva prevalencia a nivell mundial com a conseqüència del mal maneig dels casos susceptibles. La transmissió primària de TB amb resistències a la comunitat estan posant en risc el control global de la TB. La majoria de malalts procedeixen de països en desenvolupament amb sistemes de salut insuficients per a diagnosticar i tractar aquesta enfermetat. Les eines diagnòstiques i terapèutiques actuals estan obsoletes i les eines futures poden trigar dècades en aparèixer i fer-se servir en context d'escassos recursos.

Objectius
L'objectiu general d'aquesta tesis doctoral és profunditzar en el tema de la TB-MDR en països en desenvolupament i aportar a la comunitat científica i clínica, nous coneixements que col·laborin en l'objectiu comú de prevenir l'adquisició de resistències i millora els resultats del tractament.

Hipòtesi
Encara que es facin servir eines obsoletes, els resultats en prevenció i tractament de la TB-MDR podrien ser millor del que actualment són en països en desenvolupament. L'ús més eficient dels coneixements i eines actuals podria contribuir a la creació d'estratègies i activitats d'impacte en prevenció i major curació de casos. S'identifiquen tres possibles hipòtesis:

- Hipòtesi 1. Els medicaments combinats en dosis fixes (MCFs) poden tenir una eficàcia similar que els medicaments solts a menys cost i amb potencials avantatges operatives i prevenció de resistències.
- Hipòtesi 2. Els tractaments estandarditzats per a TB-MDR poden aportar uns resultats similars que els tractaments individualitzats també amb avantatges operatives i menor cost.
- Hipòtesi 3. És possible crear eines i documents de qualitat tècnica per accelerar la auto-formació i l'actualització de clínics en el maneig de TB-MDR i així obtenir millors resultats derivats de millor formació i maneig.

Metodologia
En funció dels objectius i hipòtesis plantejats, aquesta tesi ha treballat en tres línies d'investigació principals:

1. Revisió sistemàtica de l'eficàcia dels MCFs respecte a medicaments solts.
2. Estudi de cohorts de pacients en tractament per a TB-MDR i avaluació d'eficàcia, efectivitat, recaigudes i efectes adversos respecte a l'ús de tractaments estandarditzats i individualitzats.
3. Creació de documents senzills d'alta qualitat tècnica per augmentar l'accés al coneixement del maneig de la TB amb resistències, orientat a clínics en països en desenvolupament.

Resultats
Estudi 1: Revisió sistemàtica d'eficàcia dels MCFs. Els resultats en eficàcia de conversió de cultiu i cura son similars en el 100% dels estudis trobats en que es comparen MCFs i medicació separada. Les recaigudes semblen similars en ambdós

grups. Adherència, acceptació i capacitat per reduir resistències estan a favor dels MCFs. Altres avantatges operatives també afavoreixen l'ús de MCFs.

Estudi 2: Estudi de cohort i avaluació de tots els pacients amb TB-MDR tractats a República Dominicana entre agost 2006 i juny 2010. No va haver-hi diferències estadísticament significatives entre tractaments estandarditzats i individualitzats en conversió de cultius. En pacients amb tractaments finalitzats, els estandarditzats van obtenir una taxa d'èxit terapèutic del 74% respecte a un 66% dels individualitzats ($p>0,05$). Cada malalt va presentar una mediana de 5 efectes adversos. La presència de cavitació en radiografia de tòrax i no negativizar el cultiu abans del segon mes va ser trobat com a factor de risc per a resultat desfavorable. La taxa de recaigudes va ser aproximadament de un 1% després d'un any de seguiment a la majoria de casos.

Estudi 3: Es va portar a terme una revisió crítica sobre el maneig de pacients amb TB resistent. Llistat i presentació de les bases bacteriològiques del tractament i mínims coneixements a tenir en compte per un correcte maneig de casos amb altes taxes de cura.

Estudi 4: Elaboració d'un article científic abordant de forma simplificada el correcte maneig de pacients amb coinfecció TB-MDR i VIH en contexts africans d'escassos recursos terapèutics i diagnòstics.

Estudi 5: Es van analitzar les diferències en presentació i maneig de pacients amb TB-MDR procedents de països rics i pobres. Les solucions de països rics, actualment el *gold standard* probablement no siguin exportables a països amb escassos recursos.

Conclusió

Els articles científics inclosos en la present tesi doctoral presenta un conjunt de mesures bàsiques de baix cost que suposen un recolzament científic fonamental per:

- Polítiques sanitàries d'ús massiu de MCFs en el tractament per la TB que presenten taxes de cura i recaiguda similars, nombroses avantatges logístiques i operatives i probablement menys adquisició de resistències a menor preu i major simplicitat de maneig.
- Ús d'estratègies de tractaments estandarditzats per TB-MDR ja que son capaços d'obtenir alts índex d'èxit terapèutic a països d'escassos recursos econòmics amb major simplicitat de maneig i menor cost.
- La formació de clínics es pot millora mitjançant l'elaboració d'articles científics de qualitat que de manera breu i simplificada aborden el difícil maneig de la TB-MDR orientat a països en desenvolupament.

Els articles resultants d'aquesta tesi doctoral aporten informació científica rellevant per un millor control de la tuberculosi multidrogoresistent en països en desenvolupament, objectiu principal de la tesi.

Paraules clau

Tuberculosi, TB, Tuberculosi multidrogoresistent, TB-MDR, Combinacions de medicaments fixes, Països en vies de desenvolupament.

THESIS ABSTRACT (English)

Introduction

The prevalence of Multidrug resistant Tuberculosis (MDR-TB) is globally increasing mainly as a result of mismanagement of susceptible TB cases. The transmission of resistant strains into the community is jeopardizing global TB control. The vast majority of cases are from developing countries where health systems are insufficient to diagnose, treat and support the patients. Current diagnose and treatment tools are obsolete while future tools may delay decades to appear and be used in scarce resource settings

Object

The main objective of this doctoral thesis is to analyze in deep the MDR-TB problem in developing countries and provide to the clinical and scientific community new knowledge that may support the common objective of TB resistance prevention and better MDR-TB treatment results.

Hypothesis

Even with obsolete tools, results in prevention and MDR-TB treatment might be better that currently are in developing countries. The more efficient use of current knowledge and tools may contribute to the creation of health policies with impact on resistance prevention and better cure rates. Three different hypotheses were identified:

- Hypothesis 1.The anti-TB fixed dose combinations (FDCs) may obtain similar efficacy than single drugs with operative advantages, reduced cost and reducing the resistance acquisition.
- Hypothesis 2. Standardized MDR-TB treatments may obtain similar results than individualized also with operative advantages and less cost.
- Hypothesis 3. It is possible to create quality tools and documents for quick self-training and up date of clinicians in the management of MDR-TB cases in order to obtain better results due to better disease understanding.

Methods

According to the objective and hypothesis formulated, this thesis had worked in three research lines:

1. Systematic review on the FDCs efficacy for the TB treatment respect to single drugs
2. Cohort study and evaluation in terms of efficacy, effectiveness side effects and relapses of MDR-TB patients under standardized and individualized regimens
3. Creation of simple but high quality documents to increase the access of developing countries clinicians to most relevant knowledge regarding MDR-TB to avoid therapeutic errors and resistance amplification.

Results

Study 1: Systematic review on FDCs efficacy. The 100% of the studies found revealed equal efficacy in terms of culture convertion and cure. Relapses appear to be similar. Adherence acceptance and capacity to reduce resistance acquisition go in favour of FDCs. Other operative and logistic advantages and cost favour FDCs as well.

Study 2: Cohort study and evaluation of all MDR-TB patients treated in Dominican Republic between august 2006 and June 2010. There were not found significative

statistically differences in culture conversion regarding standardized or individualized treatments. Concerning patients with ended treatments, standardized obtained a treatment success rate of 74% whereas 66% was obtained for individualized. Each patient presented a median of 5 side effects. Cavitation on the chest x ray and more than 2 months for culture conversion were found as risk factor for unfavourable result. Relapse rate was close to 1%.

Study 3: Creation of a review article on the subject of drug resistant TB management. List and presentation of the bacteriological bases for TB treatment and minimum requirements and knowledge to take into account to achieve high cure rates.

Study 4: Scientific article addressing the simplification of the most correct and updated management of co-infected patients with MDR-TB and HIV in African scarce therapeutic and diagnose resource contexts.

Study 5: Perspective article showing the differences on the presentation and management of MDR-TB patients coming from rich and poor countries. Solutions from rich countries, usually the only ones available on the literature or the gold standard are probably not the best solutions or can not be extrapolated to poor countries.

Conclusion

The articles included in this doctoral thesis represent a scientific back up of a comprehensive package of basic and low cost interventions:

- Presenting similar efficacy and better profile regarding acceptance, adherence and probably on resistance acquisition health policies on anti-TB FDCs for the treatment of susceptible TB should be expanded and prioritized over single drug use.
- The use of standardized MDR-TB treatments obtains high treatment success rates even in scarce reduced settings comprising much more simple management and less cost.
- The MDR-TB knowledge of clinicians in developing countries can be improved through key and brief materials with simple and quality messages for the self training on the difficult management of drug resistance TB.

The articles comprised in this doctoral thesis provide relevant scientific information towards a better control of MDR-TB in developing countries, which was the main thesis objective.

Key words:

Tuberculosis, TB, multidrug resistant tuberculosis (MDR-TB), fixed dose combinations (FDCs), developing countries

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PRODUCCIÓN CIENTÍFICA

Los resultados obtenidos durante el proceso de investigación que ha llevado a la elaboración de esta tesis doctoral han sido publicados previamente en revistas científicas y de amplia divulgación:

1. Evidence for promoting fixed-dose combination drugs in tuberculosis treatment and control: a review. Monedero I, Caminero JA. Int J Tuberc Lung Dis. 2011 Apr;15(4):433-9
   Publicado: Abril de 2011. Factor de impacto: 2.73

2. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. Rodriguez M, Monedero I, Caminero JA, Encarnacion M, Dominguez Y, Acosta I, et al. Int J Tuberc Lung Dis. 2013 Apr;17(4):520-5.
   Publicado: Marzo de 2013. Factor de impacto: 2.73

3. Management of multidrug-resistant tuberculosis: an update. Ignacio Monedero, José A. Caminero. Ther Adv Respir Dis 2010 4: 117-127.
   Publicado: Abril de 2010. Factor de impacto de acuerdo a Scopus: 6.85

4. A basis for the clinical management of complicated MDR–TB cases. Monedero I, Holkar S. Africa Health. 2010 Sept; Vol 32 No 6: 20-25
   Publicado: Septiembre de 2010. Impacto: Revista de la Asociación Africana de Medicina bajo auspicio del Fondo Mundial

5. Tuberculosis Multidrogorresistente: una enfermedad, dos realidades diferentes. Monedero I, Caminero JA, Palomares FA, Alonso E, Mazario S. Enfermedades Emergentes. 2011; 13(2):68-73
   Publicado: Junio de 2011. Factor de impacto: 0.25

Estos 5 artículos científicos cuerpo principal de esta tesis doctoral, están reproducidos íntegramente en la sección resultados.

Producción científica adicional

De forma adicional durante el tiempo de estudios de doctorado, el doctorando ha participado en la creación de otros 7 documentos científicos, 5 de ellos publicados y otros 2 pendientes de revisión, todos ellos en relación con temática y objetivos de esta tesis. Dicho material científico se adjunta a esta tesis en forma de anexos e información complementaria.

Artículos originales

6. Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? Trébucq A, Enarson D A, Chiang C Y, Van Deun A, Harries A D, Boillot F, Detjen A, Fujiwara P I, Graham S, Monedero I, Rusen I D, Rieder H L. Int J Tuberc Lung Dis 15(12):1567–1571
   Publicado: Octubre 2011. Factor de impacto: 2.73

7. Common errors in MDR-TB management and how to avoid them. I. Monedero, JA. Caminero.
Sujeto a revisión.

8. Treatment of Patients with multidrug-resistant/extensively drug-resistant tuberculosis. Management of patients with M/XDR TB in Europe. A TBNET consensus statement. Jose A. Caminero, Kwok-Chiu Chang, I. Monedero, A. Scardigli, Wing-Wai Yew.
Sujeto a revisión.

Coautor en Guías Internacionales de TB

9. Guideline for the Clinical and Operational Management of Drug Resistant Tuberculosis. JA Caminero, A van Deun, PI. Fujiwara, I Monedero, CY Chiang, HL Rieder, D Enarson, A Harries, E Heldal, A Trebucq, E Alarcón, R Armengol, C Macé, C Perrin, RA Dlodlo, NE. Billo Paris, France: Internacional Union Against Tuberculosis and Lung Diseases.
En prensa 2013. Doctorando responsable de 3 capítulos de alta relevancia.

10. Management of Tuberculosis: A Guide to the Essentials of Good Clinical Practice. Authors: N. Aït-Khaled, E. Alarcón, R. Armengol et al. Publisher: International Union Against Tuberculosis and Lung Disease (The Union). Edition: 6th edition (English), 5th edition (Other languages)
Publicado: Febrero 2010.
Acceso desde:
http://www.theunion.org/index.php/en/resources/scientific-publications/tuberculosis

Colaboraciones en otras guías internacionales de TB y TB/VIH

11. Implementing collaborative TB-HIV activities: a programmatic guide. Fujiwara PI, Dlodlo RA, Ferrousier O, Nakanwagi-Mukwaya A, Cesari G, Boillot F. Paris, France: International Union Against Tuberculosis and Lung Diseases, 2012.
Publicado: Abril de 2012
Acceso desde:
http://www.theunion.org/index.php/en/resources/technical-publications

12. Manual on use of Routine Data Quality Audit (RDQA) tool for TB monitoring. WHO 2010.
Publicado: Junio de 2011
Acceso desde:
http://whqlibdoc.who.int/publications/2011/9789241501248_eng.pdf

ABREVIATURAS

ARV:	Antiretrovirales
DM:	Diabetes mellitus
DOTS:	Directly observed treatment short-course strategy
E o EMB:	Etambutol
FQ:	Fluoroquinolonas
FPL:	Fármacos de primera línea
FSL:	Fármacos de segunda línea
H o INH:	Isoniazida
I+D+I:	Investigación, desarrollo e innovación
La Unión:	Unión internacional contra la tuberculosis y enfermedades respiratorias
MCFs	Medicamentos combinados en dosis fijas
OMS:	Organización mundial de la salud
PSF:	Prueba de sensibilidad a fármacos
PVD:	Países en vías de desarrollo
R o RIF:	Rifampicina
SIDA:	Síndrome de inmunodeficiencia adquirida
Sm:	Estreptomicina
TARGA:	Tratamiento antirretroviral de gran actividad
TB	Tuberculosis
TB-MDR	Tuberculosis multidrogorresistente
TB-XDR	Tuberculosis extensamenterresistente
TDO	Tratamiento directamente observado
VIH	Virus de la inmunodeficiencia humana
Z	Pirazinamida

1. INTRODUCCIÓN

La Tuberculosis (TB) sigue afectando a millones de personas en todo el mundo. Se estima que cerca de 9 millones de personas enferman y aproximadamente 1.4 millones fallecen cada año (1, 2). Tratar la enfermedad cuando es sensible a fármacos de primera línea (FPL) no es clínicamente complicado en la mayoría de los casos y la curación es posible en más del 95%. Casi todos los medicamentos contra la TB de los que se dispone hoy día fueron descubiertos en las décadas de los años 50 y 60. Por otro lado, las medidas para el control comunitario de la enfermedad fueron diseñadas en los años 50 y básicamente son las mismas en la actualidad (3). Sin embargo en el año 2013, todavía estamos lejos de poder controlar esta vieja enfermedad.

Para conseguir tasas de curación adecuadas, la TB necesita un tratamiento de 6 meses, en ocasiones con tratamiento directamente observado (TDO). Por lo tanto desde un punto de vista de salud pública, requiere servicios de atención médica sólidos. Sin embargo, en los países de rentas medias y bajas, de donde procede la mayoría de pacientes, los servicios de atención médica más básicos no son universales o de una calidad aceptable. Complementariamente, la TB está fuertemente ligada a pobreza y a su vez la pobreza está fuertemente ligada a barreras en el acceso a servicios de salud (4). Igualmente, las clases más desfavorecidas, no son un grupo de presión importante que pueda influenciar en la agenda internacional o acelerar la investigación de nuevos productos farmacéuticos. Con el uso masivo de la rifampicina (RIF) a finales de los años 60, la TB fue prácticamente eliminada como un problema de salud pública en muchos países desarrollados con fuertes sistemas de salud. Consecuentemente, la investigación en TB paró. Desde entonces, no ha habido grandes inversiones ni investigación dirigida hacía la TB (5).

Por lo tanto, los medicamentos más específicos y efectivos contra la TB datan de los años 60. El tratamiento no es caro, (medicación completa cuesta 22 € de media para países de escasos recursos a través del Global Drug Facillity) y generalmente es bien tolerado. Sin embargo, es un tratamiento largo que necesita 6 meses de toma diaria de medicación y un sistema de salud capaz de apoyar al enfermo durante todo el proceso. Por otro lado, la herramienta diagnóstica más utilizada a nivel mundial, la baciloscopia de esputo, fue diseñada por Robert Koch, el mismo bacteriólogo que descubrió el bacilo causante de la dolencia en 1882. Es una prueba que desde el punto de vista técnico es sencilla de realizar e interpretar, barata, relativamente rápida y especifica. Sin embargo como prueba es muy poco sensible y apenas consigue diagnosticar al 65% de los enfermos (3). Es decir uno de cada 3 pacientes puede quedar sin diagnóstico. Esto es especialmente relevante porque las formas clínicas de TB más letales como la TB meníngea, la miliar o en el paciente severamente inmunodeprimido con frecuencia presentan baciloscopias negativas.

En el momento actual y en comparación con otras enfermedades, para luchar contra la TB apenas se cuenta con herramientas obsoletas y desfasadas (5). Teniendo en cuenta el número de muertos y afectados por la TB, la baja inversión y la ausencia de nuevos avances, sin duda la TB podría ser considerada como la enfermedad más olvidada o abandonada de nuestro tiempo (6). A pesar de constantes críticas de médicos, agentes de salud pública y ONGs han sido prácticamente 40 años de inmovilismo (6). El resultado de ausencia de innovaciones y escasez de interés político internacional, es una

enfermedad potencialmente curable que sigue acabando con la vida de millones de personas y perpetuando un círculo vicioso de pobreza y baja salud mantenida.

Afortunadamente, parece que la TB vuelve a estar otra vez en la agenda internacional y se prevén importantes cambios en los próximos 5-20 años. Este renovado interés de los países desarrollados y la industria farmacéutica por la TB, no es fortuito. Tras años de uso de las pocas medicaciones disponibles para TB, la emergencia de resistencia antibióticas está poniendo en serías dificultades el control de la TB y no solo en países en vías de desarrollo (PVD) (7). Adicionalmente, el proceso conocido como globalización y los movimientos poblacionales hace que una enfermedad de transmisión aérea como la TB suponga un riesgo para cualquier nación (8).

Además en estos últimos 30 años las dinámicas de la epidemia de TB se han visto influenciadas fuertemente por una nueva enfermedad, el Síndrome de Inmunodeficiencia Adquirida (SIDA) (9). El SIDA está alterando la progresión de la epidemia tuberculosa, cambiando las tendencias positivas de los años anteriores y creando epidemias de TB con alta letalidad (10). La presencia de virus de Inmunodeficiencia adquirida (VIH), el cual reduce la capacidad de defensa contra del cuerpo humano al ataque de otras infecciones ha actuado de forma sinérgica con la TB. La complementariedad entre ambas enfermedades se explica entre otros, porque el VIH destruye los macrófagos tisulares y los linfocitos CD4, que a su vez son las principales barreras para frenar la infección tuberculosa y también para frenar la progresión de infección latente a enfermedad. Las personas viviendo con VIH tienen más probabilidad de quedar infectadas tras un contacto y de 100 a 140 veces más probabilidad de desarrollar la enfermedad y también más probabilidad de morir por TB (3, 11, 12).

Durante los primeros años de la epidemia de VIH en los países desarrollados la sinergia entre ambas enfermedades fue puesta de manifiesto y documentada (9). Los programas de control de la TB fueron reforzados y al mismo tiempo hubo una introducción mantenida de tratamientos anti-retrovirales. Además se hicieron grandes esfuerzos en la prevención de VIH en grupos de riesgo (13). La situación fue parcialmente controlada mientras que en los países en desarrollo poca o ninguna información existía al respecto.

Tanto es así que en los países de África Subsahariana con altos niveles de infección por VIH, las tasas de TB se han multiplicado exponencialmente pasando de 100 casos por cada 100.000 habitantes a niveles de 500 o incluso 1000 casos por cada 100.000 (14). Un crecimiento de las tasas de TB que siguen en aumento y que además en casos no tratados de VIH comporta un aumento considerable de la mortalidad. De hecho la TB es actualmente la principal causa de muerte en pacientes infectados por el VIH (15). La mortalidad por TB con resistencia a fármacos en pacientes seropositivos en países africanos ha llegado a ser el 98% en unas 2 semanas tras el diagnóstico (10).

En PVD, hay otra enfermedad que puede a medio plazo condicionar seriamente las dinámicas de la epidemia por TB y es la Diabetes Mellitus (DM). Los países en vías de desarrollo están pasando por un proceso denominado transición epidemiológica. Es decir apenas han conseguido superar las enfermedades infecciosas y sus países ya presentan enfermedades no comunicables hasta ahora principalmente observados en países occidentales, como la hipertensión arterial, la obesidad y la DM. Las proyecciones y tendencias actuales de obesidad y DM son particularmente alarmantes en América Latina, Sudeste Asiático y en general los países con economías emergentes.

La DM de una forma que pudiera compararse con el VIH aumenta la susceptibilidad de los pacientes a infectarse y también a desarrollar TB (16, 17). Como factor de riesgo de TB la DM es menos potente que el VIH, sin embrago su presencia en la población es mucho más prevalente (17). Lo que podría implicar un incremento considerable de TB en la población general.

Ahora más que nunca es necesario el trabajo conjunto y fondos dirigidos hacía investigación, desarrollo e innovación (I+D+I) en TB. Sin embargo, tras todas estas décadas de retraso por mucho empeño que se ponga las medidas probablemente van a llegar tarde. La epidemia de TB sigue creciendo en países en desarrollo, las formas de TB en pacientes inmunocomprometidos (sea por VIH o DM) son más difíciles de diagnosticar y presentar peor pronóstico mientras que las resistencias a medicamentos reducen las opciones terapéuticas, complican el manejo y ensombrecen el pronóstico.

Durante los años que puede demorar la aparición de soluciones definitivas (5) se deben optimizar los actuales conocimientos y herramientas de que se disponen para aumentar el acceso a diagnóstico y tratamiento oportuno de pacientes, a la vez que reducir en la medida de lo posible la aparición de resistencias medicamentosas. Incluso con herramientas obsoletas en países de escasos recursos, hay todavía mucho por hacer. Optimizar las herramientas y conocimientos actuales, principal objetivo de esta tesis, pueden marcar una diferencia en la evolución de la epidemia de TB sensible y resistente.

La TB resistente a fármacos

El tratamiento actual promulgado por la Organización mundial (OMS) para TB sensible consta de 4 fármacos en la fase inicial de 2 meses de duración y 2 fármacos en la fase de continuación que dura 4 meses (18). Se denomina tratamiento de Categoría I e incluye los siguientes medicamentos considerados de primera línea: isoniazida (H o INH), rifampicina (R o RIF), pirazinamida (Z) y etambutol (E o EMB). De forma abreviada se escribe: 2RHZE / 4RH.

Los fármacos de primera línea (FPL), son actualmente los medicamentos más potentes, menos tóxicos y de menor coste que existen. De ellos la INH y especialmente la RIF son los más importantes. La INH es el medicamento con mayor actividad bactericida, es decir la que tiene mayor capacidad para destruir bacilos metabólicamente activos con una capacidad alta de replicación. Por lo tanto, salva la vida del paciente y clínicamente cura al enfermo. Sin embargo su capacidad para destruir bacilos metabólicamente inactivos o durmientes es muy limitada (3). Esta se denomina capacidad esterilizante y determina curaciones sin recaídas de enfermedad. La RIF desarrollada en 1963 tiene una fuerte capacidad bactericida y una inigualable capacidad esterilizante. De hecho, la RIF es el medicamento fundamental para acortar el tratamiento y conseguir curaciones sin posteriores nuevos episodios de enfermedad o recaídas (19). La duración del tratamiento se puede limitar a 6 meses debido a la potente acción esterilizante de la RIF. Aunque 6 meses pudiera parecer un tratamiento largo, es la menor duración de un tratamiento de TB de alta eficacia sin recaídas posteriores (20). La RIF ha demostrado ser una herramienta esencial en la curación de enfermos. Tanto es así que en países con fuertes sistemas de salud capaces de apoyar y supervisar al enfermo durante los 6 meses de tratamiento ha conseguido controlar la epidemia y encaminarla hacia la eliminación.

La RIF es también la piedra angular del tratamiento de la TB en el paciente coinfectado con VIH (15, 21). El tratamiento diario con RIF es un factor pronóstico fundamental para evitar muertes, fracaso de tratamiento y recaídas (21).

Sin embargo, después de décadas utilizando los FPL, se han ido seleccionando poblaciones bacilares resistentes a estos antibióticos mediante un proceso de adaptación inter-especie y presión Darviniana. Las causas de emergencia y selección de bacilos resistentes naturales se deben principalmente al uso de tratamientos inadecuados (22). La monoterapia real o encubierta entre otros medicamentos no eficaces, es uno de los principales mecanismos por los que se seleccionan cepas resistentes (22).

El uso de medicamentos en monoterapia en presencia de altas cantidades de bacilos (10^{9-10}) hace que todos los bacilos susceptibles a dicho medicamento sean destruidos pero una mímima proporción de ellos (de 100 a 1000 bacilos) sobreviven por ser mutantes resistentes naturales. Esos pocos bacilos supervivientes en los meses siguientes crecerán hasta formar ser otra vez 10^{9-10} creando enfermedad siendo todos los bacilos resistentes al medicamento dado en monoterapia. Este proceso se conoce con el nombre de "fall and rise"(23, 24) y es la base de la amplificación de resistencias o creación de resistencias secundarias al tratamiento.

El uso masivo de INH en los últimos 50 años ha acabado por generar altas tasas de resistencia inicial a INH (13% a nivel mundial) (25). Por este hecho a los tratamientos de TB iniciales actualmente se asocia EMB en la fase de inicio. Sin embargo, las altas tasas de resistencia a INH son un considerable peligro y una fuente de ampliación de resistencias. En el actual esquema de categoría I la fase continuación se realiza solo con INH y RIF. Por lo tanto, si hay resistencia inicial a INH de forma efectiva solo estamos tratando con RIF en monoterapia. Si la carga bacilar es alta o las tomas son inadecuadas existe un riesgo importante de desarrollar resistencia a RIF. Cuando surge resistencia a los dos medicamentos más potentes a la vez (RIF e INH), esta situación se define como multidrogorresistencia (MDR) (26). Sin la capacidad esterilizante de la RIF, actualmente la duración del tratamiento de la TB pasa de 6 a18 y 24 meses con medicamentos más caros, más tóxicos, menos eficaces (22). El manejo de la TB pasa a ser mucho complejo, tanto que grupos como Médicos sin Fronteras lo han dado en comparar con los tratamientos quimioterapeúticos contra el cáncer. La TB-MDR está poniendo en peligro el control de la TB países en desarrollo ya que las cifras de pacientes son mucho mayores que las inicialmente pensadas (27). Se estima que para el año 2011 el número de pacientes con TB-MDR ascendencia a 650.000 (1). Desde un punto de vista epidemiológico, estos pacientes al no haber fallecido pero tampoco estar curados contribuyen a una expansión primaria de la epidemia resistente en la comunidad ya que los bacilos que expelen son resistentes.

A pesar de los vastos beneficios de la estrategia DOTS (del ingles Directly Observed Treatment Short-course Strategy), introducida a nivel mundial por la OMS en 1992, la preocupación por una TB de difícil curación no ha parado de crecer desde años 90 (28). Los tratamientos irregulares o de escasa calidad y otras circunstancias (vea *Tabla n.1*) han convertido un problema de pacientes concretos en una preocupación de salud pública mundial (6). Esta situación es particularmente alarmante en las repúblicas de la antigua Union Soviética (29). A pesar de los progresos en el control de la TB-MDR (30) y del desarrollo de políticas internacionales para tratar la enfermedad, han aparecido formas con patrones de resistencias aún más severas como la TB extensamente

resistente (TB-XDR) (9, 10, 31, 32) y la TB totalmente resistente (33). TB-MDR más resistencia a alguna fluoroquinolona (FQ) y al menos a un inyectables de segunda línea, es la actual definición de TB-XDR (7). En estos casos, los pacientes tienen bacilos resistentes a los fármacos más potentes tanto de primera, como de segunda línea. Obviamente los pacientes con TB-XDR tienen menos opciones terapéuticas y también un pronóstico peor (32).

Tabla 1: Causas frecuentes asociadas a la selección de resistencias en la comunidad (5, 34):

1. Mala implementación de la estrategia DOTS:
Mala adherencia y supervisión del tratamiento
Tratamientos no estandarizados
Historia frecuente de falta de suministros de medicación en el país
2. Mala calidad de los medicamentos anti-tuberculosos
3. Tratamiento de la TB principalmente en el sector privado
4. Deficientes condiciones de control de infección hospitalaria
5. Alta prevalencia de cepas de *M.* TB de alta virulencia
6. Virus de inmunodeficiencia humana en algunas áreas concretas

El peligro de las epidemias de TB resistente entre pacientes VIH positivos saltó a la agenda internacional en el año 2006 aunque ya se habían documentado numerosos casos de epidemias en todo el mundo (35-37). En aquel año se publicó en la revista semanal del Centro para el control de enfermedades de Atlanta (CDC) la aparición de la TB-XDR (38) y poco después, se publicó un brote epidémico intrahospitalario de TB-XDR con una alta letalidad en Sudáfrica (10). La mortalidad fue del 98% en menos de 4 semanas tras el diagnóstico. Los estudios genotípicos revelaron que las cepas eran prácticamente las mismas, demostrando un patrón de transmisión persona a persona probablemente dentro de un centro sanitario. Parece que los colectivos de enfermos de VIH y también la industria farmacéutica empieza a considerar que todos los éxitos alcanzados con los tratamientos anti-retrovirales (ART) podrían convertirse en nada por culpa de una TB intratable. Es necesario una aceleración en I+D+I antes de que la emergencia de resistencias hagan el manejo aún más difícil y económicamente inaccesible especialmente en países pobres.

Factores de riesgo para la TB resistente

Hasta la fecha, el factor de riesgo mejor documentado para resistencia es haber sido tratado previamente contra la TB (26, 29, 34, 39-41). En algunas áreas geográficas, el sector privado al trabajar fuera de los programas, sin realizar TDO y sin seguir los estándares internacionales puede estar jugando un papel deletéreo (42, 43).

En cuanto a las resistencias primarias, es decir enfermos que primariamente se infectaron con cepas resistentes, parece estar aumentando. De hecho, ser contacto próximo de un paciente con enfermedad resistente es un también un importante factor de riesgo (44, 45). Existen numerosas referencias a casos en niños y convivientes en la misma casa (46).

A un nivel de datos agregados o individuales, actualmente la infección por VIH en si mismo no se considera un factor de riesgo (26, 39, 47) . Contrariamente y teniendo en cuenta datos más recientes pero limitados, sí podría ser considerado un factor de riesgo (29) no por el virus en sí, sino por factores ambientales como la transmisión aérea en lugares con grandes concentraciones de personas (salas de espera, hospitales...). El VIH está implicado en gran número de epidemias nosocomiales de TB y TB resistente. Según algunas experiencias limitadas, la malabsorción medicamentosa en pacientes con SIDA avanzado puede condicionar un alto número de fracasos terapéuticos y amplificación de resistencia (48). Los países con alta carga de VIH tienen por tanto, un mayor riesgo tanto de TB sensible como de TB resistente, todo ello en un contexto de coinfección donde es más difícil de diagnosticar y el tratamiento ofrece peores resultados.

Desde otro punto de vista, más social y menos clínico existen múltiples razones para la emergencia de resistencias a nivel internacional, especialmente asociadas a pobreza: falta de acceso a servicios básicos de atención primaria, programas nacionales de TB subóptimos, rupturas de stock de medicamentos, tratamientos inadecuados, uso irracional de medicamentos, amplia monorresistencia a INH, falta de investigación en nuevos medicamentos y pruebas diagnósticas, etc (26, 34, 49).

Diagnóstico de la TB-MDR

Como ya se ha comentado, la TB-MDR se define como TB con resistencia a INH y RIF. Es por tanto un diagnóstico bacteriológico. Desde un punto de vista, clínico, radiográfico o mediante baciloscopia de esputo la TB y la TB resistente a fármacos son indistinguibles. A pesar de que los anteriores factores de riesgo puedan orientar el diagnóstico (50), este solo es de certeza realizando un antibiograma o prueba de sensibilidad a fármacos (PSF). Consecuentemente, para diagnosticar un paciente de TB-MDR es necesario la toma de una muestra biológica (preferentemente esputo) cultivarlo y una vez cultivado exponer distintas muestras a diferentes antibióticos e incluso a distintas concentraciones. Si el germen crece sería una cepa resistente a dicho medicamento.

Mycobacterium tuberculosis es un bacilo de crecimiento lento que necesita de 15 a 40 días para crear colonias en medio sólido de Lowenstein-Jensen y de 5 a 20 días en medios líquidos. Este crecimiento lento condiciona una alta demora en los resultados que limita el uso de rutina de los cultivos (3). Realizar la prueba de sensibilidad a medicamentos puede doblar en el tiempo de duración en la obtención de resultados. Por tanto el tiempo en laboratorio para obtener resultado puede ser entre uno y tres meses. Posteriormente, hay que hacer llegar los resultados a los médicos y pacientes proceso que según los sistemas y burocracia del país puede ser inmediato en lugares trabajando con intranets que comuniquen laboratorio y hospitales o puede ser de 6 meses si funcionan con sistemas de cartas en papel con puesto intermedios. En el caso de la India, de donde proceden gran parte de los pacientes con TB-MDR del mundo, de media se puede tardar 5 meses en el diagnóstico y otros 3 más para iniciar el tratamiento tras la confirmación de las resistencias, total 8 meses (51). Es una demora inaceptable desde el punto de vista clínico para el tratamiento de una enfermedad mortal y con importantes

secuelas en caso de diagnóstico tardío. Por otro lado, el actual gold estándar para el diagnóstico de resistencias que es el método de las proporciones de Cannetti tiene más de 50 años y presenta importantes limitaciones técnicas que reducen su fiabilidad (52, 53). La fiabilidad de estas pruebas es mayor para RIF e INH. Fiabilidad y reproducibilidad es mediana para FQs e inyectables pero muy escasa para el resto de medicamentos presentando alto número de falsos positivos y falsos negativos (53, 54).

Tabla 2. Limitantes de las pruebas de sensibilidad a fármacos anti-TB (22, 53-55):

DEL INÓCULO	El *tamaño* del inoculo se correlaciona con la carga bacilar cultivada pudiendo modificar los resultados Una buena *dispersión del inoculo* por el medio, es necesaria para que todas las colonias tengan contacto con el fármaco *Viabilidad* de los bacilos dependiente de: retraso en envío de muestra o excesiva decontaminación *Representatividad* de la muestra respecto a la población de bacilos que presenta el enfermo. Bacilos con grandes patrones de resistencias tienen un comportamiento de *pobres crecedores.* Pueden tardar más de 5 semanas en crecer en cultivo
DEL MEDIO DE CULTIVO Y CAPACIDAD DEL LABORATORIO	Medio de Lowenstein-Jensen *no estándar* y con frecuencia elaborado en laboratorio. El uso de huevos sin trazas de antibióticos puede ser difícil *Tiempo de incubación* prolongado Suministro constante de energía eléctrica durante40 días Tasas de contaminación excesivamente altas o excesivamente bajas según procedimientos
APLICACIÓN DE LA MEDICACIÓN	*Disolución* del medicamento Falta de *concentración crítica* estándar para asumir un umbral de resistencia *Almacenaje y calidad* de la medicación
EFICACIA DE LA MEDICACIÓN	*Mala correlación in vivo – in vitro*. Malos valores predictivos Dependiente de la *vida media* del medicamento Diferentes de Falso positivos y negativos en función de la *eficacia de la medicación.* Resultados más fiables para las medicaciones más efectivas: Isoniazida y Rifampicina

En conclusión, las PSF como test diagnóstico presentan un importante retraso, no tienen una buena correlación clínica excepto para RIF e INH, son caras y precisan de laboratorios de alta calidad y seguridad de los cuales tal vez carecen o son deficitarios en gran número de países en desarrollo. Consecuentemente no se diagnóstica a la mayoría de enfermos con TB- MDR y de los diagnosticados muchos mueren esperando resultado o ya padecen enfermedad avanzada o no hay acceso a medicamentos (27, 51). Actualmente la OMS limita la recomendación de PSF a RIF e INH. En un segundo paso si el país lo considera oportuno se amplia a EMB, Estreptomicina (Sm), otros inyectables de segunda línea y FQs (56). No se recomienda su uso para otros medicamentos anti-TB.

Según lo mencionado anteriormente las resistencias emergen por la selección de bacilos que de una forma natural presentan mutaciones espontáneas que les confieren resistencias a determinados medicamentos. Por tanto mediante la identificación de estas mutaciones que determinan resistencia fenotípica se podrían utilizar para el diagnóstico de resistencias medicamentosas. Está es la tecnología por la cual se llevan diagnosticando las resistencias del VIH desde hace más de 15 años. Sin embargo la aplicación en TB apenas está empezando (57-61). Con toda la falta de I+D+I en el campo de la TB de las últimas décadas, hay un importante desconocimiento en cuanto a las mutaciones que confieren resistencia a los medicamentos anti-TB. Sin duda es un campo de trabajo donde se esperan cambios en un futuro cercano. Afortunadamente las principales mutaciones que confieren resistencia a los principales medicamentos como INH, RIF y las FQ son conocidas, (ver *Tabla 3*). Aunque es escaso el conocimiento del papel que juegan las mutaciones de alto y bajo grado y se desconocen las mutaciones y mecanismos que confieren resistencias al resto de medicamentos anti-TB.

Tabla 3. Bases moleculares de la resistencia medicamentosa en *Mycobacterium tuberculosis (57):*

MEDICAMENTO	GEN	FUNCIÓN	PREVALENCIA (%)
Isoniazida	kat G	Catalasa-Peroxidasa	40-60
	inh A	enoil-ACP reductasa	25
	ahp C	Alfil-hidroperoxidasa reductasa	10
	kas A	Sintetasa de la proteina carrier cetoacil-acil	
Rifampicina	rpo B	Subunidad ß de la ARN polimerasa	95
Pirazinamida	pnc A	Pirazinamidasa	95
Etambutol	emb CAB	Arabinosil transferasa	60
Estreptomicina	rps L	Proteina ribosomal S12	60
	rrs	ARNr 16S	20
Fluoroquinolonas	gyr A, gyr B	ADN girasa	80-90
Amikacina/Kanamicina	rrs	ARNr 16S	70-90
Capreomicina	rrs	ARNr 16S	90
	tly A	ARNr metiltransferasa	

Si el laboratorio que hace pruebas fenotípicas clásicas no trabaja sobre altos estándares de calidad, posiblemente las nuevas pruebas genotípicas sean más sensibles y específicas especialmente para RIF (62). Los nuevos test genotípicos para detección de resistencias además de tener un grado alto de fiabilidad son rápidos. Tanto es así que pueden aportar resultados entre 2 horas y 2 días. Globalmente al necesitar menos tiempo y personal pueden ser más baratos que las PSF tradicionales (60).

Las pruebas genotípicas actualmente en mayor uso son el *Genexpert* y el *Genotype*. El Genexpert es un test que realiza una detección de ADN de Mycobacterium tuberculosis complex mediante una PCR a tiempo real. Demora solo 2 horas en dar resultados. Se realiza directamente desde esputo y tiene una sensibilidad diagnóstica cercana al cultivo incluso en pruebas con baciloscopia negativa (63). Es capaz de diferenciar tuberculosis de Mycobacterias atípicas y testar resistencia a rifampicina mediante detección de mutaciones en el gen rpo B. La principal ventaja que presenta es su fácil uso, muy reducido riesgo de contagio para los trabajadores y sus escasos requerimientos (electricidad constante y temperaturas menores de 25ºC). Las limitaciones principales para su implantación en países en desarrollo es su coste y re-calibración anual (64).

El Genotype MDR-TB line probe assay es también una PCR pero necesita un laboratorio de biología molecular, personal altamente especializado y demora aproximadamente 2 días en ofrecer resultados. En cambio aporta información en cuanto a resistencias a INH (detección de mutaciones en kat G y en inh A) y RIF (rpo B) e identifica más de 40 mycobacterias atípicas (58). Sus nuevas versiones aportan información sobre resistencias a EMB, kanamicina y ofloxacina.

Manejo de la TB-MDR

En el manejo de la TB-MDR no existen fuertes evidencias científicas ya que la gran mayoría de pacientes tratados durante las décadas de los ‘60, ‘70, ‘80 y ‘90, lo fueron de forma individual en los centros de referencia de los países desarrollados. Por tanto, los datos científicos son limitados. El manejo de estos pacientes suele estar basado en la opinión de expertos, que con frecuencia muestran desacuerdo y controversia (30). Existen muy pocos ensayos clínicos aleatorizados posteriores que evalúen los distintos esquemas de tratamiento. De hecho, además de la mencionada falta de interés por la comunidad científica e industria farmacéutica, el tratamiento prolongado de la MDR y la necesidad de evaluar las recaídas un año tras el tratamiento hacen los estudios en TB-MDR largos y costosos (5). El marco básico sobre el que establecer el tratamiento estandarizado de la TB-MDR son un éxito reciente (65) (22) y la eficacia de los mismos sigue en entredicho por gran parte de los clínicos.

En países desarrollados para tratar a estos escasos pacientes con resistencias se utilizaron fármacos también desarrollados en los años ‘50 y ‘60 antes del descubrimiento de la RIF. De hecho con excepción de las FQs, no han aparecido nuevos fármacos contra la TB que pudieran ser utilizados en casos de resistencias. En países en vías de desarrollo estos enfermos eran denominados pacientes crónicos o directamente casos incurables.

A largo de las décadas, el mal uso de las FPL, la inexistencia de medicación para TB-MDR o los tratamientos ineficientes para ésta han ampliado el patrón de resistencias aún más. Añadido a la transmisión de cepas resistentes en la comunidad, se ha creado una situación preocupante de alta prevalencia de casos resistentes en países en desarrollo. En estos países no solo la capacidad diagnóstica es reducida, también existe un escaso número de médicos formados para el manejo de la TB resistentes. Además los sistemas de salud son insuficientes para la retención y el TDO de pacientes en los 20 a 24 meses que duran los regimenes propuestos por la OMS (5, 66). Actualmente en

Bangladesh y ciertos países de África se está llevando a cabo tratamiento para pacientes con TB-MDR de una duración de 9 a 12 meses con tasas de curación superiores al 85% (67). La Unión Internacional contra la TB y Enfermedades Respiratorias está llevando a cabo un ensayo clínico con estos regímenes acortados pero los resultados no serán definitivos hasta el año 2017.

Por otro lado, los fármacos de segunda línea (FSL) de los que se dispone son menos eficaces, más tóxicos, peor tolerados y mucho más caros (22). Estos medicamentos se clasifican en 5 grupos principales (ver *Tabla* 4) (22).

Tabla 4. Clasificación de OMS de medicamentos con actividad frente a la TB (5, 22, 30, 55):

GRUPO	MEDICAMENTOS
Grupo 1: Medicamentos orales de primera línea	isoniazida (H); rifampicina (R); etambutol (E); pirazinamida (Z)
Grupo 2: Medicamentos inyectables	kanamicina (Km); amikacina (Am); capreomicina (Cm); estreptomicina (Sm)
Grupo 3: Fluoroquinolonas	ofloxacina (Ofx) moxifloxacina (Mfx); levofloxacina (Lfx); gatifloxacina (Gtx)
Grupo 4: Bacteriostáticos orales	etionamida (Eto); protionamida (Pto); cicloserina (Cs); terizidona (Trd); ácido para-aminosalicílico (PAS)
Grupo 5: Medicamentos poco eficaces o con escasa evidencias	clofazimina (Cfz); amoxicilina/clavulánico (Amx/Clv); linezolid (Lzd); imipenem/cilastatin (Ipm/Cln); altas dosis de isoniacida (>H); tioacetazona (Thz); claritromicina (Clr)
Medicamentos a estudio (fase III), actualmente solo uso compasivo	bedaquilina, delamanid

La base del tratamiento de la TB-MDR es crear esquemas con los siguientes medicamentos más activos tras los de primera línea. Estos son en primer lugar las quinolonas de tercera y cuarta generación y después los inyectables de segunda línea. Quinolonas e inyectables son la base del tratamiento. Posteriormente hay que añadir más medicamentos potencialmente activos para proteger a los medicamentos anteriores de la selección de resistencias (19). Finalmente los esquemas contarán con al menos 4 medicamentos efectivos. Ver más información sobre buenas prácticas en manejo de TB-MDR en la T*abla* 5.

Bajo esquemas inadecuados o con deficiente adherencia a la medicación, existe la posibilidad de ampliar los patrones de resistencia. Por eso cuando las cepas de bacilos se hacen resistentes a quinolonas e inyectables, medicamentos que son la base del tratamiento de la TB-MDR, el pronóstico se ensombrece y pasa a denominarse TB-XDR. A finales de 2011, 77 países habían reportado casos de TB- XDR (68). Pero la existencia de casos TB-XDR permanece siendo una incógnita en más de 100 países debido a la poca capacidad de sus laboratorios. Por lo tanto, las estimaciones tienen un considerable grado de incertidumbre y muy probablemente están infraestimados (40).

Para el manejo de la TB-XDR es necesario realizar esquemas individualizados, que a su vez son aún más caros y por lo tanto con menor acceso a tratamiento en países de escasa renta (5). Sin duda es necesario para un futuro próximo contar con nuevos medicamentos y mejores y más sencillos regímenes contra la TB.

Tabla 5. Resumen de buenas prácticas actuales en el manejo de TB-MDR (55)

PASOS	CONSIDERACIONES
1. Diagnóstico	Tener en cuenta • Historia de drogas: un mes de monoterapia es el indicador de resistencia más importante • PSF: Más fiable para RIF e INH; bastante fiable para Km y FQ; Menos fiable para E y Z; muy poco fiable para drogas del grupo 4 y 5. No recomendado). • Realizar test de VIH. Si es positivo iniciar cuanto antes co-trimoxazol y ART
2. Número de medicamentos	Al menos 4 medicamentos efectivos: nunca usados en el pasado o con susceptibilidad demostrada por PSF, teniendo en cuenta fiabilidad de la PSF y resistencias cruzadas
3. Selección de medicamentos	• Usar medicamentos de primera línea si todavía son efectivos • Una quinolona de tercera o cuarta generación (considerar doble dosis) • Un inyectable de segunda línea • Usar medicamentos del grupo 4 hasta completar las 4 drogas efectivas • Si es necesario usar medicamentos del grupo 5 para reforzar el esquema o cuando no se llega al número de 4 drogas efectivas. Actualmente se considera que cada 2 medicamentos del grupo 5 cuentan como 1 medicamento efectivo.
4. Duración del inyectable	• Al menos 4 meses tras la conversión del esputo o cultivo • Aún mayor duración si no hay 3 medicamentos efectivos en la fase continuación o son del grupo 5 o hay sospechas de resistencias a FQ
5. Cirugía	Considerar solo si se cumplen todas las siguientes condiciones • Se disponen de muy pocas drogas efectivas • Lesiones localizadas • Reserva respiratoria suficiente tras la resección
6.Régimen ideal	• *Estandardizado*: si no hay uso de medicamentos de segunda línea en el pasado • *Individualizado*: si hay uso de medicamentos de segunda línea en el pasado o contacto con un paciente MDR que los ha usado (tratar con el régimen que fue efectivo en el caso índice).

ART: tratamiento antirretroviral; PSF: prueba de sensibilidad a fármacos; E: Etambutol; FQ: fluoroquinolonas; H: isoniacida; Km: kanamicina; R: rifampicina; Z: pirazinamida

Perspectivas en la TB con resistencias

Ante la ausencia de nuevos medicamentos, vacunas y pruebas diagnósticas, la TB-MDR/XDR es una preocupación real de salud pública global (69). Los modelos matemáticos indican además que existe un riesgo real de un cambio desde cepas

susceptibles hacia resistentes (70). Dada la baja capacidad actual para diagnosticar y las reducidas tasas de curación de los casos TB-MDR, de acuerdo a otros modelos, cuanto más MDR se diagnostique, más XDR se crea (71). Se predice un incremento exponencial a nivel internacional de la TB-XDR como resultado sinérgico de la interacción entre la resistencia adquirida por un mal uso de medicamentos de segunda línea más las resistencia transmitidas por vía aérea (71-73). Sin medidas de calidad, las epidemias la TB-MDR y XDR puede llegar a ser incontrolable (71).

Este problema se podría solventar con un incremento sustancial de la monitorización y evaluación y creación de capacidades locales. Sin embargo podría contribuir a otro riesgo mayor: el desvío de recursos (humanos y económicos) desde los programas de TB sensible a los de TB resistente. Si la implementación de un programa de MDR viene acompañado tan solo de un descenso del 5% en la efectividad de programa de TB sensible, el número de muertos totales se incrementaría considerablemente más que si solo se implementara DOTS y se crearían más casos de TB-MDR como consecuencia del fracaso del DOTS (73). De hecho, el éxito de abogacía y financiación sobre los programas de TB-MDR ha forzado a algunos gobiernos a iniciar de forma prematura programas de TB-MDR sin tener previamente programas DOTS de calidad (74). La falta de experiencia y conocimientos en el manejo de la TB-MDR en países en desarrollo es un serio problema. Un enfoque limitado en el tratamiento de la TB-MDR, sin garantizar su calidad o altas tasas de curación puede paradójicamente convertir una mala situación en una aún peor (74, 75).

2. JUSTIFICACIÓN

Para cortar la cadena epidemiológica de la TB-MDR la primera medida a tomar sería lograr altas de tasas de diagnóstico de TB sensible y después alcanzar altas tasas de curación que eviten la transmisión pero además no generan resistencias a los medicamentos utilizados (18, 76).

Una vez creadas las resistencias por tratamientos no efectivos (resistencias secundarias) la TB-MDR se puede transmitir por vía aérea. Por tanto el diagnóstico precoz es necesario en la comunidad y tratar aquellos casos de forma eficaz para evitar transmisión y aún mayor amplificación de resistencias (5, 77). De una forma general áreas potenciales para reducir la epidemia de TB-MDR se podrían resumir en estos 3 grandes campos.

Campos de actuación contra la epidemia de TB-MDR

A. TRABAJAR SOBRE CONDICIONANTES DE LA EPIDEMIA DE TB
1. *Medidas sociales y económicas.* Históricamente el mayor declive en la epidemia mundial de TB sucedió en Europa tras la revolución industrial de la mano de los cambios en los estándares de vida, mejora de la alimentación y condiciones higiénico-sanitarias tanto en grandes ciudades como en áreas rurales (4). De hecho pobreza, malnutrición y exclusión social son los mayores condicionantes de la epidemia de TB (3) y tan solo actuando en este punto se podría limitar la epidemia de TB con o sin resistencias e incluso encaminarla por si sola hacia la eliminación (ver *figura* 1).

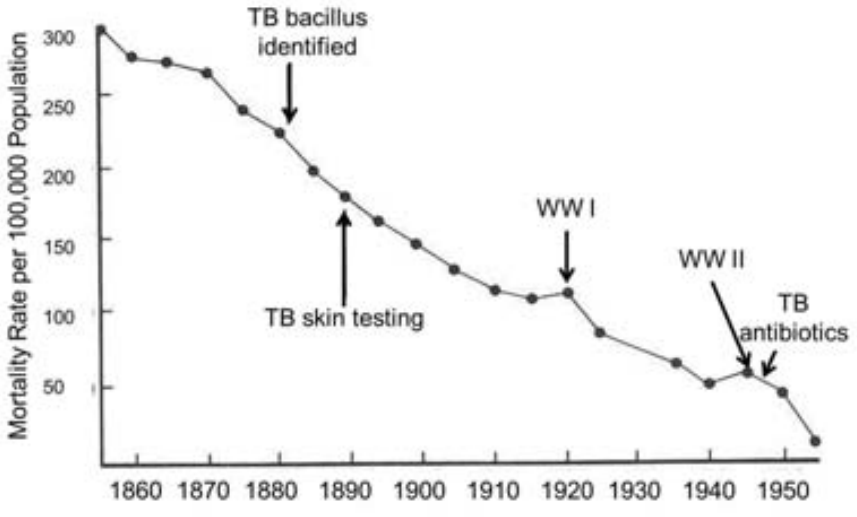

Figura 1. Descenso en la mortallidad por TB en Inglaterra y Gales entre los años 1850 y 1960 (78)

2. Medidas sobre otras enfermedades que condicionan la epidemia de TB. Clásicamente la silicosis estaba fuertemente implicada en la TB (3). Sin embargo en el momento actual las enfermedades que reducen la capacidad del sistema inmune están influenciando aún con más fuerza la epidemia de TB. Como se comentó previamente la

falta de control y tratamiento de la epidemia de VIH en países de África Sub-sahariana ha creado un incremento de las tasa de TB sin precedentes en la historia (9). En estos países con altas cifras de VIH, el control de la TB con medidas exclusivas centradas en la TB sin tener en cuenta el control del VIH, es insuficiente. La DM en plena tendencia alcista en países en vías de desarrollo posiblemente en un futuro cercano puede traer de la mano un incremento sustancial de las tasas de TB (17). Tanto VIH como DM y falta de acceso a su tratamiento están fuertemente asociados con los factores anteriores de pobreza y exclusión social presentes en los pacientes con TB-MDR (6, 50).

B. OPTIMIZACIÓN DE HERRAMIENTAS Y CONOCIMIENTOS ACTUALES

Los conocimientos, estrategias y medicamentos actuales si fueran optimizados se lograrían mejores resultados de los actualmente obtenidos tanto en prevención de casos con TB-MDR como en la curación una vez aparecidos (5, 79). Algunas de las principales medidas necesarias de optimización son (5):

1. Fortalecer la estrategia DOTS. La estrategia DOTS ha sido y sigue siendo uno de los pilares básicos para el control de la epidemia de TB (18). Por si solo ha sido insuficiente para controlar las resistencias pero también es cierto que su implementación no ha sido adecuada, precisamente en los países donde más resistencias existen. Ahora más que nunca es necesario un DOTS de calidad para encarar los nuevos retos que presenta la epidemia de TB como la prevención de casos de TB-MDR (34).

2. Uso global de los Medicamentos Combinados en dosis Fijas *(MCFs).* Los MCFs tienen ventajas clave a nivel logístico y práctico (ver *tabla 6*) y probablemente la capacidad para evitar la monoterapia (80). Basado en un análisis de no inferioridad se ha demostrado que los medicamentos sueltos y combinados en una sola pastilla, obtienen similares resultados (81). Añadido a un menor precio, facilidad de toma y cumplimiento de esquemas estándar, facilidad de cálculo de dosis, se puede especular que si los MCFs se usaran a gran escala y especialmente en países con escasos recursos y mala supervisión de la toma de tratamiento, los esquemas terapéuticos serían más curativos a la vez que una proporción sustancial de resistencias podrían ser evitadas (5). Sin embargo los MCFs siguen sin ser utilizados ampliamente a nivel internacional (82, 83).

Tabla 6. Ventajas operativas de los medicamentos combinados en dosis fijas (84) (80):

1. Prevención de monoterapias y selección de resistencias
2. Prevención de errores en el cálculo de dosis
3. Simplificación y estandarización de los regimenes de quimioterapia
4. Facilita la educación del paciente y cumplimiento de tratamiento
5. Mejora la aceptación por pacientes y trabajadores de salud
6. Prevención de escasez y ruptura de stock de medicaciones individuales
7. Mejora el manejo de medicamentos, pedidos, envíos y suministro
8. Facilitan la planificación y gestión de medicamentos.

3. Involucrar a todos los proveedores de salud en el tratamiento de la TB, especialmente neumólogos y médicos del sector privado. Por si solos los programas nacionales no tienen capacidad en muchos países para atajar la complejidad de la TB por lo tanto el sector privado es importante para el control de la TB (85). Pero a su vez

el sector privado a menudo trabajando fuera de las normativas, sin hacer TDO y con una formación muy heterogénea podría estar jugando un papel importante en la creación de TB-MDR (86). El uso de MCFs bajo protocolos adecuados y con sistema de referencia efectivos, junto con la creación de capacidades puede traer consigo importantes beneficios en la curación de pacientes y en la reducción de resistencias (5).

4. Aumentar la formación en TB-MDR de los clínicos en países en vías de desarrollo. El manejo de la TB-MDR actualmente es complejo y la formación de especialistas que puedan hacerse cargo de estos pacientes es a menudo cara y reducida. Sin embargo la carga de enfermedad es tal en países en vías de desarrollo que la gran mayoría de enfermos MDR son llevados por personal con poca experiencia en el uso de medicaciones de segunda línea y muy poca formación (87). Clínicos de todo el mundo tienden a actuar en base a su propia experiencia, en muchos casos cometiendo importantes errores clínicos y programáticos que se transfieren de unos a otros. La capacidad de autoformación es limitada y los materiales didácticos sencillos prácticamente no existen (5). En general los documentos y líneas guías que existen son demasiado amplios (22) y por tanto se usan poco especialmente si los clínicos tienen una gran presión asistencial.

5. Facilitar y estandarizar el manejo de la TB-MDR tanto a nivel clínico como programático. Los tratamientos de TB-MDR duran de 18 a 24 meses y se suelen usar 4 o más fármacos con importantes efectos adversos (22). Hoy por hoy los tratamientos individualizados son el estándar de países desarrollados con fuertes sistemas de salud. Las escasas evidencias existentes son principalmente en tratamientos individualizados (88, 89) a pesar de que la mayoría de enfermos son tratados en países pobres con acceso reducido a las necesidades de diagnóstico y medicación que exigen los individualizados. No hay grandes evidencias en la literatura de la efectividad de tratamientos estandarizados con medicamentos de segunda línea.

6. Nuevos regimenes de tratamiento con medicaciones actuales. Tanto la TB sensible como la TB resistente podrían beneficiarse de las medicaciones actuales si se consiguieran esquemas de similar efectividad pero siendo más cortos. Así se podrían reducir el número de abandonos y efectos adversos (67). Si a su vez el acortamiento del tiempo de tratamiento trae consigo un menor coste tanto en medicación como en uso de los servicios de salud, permitiría una atención de mayor calidad y un aumento de los pacientes que podrían entrar en tratamiento y por tanto curar.

C. INNOVACIONES

1. Nuevos medicamentos. Existen varios fármacos prometedores en investigación con mecanismos de acción innovadores (90, 91) que podrían transformar el futuro de la MDR. Actualmente en 2013 los medicamentos bedaquilina (92) y delamanid (93) han demostrado una potente actividad frente a poblaciones metabólicamente activas y durmientes, están en fase III y se están empezando a utilizar en lugares concretos como medicación compasiva (93). También las nuevas Rifamicinas como el rifalazil (KRM-1648) han demostrado buenos resultados preliminares. Otros compuestos como el SQ109 y los Nitrofuranylamidas han demostrado actividad in vitro (94). Sin embargo es muy improbable que estas y otras moléculas estén preparadas para su uso masivo y a precio accesible para países de bajos recursos en menos de 10 o 15 años (5).

2. Vacunas y otras líneas por descubrir. Se están realizando esfuerzos significativos en busca de una vacuna contra la TB, que podría ser la mejor herramienta para la lucha contra la enfermedad. Sin embargo los recursos empleados en las mismas son escasos y poniéndonos en el mejor escenario, es altamente improbable que una vacuna esté ampliamente disponible en menos de 10 o 20 años (95).

Justificación del estudio

Generar resistencias y crear un paciente con TB-MDR puede llevar apenas 4-6 meses de malas prácticas terapéuticas. Curar a un paciente con TB-MDR puede llevar de 18 a 24 meses.

Tanto la pobreza como la exclusión social y las medidas alimentarías e higiénico-sanitarias producidas en Europa tras la revolución industrial están lejos de poder cumplirse a corto o medio plazo en países en desarrollo (4). Tanto el VIH como la DM están aumentando en países pobres y su control necesitará grandes esfuerzos a lo largo de las décadas venideras (17, 96). Los nuevos fármacos y vacunas, pueden tardar años en aparecer y décadas en salir al mercado y de momento no está muy claro si serán completamente accesibles para países de escasos recursos (95). Los resultados del *STREAM trial* de la Unión con esquemas para TB-MDR de 9 meses aparecerán en torno a 2017.

Por todo ello en un futuro a corto/medio plazo no va a aparecer una única solución que controle la TB MDR/XDR (97). Teniendo en cuenta los retrasos en nuevas soluciones contra la TB, probablemente uno de las mejores actitudes para frenar el avance de la TB-MDR sea optimizar el manejo de la TB con las herramientas que contamos actualmente. Simplificar y expandir al máximo los conocimientos que poseemos es fundamental. Mediante la introducción de medidas sencillas, baratas y de bajo riesgo se podría reducir el daño previniendo la emergencia de resistencia y una vez aparecidas haciendo más sencillo su manejo para mejorar los resultados actuales (5, 30).

Podrían ser medidas con impacto en vidas salvadas si se reduce la creación de resistencias y si se incrementa el acceso de pacientes a un tratamiento de calidad. Estas medidas deben tener una base científica sólida y deben ser difundidas a clínicos y tomadores de decisiones. Esta tesis, sus recursos y personal no permiten trabajar en los puntos A y C pero si puede aportar nuevos conocimientos que apoyen medidas efectivas en la optimización de las actuales herramientas (punto B) mientras soluciones más definitivas como las comentadas aparecen en los próximos 5 a 20 años.

3. OBJETIVOS

El *objetivo general* de esta tesis doctoral es profundizar en el tema de la TB-MDR en países en desarrollo y aportar a la comunidad científica y clínica, nuevos conocimientos que colaboren en el objetivo común de prevenir la generalización de la epidemia y tratar con mejores resultados a los enfermos en PVD.

Para llegar a este objetivo general esta tesis doctoral trabajará en la búsqueda de dos objetivos específicos:

- *Objetivo especifico 1*: Desarrollo o promoción de estrategias para mejorar el control de la TB sensible y por tanto prevención de la TB resistente.

- *Objetivo específico 2:* Aportar herramientas o evidencias científicas que con una similar eficacia ayuden a la simplificación del manejo de la TB-MDR y por tanto hagan su tratamiento más accesible a un mayor número de enfermos en PVD.

4. HIPÓTESIS

Como se ha comentado en la introducción las soluciones que podrían ser definitivas para la TB llevaran años en poder implementarse en PVD mientras que las herramientas actuales no obtienen resultados óptimos. Si las herramientas actuales no obtienen resultados óptimos en PVD es por la existencia de barreras o problemas de acceso tanto a los principales conocimientos científicos en las que podrían basarse mejores políticas sanitarias como acceso a diagnóstico y medicación especifica. Durante el planteamiento de esta tesis mediante la experiencia clínica y de salud pública de los directores de tesis y la experiencia de cooperante en terreno del doctorando se han identificado algunas de esas barreras. Los estudios que surgen de este trabajo pretenden aportar soluciones concretas a esos problemas o barreras para llegar a un mejor control de la TB-MDR en PVD.

Las ***barreras identificadas*** en las que se van a basar las hipótesis de trabajo para alcanzar los objetivos propuestos son:

> *Barrera 1.* Los medicamentos combinados en dosis fijas (MCFs) facilitan la toma, cumplimiento y abastecimiento de medicación anti-TB (80, 84) . Sin embargo en muchos PVD los MCFs no se introducen en los programas nacionales de TB argumentando falta de evidencias científicas en cuanto a su eficacia (98) (82).
>
> *Barrera 2.* El manejo de la TB-MDR se basa en esquemas de tratamiento complicados (22). Hay escasas evidencias respecto al manejo estandarizado más económico y sencillo de estos enfermos y que por tanto podría ser más accesible y sostenible en PVD.
>
> *Barrera 3.* Con frecuencia los clínicos manejando casos en países en desarrollo carecen de entrenamiento específico en TB-MDR (22). Hay una falta y necesidad de documentos que de una forma breve y ordenada recojan la información esencial en cuanto al manejo y tratamiento de estos pacientes especiales (5).

En relación a los objetivos planteados y las barreras identificadas para su consecución han surgido las siguientes hipótesis de trabajo:

> *Hipótesis 1.* Los MCFs pueden tener similar eficacia que los medicamentos sueltos a un menor coste y con potenciales ventajas operativas para el programa y también para el paciente.
>
> *Hipótesis 2.* Los tratamientos estandarizados pueden aportar similares resultados que los tratamientos individualizados.
>
> *Hipótesis 3.* Es posible crear herramientas y documentos de calidad técnica para acelerar la auto-formación y actualización de clínicos en el manejo de TB-MDR.

De las previas hipótesis surgen ***3 líneas de trabajo*** e investigación de los cuales surgirán estudios científicos que colaboren con el objetivo general establecido. Las líneas investigación son:

> *Línea 1:* Aportar evidencias científicas que evalúen el papel real que puedan tener los MCFs en cuanto a su eficacia y efectividad en el tratamiento de la TB sensible y capacidad para evitar resistencias.
>
> *Línea 2:* Aportar evidencias científicas sobre la eficacia y efectividad de los tratamientos estandarizados para tratar TB-MDR en países en desarrollo.
>
> *Línea 3:* Crear nuevas herramientas de calidad científica y técnica que mejoren el acceso a información y simplifiquen formación en manejo de pacientes con TB-MDR en países en desarrollo.

Objetivos, hipótesis y metodología general de esta tesis doctoral pueden observarse de forma resumida bajo matriz de marco lógico en la *tabla 7.*

Tabla 7. Objetivos, hipótesis, líneas de investigación y resultados de la tesis doctoral planteada mediante matriz de marco lógico

OBJETIVO GENERAL	OBJETIVOS ESPECIFICOS	BARRERA	HIPOTESIS Y LINEA DE INVESTIGACIÓN	METODOLOGÍA Y RESULTADO
Aportar a la comunidad científica y clínica, nuevos conocimientos que colaboren en la prevención y tratamiento de los pacientes con TB-MDR.	1.Desarrollo o promoción de estrategias para mejor control de la TB sensible y prevención de resistencias	Dificultad para la inclusión de MCFs en los programas nacionales de TB argumentando falta de evidencias en cuanto a su eficacia.	1. Los MCFs pueden tener similar eficacia que los medicamentos sueltos y capacidad para evitar resistencias.	Estudio 1: Revisión sistemática y Meta-análisis de la eficacia de los MCFs respecto medicación suelta
	2. Aportar herramientas o evidencias científicas que a igualdad de eficacia ayuden a la simplificación el manejo de la TB-MDR	El manejo de la TB-MDR consta de esquemas complicados. Hay escasas evidencias respecto al manejo estandarizado más económico y sencillo	2. Los tratamientos estandarizados pueden aportar similar resultados que los individualizados en países en desarrollo.	Estudio 2: Estudio de cohortes retrospectivo comparando tratamientos estandarizado respecto a individualizados
		Los clínicos en países en desarrollo carecen de entrenamiento específico en TB-MDR. Falta de documentos breves que recojan una forma global la información esencial para el manejo de pacientes	3. Se pueden crear herramientas de calidad técnica para simplificar y acelerar la formación de clínicos en TB-MDR	Estudios 3, 4 y 5: Revisión crítica de TB-MDR, TB-MDR/VIH

MCFs: Medicamentos combinados en dosis fija; TB-MDR: Tuberculosis Multidrogorresistente; VIH: virus de la inmunodeficiencia humana

5. METODOLOGÍA

Metodología específica de cada estudio concreto

En el ***estudio 1*** mediante una revisión sistemática se evalúa la eficacia y tolerancia de los MCFs para el tratamiento de la TB sensible y la capacidad de prevención de resistencias. Se realizó una revisión sistemática siguiendo los criterios de declaración PRISMA (99). Fue llevada a cabo por 2 investigadores (doctorando y coautor) a través de PubMed. Se buscaron los términos: "Tuberculosis", "fixed-dose combination", "drug resistance", "multidrug-resistance", "risk factor" y/o "private sector". La elección de estudios fue basada en título y abstract según relevancia con la pregunta de investigación. En cuanto a los criterios de inclusión se aceptaron estudios publicados en revistas revisadas por pares que fueran ensayos clínicos aleatorizados, cuasi-aleatorizados o ensayos sobre terreno (field trials) e incluyeran pacientes adultos con TB. La intervención debía ser comparación entre MCFs y medicamentos sueltos y que las medidas de resultado comprendieran: conversión de esputo o cultivo, curación, recaída, adherencia, efectos adversos, adquisición de resistencia o coste. Se aceptaron publicaciones en cualquier idioma. Inicialmente se planteo como un metanálisis pero la heterogeneidad de los estudios no lo permitió.

En el ***estudio 2*** con metodología de cohortes retrospectiva procedió a caracterizar y comparar los resultados de todos los tratamientos estandarizados vs. individualizados en el manejo de la TB-MDR en Republica Dominicana. Se incluyeron en el estudio todos los pacientes con TB-MDR diagnosticados por laboratorio y que empezaron tratamiento en el país entre Agosto de 2006 y hasta el final de Junio de 2010. Fueron excluidos segundas o terceras entradas del mismo paciente en tratamiento. La muestra fue descrita en términos socio-demográficos y clínicos. Se evaluó el tiempo de conversión del cultivo en relación a haber recibido tratamiento estandarizado o individualizado. Para los pacientes de las cohortes 2006-08 (un año de seguimiento tras finalización del tratamiento) también se evaluaron resultados de tratamiento, efectos secundarios, factores de riesgo de mal pronóstico y recaídas al año de curación.

Como fuentes se información se utilizaron los datos de rutina del programa nacional de TB: registros clínicos y documentos operativos del programa de acuerdo a los formatos y definiciones de la guías de la OMS. La recogida de datos fue llevada a cabo entre Enero y Junio de 2011 por personal del programa nacional. Los principales datos de resultado fueron cotejados por 3 investigadores usando 3 fuentes distintas de información. El estudio cumple criterios de calidad de la declaración STROBE (100). Los análisis estadísticos fueron realizados en Marzo-Julio de 2011. El valor p considerado significativo fue al nivel igual a 0.05. El cálculo estadístico fue realizado usando los programas *SPSS 18.0* y *R statistical package* (v2.12.1). En cuanto al cálculo de factores de riesgo clínico o socio-demográficos se emplearon modelos de riesgos proporcionales de Cox: asociación de variables con resultado desfavorable e intervalos de confianza del 95%. La proporcionalidad de los riesgos en los modelos fueron verificados gráficamente usando residuos de Schoenfeld.

En el ***estudio 3*** se procede a crear un compendio simplificado de buenas prácticas en el manejo de la TB-MDR en países en desarrollo orientado a la docencia mediante una revisión crítica de la literatura.

El ***estudio 4*** de manera similar aborda de manera simplificada y didáctica el manejo de la TB-MDR en pacientes con infección por el VIH en contextos africanos de alta carga de coinfección.

El ***estudio 5*** explora las diferencias existentes entre el manejo de la TB-MDR en países desarrollados y países en vías de desarrollo a través de revisión de la literatura y experiencias personales de trabajo cooperante en terreno, poniendo de manifiesto barreras que dificultan el manejo adecuado de esta enfermedad en países en desarrollo.

Para más detalles sobre la metodología específica de cada estudio, acceda directamente a la sección de metodología en los estudios originales publicados (ver en la sección de *Resultados* de esta tesis)

Consideraciones éticas

En los estudios en que se han usado datos del dominio público sin interacción directa con pacientes, no existen consideraciones éticas ya que no hay posibilidad de identificación o potencial agravio. En los estudios que han necesitado datos concretos de pacientes se ha solicitado y obtenido aprobación del estudio por las autoridades y comités de bioética locales así como del comité de bioética de La Unión Internacional contra la Tuberculosis y Enfermedades Respiratorias (101) y en todos los casos se ha guardado la confidencialidad de datos personales o que pudieran identificar personas.

Fuentes de financiación y conflictos de interés

La presente tesis doctoral y los artículos científicos que la componen se han llevado a cabo sin ninguna fuente externa de financiación. No existen ningún tipo de conflicto de interés por parte del doctorando, directores de tesis o co-autores de los estudios que la componen.

6. RESULTADOS

Partiendo de las hipótesis de trabajo, se ha llegado a 3 líneas de investigación principales que han dado como resultado 5 estudios publicados que son la base de la presente tesis doctoral (102) (103) (55) (104) (105) . Como resultados complementarios se añaden en los anexos la siguiente producción científica donde el doctorando ha sido co-autor durante el tiempo de los estudios de doctorado: una publicación en revista de segundo cuartil (64), dos artículos pendientes de revisión y 2 guías clínicas internacionales (76, 106). De forma también complementaria el doctorando ha sido colaborador de otros dos guías internacionales (107, 108) y otros documentos de interés científicos relacionados con el tema de la tesis. Tanto las publicaciones principales como las complementarias (añadidas en los anexos) tratan de dar respuesta a los objetivos planteados.

1. Evidence for promoting fixed-dose combination drugs in tuberculosis treatment and control: a review. Monedero I, Caminero JA. Int J Tuberc Lung Dis. 2011 Apr;15(4):433-9
   Publicado: Abril de 2011. Factor de impacto: 2.73

2. Rodriguez M, Monedero I, Caminero JA, Encarnacion M, Dominguez Y, Acosta I, et al. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. Int J Tuberc Lung Dis. 2013 Apr;17(4):520-5.
   Publicado: Marzo de 2013. Factor de impacto: 2.73

3. Management of multidrug-resistant tuberculosis: an update. Ignacio Monedero, José A. Caminero. Ther Adv Respir Dis 2010 4: 117-127.
   Publicado: Abril de 2010. Factor de impacto de acuerdo a Scopus: 6.85

4. A basis for the clinical management of complicated MDR–TB cases. Monedero I, Holkar S. Africa Health. 2010 Sept; Vol 32 No 6: 20-25
   Publicado: Septiembre de 2010. Impacto: Revista de la Asociación Africana de Medicina bajo auspicio del Fondo Mundial

5. Tuberculosis Multidrogorresistente: una enfermedad, dos realidades diferentes. Monedero I, Caminero JA, Palomares FA, Alonso E, Mazario S. Enfermedades Emergentes. 2011; 13(2):68-73
   Publicado: Junio de 2011. Factor de impacto: 0.25

Estudio 1

INT J TUBERC LUNG DIS 15(4):433–439

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UNRESOLVED ISSUES

Evidence for promoting fixed-dose combination drugs in tuberculosis treatment and control: a review

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SUMMARY

Uptake of fixed-dosed combinations (FDCs) of anti-tuberculosis drugs remains low worldwide, despite decades of recommendations. FDCs are thought to be important tools for tuberculosis (TB) control and drug resistance (DR) prevention. However, evidence relating to this is limited. This article provides a critical review of the most relevant studies on anti-tuberculosis FDCs. The majority of published studies have sought to demonstrate that FDCs and single drugs have similar efficacy. This hypothesis has been proved with relation to similar sputum conversion, cure and relapse rates in a range of studies over the last 20 years using FDCs of two, three and four anti-tuberculosis drugs. However, one of the most relevant features of FDCs, the prevention of DR, has been addressed in only one study. Nevertheless, based on their similar efficacy, user-friendliness, lower costs, and operational and logistical advantages, generalised use of FDCs should continue to be recommended.

KEY WORDS: tuberculosis; TB; fixed-dose combinations; FDC; multidrug resistance; MDR

THE FIRST and most important intervention in tuberculosis (TB) control in the community is the attainment of high cure rates. To cure as many patients as possible, two equally important measures are necessary: 1) short-course standardised treatment regimens, which are highly effective, particularly if rifampicin (RMP) is used throughout;[1] and 2) ensuring that all patients complete treatment correctly. The greatest challenge for all National Tuberculosis Programmes (NTPs) is ensuring treatment adherence. Poor adherence not only reduces cure rates, it also creates a selection of naturally resistant mutant bacilli.[2] Several methods have been adopted to ensure and facilitate the correct intake of medications during the 6–8 months of anti-tuberculosis treatment. Of these, the DOTS strategy is one of the most effective.[3] Another widely recommended intervention is the use of fixed-dose combinations (FDCs) of two anti-tuberculosis drugs (2FDCs, usually RMP + isoniazid [INH]), three drugs (3FDCs, RMP + INH + pyrazinamide [PZA]) and four drugs (4FDCs, RMP + INH + PZA + ethambutol [EMB]).

During the 1980s and 1990s, the quality of FDCs was a matter of concern, as substandard FDCs and relatively poor bioavailability of RMP were documented in the global market.[4,5] However, current FDCs are fully bioequivalent to single-drug reference products,[6–9] with stable efficacy even after 6 months in tropical conditions.[10–12]

The rationale for recommending FDCs[9,13,14] is that if all drugs are provided in the same tablet, drug selection by the patient and consequent monotherapy can be avoided. Furthermore, FDCs facilitate dosage calculation and prevent prescription errors due to the simplified, standardised chemotherapy regimens. The pill burden is also drastically reduced, increasing acceptance by patients while facilitating health education and adherence. FDCs offer several logistical advantages for NTPs, such as the facilitation of drug planning, ordering, storage and management. These improve drug handling and delivery and reduce the likelihood of drug shortages. If widely applied in the field, FDCs result in improved TB outcomes and prevent anti-tuberculosis drug resistance (DR).

As the logic that FDCs prevent selection of resistance in the field was considered unequivocal, very few doubts have been expressed about this aspect; studies undertaken in the 1980s and 1990s did not seek to demonstrate the prevention of resistance, but only their similar efficacy.

This article provides a critical review of available evidence on the efficacy and other aspects of anti-tuberculosis FDCs in comparison with separate drugs.

METHODS

A review of the literature was conducted between May and July 2009 using PubMed. The terms 'tuberculosis',

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Table 1 Description and clinical outcomes of the studies reviewed

Study, reference, year, country	Design	Study duration	Intervention		Comparison		Clinical outcomes	Intervention, FDCs vs. comparison regimen, separate drugs	*P* value
			n	Treatment	*n*	Treatment			
Geiter et al.,[15] 1987, USA	RCT SAT	6 months	169	2 months 3FDC/4 months 2FDC	532	Separate drugs	Sputum conversion at 2 months	86.6% vs. 77.7%, absolute difference 8.9% (95%CI 1.1–16.7)	<0.05
Bellabas et al.,[16] 1989, Algiers	RCT DOT	2 months	125	3FDC	125	Separate drugs	Culture conversion at 2 months (193 susceptible cases)	95% vs. 91%	>0.05
Agounitestane et al.,[17] 1990, Algiers (*continuation of previous study*[16])	RCT DOT	12 months	125	2 months 3FDC/4 months 2FDC	125	2 months separate drugs/ 4 months 2FDC	Failures and relapses after 6 months among INH-susceptible patients	0% vs. 0% 0% vs. 0%	ND ND
Chaulet et al.,[18] 1995, Algiers	RCT DOT	24 months	124	2 months 3FDC	126	2 months separate drugs	Failure at 6 months and relapse at 24 months (combined)	2% vs.1%	>0.05
Hong Kong Chest Service/BMRC,[19] 1989, China	RCT DOT	2–4 months	314	2 months 3FDC + SM three times weekly	313	2 months separate drugs three times weekly	No clinical outcomes included		
Hong Kong Chest Service/BMRC,[20] 1991, China	RCT DOT	30 months follow up	420	Different treatment protocols, including 3FDC three times weekly	966	Different treatment protocols with separate drugs three times weekly	Culture conversion at 2 months Relapse after 30 months (in initially susceptible cases)	93% vs. 91% 5.1% vs. 4.6%	>0.05 >0.05
Singapore Tuberculosis Service/BMRC,[21] 1991, Singapore	RCT DOT	18 months	155	Different treatment protocols, including daily 3FDC for first 2 months	155	Same protocols with separate drugs daily for first 2 months	Culture conversion at 2 months Relapse at 18 months	96% vs. 95% 6% (*n* = 8) vs. 1% (*n* = 2)	>0.05 0.04
Teo,[22] 1999, Singapore; (*continuation of previous study*[21])	RCT DOT	60 months	155	Different treatment protocols, including daily 3FDC for first 2 months	155	Different treatment protocols with separate drugs daily for first 2 months	Relapse at 60 months (per sputum and culture)	7.9% (*n* = 12) vs. 2.2% (*n* = 3)	0.03
Zhu et al.,[23] 1998, China	RCT	6 months	227	2 months 3FDC/4 months 2FDC	81	Separate drugs	Sputum conversion 1) at 2 months 2) at 6 months CXR improvement Default rates	91.2% vs. 86.4% 98.7% vs. 97.5% 95.2% vs. 93.8% 4.3% vs. 7.8%	NA NA NA NA
Su & Perng,[24] 2002, Taiwan, China	RCT SAT	2 years	57	2 months 3FDC + EMB/ 4 months 2FDC	48	Separate drugs	Sputum conversion 1) at 2 months 2) at 6 months	95.0% vs. 100% 100% vs. 100%	>0.05 ND
Gravendeel et al.,[25] 2003, Indonesia	RCT DOT	6 months	198	Initial phase daily 4FDC/ continuation phase three times weekly 2FDC	162	Separate drugs daily	Sputum conversion at 2 months Treatment success	94% vs. 89% 95% vs. 95%	0.23 ND

Suryanto et al.,[28] 2008, Indonesia (*continuation of previous study*[27])	RCT	4.3 years	236	Initial phase 4FDC/ continuation phase three times weekly 2FDC	198	Separate drugs	Bacteriological relapse	10.1% vs. 2.7%	0.074
Moulding et al.,[27] 2004, USA	Multicentre field study/ SAT	5 years intervention 2 years follow-up	4000 (estimation)	Self-administered intermittent 2FDCs Group A: patients only on FDCs Group B: patients mostly using FDCs + all patients in Group A Group C: all patients on FDCs	1337	SAT separate drugs	Acquired drug resistance	Creation of MDR-TB: Group A: 0.1% vs. 1% Group B: 0.2% vs. 1% Group C: 0.47% vs. 1%	NK
The Union,[26,31] 2008, multicentre	Multicentre RCT DOT	6–12 months		Initial phase 4FDC/ continuation 2FDC ($n = 583$)		Separate drugs ($n = 581$)	Cure, relapse after 12 months, complaints	Preliminary results, FDC non inferior to separate drugs in cure and relapse rates after 1 year	
Bartacek et al.,[29] 2009, multicentre	Multicentre RCT	12 months	582	Initial phase 4FDC (Rimstar®)/ continuation 2FDC (Rimatazid®) Daily	577	Separate drugs Daily	Cure Relapse at 12 months	ITT: 80.4% vs. 82.7% PP: 98.1% vs. 98.6% (non inferior) ITT: 1.75% vs. 0.97% PP: 1.74% vs. 0.87% (non inferior)	

FDC = fixed-drug combination; RCT = randomised controlled trial; SAT = self-administered treatment; 3FDC = RMP+INH+PZA; 2FDC = RMP + INH; CI = confidence interval; DOT = directly observed treatment; INH = isoniazid; ND = no difference; BMRC = British Medical Research Council; EMB = ethambutol; NA = not available; SM = streptomycin; 4FDC = RMP+INH+PZA+EMB; CXR = chest X-ray; MDR-TB = multidrug-resistant tuberculosis; NK = not known; ITT = intention-to-treat population; PP = per-protocol population; RMP = rifampicin; PZA = pyrazinamide.

'fixed-dose combination', 'drug resistance', 'multidrug resistance', 'risk factor' and 'private sector' were used in a range of combinations. Two researchers selected articles by title and abstract according to their relevance to the research question. Randomised or quasi-randomised controlled trials (RCTs) and field trials that met the following review inclusion criteria were included: adult TB patients, comparisons of FDCs and single drugs and study outcome measure, including at least one of the following: smear conversion, culture, cure, relapse, adherence, side effects, acquisition of drug resistance and cost. No measures of methodological quality, language or date were applied in the selection of studies.

RESULTS

Of 15 articles published between 1987 and 2009 identified,[15–29] 12 were original research studies and the remainder were re-evaluations of previous studies at different points in time.[17,22,26] The key results and methodology of these articles are summarised in Tables 1 and 2. Almost all studies were unblinded and involved smear-positive and new, probably susceptible cases. Three studies were conducted under programme conditions, without complete directly observed treatment (DOT) or self supervision.[15,24,27] Information on treatment modality was not available for two articles,[23,29] while the remaining studies were performed under DOT and controlled study conditions.[16,18–21,25,28] Of these, one was an unpublished RCT,[28] with only preliminary results available.[30] No studies measuring the possible impact of FDCs in the private sector were found.

Studies comparing the efficacy of FDCs vs. single drugs

All the 11 original trials comparing efficacy, all of which compared sputum conversion, culture and cure rates, obtained similar results regardless of the drug formulation (no statistically significant difference at $P > 0.05$ or non-inferiority to single drugs).[15–18,20,21,23–25,27–30] Of these, only three studies compared 4FDCs, recommended in the current standard treatment regimen.[25,28,29]

Studies comparing relapses with FDCs vs. single drugs

Relapses are probably the most controversial issue in FDC use. Of the seven original studies that address this issue, six (85%) obtained a statistically ($P > 0.05$) similar number of relapses or non-inferiority after 6 months,[16,17] 12 months,[29,30] 24 months,[18] 30 months[20] and 4.3 years.[25,26] Only one trial using 3FDCs[21] found statistically significant differences ($P = 0.04$) in relapse rates 18 months after treatment initiation (6% relapses with FDCs vs. 1% with separate drugs). However, absolute numbers were small (310 total patients: 8 relapses with FDCs vs. 2 with separate drugs) and

Table 2 Other outcomes and methodological issues in the studies reviewed

Study, reference, year, country	Other outcomes	Intervention, FDCs vs. comparison regimen, separate drugs	*P* value	Methodological and results issues
Geiter et al.,[15] 1987, USA	Adherence measures (urine testing, pill counting, self reporting)	At 2 months: 96.5% vs. 98.1% At 6 months: 88.5% vs. 87.3%	>0.05 >0.05	Treatment and comparison groups enrolled at different times Exclusion and loss to follow-up >30% ITT analysis not reported
Bellabas et al.,[16] 1989, Algiers	Side effects Patient satisfaction interview	20% vs. 36% 97% vs. 95%	<0.02 >0.05	ITT analysis not reported Exclusion and loss to follow-up >20%
Agounitestane et al.,[17] 1990, Algiers (*continuation of previous study*[16])	Not measured			ITT analysis not reported Loss to follow-up >40% in clinical outcome
Chaulet et al.,[18] 1995, Algiers	Side effects at 2 months	19% vs. 36%	<0.02	ITT analysis not reported Exclusion and loss to follow-up >20%
Hong Kong Chest Service/BMRC,[19] 1989, China	Clinical side effects Difficulty swallowing Brought own drink to swallow pills	38% vs. 39% 1% vs. 5% 32% vs. 45%	>0.05 <0.05 <0.01	ITT analysis not reported
Hong Kong Chest Service/BMRC,[20] 1991, China	Not measured			Treatment and comparison groups enrolled at different times Exclusion and loss to follow-up >30% ITT analysis not reported
Singapore Tuberculosis Service/BMRC,[21] 1991, Singapore	Side effects at 2 months	8% vs. 7%	>0.05	ITT analysis not reported
Teo,[22] 1999, Singapore; (*continuation of previous study*[21])	Not measured			Re-infection not evaluated despite long-term (>2 years) relapse assessment HIV not measured in original study and follow-up population Lower number of relapses: 12 vs. 3 *P* = 0.03, 95%CIs overlap on the main result (7.9%, 95%CI 4.1–14.7 vs. 2.2%, 95%CI 0.7–6.4)
Zhu et al.,[23] 1998, China	Not measured			Limited information in methodology
Su & Perng,[24] 2002, Taiwan, China	Adherent: not lost to follow-up or no change in treatment	70.2% vs. 66.7%	>0.05	Considerable loss to follow-up (50% by 2 years) ITT analysis not reported
Gravendeel et al.,[25] 2003, Indonesia	Complaints during initial phase Gastrointestinal Muscle-joint	41% vs. 56% 32% vs. 46%	<0.01 <0.01	
Suryanto et al.,[26] 2008, Indonesia (*continuation of previous study*[25])	Not measured			Differential length of follow-up (0.1–5.8 years) Relapse assessment not the original design, including 74 additional patients without clear inclusion criteria Possible observation bias: proxy interviews, verbal autopsy Bacteriological measures in only 39% of the population study Re-infection not evaluated
Moulding et al.,[27] 2004, USA	Not measured			Programme conditions. Failure to find cases and migration of cases during treatment not evaluated. Numbers based on estimations. Retrospective study. Difficulties differentiating acquired from primary drug resistance (7/25 patients with acquired drug resistance were treated previously)
The Union,[28,30] 2008, multicentre	Information not available			Non-inferiority test Preliminary results
Bartacek et al.,[29] 2009, multicentre	Patient satisfaction (difficulty swallowing, number of tablets and taste) Drug-related adverse events	Statistically significant differences in PP and ITT favouring FDC 73.3% vs. 63.5%	0.03	Non-inferiority test. Missing data imputed to relapses and no information about DOT practices. Differential number of deaths not completely addressed

FDC = fixed-drug combination; ITT = intention-to-treat population; BMRC = British Medical Research Council; HIV = human immunodeficiency virus; CI = confidence interval; PP = per-protocol population; Union = International Union Against Tuberculosis and Lung Disease; DOT = directly observed treatment.

just one addition relapse could have affected the statistical significance. A re-evaluation of the cohort after 60 months[22] found greater differences ($P = 0.03$), with 12 cases on FDCs vs. 3 on separate drugs. However, the 95% confidence intervals (CIs) overlapped within the estimated proportions (7.9%, 95%CI 4.1–14.7 vs. 2.2%, 95%CI 0.7–6.4). Despite a long-term assessment of relapse (>2 years), re-infection and human immunodeficiency virus (HIV) status were not evaluated. As in the original study, slight differences could have affected the statistical significance.

The role of re-infection confirmed by DNA fingerprinting was mentioned in only one study.[30] According to the studies reviewed, FDCs and separate drugs have similar efficacy in terms of sputum conversion, cure and probably relapse rates.

DISCUSSION

Efficacy and other secondary outcomes were evaluated in the studies reviewed. Acceptability, side effects and adherence were measured in nine studies;[15,16,18,19,21,24,25,28,29] all obtained similar or better results in patients treated with FDCs. Only one study reported on the possible role of FDCs in the prevention of drug resistance, one of the principal motives for recommending FDCs worldwide.[27] This study reported lower levels of acquired DR (0.47% vs. 1%) in patients taking self-administered 2FDCs or mostly 2FDCs. Despite its limitations in methodology (Table 2), the main advantage of this study is that it reproduces the real circumstances of a well-performed NTP, without using DOT. Although all studies reported similar efficacy regardless of drug formulation, studies that included DOT[16,18–21,25,28] obtained outstanding cure rates (between 93% and 100%). Efficacy results differ widely between controlled studies and those conducted under real conditions. For example, an RCT comparing trial results with national rates found highly disparate treatment success rates (95% vs. 74%, $P < 0.01$).[25] As it was unlikely that patients enrolled in DOT-based studies would be subjected to drug shortages, prescription errors, monotherapy or allowed to select drugs, such studies measured efficacy rather than the effectiveness of FDCs as compared to single drugs.

Ten of the 22 high-burden countries reported shortages of first-line drugs to the World Health Organization (WHO) in 2007, and the logistical benefits of FDCs, which remain an unresolved issue, could play a crucial role at the policy level.[31] However, it is likely that the key issue is not the type of formulation administered, but the kind of formulation used in settings with substandard DOT.

The only study to report slightly poorer results on FDCs (relapses), mentions that when DOT is deficient, the other advantages of FDC-based regimens would probably compensate for the small difference in efficacy.[22] The WHO estimates that 37% of incident TB cases are not being treated in DOTS-based programmes.[31] It is well known, however, that DOT is incorrectly applied in many countries that apply the DOTS strategy. Moreover, DOT is rarely performed in the private sector, which covers more than 15% of the global TB burden[32] and is associated with substandard TB care.[32–35] Most low- and middle-income countries have a large and growing private sector.[34] Under suboptimal DOTS conditions, FDCs are likely to play a relevant role in cure rates and prevention of DR. However, no evidence was found in this regard. Furthermore, evidence of the prevention of DR in treatment with FDCs was limited to one study,[27] and no RCTs have been conducted to support this hypothesis. Nevertheless, effectiveness could be key in the application of this intervention given the similar efficacy of the two approaches.

Global uptake of FDCs

Although many countries have adopted FDCs over the past decades, uptake remains extremely low, despite international recommendations.[36] According to the Global Drug Facility (GDF),[36] FDCs were being used by only half of the 136 countries reporting TB to the WHO in 2007. Moreover, globally only 15% of new cases were being treated with FDCs.[36] Treatment with FDCs was infrequent not only in developing countries but also in the United States, where in 2006 the ratio of money spent on RMP was 1 to 10 for single formulations.[37] Infrequent use of FDCs in the private sector is also thought to be an important and neglected cause of DR.[27,37]

There is a multitude of potential reasons for this low uptake. Issues such as the perceived inferiority of treatment and the need for separate drugs in case of toxicity during FDC use may have discouraged NTPs. At least 2% of adults experience adverse reactions, requiring cessation of treatment and the subsequent reintroduction of treatment using separate drugs.[38] NTPs therefore always retain a certain supply of single drugs for this limited but constant number of cases.

As a disease of the poor, for many decades TB has been considered an unprofitable market, and 'old' tools such as FDCs are still unavailable in many settings. Conversely, such a prevalent disease has a potentially large treatment market, especially for FDCs.[39] A full FDC-based treatment regimen for susceptible TB patients bought through the GDF currently costs about US$22.40.[40] According to 2000 data, the cost of FDCs was approximately 50% less than for single drugs.[41] As this appears to still hold true, use of FDCs could increase access to quality TB treatment for even the poorest programmes.

Limitations

The findings of this review are subject to limitations, as most of the studies faced methodological

constraints (see Table 2), while one of the best studies[30] reported only preliminary results. Most of the studies were published 10–20 years ago and some of the compounds tested are no longer on the market in the same dosages. As the logistical advantages of FDCs remain unevaluated, it is probable that RCTs comparing FDCs and single drugs under self-administered treatment, family supervised DOT or the private sector would provide stronger evidence of their impact in terms of effectiveness and averted DR.

CONCLUSIONS

According to the studies reviewed, and taking into account their important limitations, anti-tuberculosis FDCs appear to have similar clinical efficacy to separate drugs in terms of sputum conversion, cure and probably relapse rates. The role of FDCs in averting drug resistance by preventing monotherapy and patient selection remains unclear, and evidence was reduced to a single, limited study. Other issues, such as acceptability, adherence, logistical or operational advantages and costs, make FDCs a better option than single drugs. Nevertheless, global uptake of anti-tuberculosis FDCs remains extremely low. If FDCs and separate drugs deliver the same outcomes and secondary issues favour FDCs, global access to FDCs should be advocated. Promotion should be particularly strong in those settings where DOT is not fully guaranteed, such as the private sector and weaker health care systems.

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RÉSUMÉ

En dépit de décennies de recommandations, l'utilisation de combinaisons de médicaments antituberculeux à dose fixe (FDC) reste faible au niveau mondial. Les FDC sont considérées comme des outils importants pour la lutte antituberculeuse et la prévention de la résistance aux médicaments. Toutefois, les éléments probants sont limités à ce sujet. Cet article constitue une revue critique des études les plus pertinentes concernant les FDC antituberculeuses. La grande majorité des études publiées ont cherché à démontrer que les FDC et les médicaments isolés ont une efficacité similaire. Cette hypothèse a été démontrée par une négativation similaire des expectorations et des taux similaires de guérison et de rechute dans une série d'expériences au cours des 20 dernières années utilisant des FDC avec deux, trois ou quatre médicaments antituberculeux. Toutefois, une des caractéristiques les plus importantes des FDC est d'éviter la résistance ; celle-ci n'a été envisagée que dans une seule étude. Néanmoins, en se basant sur une efficacité similaire, la facilité d'emploi, les coûts plus faibles, les avantages opérationnels et logistiques, il y a lieu de continuer à recommander la généralisation des FDC.

RESUMEN

A pesar de décadas de recomendaciones, el uso de medicación anti-tuberculosa en combinaciones de dosis fijas (FDC) sigue siendo bajo a nivel mundial. Se cree que los FDC son herramientas importantes en el control de la tuberculosis y en la prevención de resistencias. Sin embargo, las evidencias al respecto son limitadas. Este artículo proporciona una revisión crítica de los estudios más relevantes sobre los FDC de medicamentos antituberculosos. La gran mayoría de los estudios publicados ha buscado demostrar que los FDC y los medicamentos sueltos tienen la misma eficacia. Esta hipótesis se ha comprobado en relación a la conversión del esputo, tasas de curación y recaídas en distintas experiencias durante los últimos 20 años usando FDC de dos, tres y cuatro medicamentos anti-tuberculosos. No obstante, una de las características más relevantes de los FDC, la capacidad para evitar resistencias medicamentosas, solo ha sido tratada en un estudio. A pesar de ello, basado en similar eficacia, uso sencillo, menor coste y ventajas logísticas y operacionales, el uso generalizado de los FDC debería continuar recomendándose.

Estudio 2

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Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic

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SUMMARY

SETTING: The Dominican Republic is a high-incidence area for multidrug-resistant tuberculosis (MDR-TB; 6.6% of initial cases). Standardised treatment regimens for MDR-TB may be a potential solution.

OBJECTIVE: To present the effectiveness of standard regimens under routine national conditions.

DESIGN: We reviewed all MDR-TB patients treated under routine conditions from 29 August 2006 to 30 June 2010, showing interim and final outcomes. Patients were treated with regimens that were standardised or individualised based on previously received second-line anti-tuberculosis drugs.

RESULTS: Population description and culture conversion data are reported for the 289 MDR-TB patients. The median patient age was 31 years. Most had failed first-line treatment (72.6%). Culture negativity was obtained within 4 months (median 2 months) in 78.6%. Among the 150 patients treated between 2006 and 2008, 74% had favourable results on standardised and 66% on individualised regimens ($P = 0.211$). The efficacy of the standardised and individualised regimens was respectively 92.8% and 81% ($P = 0.056$). The relapse rate was approximately 1%. A median of five drug side effects occurred per patient. More than 2 months to culture conversion and bilateral cavitation on chest X-ray were found to be unfavourable outcome risk factors.

CONCLUSIONS: Standardised MDR-TB regimens may be effective at the national level, even in resource-poor settings.

KEY WORDS: Dominican Republic; multidrug-resistant tuberculosis; MDR-TB; standardised treatment; tuberculosis; TB

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB), defined as *Mycobacterium tuberculosis* strains with in vitro resistance to the two most effective anti-tuberculosis drugs, isoniazid (INH) and rifampicin (RMP), has become a major barrier to achieving successful tuberculosis (TB) control.[1] Among the estimated 500 000 new MDR-TB cases emerging annually worldwide, most are from low- and middle-income countries.[1,2] There are no randomised clinical trials showing the best drug combinations to achieve cure. Anti-tuberculosis treatment based on second-line drugs (SLDs) is less effective, more costly and associated with more adverse events than first-line regimens.[3,4] These difficulties are clearly greater in low- and middle-income countries, which have less access to care and affordable drugs. Even when SLDs are subsidised, programmatic challenges can prevent the completion of the required 18–24 months of treatment.[4] Despite these limitations, by following clinical management principles and with sufficient programme support, MDR-TB can be treated successfully.[5,6] Treatment success can vary from <50%[7–9] to >70%.[10–12]

The Dominican Republic is a Caribbean middle-income country with high rates of human immunodeficiency virus (HIV) co-infection (4.2%–8.3%) in the adult population.[13] The only survey available on drug resistance was published in 1998, where MDR-TB was diagnosed in 6.6% of new TB patients.[14] In April 2005, the World Health Organization (WHO)/Stop TB Partnership's Green Light Committee (GLC) approved an MDR-TB project in the country. The first patients initiated treatment at the end of August 2006.

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The present article assesses the implementation of MDR-TB treatment under routine low-resource programme conditions in the Dominican Republic in terms of effectiveness, side effects and risk factors associated with poor outcomes.

METHODS

This was a retrospective cohort study of all 289 MDR-TB laboratory-confirmed patients who started treatment in the Dominican Republic from 29 August 2006 until 30 June 2010. Only patients starting MDR-TB treatment within the programme for the first time were considered. Socio-demographic and clinical features are reported and the time to culture conversion is evaluated. Final treatment outcome (favourable or unfavourable) was available for the 150 patients entering treatment in 2006–2008. For those with favourable outcome, relapse at 6 months after treatment completion was assessed. Other variables evaluated included adverse drug reactions and risk factors for unfavourable outcome. The flow chart of enrolment of study patients is shown in Figure 1.

Drug susceptibility testing (DST) results were available only for failures on Category I or II treatment or cases with persistent TB after treatment in the private sector. Before 2011, the national reference laboratory only had the capacity to test resistance to first-line drugs. Sputum samples were treated with a modified Petroff method and cultured on Löwenstein-Jensen media. DST was performed using the proportion method according to Canetti et al.[15] At baseline, *M. tuberculosis* isolates were tested for susceptibility to INH (0.2 μg/ml), RMP (40 μg/ml), ethambutol (EMB; 2.0 μg/ml) and streptomycin (4 μg/ml).

Two treatment regimens were used for MDR-TB: 1) the standardised regimen, for patients who had never previously received SLDs, comprised kanamycin (KM), ofloxacin (OFX), ethionamide, cycloserine and pyrazinamide.[3,4] EMB was added if DST showed susceptibility. In 2010, OFX was replaced by levofloxacin and KM by capreomycin (CPM). 2) Individualised regimens were given to those who had received SLDs or if they were in contact with a case who had received SLDs. All individualised regimens were based on at least four drugs that had not been used previously. As many patients had received fluoroquinolones, only 19 regimens incorporated fluoroquinolones. All individualised regimens included one injectable (KM or CPM), and most included para-aminosalicylic acid.[3,4,16] All treatments were supplemented with vitamin B6 (50 mg). Drugs with unclear efficacy (Group 5 drugs)[3,4,16] and surgery were unavailable.

The length of treatment of both regimens was

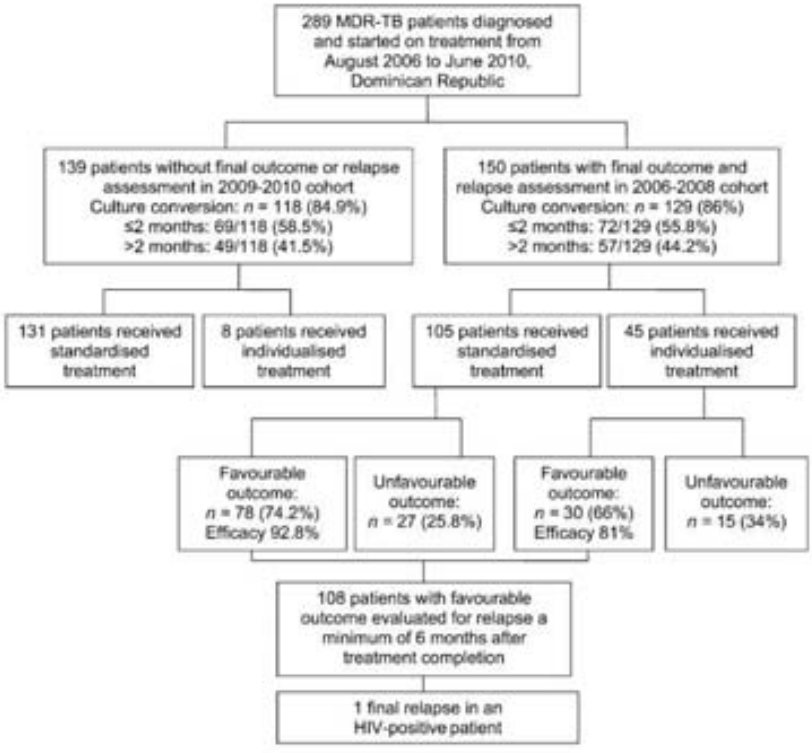

Figure 1 Enrolment, outcome and follow-up of study patients. MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus.

18–24 months. All but four of the patients began hospital-based treatment. Anti-tuberculosis medications were given under directly observed treatment (DOT) in the morning without splitting the doses. Patients remained hospitalised until they became sputum smear-negative, and tolerance to drugs was observed. All patients received at least 6 months of an intravenous injectable given daily in the initial phase. Depending on time to culture conversion or lack of adherence to treatment, some cases received the injectable for a longer period. Oral agents were continued throughout the continuation phase. After discharge, patients continued treatment in selected primary health care centres with staff trained in MDR-TB management.

Each patient underwent clinical and laboratory evaluations before enrolment, monthly during the initial phase of treatment, including smear and culture, and bimonthly during the continuation phase. Basic baseline laboratory tests included a complete blood count, hepatic and renal function and HIV testing (Determine®, Abbott Diagnostic Division, Hoofddorp, The Netherlands). Audiometric, psychiatric and ophthalmological evaluations and thyroid stimulating hormone tests were not available.

The main study outcomes were time to culture conversion and whether the patient was cured or completed treatment (favourable outcome) according to definitions in international MDR-TB guidelines.[4] A relapse assessment was performed by clinical and bacteriological screening at 3, 6 and 12 months after cure or completion of treatment.

All information used was routine data from clinical records and operational files, in accordance with WHO guideline forms and definitions.[4] Information was retrospectively reviewed, and data were collected and entered into Excel 2003 (Microsoft, Redmond, WA, USA) by programme staff from January to June 2011. All reported *P* values were two-sided. $P = 0.05$ was considered statistically significant. Clinically relevant risk factors were analysed applying Cox proportional hazards model to generate association estimates with unfavourable outcome and 95% confidence intervals (CIs). The proportionality of risks in the Cox models were verified using Schoenfeld plots.[17] Analyses were performed using *R* statistical package, version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics committee approval

Ethical approval was provided by the local authorities and by the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease.

RESULTS

A total of 289 MDR-TB patients were included. The median age was 31 years (interquartile range [IQR]

Table 1 Characteristics of a cohort of 289 patients with MDR-TB at treatment initiation, Dominican Republic

Characteristic	Patients *n* (%)	Median [IQR]
Sex		
Male	156 (54)	
Female	133 (46)	
Age, years		31 [24.5–40.0]
Diabetes mellitus	28 (9.7)	
HIV	12 (4.5)	
Incarceration	24 (8.3)	
Substance abuse	34 (11.8)	
MDR-TB contacts	46 (15.9)	
Use of SLDs in the past	37 (12.8)	
Group condition		
Failure on Category II treatment	101 (34.9)	
Failure on Category I treatment	109 (37.7)	
Others	19 (6.6)	
Relapse	28 (9.7)	
New	22 (7.6)	
Default	10 (3.5)	
BMI, kg/m² (*n* = 71)		
Men		20.96 [18.9–23.6]
Women		18.18 [15.6–23.6]
Men with BMI <20	17 (21.2)	
Women with BMI <18.5	14 (20)	
Haemoglobin, g/dl*		
Men		12.5 [11.3–12.5]
Women		10.7 [10–12]
Men with <13 g/dl	66 (43.3)	
Women with <12 g/dl	82 (61.7)	
CXR pattern (*n* = 270)		
Bilateral cavitation	128 (44.3)	
Unilateral cavitation	98 (33.9)	
Abnormal CXR without cavitation	46 (15.9)	
EMB-susceptible (*n* = 274)	146 (50.5)	
Delay in treatment from the time of diagnosis, months		7.3 [4.2–12.0]
Number of patients included per year		
2006 (starting end of August)	24 (8.3)	
2007	57 (19.7)	
2008	69 (23.9)	
2009	89 (30.8)	
2010 (until the end of June)	50 (17.3)	
Type of treatment		
Standardised	135 (46.7)	
Standardised + EMB	101 (34.9)	
Individualised	53 (18.3)	
Time to culture conversion, months		2 [2–3]†
0–2	141 (48.8)	
3–4	84 (29)	
5–6	22 (7.6)	
≥7	3 (1)	
Never converted‡	39 (13.5)	
Total	289 (100)	

*Data on some of the characteristics were missing for some patients. Data on total haemoglobin levels were available for 90 patients; normal or abnormal haemoglobin values were available for 259 patients.
†Median time to conversion in months. Includes only those achieving conversion.
‡Patients who never culture converted: early deaths and defaults plus real treatment failures.
MDR-TB = multidrug-resistant tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus; SLD = second-line drugs; BMI = body mass index; CXR = chest X-ray; EMB = ethambutol.

Table 2 Outcomes of a cohort of 150 patients with multidrug-resistant tuberculosis by year of entry into treatment and type of treatment, Dominican Republic

Characteristic	Total *n* (%)	Cure *n* (%)	Treatment completed *n* (%)	Treatment success *n* (%)	Failure *n* (%)	Death *n* (%)	Default *n* (%)	Treatment efficacy*	*P* value†
Results by year of treatment entry									0.656
2006	24 (16)	18 (75)	0	18 (75)	3 (12.5)	3 (12.5)	0		
2007	57 (38)	40 (70.2)	1 (1.8)	41 (71.9)	6 (10.5)	5 (8.8)	5 (8.8)		
2008	69 (46)	45 (65.2)	4 (5.8)	49 (71)	4 (5.8)	9 (13)	7 (10.1)		
Results by type of treatment									0.211
All standardised	105 (70)	73 (69.5)	5 (4.7)	78 (74.2)	6 (5.7)	12 (11.4)	9 (8.6)	92.8	
Standardised	55 (36.7)	40 (72.7)	3 (5.4)	43 (78.2)	4 (7.3)	6 (10.9)	2 (3.6)	91.5	
Standardised+EMB	50 (33.3)	33 (66)	2 (4)	35 (70)	2 (4)	6 (12)	7 (14)	94.6	
All individualised	45 (30.3)	30 (66)	0	30 (66)	7 (15.6)	5 (11.1)	3 (6.7)	81	
Total	150	103 (68.6)	5 (3.3)	108 (72)	13 (8.6)	17 (11.3)	12 (8)	89	

*Calculated as cured + treatment completed/(cured + treatment completed + failures).
†Pearson's χ^2 test.
EMB = ethambutol.

24.5–40.0), with similar sex proportions (54% men). Most of the patients were from Santo Domingo, the capital city (71.6%). Most (72.6%) had previously failed treatment, 9.7% had relapsed and 3.5% had defaulted from treatment; 7.6% were new incident MDR-TB cases. A high proportion of the sample population (15.9%) were contacts of MDR-TB patients. Approximately 7% had no information on previous treatment, as most were from the private sector.

At least 37 patients had used SLDs in the past, particularly fluoroquinolones. Twelve (4.5%) were HIV-infected. Illicit substance abuse was recorded for 34 (11.8%) and 24 (8.3%) had a history of incarceration. On chest X-ray, 78.2% of the patients had cavitation, and for the 259 with an available haemoglobin test, levels were low in 57.1% (<13 g/dl for men and <12 g/dl for women, Table 1).

The median time between requesting DST and starting treatment was 7.3 months (IQR 5.4–14.2); however, this delay steadily decreased over the years. Most patients were treated using a standardised regimen (81.7%). Culture conversion was obtained in 250 patients (86.5%). The median time to culture conversion was 2 months (IQR 2–3), and 78.6% of patients had achieved culture negativity by the fourth month. There were no statistically significant differences in speed of conversion as regards type of regimen or year of treatment. Among the 39 cases (13.5%) who did not convert, 17 were early deaths, 10 defaulted from anti-tuberculosis treatment, and one completed treatment (MDR-TB confirmed by biopsy). Only 11 of those who did not convert were assumed to be failures (nine of these were from the early cohorts, 2006–2008).

Final outcome data were available for all 150 patients who entered into treatment during 2006–2008. Of these, 129 (86%) achieved culture conversion. Overall, 72% (n = 108) achieved a favourable outcome within a median treatment time of 20.7 months (IQR 19–22). Table 2 summarises these results by year of entry and type of treatment. Among the 105 MDR-TB patients who received the standardised regimen, a favourable outcome (cured or completed treatment) was achieved by 74.2% (78.2% standardised vs. 70% standardised+EMB). Of the 45 (30%) patients who received individualised regimens, 66% had favourable outcomes. There were no statistically significant differences in outcome or survival time by type of treatment or previous use of SLDs. Appendix Figure A.1 shows the survival curve by type of MDR-TB regimen.*

Treatment efficacy was calculated as the sum of cured + treatment completed divided by the sum of cured + treatment completed + failures. According to the results for the 150 patients with final outcomes, overall treatment efficacy was 89%. The efficacy of the individualised regimen was 81%, while the efficacy of the standardised regimen was 92.8% (P = 0.056).

Unfavourable outcomes (defined as death, failure or default) occurred in 28% of the 150 patients: 11.3% died, 8.7% failed and 8% defaulted. Death occurred at a median of 7 months after initiating treatment (IQR 3–7), default mostly occurred at 7.5 months (IQR 3.25–17), and failure occurred mainly at 14 months (IQR 12.5–20.5). Among the two HIV-infected cases, one was cured and the other defaulted.

In univariate analysis (Appendix Table A.1), culture conversion after >2 months was found to predict an unfavourable outcome, with a hazard ratio of 2.65 (95%CI 1.37–5.29, P = 0.005). Low haemoglobin and bilateral cavitation on chest X-ray were also predictive of an unfavourable outcome, but with borderline significance. After adjusting for potential confounders in the final multiple regression model,

*The Appendix is available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2013/00000017/00000004/art00017

conversion after >2 months ($P = 0.011$) and bilateral cavities ($P = 0.031$) were significantly associated with unfavourable outcome (Appendix Table A.1).

All but two patients reported some kind of adverse event, with a median of five side effects per patient (IQR 3–6). Most cases presented mild and manageable adverse events, mainly gastrointestinal disturbances. In only one case did the causative anti-tuberculosis medication need to be suspended (psychotic episode); treatment was resumed without cycloserine once the patient's condition had stabilised. A complete description and frequency of the side effects are shown in Appendix Table A.2 and Figure A.2.

A relapse assessment was performed in the 108 patients with a favourable outcome. At least 6 months of follow-up was considered acceptable;[18] however, 83.3% were followed for >1 year (range 8–34 months). Of these patients, 100 were asymptomatic, 4 died, 2 were symptomatic and 2 were lost to follow-up. Overall, only one case was confirmed as an MDR-TB relapse.

DISCUSSION

The question of whether national TB programmes should invest in SLDs and MDR-TB management has been widely discussed.[19] Only when MDR-TB was recognised as a global epidemic was there a need to face this problem under programme conditions.[20] Our experience in the Dominican Republic, working under programme conditions with many limitations, can be considered encouraging, as the country has achieved treatment successes (72%) comparable to the best experiences published to date with individualised management in reference and high-resource settings.[10,12,21–25] Moreover, the success rates are higher than that estimated for GLC-approved programmes (60%),[22] and higher than those gathered in the two meta-analyses analysing MDR-TB treatment outcomes.[5,6] In the meta-analysis published by Johnston et al.,[5] including 31 programmes from 21 countries, a treatment success rate of 62% (95%CI 57–67) was achieved, while in the meta-analysis published by Orenstein et al., studies that combined treatment duration of at least 18 months and DOT throughout had significantly higher pooled success rates (69%) than those who did not (58%).[6] Our experience seems to confirm these results, as the use of DOT and prolonged treatment achieved a similar outcome (72%). Conversely, our experience achieved higher results with standardised regimens than those reported in the meta-analysis (74.2% vs. 54%), while patients in our study who received individualised treatment achieved similar outcomes (66% vs. 64%). At the time of the study, access to some SLDs was limited and high-dose fluoroquinolones were not indicated. Patients receiving individualised treatment may have had *M. tuberculosis* strains with a more extensive pattern of resistance. All of these factors could have contributed to the relatively reduced effectiveness of individualised regimens.

Before 2010, patients waited many months to enter into treatment. Some died during the delay, and the rest were aware of that. This may be why our patients were particularly adherent and able to endure side effects. In addition, as these patients had lived with the disease for many years, some kind of survival effect may have existed.

Regarding the efficacy of the regimens used, our overall result of 89% is among the highest published.[3] The median time to achieve culture negativity, also a reflection of efficacy, was as early as 2 months (IQR 2–3), similar to the 58–99 days published in the TBNET (Tuberculosis European Network) systematic review.[26] The effectiveness of the regimen might have been even better, with fewer deaths and defaults, had intensive care and social support accompanied the treatment.

In the multivariate analysis, only conversions that took place after 2 months ($P = 0.008$) and bilateral cavities ($P = 0.032$), factors not usually analysed in other studies, were significantly associated with unfavourable outcome. Bilateral cavitation was linked to death (15%) and failures (10%), while culture conversion after 2 months was found to be an even stronger risk factor for both (15.6% death, 16.9% failures). Borderline significance was obtained for low haemoglobin ($P = 0.075$), which has been shown to be a worse outcome predictor in other studies.[10,23] Using an EMB-containing standardised regimen also acted as a borderline significant risk factor ($P = 0.054$). Nonetheless, we believe that adding EMB was not in itself a risk factor for defaulting, but a result of residual confounding.

The anarchic use of SLDs in the past was notably frequent in the early years of implementation. The use of individualised regimens fell from 58.3% in 2006 to only 16% in 2010. It appears that the introduction of MDR-TB treatment by the National Tuberculosis Control Programme has reduced the uncontrolled use of anti-tuberculosis SLDs, making individualised regimens, which are often more lengthy and much more expensive, less necessary. The proportion of side effects (median five per patient) observed was greater than in other studies,[27,28] but treatment had to be interrupted for only one patient. Aggressive treatment of side effects and correct drug dosages might have been crucial in preserving treatment activity.

The current study is subject to several limitations, mainly due to use of routine data and resource constraints. Some key information, such as the number of drugs to which each patient was resistant and other potential risk factors, is missing, and data on specific causes of death or default during treatment were unavailable. However, other typical factors associated with worse outcome in MDR-TB management were

probably not significant due to the size of our population. The relapse assessment was performed with many restrictions and with inconsistent availability of culture confirmation in asymptomatic patients. Furthermore, the lack of funding made it impossible to assess the role of reinfection. Nonetheless, the use of routine data and field limitations do not diminish the interest of the findings; on the contrary, they bring them closer to the reality of MDR-TB in low- and middle-income countries.

In conclusion, based on programme conditions and with effective standardised treatment, successful, low-cost MDR-TB management can be achieved even in resource-constrained settings with high initial MDR-TB rates. The overall 86.4% culture conversion and 74.3% treatment success rates achieved with standardised treatment regimens in the Dominican Republic are good examples.

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APPENDIX

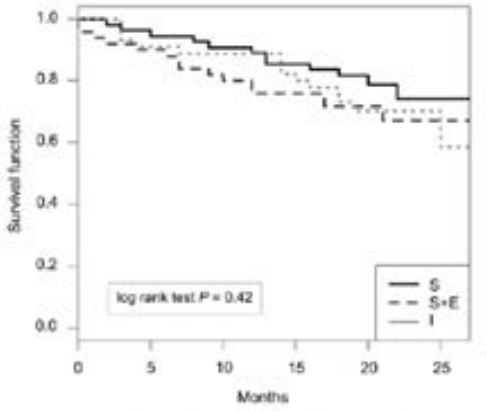

Figure A.1 Kaplan-Meier survival estimates and treatment length in a cohort of 150 patients with multidrug-resistant tuberculosis, Dominican Republic, by type of treatment regimen.

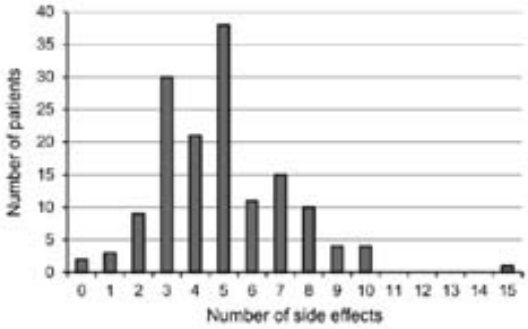

Figure A.2 Number of adverse events reported per case in a cohort of 150 multidrug-resistant tuberculosis patients, Dominican Republic.

Table A.1 Univariate and multivariate analysis of risk factors associated with unfavourable outcome during treatment in a cohort of 150 patients with multidrug-resistant tuberculosis, Dominican Republic

Risk factor	Patients with unfavourable outcome *n/N* (%)	Univariate analysis* Crude HR (95%CI)	*P* value†	Multivariate analysis* adjusted HR (95%CI)‡
Sex				
Female	23/80 (28.7)	1		
Male	19/70 (27.1)	1.01 (0.55–1.85)	0.984	—
Age, years				
≤30	20/78 (25.6)	1		
>30	22/72 (30.6)	1.21 (0.66–2.24)	0.54	—
Diabetes mellitus				
No	38/136 (27.9)	1		
Yes	4/14 (28.5)	1.16 (0.41–3.27)	0.775	—
Substance abuse				
No	35/132 (26.5)	1		
Yes	7/18 (38.9)	1.60 (0.71–3.61)	0.261	—
Contact with MDR-TB case				
No	35/121 (28.9)	1		
Yes	7/29 (24.1)	0.79 (0.35–1.79)	0.571	—
Use of SLDs in the past				
No	32/119 (26.9)	1		
Yes	10/31 (32.3)	1.05 (0.51–2.15)	0.889	—
BMI				
Normal	9/40 (22.5)	1		
Low	13/31 (41.9)	1.93 (0.82–4.52)	0.13	—
Haemoglobin				
Normal	10/49 (20.4)	1		
Low	29/74 (39.2)	2.04 (1.00–4.20)	0.051	2.13 (0.93–4.92)
CXR findings				
Abnormal CXR without cavitation	4/26 (15.4)	1		
Unilateral cavitation	14/51 (27.5)	1.77 (0.58–5.42)	0.315	—
Bilateral cavitation	22/60 (36.7)	2.64 (0.91–7.68)	0.075	3.62 (1.12–11.65)
EMB-susceptible				
Yes	22/80 (27.5)	1		
No	20/70 (28.5)	0.89 (0.48–1.65)	0.718	—
Delay in treatment after diagnosis, months				
≤10	19/75 (25.3)	1		
>10	23/75 (30.7)	1.19 (0.65–2.18)	0.584	—
Type of treatment				
Standardised	12/55 (21.8)	1		
Standardised+EMB	15/50 (30)	1.56 (0.73–3.33)	0.252	2.62 (0.98–7.02)
Individualised	15/45 (33)	13.46 (0.68–3.17)	0.334	—
Speed of conversion, months				
≤2	11/72 (15.3)	1		—
>2	31/72 (40.3)	2.65 (1.33–5.29)	0.005	2.69 (1.25–5.78)
Side effects				
≤5	27/104 (26)	1		
>5	15/46 (32.6)	1.35 (0.72–2.56)	0.351	—

*Cox proportional-hazards regression analyses.
†Log-rank test.
‡The multivariate model included haemoglobin levels, CXR findings, conversion delay, type of treatment, age, treatment delay, SLDs used in the past, illicit drug abuse, diabetes mellitus and contact with MDR-TB case. The variable BMI was not included in the multiple logistic regression model due to the large number of missing values. EMB susceptibility, sex and number of side effects also disrupted the proportionality of the analysis, and were not included.
HR = hazard ratio; CI = confidence interval; SLD = second-line drugs; BMI = body mass index; CXR = chest X-ray; EMB = ethambutol.

Table A.2 Adverse events reported per case in a cohort of 150 patients with multidrug-resistant tuberculosis, Dominican Republic

Organ or system affected	Description of side effect	Frequency *n* (%)
Gastrointestinal	Nausea	144 (96)
	Vomiting	104 (69.3)
	Loss of appetite	51 (34)
	Gastritis	47 (31.3)
	Abdominal pain	46 (30.6)
	Diarrhoea	7 (4.6)
	Constipation	1 (0.7)
Oto-vestibular	Dizziness (motion sickness)	54 (36)
	Hearing loss reported by patient	31 (20.6)
	Tinnitus	12 (8)
	Otalgia	2 (1.3)
Musculoskeletal	Arthralgia (joint pain)	46 (30.6)
Neurological	Peripheral neuropathy	41 (27.3)
	Headache	45 (30)
	Abnormal tremors or shaking	3 (2)
	Vision loss confirmed by physician	1 (0.7)
	Convulsions	1 (0.7)
Neuro-psychiatric	Anxiety	35 (23.3)
	Insomnia	15 (10)
	Depression diagnosed by physician	11 (7.3)
	Psychotic episodes with visual or auditory hallucinations	4 (2.6)
Dermal	Dermatitis and cutaneous eruption	21 (14)
	Alopaecia	1 (0.7)
Renal	Hypokalemia (potassium <3.5 mEq/l)	8 (5.3)
	Renal failure (creatinine >141 mmol/l)	6 (4)
	Hyponatraemia (sodium <136 mEq/l)	1 (0.7)
Cardiovascular	Tachycardia and/or palpitations reported by the patient with or without findings on ECG	8 (5.3)
Endocrine and metabolic	Mastalgia and gynaecomastia (breast pain or increase in size reported by patient)	3 (2)
	Hyperglycaemia (glycaemia >120 mg/dl)	1 (0.7)
	Amenorrhoea	1 (0.7)
Hepatic	Elevation of serum transaminases (<5 times normal levels without other signs of hepatitis)	2 (1.3)
Genitourinary	Dysuria	1 (0.7)

ECG = electrocardiogram.

RÉSUMÉ

CONTEXTE : L'incidence de la tuberculose multirésistante (TB-MDR) est élevée en République Dominicaine (6,6% de cas initiaux). Des régimes standardisés de traitement de la TB-MDR peuvent constituer une solution.

OBJECTIF : Exposer l'efficience des régimes standards dans les conditions nationales de routine.

SCHÉMA : Nous avons revu l'ensemble des patients TB-MDR traités dans des conditions de routine entre le 29 août 2006 et le 30 juin 2010 ainsi que les résultats intermédiaires et finaux. Les patients ont bénéficié de régimes standardisés ou individualisés en fonction de l'utilisation antérieure de médicaments antituberculeux de deuxième ligne.

RÉSULTATS : Nous rapportons la description de la population et les données de négativation des cultures chez les 289 patients TB-MDR. L'âge médian des patients était de 31 ans ; chez la plupart d'entre eux, le traitement par les médicaments de première ligne avait échoué (72,6%). On a obtenu une négativation des cultures dans 78,6% des cas à 4 mois (valeur médiane 2 mois). Parmi les 150 patients traités entre 2006 et 2008, les résultats ont été favorables chez 74% avec un régime standardisé et chez 66% avec un régime individualisé ($P = 0,211$). Les efficacités respectives du régime standardisé et individualisé ont été de 92,8% et de 81% ($P = 0,056$). Le taux de rechute a été d'environ 1%. On a noté une valeur médiane de cinq effets collatéraux des médicaments par patient. Les facteurs de risque de résultats défavorables ont été une durée supérieure à 2 mois avant la négativation des cultures et la présence de cavités bilatérales au cliché thoracique.

CONCLUSIONS : Les régimes TB-MDR standardisés peuvent être efficaces au niveau national, même dans des contextes à ressources limitées.

RESUMEN

MARCO DE REFERENCIA: La República Dominicana es un país de alta tasa de tuberculosis multidrogorresistente (TB-MDR; 6.6% de los casos iniciales). Los tratamientos estandarizados pueden ser una potencial solución para la TB-MDR.

OBJETIVO: Presentar la efectividad de los regímenes estandarizados en condiciones rutinarias a nivel nacional.

DISEÑO: Se revisaron los pacientes tratados de TB-MDR en condiciones de programa desde el 29 de agosto de 2006 al 30 de junio de 2010 mostrando resultados provisionales y finales. Los pacientes recibieron tratamientos estandarizados o individualizados según el uso previo de medicamentos antituberculosos de segunda línea.

RESULTADOS: Se describe una población de 289 pacientes con TB-MDR y se reporta su tiempo de conversión de cultivo. La mediana de edad de los pacientes fue de 31 años, la mayoría procedentes de tratamientos fallidos con medicaciones de primera línea (72,6%). La negativización del cultivo fue obtenida en 4 meses por el 78,6% (mediana 2 meses). De los 150 pacientes tratados entre 2006 y 2008, obtuvieron resultados favorables el 74% de los que recibieron tratamiento estandarizado y el 66% de los que recibieron individualizados ($P = 0,211$). La eficacia de los regímenes estandarizados e individualizados fue 92,8% y 81% respectivamente ($P = 0,056$). La tasa de recaídas fue aproximadamente del 1%. Hubo una mediana de cinco efectos adversos por cada paciente. Más de 2 meses en negativizar el cultivo y la presencia de cavitación bilateral en la radiografía de tórax resultaron como factores de riesgo independientes.

CONCLUSION: Los regímenes estandarizados pueden ser efectivos para el tratamiento de la TB-MDR a nivel nacional, incluso en países de escasos recursos.

Estudio 3

Therapeutic Advances in Respiratory Disease Review

Management of multidrug-resistant tuberculosis: an update

Ther Adv Respir Dis
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Ignacio Monedero and José A. Caminero

Abstract: Multidrug-resistant tuberculosis (MDR-TB) is threatening control of TB in many parts of the world. As a result of limited treatment options, patients have a poor prognosis and low chances of cure. This situation can be exacerbated by HIV epidemics. In some cases, the risk exists of a real shift from susceptible to resistant strains. Despite its relevance, currently there are more contradictions and confusion surrounding MDR-TB than hard evidence. No randomized controlled trials have been performed and published evidence is limited. Rather than just the selection of expensive drugs, MDR-TB management requires well-structured programmes with a comprehensive approach, which involve the actions of a wide range of participants. Even with current investments in research and development, new drugs and vaccines will take many years to be applied in low and middle income countries. The most successful results will depend on the optimization of existing tools. The majority of the patients, even those with extensive patterns of bacilli resistance, have a possibility of cure if current clinical knowledge and effective logistics are applied. This paper is a critical review of current best practice regarding the diagnosis and treatment of MDR-TB.

Keywords: tuberculosis, multidrug resistance, extensive drug resistance, review, treatment

Background

Tuberculosis (TB) still affects more than 9 million people every year and kills nearly 2 million [WHO, 2009b]. At present, in 2010, we are still for beyond from controlling this old disease. The most concerning fact is that treating TB is not clinically complicated and a cure is possible for more than 95% of patients with first-line drugs (FLDs). FLDs were discovered in the 1950s and 1960s, whilst community control measures have been well known since the 1950s [Caminero Luna, 2004].

FLDs are currently the most potent and least toxic remedies for treating TB. The new case standard treatment is based on the use of four FLDs for 6 months [WHO, 2009c]. The duration can be limited to 6 months because of the powerful sterilizing capacity of rifampicin (RIF), which is the quickest effective TB treatment [Fox, 1981]. From a public health perspective, a 6-month treatment that needs full supervision requires strong primary health services. In 2010 however, basic primary health services are not universal, particularly in low- and middle-income countries (LMICs). Moreover, TB is a disease strongly linked to poverty, whilst poverty is strongly linked to barriers in access to health services.

The result is that a curable disease with cheap (the average cost of full drug treatment is US$20) and well-tolerated drugs is still rampaging through many societies. Furthermore, being a disease of the poor, little research and funding have been directed to TB since it was eliminated as a public health problem in developed countries [Monedero and Caminero Luna, 2009]. It is notable that the most effective drugs date from the 1960s and the most common diagnosis tool, the sputum smear, was discovered by Robert Koch himself.

After decades of FLD use, resistant bacilli populations are being selected mainly due to inappropriate treatments, such as monotherapy or masked monotherapy [WHO, 2008a]. The major problem arises when resistance to RIF and isoniazid (INH) occurs. This situation is defined as multidrug-resistant tuberculosis (MDR-TB). INH is the drug with the quickest and most bactericidal activity, thus it clinically

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cures and saves patients' lives. RIF is a strong bactericide. On top of it has the most effective sterilizing activity, killing the dormant and semi-dormant bacilli population [Caminero, 2005]. Accordingly, this results in a cure almost free of relapses. Once resistance to RIF occurs, 18–24-month treatments are required to kill dormant populations and achieve a cure without relapses.

MDR-TB used to be a limited problem localized in TB reference centres. However, after decades of use and misuse of FLDs, more than 500,000 MDR-TB cases emerge annually [WHO, 2008a]. This trend is rising in many settings. MDR-TB status remains unknown in more than 100 countries as a result of restricted laboratory capacity. Therefore, these estimates have a considerable degree of uncertainty and are most probably an underestimation [Zignol *et al.* 2006]. Mathematical models indicate that a change in strains from susceptible to resistant is possible [Blower and Chou, 2004]. In the absence of widely available new drugs, vaccines and diagnosis tools, MDR-TB is a major global public health concern.

As mentioned above, to cure an MDR patient takes 18–24 months with second-line drugs (SLDs), which are less efficacious, more toxic, less tolerated and considerably more expensive [WHO, 2008b]. Nevertheless, with improper treatment schedules or under certain circumstances, resistance could be amplified to SLDs. If fluoroquinolones (FQs) and second injectables, which are the most powerful SLDs, are lost, the prognosis of the patient is severely undermined. This pattern of bacilli resistance (MDR plus one of the FQs and at least one second-line injectable) is the current definition of extensive drug resistance TB (XDR-TB) [WHO, 2007]. Obviously patients with XDR-TB have fewer drugs available for their treatment and their prognosis tends to be poorer.

In September 2009, XDR-TB was reported in 57 countries [WHO, 2009a]. Given the current low capacity to diagnose and the reduced MDR-TB cure rates according to mathematical models, it is possible that the more MDR-TB is diagnosed, the more XDR-TB is created [Blower and Supervie, 2007]. There is a real risk of a TB difficult to cure and expensive. This should be considered a call to arms for better MDR management worldwide.

This article is a comprehensive and critical review of the most relevant and valid evidence in MDR-TB according to two independent researchers working internationally in this field. The aim of this paper is to provide a range of updated practices in MDR-TB management.

Approach to diagnosis

Unfortunately the current tools for MDR-TB confirmation are not easy to use, nor are they completely reliable, cheap or quick [Kim, 2005]. Hence diagnoses need to be optimized, especially in LMICs. To make a diagnosis more cost effective, the suspicion (the first step in diagnosis) should be based on a patient presenting the main risk factors for MDR-TB [Caminero, 2010]. To date the major risk factor is having had previous treatment for TB. The key risk factors in contracting MDR are failure to WHO Category II treatment and chronic cases (more than two cycles of RIF-containing treatment without getting cured) [WHO, 2008b]. The subsequent risk group corresponds to patients who are WHO Category I failures and TB patients probably infected by an MDR-TB index case. The third risk group in MDR-TB is represented by relapses, defaulters, patients who are smear positive at the end of the second month and have previously been treated in the private sector, those working in institutions with MDR outbreaks, patients coming from high primary MDR areas or patients treated under poor National Tuberculosis Control Programme (NTP) conditions [Caminero, 2010]. See Table 1 for more information regarding individual risk factors for TB resistance.

HIV is known to be linked to MDR-TB outbreaks but is not itself a risk factor [Suchindran *et al.* 2009]. Given that HIV is a disease that destroys the CD4 and macrophage (principal barriers to TB disease progression), the susceptibility of HIV patients towards TB disease increases by a hundred [Caminero Luna Ja. Paris, 2004; Selwyn *et al.* 1989]. A significant number of MDR-TB and even XDR-TB outbreaks with high mortality rates among HIV patients have been documented [Gandhi *et al.* 2006; Samper *et al.* 1997; CDC, 1994; Coronado *et al.* 1993].

Once the risk groups have been identified, it is important to note that sputum smear, chest X-ray or clinical facts do not differ from susceptible to resistant TB. MDR-TB is just a distinctive form of TB, which cannot be cured

Table 1. Individual risk factors for resistance.

[1]	Category II* and chronic patients
[2]	Tuberculosis (TB) cases with known close exposure to a multidrug-resistant tuberculosis (MDR-TB) case
[3]	Category I** failures
[4]	Failure of anti-TB treatment in the private sector
[5]	Patients who remain smear positive at second or third month of treatment
[6]	Relapses and returns after default
[7]	Exposure to institutions with MDR-TB populations or outbreaks (e.g. prisons)
[8]	Living in areas with high MDR-TB prevalence
[9]	History of using anti-TB drugs of poor or unknown quality
[10]	Treatment in programmes that operate poorly (especially drug stock-outs)
[11]	Co-morbid conditions associated with malabsorption
[12]	HIV in some settings

*Category II: World Health Organization (WHO) standard treatment for previously treated patients. **Category I: WHO standard treatment for new patients.
Adapted from Monedero and Caminero Luna [2009], Faustini *et al.* [2006], WHO [2004, 2008b].

with RIF and INH. MDR diagnose can, therefore, only be based on a bacteriological assessment.

The most common way to determine resistance is specimen culture and subsequently to confront the bacilli with different antibiotics, known as drug sensitivity testing (DST). DST can be performed in solid or more rapid liquid culture media. These types of techniques are still considered the gold standard. Nevertheless, DST in either modality presents important limitations [Kim *et al.* 2004]. Firstly testing could take from 10 days to 2 months, which for clinical purposes and decision making is clearly too long. In many instances, this period is frequently subject to further delays due to information, logistical and resource deficiencies [Yagui *et al.* 2006; Caminero Luna 2004]. Secondly, DST is a difficult and expensive technique. Regular DST should be performed only at quality-assured laboratories with safe facilities. Finally, *in vitro* DST often shows poor inter-laboratory reproducibility and low correlation with clinical response. *In vitro* and *in vivo* correlation is not optimal, especially for SLDs [Kim *et al.* 2004]. Fortunately, INH and RMP give the most reliable results [Caminero, 2005, 2006; Kim, 2005].

To complement the information given by DST, a complete history of the anti-TB drugs used by the patient and their availability in the country is needed. This is particularly relevant as the use of an anti-TB drug monotherapy for more than 1 month is thought to be one of the main predictors of resistance [Caminero, 2005, 2006; Kim, 2005].

To solve these disadvantages, new genotypic techniques are being designed. Fundamentally, these techniques identify mutations linked to phenotypic resistance. For instance, *rpoB* gene mutation is responsible for 95% of RIF resistance [Telenti *et al.* 1993]. The main advantage of genotypic DST is that it provides results in under 24 hours. In addition, it is relatively cheap and identifies resistance with a high level of reliability [Richter *et al.* 2009]. RIF resistance itself is a strong indicator of MDR, especially in patients previously treated for TB [Aziz *et al.* 2006; Skenders *et al.* 2005]. With knowledge of RIF status, an appropriate treatment can be rapidly identified, improving a patient's prognosis, avoiding amplification and interrupting MDR-TB transmission [WHO, 2008b]. These innovative methods have the potential to change practices in the treatment of MDR-TB.

Current evidence supports these findings [Barnard *et al.* 2008; Miotto *et al.* 2008]. As an example, in a busy TB clinic in South Africa, genotypic DST was tested under routine conditions. The study obtained high sensitivity (98.8%), specificity (100%) and positive (100%) and negative (99.7%) predictive values for MDR detection compared with conventional procedures. However, results for INH are not very sensitive as resistance can be linked to many different mutations [Richter *et al.* 2009].

Rapid testing, not only for INH and RIF, but also for ethambutol, FQ and second-line injectable resistance mutations, is available and currently under research. Initial publications on this issue reveal a high level of agreement with reference techniques, at least for FQ and injectables

[Hillemann *et al.* 2009]. By the time all gene mutations linked to resistance are identified and techniques are standardized, genotypic DST will probably be the best practice, due to its accuracy, reliability, quick results and cost effectiveness. Nevertheless, good quality and proficient laboratories are needed to perform genotypic DST, which could be a barrier for high burden countries.

Focusing on high burden LMICs, novel culture-based DST techniques are being developed and have been demonstrated to be highly cost effective. Principally these are the nitrate-reduction assay and the microscopic observation drug-susceptibility assay (MODS), which have obtained good results in several studies with regard to accuracy, sensitivity and specificity [Richter *et al.* 2009]. These are noncommercial and cheap laboratory techniques. However, relevant work on standardization and biosafety validation remains to be performed.

Approach to treatment

On the whole, either from a clinical or public health perspective, managing MDR-TB requires the application of the same principles as those for an susceptible TB. There are two main requirements for an effective TB treatment: multiple drugs to avoid further resistance and lengthy treatments to kill dormant forms and thus avoid relapses [Caminero, 2005]. Find in Table 3 the main aspects for correct MDR-TB management. Consequently, management of MDR/XDR-TB is long lasting and complicated. Experienced staff should take responsibility for these cases. However, given the high number of cases in LMICs, it is unrealistic for only specialists to treat such cases. Thus a standardized management approach is necessary [Caminero, 2005, 2006; Caminero Luna, 2004]. Standardized SLD regimens are fully appropriate if the MDR-TB patient has received only FLDs in the past. On the other hand, if the patient received FLDs and SLDs, an individualized SLD regimen could be more appropriate.

As mentioned above, TB is one of the most neglected diseases in terms of research and development. This is especially true for MDR-TB. In fact there are probably more contradictions than evidence [Caminero, 2006]. Randomized controlled trials (RCTs) on which the main clinical and control measures should be based should be simply nonexistent. In fact, the vast majority of research knowledge was obtained from INH-resistant TB studies carried out during the 1950s and 1960s prior to the discovery of RIF and FQs. However, once a patient is diagnosed with MDR/XDR-TB, a treatment schedule based on the following logical steps, or similar, should be followed [Monedero and Caminero Luna, 2009; Caminero, 2006].

Step 1. Selection of number of drugs

To cure and avoid resistance amplification, a patient requires a treatment based on new and effective drugs. This relates to the application of anti-TB drugs that have not previously been applied in real or masked monotherapy or with effectiveness assured by DST. From a bacteriological perspective, three new and effective drugs would be sufficient to cure and avoid amplification. However, in the field, not infrequently the effectiveness of the drugs is compromised, especially with SLDs that have a reduced capacity to reach high tissue concentrations and have weak bacteriostatic activity [Caminero, 2006]. Thus, at least four new and effective drugs are necessary to remove all probability of amplification [WHO, 2008b; Caminero, 2006]. Once a patient has MDR-TB, in many setting the only available SLD schedule represent the very last chance of cure. Hence, treatment should not be started until four effective drugs are available for the whole duration of the treatment.

Step 2. Drugs to use

Not all anti-TB drugs have the same effectiveness and toxicity and thus are classified into five different groups [WHO, 2008b; Caminero, 2006] (see Table 2). A rational way to select use is to employ drugs from the most powerful and least toxic to the least powerful and most toxic. For instance, to use as many drugs as possible from group 1 (FLDs), only one drug from group 2 (FQ), only one drug from the group 3 (injectables) and whatever else is needed until reaching four effective drugs from group 4 (toxic and low activity drugs). Finally, use group 5 drugs (low evidence or very low activity) if four effective drugs were not reached with the previous groups. Nevertheless, being very low activity drugs, use 2 group 5 drugs every time you need one extra effective drug.

There is significant controversy on the role of FLDs in MDR/XDR-TB treatment, including high dosages of INH. A recent RCT has demonstrated quicker smear negativation in MDR cases with same side effect profile [Katiyar *et al.* 2008]. Different mutations are linked to INH resistance

Table 2. Rational classification of antituberculosis drugs.

Grouping	Drugs
Group 1: first-line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z)
Group 2: injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3: fluoroquinolones	ofloxacin (Ofx); moxifloxacin (Mfx); levofloxacin (Lfx)
Group 4: oral bacteriostatic second-line agents	ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS)
Group 5: agents with unclear efficacy	clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); clarithromycin (Clr)

Adapted from: Monedero and Caminero Luna [2009], WHO [2008b], Caminero [2006].

Table 3. Fundamental aspects of multidrug-resistant tuberculosis management.

Steps	Considerations
1. Diagnose	Confront information History of drugs: 1 month of monotherapy or single drug intake over a failure regimen could be a strong predictor of resistance. DST: most reliable for R and I; also reliable for Km and FQ; less reliable for E and P; very low reliability for group 4 drugs.
2. Number of drugs	'At least four effective drugs': never used in the past or susceptible by DST taking into account DST reliability and cross-resistance.
3. Drug selection	Use FLDs if still effective. One injectable. One FQ. Use group 4 drugs until complete four effective drugs. If necessary, use group 5 drugs to strengthen the regimen or when four effective drugs are not reached with the previous groups.
4. Length of the injectable	At least 4 months after smear or culture conversion. Longer if there is not three effective drugs during the continuation phase or drugs are from group 5.
5. Surgery	Consider only if: few effective drugs are available; localized lesions; sufficient respiratory reserve.
6. Ideal regimen	Standardized: if there is no use of SLDs in the past. Individualized: use of SLDs in the past or contact with a multidrug-resistant patient who was treated with them (treat with the effective regimen of the index case).

DST, drug sensitivity test; E, ethambutol; FLD, first-line drugs; FQ, fluoroquinolone; I, isoniacid; Km, kanamycin; P, pyrazinamide; R, rifampicin; SLDs, second-line drugs.
Adapted from: Monedero and Caminero Luna [2009], WHO [2008b], Caminero [2006].

and cross resistance with ethionamide through an intricate process. It is becoming clear that a high INH dosage could play a relevant role in MDR treatment [Schaaf *et al.* 2009; Van Deun *et al.* 2004]. In addition, there is a lack of consensus regarding the role of other FLDs such as pyrazinamide (Z) and ethambutol (E) on MDR/XDR-TB, especially taking into account that their DST is not very reliable. Nonetheless, some articles have reported good outcomes in patients using Z and E when they have susceptible DST [Migliori *et al.* 2007; Mitnick *et al.* 2003]. Thus, it is probably justified to include these drugs in the MDR/XDR-TB treatment when the DST demonstrates susceptibility. However, they should not be counted as part of the four new effective drugs as they had been administered for more than 1 month in a treatment that did not cure the patient.

Only one FQ should be used, given that all FQs have the same phenotypic target. Hence, no benefit is achieved by adding more than one while toxicity and cost are increased. The same reasoning applies to second-line injectables. With reference to cross resistance, it is important to consider that old generation FQs probably have complete cross resistance with other FQs of the same generation, but not with other newer FQ. This is particularly important for ofloxacin (Ofx), the FQ most frequently used to date.

Its resistance added to injectable resistance defines XDR-TB, but with the limited evidence available it is probable that 50% of Ofx-resistant cases are still susceptible to levofloxacin (Lfx) and moxifloxacin (Mfx) [Kam *et al.* 2006; Cheng *et al.* 2004]. There are clinical experiences reporting good outcomes with Lfx even in proven Ofx-resistant patients [Yew *et al.* 2003].

Another key issue is an awareness of the best FQ to use in MDR/XDR-TB patients. After a major review it is commonly accepted that ciprofloxacin is a very weak drug in TB and should no longer be recommended in MDR-TB management [Ziganshina and Squire, 2008]. Evidence is scarce regarding other FQ generations as the previous study is the only one that compared Ofx and Lfx in MDR patients [Yew *et al.* 2003]. Results were clearly in favour of Lfx. Given the lack of RCTs, there are two pharmacodynamic and pharmacokinetic studies comparing several FQs *in vitro* [Peloquin *et al.* 2008; Johnson *et al.* 2006], which have reported the best effectiveness surrogate parameters to high dosage Lfx (1000 mg). This is superior even to Mfx. Probably in terms of cost effectiveness the best drug to use is Lfx at 750–1000 mg per day.

The initial approach with regard to injectables is unclear. Probably, according to the limited literature available, the best choice of injectable in terms of cross resistance and toxicity could be the following sequence: capreomycin, then kanamycin and finally amikacin [Tsukamura and Mizuno, 1980; Tsukamura, 1969]; however, capreomycin is usually very expensive and difficult to acquire. Streptomycin is no longer recommended in MDR treatment mainly due to worldwide high levels of primary resistance and linked INH resistance [WHO, 2004, 2008b].

Step 3. Length of injectable treatment (intensive and continuation phases)

Basically, the difference between the intensive and continuation phases is injectable use. Together with FQs, injectables are the most powerful drugs for use in MDR-TB, although the longer they are used, the higher the toxicity becomes. In theory, it is safe to suspend the injectable and pass to the continuation phase when the bacilli burden has been reduced to an almost undetectable level. This occurs when the microscopic observations are negative and specifically when there are two negative microscopic observations with 1 month in between. However, in the field, a more prudent approach is recommended to preserve the effectiveness of the continuation phase: retain the injectable for at least 6 months and at least 4 months after negative culture [WHO, 2008b]. In this way, the cure is maximized and resistance amplification probabilities are minimized. The injectable can be withdrawn safely only when at least three effective drugs remain in the regimen. Lengthy treatments with injectables should be considered if fewer than three effective drugs remain in the continuation phase or are very weak drugs [Caminero, 2006]. This could be relevant in XDR management where if the injectable is withdrawn, the remaining treatment schedule is weak. The risk of resistance amplification exists on a weak continuation treatment schedule. In such cases long injectable treatments of 6, 12 or even 18 months are to be assumed. Intermittent therapy (three times a week) can be considered in very long treatments or where there is a high risk of toxicity [WHO, 2008b]. When smears and cultures turn negative, the bacillary load is notably reduced. After two negative cultures or smears separated by 1 month, the intensive phase of treatment can be stopped. The continuation phase without injectables ought to last for 18 months.

Step 4. Surgery

The role of the surgery in MDR-TB is limited to exceptional circumstances [WHO, 2008b; Caminero, 2006]. These are mainly cases with fewer than four effective drugs available for their schedule (mostly XDR), if lesions are isolated and localized and where there is sufficient respiratory reserve [WHO, 2008b; Caminero, 2006]. The appropriate selection of candidates was the key factor for good performance in the only study carried out in LMICs [Somocurcio *et al.* 2007]; however, morbidity and mortality were often considerable.

Special cases

Given that the evidence for standard cases is limited, the approach for special cases is particularly controversial. At the moment the same rules as for adults are applied to children [WHO, 2008b]. Apparently children have lower levels of side effects with SLDs. Many professionals have significant doubts about use of FQs in children, but current evidence has proved that FQs were safe in more than 7000 cases [Burkhardt *et al.* 1997].

Special consideration should be given to pregnant women. Nowadays, the best practice is to avoid pregnancy during TB disease, but if this occurs, ideally MDR treatment should be delayed until after the second trimester. Injectables have proven to be teratogenic drugs and doubts remain about thioamides (ethionamide and protionamide). If possible, both groups should be avoided. If there is no other option, the best recommendation is to use capreomycin out of the injectables because of its lower teratogenic profile [WHO, 2008b].

Little information is available regarding comorbidity conditions common to MDR-TB such as diabetes mellitus. However, some publications have reported worse outcomes and greater rates of relapse [Bashar *et al.* 2001]. Concerning MDR-TB and HIV, there are contradictory opinions as regards additive toxicities, malnutrition and other critical comorbidities. Probably the most controversial issues concern when to start antiretroviral therapy, how best manage (IRIS) and prevent immune reconstitution syndrome. There is as well a great lack of knowledge, for instance concerning drug to drug interaction while funding is very limited for these programmes in LMICs [Harries *et al.* 2009; Scano *et al.* 2008]. However, more is starting to become known about the interactions between SLDs and antiretroviral agents [Coyne *et al.* 2009], and it is expected that some of these questions will be answered in the near future.

In the case of new TB patients being MDR close contacts, treatment should be based on the same pattern of bacilli resistance of the index case if known, or on the effective regimen given to the former [Caminero, 2006]. Amendments can be made after DST results in case of susceptibility.

One important and unresolved issue is what to do with MDR-infected contacts (latent TB infection). Once again, evidence is limited to expert opinions [Fraser *et al.* 2006]. This could be crucial in HIV HBCs. To date there is no approved chemoprophylaxis schedule for contacts and the current recommendation is to be under close supervision [WHO, 2008b].

No clear guidelines exist for XDR cases since no RCTs are available. In addition, XDR conditions can be quite different from patient to patient depending on the pattern of resistance and previous drugs used. As well as issues relating to the patient, the TB programme, resources, availability of drugs and social support prognosis will have an impact. In fact there are settings where XDR cases have obtained similar cure rates than MDR cases. Conversely, in other settings, XDR cure rates were extraordinary low [Sotgiu *et al.* 2009]. As a common approach, previous guidance for MDR diagnosis and treatment is suitable to perform diagnose and treatment for XDR cases. However, in XDR management, as four effective drugs are often not available, the use of multiple drugs (more than 6–8 in some settings), lengthy treatments (often more than 24–30 months), lengthy injectable use, surgery and others have to be considered [Sotgiu *et al.* 2009; WHO, 2008b].

Other key tools for MDR-TB success

Something that might seem obvious, yet is crucial, is the presence of a strong TB programme. It is thought that introduction of an MDR component into a weak Tuberculosis Directly Observed Treatment Short-course (DOTS) programme could quickly lead to the development of XDR with decreasing effectiveness of the susceptible TB programme [Sterling *et al.* 2003]. Clinical experiences and mathematical models conclude that poor treatments paradoxically are worse than no treatment. A narrow focus on MDR-TB therapy could make a bad situation worse by increasing the number and pattern of resistance of circulating strains in the community [Coker, 2004; Pablos-Mendez *et al.* 2002].

Without an integrated programme structure, all the approaches mentioned here are likely to fail. The DOTS strategy is at present the best framework for managing susceptible and resistant TB. Without a good DOTS framework, failures, defaults and drug shortages are more likely to occur. At the same time MDR committees comprising laboratory staff, pharmacists, clinicians and social workers are needed to increase the chances of success [Nathanson *et al.* 2004], improve decision making and ensure a coordinated approach. On the other hand, strong side effect management is needed since many of the SLDs have a toxic profile. Ancillary drugs need to be easily available. In addition, to avoid defaults, regular monitoring visits with basic clinical blood tests, and treatment support are required and ancillary drugs need to be easily available [WHO, 2008b].

At the same time, having a strong DOTS programme limits the creation of new MDR cases. Actions to limit the creation of MDR cases under

programme conditions are essential [Caminero, 2008]. For instance, in the case of an intermittent continuation phase, adherence to the maximum and assuring at least three intakes per week is necessary. Other basic practices to avert MDR is the use of anti-TB fixed-dose combinations, and extend the intensive phase by 1 month in the case of smear positivity at the end of the second month [Caminero, 2008].

Another key tool in limiting the burden of MDR/XDR-TB is the use of infection control measures. The importance of infection control was highlighted after the Tugela Ferry deadly XDR outbreak among HIV-positive patients [Gandhi *et al.* 2006]. It was discovered that most of the cases were infected at health facilities. In fact, not all hospitals are prepared to admit MDR/XDR cases. In many settings the most simple, essential and effective administrative infection control measures are not followed [WHO, 2009d]. In terms of risk reduction, simply separating the MDR/XDR patients into a different room, which is well ventilated and has natural light, can make a vast difference [Bock *et al.* 2007].

Finally, it is important to mention that TB, and especially MDR-TB, is more than a clinical problem. Programmes have to deal with patients with social difficulties and poverty [Atre and Mistry, 2005; Yong Kim *et al.* 2005]. Behind an MDR patient, there is always a sad story. Clinicians should open their minds to social diseases and social solutions. Supportive nurses, counsellors and social workers play a relevant role in MDR-TB [Farmer *et al.* 1998]. Economic aid and food support as well as comprehensive and psychosocial approaches are strongly linked to positive outcomes in these lengthy and toxic treatments [Mitnick *et al.* 2008; WHO, 2008b]. It makes no sense to spend thousands of dollars on an expensive drug cocktail if the patient defaults because of hunger. Unfortunately, this tends to happen in many MDR programmes all around the world.

Promising approaches and tools

Concerning current drugs, an important issue to solve is the role of new generation FQs such as gatifloxacin and Mfx. If these have a similar sterilizing activity to RIF it should be possible to shorten MDR treatments. Ongoing RCTs will provide answers to some of these questions in the near future.

Another promising approach, as previously mentioned, is the use of high dosages of INH, which proved effective in an RCT on MDR-TB [Katiyar *et al.* 2008]. In another study, a treatment using a schedule of high INH dosages and clofazimine demonstrated optimal cure results [Van Deun *et al.* 2004]. Clofazimine could be a relevant MDR drug in the near future according to clinical experiences, although to date, limited published evidence is available.

Linezolid (Lzd) a group 5 drug, could be a potential tool, especially in XDR-TB treatment [Condos *et al.* 2008; Ntziora and Falagas, 2007]. More evidence of its benefits is emerging, especially when used in lower and safer dosages [Migliori *et al.* 2009; Park *et al.* 2006]. Lzd is suitable for XDR and MDR cases, but its use should probably be limited to severe cases, for example, those resistant to more than seven drugs [Migliori *et al.* 2009]. However, Lzd has only proved so far to have poor bactericidal activity [Dietze *et al.* 2008]. In addition, due to its price and toxicity profile (lactic acidosis and optic or peripheral neuropathy and others) [De Vriese *et al.* 2006], it is not a suitable drug for most LMICs, where the majority of MDR cases exist.

There are several drugs emerging with innovative actions [Coyne *et al.* 2009; Van Den Boogaard *et al.* 2009], which could transform the MDR landscape in the future. New Rifamycins, such as rifalazil, have had good preliminary results. New family drugs such as diarylquinolines have demonstrated early bactericidal activity against susceptible and MDR-TB. From these, the component TMC207 is one of the most promising future TB drugs [Diacon *et al.* 2009]. Nitroimidazoles, another new class of drugs, have candidate molecules such as PA-824 and OPC-67683, which have demonstrated potent activity against active and dormant forms. Others compounds such as SQ109 and nitrofuranylamides have demonstrated activity *in vitro* [O'Brien and Spigelman, 2005]. Nevertheless these and other molecules are unlikely to be ready at an affordable price for clinical use in LMICs in the next 10–15 years [Monedero and Caminero Luna, 2009].

Significant efforts have been made towards a vaccination, which would probably be the best tool for tackling TB. Likewise, this scenario would take no less than 10–20 years to be introduced into LMICs. In 2010, taking into account the delays in the introduction of new solutions, probably the wisest approach in TB and MDR-TB

management is to optimize the current tools through low-cost and low-risk policies such as those mentioned in this paper to prevent an increase in drug resistance and, once it has appeared, to improve its management [Monedero and Caminero Luna, 2009].

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Estudio 4

MDR-TB

A basis for the clinical management of complicated MDR–TB cases

Ignacio Monedero and Sandya Holkar summarise best practice in the often lengthy and complex managemenet of multidrug-resistant tuberculosis

Summary

Successful multidrug-resistant tuberculosis (MDR-TB) treatment and programme performance is possible even in complex circumstances. Governments are subject to strong pressure from donors concerning both DOTS (directly observed treatment, short course) expansion initiatives and especially MDR management.[1] Nevertheless, anyone assuming an MDR programme can be launched just with money and drugs is probably labouring under a grave misapprehension. A sound understanding of the clinical management of both susceptible and resistant TB is one of the basic fundamentals. The substandard use of second-line drugs is not only measured in low cure rates but in drug resistance amplification in the community, and hence potentially circulating extensively drug-resistant (XDR) TB strains.

From a clinical point of view, MDR management is lengthy and complicated, involving the entire range of problems attendant upon chronic disease plus the high toxicity profile of second-line drugs. In addition, in developing countries with high HIV/TB co-infection levels, the complexity in terms of clinical and drug management issues increases. Poverty and lack of access to care and treatment can reduce adherence and further complicate the recovery process. This paper provides a brief summary of the best practice in MDR-TB patients including the most frequent side-effects and practical advice on managing TB/HIV co-infection based upon the most recent evidence.

MDR-TB often requires complex drug management

Background

Multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to isoniazid (H) and rifampicin (R) is a major concern in global TB control. It is thought that more than half a million MDR-TB cases emerge per year.[2] The issue is more serious taking into account the length and cost of treatment, the serious side-effects and the low cure rates compared with susceptible cases. Unfortunately, low cure rates are especially common in those countries with high TB/HIV co-infection rates.[3] HIV per se is not a risk factor for MDR-TB.[4,5] However, it is has been widely linked to MDR or even XDR-TB outbreaks.[6,7] People living with HIV, by reason of their impaired immunity, are more likely to become infected with TB, more than 100 times more likely to develop TB disease from infection, and also more likely to die from it.[8] Due to this synergy of HIV and TB, Africa demonstrates an unusual scenario whereby the total number of MDR cases remains relatively low but the incidence of new cases is particularly high.[9] It is thought that airborne XDR/MDR-TB transmission to primary cases is playing a crucial role in high HIV burden countries. The deadly XDR-TB epidemic of KwaZulu Natal in South Africa is probably the most studied example.[6] Around 98% of the patients died within 2 weeks of diagnosis; most having been infected by the same source. Major efforts towards infection control and appropriate MDR-TB management are urgently needed. Tackling HIV is not easy, and neither is combatting MDR/XDR-TB. Managing both at the same time is even more complex. New anti-TB medications and ideally an effective TB vaccine are desperately needed, but they will not be ready for use in developing countries within the next 10–15 years.[10]

There is a pressing need for training of healthcare workers since suboptimal clinical management of a patient can amplify resistance into MDR within a couple of months. However, curing that same patient once they have developed MDR-TB can take up to 2 years.[11] Furthermore, the cure rates for MDR-TB and specially XDR-TB tend to be less than 60%[5,12] and failure and mortality rates are high.[13]

In addition to these challenges, wide-scale MDR-TB management is comparatively a new field. Consequently, not many randomised controlled trials (RCTs) exist

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and to some extent this has generated more controversies than useful evidence.[14] It is only recently that a robust consensus on correct management is being achieved.[11] However, even in low-income settings with limited human resources, there are many effective measures which can be applied, just using the current knowledge and public health tools.

The aim of this paper is to provide a short catalogue of good practices to manage the majority of complicated MDR cases, describing the most common problems and the most likely solutions according to current literature. Given the urgent need for practical and simple approaches to managing MDR complex conditions, this paper aims to provide rapid and succinct guidance on management of MDR-TB and avoidance of common errors even where resources are most scarce. It is also hoped that it will serve as an starting point for further reading of more specialised MDR-TB guidelines and literature.

Basis for susceptible TB management

Susceptible TB is mainly diagnosed by sputum smear, which is cheap, quick and easy to accomplish even in resource-scarce settings.[15,16] It is not only highly specific but also informs whether or not a patient is contagious (specificity of 95%). However, it is not very sensitive, as it can only detect approximately 70% of active TB cases in optimal conditions. In high-HIV settings this figure can be further reduced as many people living with HIV (PLHIV) with active TB develop smear-negative forms. Culture offers a considerable increase in sensitivity (diagnoses up to 85% of cases) but in most high-prevalence settings results are unavailable before 1–3 months, and hence are of no use for immediate clinical management.

There are two basic principles for effective TB treatment:[8,17]

1. Use of *several drugs* to avoid resistance amplification. If a bacillary population is exposed to only one drug, then just by chance and spontaneous mutation 1 out 1 million of the bacilli will be a natural mutant resistant. In a patient with cavitary disease, the number of bacilli within the patient is approximately 1000 million. Hence if exposed to monotherapy, almost all of those bacilli will die but from 100 to 1000 natural mutant resistants will remain. After a couple of months there will again be 1000 million bacilli but now all will be of resistant strains. To avoid this circumstance, it is recommended that the initial phase of TB treatment contains at least four drugs. First-line drugs are to date the most powerful drugs available to treat TB.
2. Lengthy treatments: *Mycobacterium Tuberculosis* is a very slow growing bacterium. Furthermore, depending on pH and oxygen conditions on the lesions, bacilli could present different metabolic populations. Some of them are metabolically active, like in the cavities, where the bacilli divide and create disease. Conversely without oxygen and favourable pH conditions bacilli turn metabolically inactive or dormant. Dormant bacilli are not easy to kill and if they turn active will eventually create relapses. Rifampicin (R) is to date the drug with the greatest capacity to kill dormant forms. Thanks to rifampicin, treatment length can be reduced to 6 months. Without its powerful sterilising effect, the duration of TB treatment stretches to 18–24 months.[11]

Current treatment recommendations[13,16] are 2 months with four drugs (R, H, pyrazinamide (Z) and ethambutol (E)) plus 4 months with two drugs (RH). Daily treatment is preferred, especially in high-HIV settings where there are demonstrably better outcomes and reduced relapse and death rates.[18,19] For susceptible disease, this treatment combination can cure up to 97% of patients.[8]

Bases for MDR-TB management

MDR-TB is simply TB disease that can not be cured with the most effective drugs to date, i.e. isoniazid and rifampicin. Diagnosis can not be confirmed with sputum, clinical picture or chest X ray (CXR) but only from drug susceptibility testing (DST). This can be done via culture (liquid or solid), with, however, a likely delay of 1 to 4 months or more. Usually liquid culture is quicker but contamination rates tend to be higher. DST, a technique developed more than 50 years ago, is most reliable for R and H.[20] For fluoroquinolones (FQs) and second-line injectables it is very reproducible but less reliable.[21] This means results can be consistent between different laboratories, however the clinical relevance of the result can be inaccurate. Unfortunately, regular DST is not very reliable for other second-line drugs (SLDs) and in the particular case of Z, cycloserin (Cs), ethionamide (Eth) and PAS, DST can confuse clinicians more than it helps.[21,22] Consequently, having a detailed history of the previous drug history of the patient is crucial. An important issue to keep in mind is that currently the best predictor of resistance in TB is the use of a drug as monotherapy for more than 1 month.[17] In clinical practice this translates into the most common error in TB clinical practice leading to drug resistance: adding one drug to a failing regimen.

Fortunately, new rapid DST techniques based on PCR technology and genetic mutation detection are able to provide susceptibility results within 2 hours to 5 days. Being not only rapid but also offering more reliable results, these new techniques are starting to be introduced in many different settings with good results under real conditions.[23]

Before starting MDR-TB treatment, a DST result demonstrating resistance to R and H plus an accurate history of drugs is mandatory.[11] Also, identification of Mycobacterium species is fundamental. Mycobacterium other than Tuberculosis (MOTTs) can have a DST pattern of disease of MDR. These different sorts of bacilli require a different treatment that is less toxic, less expensive, and shorter than MDR-TB treatment. It is thought that in many MDR-TB programmes, a substantial proportion of the patients actually have MOTT rather than MDR-TB especially in high-HIV settings.

The principles for MDR-TB treatment are the same as for susceptible TB:[11]

1. *At least four effective drugs:* drugs should be chosen starting from the most effective and least toxic (FLDs) and scaling-up to the least effective and more toxic.

MDR-TB

Table 1 Rational classification of anti-tuberculosis drugs. Adapted from references 10, 11, and 14

Grouping	Drugs
Group 1 First-line oral agents	Isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z)
Group 2 Injectable agents	Kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (Sm)
Group 3 Fluoroquinolones (FQs)	Ofloxacin (Ofx); moxifloxacin (Mfx); levofloxacin (Lfx); gatifloxacin (Gfx)
Group 4 Oral bacteriostatic second-line agents	Ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); P-aminosalicylic acid (PAS)
Group 5 Agents with unclear efficacy	Clofazimine (Cfz); amoxicillin/clavulanate (Amx/Clv); linezolid (Lzd); imipenem/cilastatin (Ipm/Cln); thioacetazone (Thz); clarithromycin (Clr); high-dose isoniazid (high-dose H)

Anti-TB drugs are classified according into five different groups (see Table 1). The pillars of category IV treatment are FQ and second-line injectables, which are by far the most bactericidal drugs among second-line drugs. Add drugs from group 4 (weak and toxic drugs) until complete four effective drugs and use all possible first-line drugs to which the patient is or might be susceptible. When over an MDR-TB case, resistance to one FQ or one second-line injectable emerges, the disease is defined as XDR-TB.[24] In that case, drugs available are less and consequently prognosis is worst. Usually the use of group 5 drugs is necessary to treat XDR-TB cases. However, as drugs from this group are very weak or have little evidence base, use two drugs from this group, to account one new 'effective drug'.[11]

2. *Long treatment:* because the sterilisation power of R is lost, treatments are extended to 24 months. Injectables are recommended to be used for at least 4 months after culture turns negative and usually 6 months.[11] If there is resistance to FQs the continuation phase is weak after injectable withdrawal and longer treatment with injectables might be needed given the lack of a powerful drug in the continuation phase.
3. The choice between using individualised versus standardised regimens is a long and hotly debated issue. Though in developing countries, for patients who have never used SLDs in the past, standardised regimens can achieve good levels of treatment success with lower cost, less specific training, and reduced risk of treatment improvisations.[14]

Surgery is another issue to consider. This option, with the high associated mortality and morbidity, is only indicated in a limited number of patients who meet the following conditions: fewer than three or four effective drugs available for treatment, single and localised lesion, and sufficient respiratory reserve after the resection.[14,23] Few patients fulfil these criteria.

Clinicians should be alert to the problem of cross-resistance among anti TB drugs.[11,26] Rifampicin has almost full cross resistance with other rifamycins. Isoniazid and ethionamide may also have cross resistance if there is isoniazid resistance at low isoniazid concentration (inhA mutation). Old generation FQs (ciprofloxacin–ofloxacin) are generally cross resistant within them. However, some activity may still remain using new generation FQs (levofloxacin, gatifloxacin, moxifloxacin) even if resistance to old generation FQs exists. Note than ciprofloxacin is currently not recommended to treat MDR-TB due to reduced efficacy.[27]

Due to the considerations of toxicity and cross resistance, the order of preference for second-line injectables becomes: capreomycin, them kanamycin, and lastly amikacin.[28,29] Streptomycin is not recommended currently for MDR-TB treatment given the high resistance levels among initial H resistant strains.

Although clinical improvement is useful, monitoring of MDR as a disease can only be done through/by bacteriology. Follow-up of treatment should preferably be based on culture.[11] The number of colonies (solid culture) can be help to show progress or risk of failure during the treatment.

Drug side-effects and possible solutions

First-line drugs

The most common side-effects from first-line drugs is hepatoxicity.[8] High levels of liver enzymes (particularly ALT) should be an alert. Having levels four times higher than normal is considered as hepatitis and treatment should be stopped until liver enzymes return to normal. The drugs should be reintroduced one by one with gradually increasing dosage over 2 weeks, starting from the least hepatotoxic.[13,30] In this sense the rational order of introduction is E–R–H–Z.

Rifampicin is an inducer of cytocrome p450, hence can reduce the levels of other drugs including oral contraceptive, proteasa inhibitors, and nevirapine. Specific advice should be given on this in TB/HIV patient recommending ARV treatments based on efavirenz or tenofovir plus two NRTIs.[31]

Optic neuritis is an infrequent (less than 1 in 500 treatments) but concerning side-effect of ethambutol (E). It usually starts with colour distortion and blurred vision. If this happens, treatment should be stopped immediately. The use of E among children has being an issue of much debate.[32] Currently it is widely recommended to them at a 15–20 mg/kg/day dosage, where the occurrence of optic neuritis is less frequent.[13]

Table 2 MDR-TB management. Fundamental aspects. Adapted from references 10, 11, and 14

Steps	Considerations
1. Diagnose	Information required? • History of drugs: 1 month of monotherapy or single drug intake over a failing regimen could be a strong predictor of resistance. • DST: most reliable for R and H; also reliable for Km and FQ; less reliable for E and Z; very low reliability for group 4 drugs.
2. Number of drugs	'At least four effective drugs': never used in the past or shown to be susceptible by DST (taking into account DST reliability and cross-resistance)
3. Drug selection	• Use first-line drugs if are still effective • One injectable • One FQ • Use group 4 drugs until a regimen with four effective drugs has been reached. If necessary, use group 5 drugs to strengthen the regimen or when with previous groups the number of four effective drugs is not reached. One drug from group 5 accounts as 'half effective drug'.
4. Length of the injectable	• At least 4 months after smear or culture conversion; longer if there are not three effective drugs used during continuation phase or if drugs used are from group 5
5. Surgery	Consider only if: • few effective drugs are available • localised lesions • sufficient respiratory reserve
6. Ideal regimen	• *Standardised*: if there is no use of second-line drugs in the past • *Individualised*: use of second-line drugs in the past or contact with an MDR patient who used second-line drugs (treat with whichever regimen was effective for the index case)

Second-line drugs

Current evidence indicates that *FQs*, have a relatively safe profile even in children.[33]

Injectables, including streptomycin, have quite a toxic profile, and can cause vestibular toxicity (vertigo), hearing loss and renal insufficiency, plus teratogenicity (safety class C for Cm and class D for Sm, Am, Km).[11] Toxicity is mainly by cumulative dosage hence for long treatment, administration can be reduced to three times weekly. Where conditions are suitable, the drug should be administered intravenously to avoid painful injections especially among malnourished patients.

Cycloserin can cause disturbances of the central nervous system ranging from nightmares to depression, psychotic syndrome and suicidal tendencies. These symptoms are rarely but increasingly described.

Ethionamide (Eto) or prothionamide (pto): these effectively identical drugs are badly tolerated because of nausea, vomiting, stomach ache, and diarrhoea.

PAS: probably the worst-tolerated drug having extremely unpleasant (although not life-threatening) gastrointestinal symptoms. If given with Eto/Pto tolerance side-effects are even worse. Concomitant use can also lead to alteration of the equilibrium of thyroid hormones.

Tips for most frequent side-effects

Using category IV treatment, we can predict that side-effects will occur; hence clinicians must be alert to their occurrence. Nevertheless, despite the wide range of adverse events among second-line drugs, the most frequent ones which have the greatest impact on adherence are easy to diagnose and treat.[11,34]

1. *Nausea, vomiting, and diarrhoea* are the most common side-effects and are relatively easy to control if omeprazol or similar drugs are used at high doses. Antacids are not recommended due to interactions with FQs absorption. Drugs can be given with foods such as milk and banana that do not decrease absorption, while improving tolerance and possibly adherence if given for free at facilities. Drugs that are poorly tolerated such as PAS, Eto/Pto, and Cs can be introduced gradually (drug ramping).[11] The patient starts on a one-third dosage and it is increased every 4–5 days, achieving full dosage within 2 weeks.
2. *Arthralgia*, which is also a common side-effect, can be easily tackled with paracetamol or non-steroid anti-inflammatory drugs.
3. *Dizziness, vertigo, and hearing loss* are most commonly caused by second-line injectables. If early symptoms appear, particularly hearing loss (described by the patient or by audiometry), then consider reducing the injectable treatment to three times weekly. Regrettably, hearing loss is irreversible. However, early withdrawal of injectable would be a mistake if the continuation phase is weak or the smears or cultures remain positive, since the patient would probably develop amplification of resistance in the continuation phase and failure. Keep in mind that Category IV is, especially in developing countries, the last chance for this patient to achieve cure.

Other less common side-effects include *numbness and paresthesia*. A suitable approach for these is to provide from 50–150 mg of pyridoxine (Vit B6). To prevent central and peripheral nervous system alteration it is

currently recommended to use 50 mg pyridoxine for each 250 mg of cycloserine (750 mg average Cs dose). In case of seizures, even 300 mg of pyridoxine plus regular anticonvulsive therapy can be used.[11] Behavioural changes are also common, especially depression, in which Cs probably plays a major role but nevertheless, other important factors like chronic ill health and poor socioeconomic conditions also contribute. Treatment with an antidepressant plus psychotherapy and socioeconomic support improves the quality of life of the patient and this increases adherence to treatment. Regarding psychotic disorders, neuroleptics such as haloperidol or risperidone plus pyridoxine can be used. In case of hypothyroidism, replace thyroid hormones when necessary. At the end of the treatment and Eto/Pto and PAS discontinuation, hormone levels tend to return to normal.[11]

Bases for MDR-TB and HIV management

Management of these two diseases concurrently is one of the major challenges for TB control. However, this is the certain reality for many sub-Saharan African countries. Patients are usually diagnosed late in the course of HIV infection with a low CD4 count, presenting with malnutrition and several opportunistic diseases, TB among them.

According to current evidence the best clinical questions to screen for TB among HIV infected patients are: asking about cough of any duration, fever of any duration and night sweats in the last 3 weeks or more.[33] Nutrition treatment and vitamin supplementation (especially vitamin B6) should start as soon as possible together with cotrimoxazole preventive therapy which should continue at least until the end of TB treatment.[13] Other opportunistic diseases should be excluded or treated, especially Cryptococcus meningitis. Treatment of opportunistic disease also avoids development of immune reconstitution inflammatory syndrome (IRIS) when ARV treatment is commenced.

TB treatment should start as soon as possible to avoid patient death. If patient has susceptible TB disease then Category I treatment is to be order. HIV-infected patients often have problems of malabsortion hence daily treatment with rifampicin is preferred and leads to better cure rates and fewer relapses.[15,18,19]

ARV initiation is mandatory whenever TB is present, regardless of the CD4 count.[18] The timing for ARV initiation has been a subject of much debate, although currently the best cure and lowest death rates have being demonstrated among those starting ARV shortly after (2 weeks) or concomitant with TB treatment initiation.[36] Preventing and treating IRIS (1–2 mg of prednisone/kg/day) resulted in no deaths or serious side-effects in patients in the integrated treatment group. The only exception to this occurs with immune reconstitution due to cryptococcal meningitis; which *must* be treated simultaneously with TB, while in all other cases, the sooner ARVs are started, the better the cure rates obtained.

Regarding drug interactions between TB and HIV, the key issue is rifampicin which is both the best anti-TB drug ever and a powerful inductor of cytochrome P450. Cytochrome P450 reduces the concentration of many ARVs, especially protease inhibitors (PI) and NVP. Currently the recommendation while using rifampicin are 2 nrti (nucleoside reverse transcriptase inhibitors) plus efavirenz, or alternatively 3 NRTI. Where protease inhibitors are unavoidable, the ritonavir boosting dose should be increased from 100 mg to 400 mg but this regime is often poorly tolerated.[31]

MDR treatment lacking rifampicin avoids the principal interaction problems. Nevertheless, clinical complexities and second-line drug toxicities are added. MDR-TB patients tend to be in the worst clinical situation having spent longer in a deteriorating state, more so if they are HIV infected. Gastrointestinal intolerance is often severe due to malnutrition and parasitic diseases; electrolyte alterations like hypokalaemia (especially when on capreomycin treatment) and overall renal insufficiency are more frequent. Overall, evidence on drug to drug interactions between second-line drugs and ARV are still limited.[37]

Particular care and monitoring of these patients is needed especially at the beginning of treatment where other opportunistic diseases, serious clinical conditions (malnutrition, cavitary, meningeal and miliary TB), drug intolerance, side-effects, additive toxicities, and IRIS are all occurring within a short time frame. See a basic approach for TB/HIV patients in Box 1.

However, implementing these measures at the community level is not useful if patients and visitors are getting MDR-TB infected during their stay at the hospital. Good understanding of the disease plus effective administrative infection control measures are strongly needed in high-HIV-prevalence countries.[38]

Other special conditions

Regarding management of children, the same rules apply as for adults. Given that the bacillary load in children is lower, probably three effective drugs and shorter treatments could be used.[11] However, there is no robust evidence to support these statements. In terms of

Box 1 Fundamental aspects of TB/HIV patient management

1. Initiate TB treatment as soon as possible and preferably containing rifampicin on a daily basis.
2. Initiate CPT as soon as possible. Keep CPT at least for the whole TB treatment duration.
3. Nutritional support and vitamin replacement.
4. Rule out and treat other opportunistic diseases (especially Cryptococcal meningitis).
5. Start ARVs in all PLHIV with TB independently of the CD4 count.
6. Start ARV as soon as possible and in any case earlier than 8 weeks from TB treatment initiation.
7. Adjust ARV treatment in case of susceptible TB and rifampicin use.
8. Prevent IRIS (prednisone 1–2 mg/kg/day for 2 weeks).
9. Closely monitor for side-effects and toxicities.

Note: CPT: Cotrimoxazol preventive therapy; PLHIV: People living with HIV.

side-effects, it appears that SLDs are better tolerated in children.

On the subject of pregnancy and MDR, pregnancy should be avoided if possible. A pregnancy test should be requested at the beginning of treatment and family planning discussed and strongly encouraged. Deferral of treatment to the second trimester is suggested if the clinical condition allows it. Almost all first- and second-line drugs can be used during pregnancy with different levels of safety. Nevertheless, injectables should be avoided (Sm, Km, Am) or if necessary, use capreomycin where available as it has a less teratogenic profile.[11]

Diabetes mellitus is becoming a more common condition in developing countries and even among MDR-TB cases. Among diabetes patients immunity is slightly reduced, thus creating a greater chance of worse outcomes. Moreover, treatment can be more complicated if a baseline of neuropathy and renal failure exists in addition to potential drug toxicities.

Conclusions

MDR-TB management on a large scale is new for most NTPs. In addition, many countries have to face fundamental challenges such as scarce economic and human resources, weak healthcare systems and high HIV rates. In these challenging conditions clinical and programmatic errors can occur frequently. In that sense, improper TB or MDR-TB schemes are a waste of money and lives. Moreover, it leads to an increase in resistant strains circulating in the community.

Now, more than ever, good cure rates among susceptible cases are vital. Prevention of MDR with good initial treatments and follow-up are the roots of the problem and the solution. This is certainly true if HIV rates are high and infection control measures are not in place. Inappropriate MDR-TB schemes lead to low cure rates and a high number of failures. On the other hand appropriate MDR-TB schemes, which are the last chance for the patient, will result in bad adherence, unless side effects are managed promptly and the continuation phase is supportive.

Clinical MDR-TB management is challenging but feasible even in resource constrained settings. Overall, clinical knowledge is not only crucial but the starting point for an MDR-TB programme. A good working understanding of the disease process is essential.

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Estudio 5

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CASO CLÍNICO

Tuberculosis Multidrogorresistente:
una enfermedad, dos realidades diferentes

Resumen

La tuberculosis multidrogorresistente (TB-MDR) es una de las enfermedades emergentes que más alerta está causando nivel mundial. Intrínsecamente ligada a pobreza, la TB-MDR está afectando de forma diferente a países desarrollados y en vías de desarrollo. La desigual distribución de la enfermedad, forma de diagnóstico, tratamiento y especialmente pronóstico, está condicionando dinámicas de epidemia distintos a pesar de una misma etiología y patogenia. En este artículo se muestran punto por punto las diferencias y similitudes entre la presentación de la enfermedad en países ricos y pobres.
Palabras clave: Faltan. Faltan. Faltan. Faltan. Faltan. Faltan. Faltan. Faltan. Faltan. Faltan.

Summary

Multidrug resistant tuberculosis (MDR-TB) is one of the emerging infectious diseases that is worldwide creating most concern. Intrinsically linked to poverty, MDR-TB is differentially affecting developed and developing countries. Despite same aetiology and pathogenesis the differential distributions of the disease, ways of diagnose, treatment and especially prognosis is contributing to completely different epidemic dynamics. Along this article are shown in detailed similarities and differences between developed and developing countries disease presentation.
Key words: Tuberculosis. Multi Drug Resistance. MDR. Extensively Drug Resistance. XDR. Clinical. Poverty.

Introducción

La tuberculosis multidrogorresistente (TB-MDR) no es problema nuevo. La existencia de resistencias y pacientes incurables se remonta a los primeros tiempos de la era antibiótica[1]. Sin embargo la visibilidad y medida de la magnitud del problema a nivel mundial, sí es reciente y está creando una gran alarma en la comunidad científica y clínica. La TB-MDR se define como tuberculosis resistente a rifampicina (R) e isoniazida (H)[2]. Estos medicamentos descubiertos en

los años 60, son hasta día de hoy los más potentes para curar la enfermedad y en casos sensibles se consiguen tasas de curación superiores al 95% de los casos en 6 meses de tratamiento[3]. Son medicamentos bien tolerados y el coste en forma de combinaciones en dosis fijas a nivel mundial es aproximadamente de 20 euros por tratamiento[4]. Cuando los bacilos se hacen resistentes a estos medicamentos es necesario usar esquemas de tratamiento complejos con múltiples fármacos, menos eficaces, más tóxicos y más caros con una duración media de 2 años[2]. Según los medicamentos usados el costo puede variar de 2.000 a 80.000 euros/año. Cuando sobre una TB-MDR el patrón de resistencias se amplia, perdiendo la efectividad de quinolonas e inyectables de segunda línea, la enfermedad pasa a denominarse TB extensivamente resistente (TB-XDR)[5] y tiene peor pronóstico[6]. Debido a su complejidad, efectos adversos y duración, el tratamiento de la TB-MDR y XDR se tiende a comparar con la quimioterapia oncológica.

La TB es una enfermedad ligada a pobreza que afecta más a países de escasos recursos[7]. En ellos, la capacidad de los sistemas sanitarios para atajar la enfermedad son también más limitados. A nivel poblacional las dificultades para lograr buenas tasas de curación en la TB sensible, está condicionando la aparición de resistencias a nivel individual y comunitario, hecho que agrava considerablemente el problema[8].

A nivel específico cada país tiene sus particularidades. Pero de forma general la TB-MDR tiene el potencial de afectar contundentemente a pobres a pesar de una misma etiología y patogenia[9]. Como se analizará más adelante, la TB-MDR está poniendo en peligro el control de la TB, especialmente en ciertos países en vías de desarrollo[9].

Epidemiología y distribución de la enfermedad

Se estima que cada año aparecen unos 9,27 millones de casos nuevos de TB en el mundo[10]. En torno al 80-90%

CASO CLÍNICO

Tabla 1. Resumen de diferencias en la presentación y manejo de la Tuberculosis Multidrogorresistente según la capacidad económica de los países.

	Países desarrollados	Países en vías de desarrollo	Observaciones
Epidemiología	Baja carga de enfermedad	Alta carga	TB es una enfermedad intrínsecamente ligada a pobreza. La TB-MDR existe más allí donde hay más TB o peor manejo individual o colectivo.
Etiología y patogenia	*M. Tuberculosis*	*M. Tuberculosis*	Misma etiología y patogenia. Factores de riesgo de exposición, de infección y enfermedad mayores en países pobres incluyendo infección VIH y DM.
Clínica	TB pulmonar	TB pulmonar	Clínica indistinguible de la TB pulmonar sensible. Habitualmente la presentación de una TB pulmonar más avanzada debido a retraso en diagnóstico o mala evolución tras tratamiento de TB sensible.
Diagnóstico	Precoz Estudio exhaustivo de contactos de TB-MDR	Tardío Estudio de contactos limitado	El retraso en el diagnóstico está mediado por la capacidad de los laboratorios y sistemas de salud para notificar resultados. El estudio de contactos depende de las capacidades y disponibilidad de recursos humanos y económicos del país
Tratamiento	Individualizado	Estandarizado	El tratamiento estandarizado abarata el costo de los tratamientos, facilitan el pedido, distribución y las necesidades de formación en países en desarrollo.
Pronóstico	Aceptable, por debajo de los niveles de la TB sensible.	En general muy por debajo de los resultados de tratamiento de la TB sensible.	El pronóstico principalmente depende de la capacidad para proporcionar un tratamiento adecuado y del patrón de resistencias del paciente.
Impacto poblacional	Limitado	Potencialmente muy elevado	Las dificultades y limitaciones en países de escasos recursos contribuyen a que la capacidad de reacción ante la epidemia de TB-MDR sea más lenta e incapaz de cortar la cadena epidemiológica.

TB: Tuberculosis; TB-MDR: Tuberculosis Multidrogorresistente; DM: Diabetes Mellitus.

aparecen en países de renta media o baja. De ellos, aproximadamente 2 millones de pacientes mueren, principalmente también en países pobres. En cuanto a la TB-MDR, unos 500.000 nuevos casos aparecen por año, casi todos ellos localizados también en estos países[9]. Dada la heterogeneidad de contextos, la epidemiología de la TB-MDR puede ser vista de 3 formas diferentes con diferentes patrones de riesgo y dificultades[9]:

- *Por número absoluto de pacientes con TB-MDR.* Casi el 50% de casos de TB-MDR están en China y India, países que presentan el mayor número de casos de TB del mundo con casi un millón de enfermos al año en cada país.
- *Por proporción de TB-MDR respecto al total de casos de TB.* Los países de la antigua Unión Soviética presentan en general proporciones por encima del 3 o 6%. No obstante hay regiones donde la proporción de TB-MDR entre los nuevos casos ronda el 25% de los casos iniciales.
- *Por tendencias e incremento de incidencia.* Los países de África del Sur están experimentando un aumento dramático de casos de TB-MDR. La epidemia de VIH y uso de tratamiento contra la TB donde antes no existían pueden estar contribuyendo a este rápido avance de la TB-MDR[11].

En cualquiera de los casos, la TB-MDR emerge allá donde hay más TB y donde se obtienen peores resultados de tratamiento. En los países desarrollados comparativamente hay poca carga de TB junto a mejores sistemas de salud y por lo tanto la presencia de TB-MDR también es menor. No obstante, se han descrito epidemias de TB-MDR en personas con baja inmunidad incluso en nuestro país[12].

Etiología y patogenia

La TB está causada por bacilos pertenecientes al complejo *Mycobacterium tuberculosis*.

El mismo agente nosológico afecta a todos los enfermos. Con todo, los factores de riesgo de exposición, de infección y enfermedad son mayores en países pobres[13]. Las condiciones de hacinamiento y contacto estrecho con enfermos baciliferos, favorecido por condiciones de pobreza crea condiciones idóneas para la exposición a la enfermedad y posterior infección[8]. La malnutrición, edades extremas y comorbilidades como el VIH y la diabetes mellitus favorecen el paso desde infección a enfermedad[8]. Estas condiciones son similares a las de población inmigrante en malas situaciones socioeconómicos y población marginales en países desarrollados que son precisamente los principales focos de TB en estas áreas.

El VIH se comporta como un factor de riesgo de TB a todos los niveles[8,14]. De hecho la combinación de ambas enfermedades está teniendo un efecto devastador en regiones con alta carga de VIH[12,14]. Sin embargo, el efecto VIH sobre países desarrollados puede estar mitigado por la baja incidencia de TB y porque la mayoría de infectados tienen acceso a tratamiento antirretroviral gratuito en sistemas de salud de alta calidad[15].

En cuanto a patogenia, la TB y la TB-MDR, se comportan de forma similar[2]. Por lo tanto cuantas más cepas de TB-MDR circulantes haya en la comunidad, mayor será la transmisibilidad de casos de TB-MDR primaria. Pero en la gran mayoría de países la TB-MDR emerge como resultado de la selección de los bacilos mutantes resistentes naturales[9]. Estos bacilos son seleccionados mediante un proceso de presión ambiental por malos esquemas terapéuticos, mala calidad de medicamentos o toma inconsistente de medicamentos entre otros. Posteriores monoterapias irían seleccionando bacilos cada vez más resistentes ampliando el patrón de resistencias y reduciendo las posibilidades terapéuticas del paciente[13,16].

Las barreras de acceso tanto a diagnóstico precoz o como a un tratamiento de calidad

en países en desarrollo durante décadas han contribuido al bajo control de la epidemia y al aumento de las resistencias, proceso que actualmente continua[16,17].

Clínica

El patrón de enfermedad de la TB-MDR es indistinguible del de la TB sensible[13]. A pesar de ello, los casos de TB-MDR adquirida, suelen ser pacientes que han convivido con la enfermedad tuberculosa durante años, fracasando a distintos tratamientos y con una evolución tórpida. Por lo tanto, la presentación clínica y especialmente si el diagnóstico se retrasa, tiende a ser el de una TB pulmonar avanzada con grandes patrones de destrucción, con peor pronóstico aunque puedan recibir un tratamiento adecuado[17].

Diagnóstico

Al ser clínicamente indistinguible de la TB sensible, el diagnóstico de TB-MDR debe ser siempre bacteriológico bajo test de sensibilidad a fármacos (TSF) presentando resistencia a RIF e INH[2]. El TSF es básicamente un antibiograma realizado sobre un cultivo de *M. TB*. La prueba patrón oro es el TSF en medio líquido o sólido de Lowestesin-Jensen, prueba que tiene más de 50 años de antigüedad y presenta importantes limitaciones[18,19]. Es una prueba costosa, laboriosa, y precisa de un laboratorio de bioseguridad grado 2 o 3 con personal bien entrenado. No obstante, la principal limitación de la prueba es la demora de los resultados[2]. La

prueba en medio sólido, más barata y sencilla y por lo tanto más usada en países pobres, puede llegar a tardar de 2 a 4 meses en dar resultados[19]. Retraso que se incrementa con el envío de resultados. Incluso para países como Perú el retraso en el diagnóstico puede llegar hasta los 8 meses[20]. Con todo, la sensibilidad y especificidad de la prueba no superan el 85% para detectar resistencias en RIF e INH[19]. La fiabilidad de la prueba se reduce de forma importante para el diagnóstico de resistencias a medicamentos de segunda línea[21], hecho que limita de forma importante su recomendación[22].

Las nuevas tecnologías desarrolladas recientemente y disponibles en países ricos pueden presentar resultados entre 2 días y 2-3 horas con una sensibilidad similar e incluso superior, especialmente para la resistencia a RIF[18,23,24]. En muchas naciones de escasa renta, la capacidad de los laboratorios y de sus recursos humanos es muy limitada[9]. En muchos casos el TSF no existe o es de baja calidad, o la capacidad es insuficiente para la necesidad real, quedando los pacientes sin diagnóstico o diagnosticados muy tardíamente. Como ejemplo cabe destacar la escasa notificación de TB extensivamente resistente (TB-XDR) en países africanos donde muy probablemente existe pero sus laboratorios son incapaces de diagnosticarla[25].

El diagnóstico tardío o la ausencia del mismo tiene un impacto considerable en el pronóstico del enfermo y la administración de tratamientos inadecuados[17]. Todo ello favorece la transmisión de la enfermedad en la comunidad y la amplificación de los patrones de resistencias circulantes.

En países desarrollados el tratamiento de la infección latente y en el caso de la TB-MDR, el estudio de contactos, limitan la expansión de la enfermedad[9]. Mientras que en los países de escasa renta realizar estas actividades ofrece serias dificultades económicas, logísticas y de recursos humanos disponibles.

El mayor número de cepas de TB circulantes, la escasa capacidad de los laboratorios traducida en retrasos diagnósticos y el escaso estudio de casos hace muy limitada la capacidad para cortar la cadena epidemiológica de la TB-MDR en los países con más necesidad.

Tratamiento

Desde un punto de vista biológico el tratamiento de la enfermedad debería ser el mismo en ambos ámbitos. Contrariamente, la realidad y dificultades en el terreno hacen que el manejo sea diferente. En países de altos recursos el número de enfermos es más reducido, existe disponibilidad casi completa de todos los medicamentos de segunda línea y el personal de salud está altamente cualificado o tiene oportunidades para la formación en el tratamiento de estos casos complejos. En la mayoría de veces, en estos pacientes se opta por tratamientos individualizados, diseñados en función de TSF y la historia de medicamentos usados en el pasado por el enfermo[26].

Por el contrario en países pobres la escasa inversión económica en los sistemas sanitarios, limita el acceso a muchos de los medicamentos de segunda línea. Además, el personal sanitario formado es muy limitado y con frecuencia no adecuadamente pagado. Sumado a que el número de pacientes con TB-MDR es cuantioso, el manejo no puede ser dejado exclusivamente a cargo de especialistas[27]. Asimismo siendo la presión asistencial habitualmente mayor y los fondos para formación limitados, las oportunidades de un entrenamiento de calidad o tiempo de estudio son muy reducidas.

Por todo ello, se suele optar por tratamientos estandarizados con medicamentos de segunda línea que abaratan el costo, facilitan el pedido, distribución y las necesidades de formación contribuyendo a un mayor impacto colectivo de curación de pacientes[2,8,26,27]. En muchos casos ese tratamiento estandarizado es la última oportunidad para el enfermo. Con todo, las tasas de curación globalmente en los lugares reportando información es próxima a un 60%[9,28,29]. Parece ser que el patrón de resistencias inicial del paciente es uno de los principales factores asociado con el éxito del esquema[30].

Incluso en los países capaces de llevar a cabo tratamientos de pacientes con TB-MDR y su subsiguiente seguimiento diario durante 24 meses, desgraciadamente el desabastecimiento de medicamentos de segunda línea y otros problemas son frecuentes.

En países pobres donde el sector público no es suficiente por sí solo para lidiar con la complejidad de la TB, el papel del sector privado tanto en la creación, como el tratamiento de la TB-MDR sigue sin estar aclarado[31].

No obstante, en los lugares donde por escasa formación o dificultades individuales o colectivas, existen malas prácticas en TB o TB-MDR los patrones de resistencia tienden a ampliarse[11]. Se pasa así de una situación mala, a otra incluso peor precisando tratamientos más complejos y económicamente inviables. De hecho la TB-XDR se está expandiendo por todo el mundo[9].

Los nuevos medicamentos tampoco parecen ser una solución a corto plazo para los países pobres[18]. Medicamentos con actividad anti-TB como linezolid e imipenen usados en países ricos, tienen un coste que los hace totalmente inapropiados para países pobres. Igualmente, parte de las nuevas moléculas contra la TB a estudio por primera vez en décadas como el TMC207[32] tienen patente privada y se cuestiona la accesibilidad de los países pobres, para estos tratamientos[18].

La Tabla 2 incluye la clasificación de los medicamentos antituberculosos aceptados actualmente y la Tabla 3 presenta un resumen sobre buenas prácticas en el tratamiento de la TB-MDR.

Tabla 2. Clasificación racional de los medicamentos antituberculosos. Adaptado de (27) y (2)

Grupo	Medicamentos
Grupo 1: Fármacos de primera línea	isoniazida (H); rifampicina (R); etambutol (E); pirazinamida (Z)
Grupo 2: Fluoroquinolones ofloxacino(Ofx)	levofloxacino (Lfx); moxifloxacino(Mfx); gatifloxacino Gfx);
Grupo 3: Inyectables de segunda línea	capreomicina (Crm); kanamicina (Km); amikacina (Am); estreptomicina (S)
Grupo 4: Bacteriostáticos orales de segunda línea	etionamidaEto); protionamida(Pto); cicloserina(Cs); terizidona Trd); ácido para-amino salicílico (PAS)
Grupo 5: Medicamentos de baja eficacia o no comprobada	clofazimina (Cfz); amoxicilina/clavulánico (Amx/Clv); linezolid (Lzd); imipenem/cilastatin (Ipm/Cln); tioacetazona (Thz); claritromicina (Clr); altas dosis de isoniazida

Tabla 3. Resumen sobre buenas prácticas en el manejo de la Tuberculosis Multidrogorresistente. Adaptado de (17)

Pasos	Consideraciones
Diagnóstico	Tener en cuenta: Historia de drogas: un mes de monoterapia es el indicador de resistencia más importante TSF: Más fiable para Rif e INH; bastante fiable para Km y FQ; Menos fiable para E y Z; muy poco fiable para drogas del grupo 4 y 5. No recomendado). Realizar test de VIH. Si es positivo iniciar cuanto antes cotrimoxazol y ARV.
Número de medicamentos	"Al menos 4 medicamentos efectivos": nunca usados en el pasado o susceptibilidad demostrada por TSF, teniendo en cuenta fiabilidad del TSF y resistencias cruzadas
Selección de medicamentos	Usar medicamentos de primera línea si todavía son efectivos Una FQ Un inyectable Usar medicamentos del grupo 4 hasta completar las 4 drogas efectivas Si es necesario usar medicamentos del grupo 5 para reforzar el esquema o cuando no se lleva al número de 4 drogas efectivas. Cada 2 medicamentos del grupo 5 cuentan como 1 medicamento efectivo
Duración del inyectable	Al menos 4 meses tras la conversión del esputo o cultivo Aún mayor duración si no 3 medicamentos efectivos en la fase continuación o son del grupo 5 o hay sospechas de resistencias a FQ
Cirugía	Considerar solo si: Se disponen de muy pocas drogas efectivas Lesiones localizadas Reserva respiratoria suficiente tras la resección
Régimen ideal pasado	*Estandardizado*: si no hay uso de medicamentos de segunda línea en *el individualizado*: si hay uso de medicamentos de segunda línea en el pasado o contacto con un paciente MDR que las haya usado (tratar con el régimen que fue efectivo en el caso índice).

ART:tratamiento antirretroviral; TSF: test de sensibilidad a fármacos; E: Etambutol; FQ: fluoroquinolonas; H: isoniacida; Km: kanamicina; R: rifampicina; Z: pirazinamida

Pronóstico e impacto poblacional

Por todas las razones antes mencionadas y a pesar de las pocas referencias literarias el resultado de la TB y especialmente de la TB-MDR tiende a ser peor en paises de recursos escasos. A nivel clinico, los pacientes con TB-MDR son diagnosticados más tarde con una enfermedad más evolucionada y con una capacidad de tratamiento más limitada. A nivel poblacional, todas las dificultades y limitaciones mencionadas contribuyen a que la capacidad de reacción ante la epidemia de TB-MDR sea más lenta y desorganizada en los países con menos recursos y más carga de enfermedad. Por el momento el conocimiento del pronóstico a largo plazo de los pacientes curados tras una TB-MDR es limitado.

Contrariamente, la epidemia de TB-MDR está por el momento lejos de estar controlada. De hecho, del medio millón de pacientes estimados al año, tan solo el 1% han sido notificados o han entrado en tratamiento con los criterios de calidad de la Organización Mundial de la Salud[9]. Se estima que el 96% de los casos mundiales de TB-MDR no son diagnosticados[9]. En cualquier caso, el número de pacientes en tratamiento en los paises pobres es tan solo la punta del iceberg. Se cree que la mayoría fallece en la comunidad tras varios años de enfermedad. Es por ello, que el impacto de la enfermedad a nivel poblacional puede ser desmesuradamente mayor en paises pobres que ricos. Ciertamente, en algunos modelos matemáticos basados en la situación actual de capacidad de diagnóstico y tasas de curación efectiva, se argumenta el riesgo que existe en algunos paises del cambio de cepas sensibles a cepas resistentes y creación masiva de TB-XDR[33,34]. El VIH sin tratamiento en paises africanos puede complicar más una situación de por si ya compleja[12]. Las epidemias conjuntas de VIH y TB-XDR presentan una gran letalidad rondando el 97% en algunos casos[35]. El tratamiento antirretroviral y las medidas de control de infección incluyendo el tratamiento precoz y efectivo de la enfermedad se consideran cada vez más relevantes para limitar el impacto de la epidemia[18,36].

A pesar de todos estos datos, existen motivos para el optimismo. Hay documentadas experiencias exitosas en América Latina, Sudeste Asiático e incluso en regiones complejas de Rusia donde con la implementación de programas fuertes de TB-MDR se ha conseguido revertir las tendencias de incidencia[9].

Conclusiones

La TB-MDR es una enfermedad emergente ligada a pobreza, muy mediada por la capacidad económica y sanitaria, tanto clínica como de salud pública de las naciones. De no ser contenida a tiempo la epidemia de TB-MDR puede suponer nuevos retos para el control global de la TB incluyendo países de altos recursos. Reparando en la desigual presentación de la enfermedad y las diferentes posibilidades de diagnóstico y tratamiento en el terreno, la dinámica de la epidemia de TB-MDR en países pobres y ricos es prácticamente distinta.

El tratamiento y la contención de la TB-MDR es posible incluso en países con grandes dificultades. Sin embargo, puede que las soluciones empleadas para la TB-MDR en países ricos no sean totalmente extrapolables a países pobres. Nuevos esfuerzos y soluciones propias y adaptadas a cada escenario son necesarios.

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7. DISCUSIÓN

La exposición de la discusión se estructurará en 2 partes. Primeramente se analiza de forma específica que aporta cada uno de los estudios principales al conocimiento científico del manejo de la TB y la TB-MDR. Posteriormente se discute de forma global que aporta esta tesis en su conjunto para un mejor control de la tuberculosis multidrogoresistente en países en desarrollo, objetivo general de esta tesis.

7.1 Discusión específica de cada estudio realizado

Estudio 1

Evidence for promoting fixed-dose combination drugs in tuberculosis treatment and control: a review. Monedero I, Caminero JA. Int J Tuberc Lung Dis. 2011 Apr;15(4):433-9

Este artículo científico revisa el papel que pueden tener los medicamentos combinados en dosis fijas (MCFs) para mejorar el tratamiento de la TB sensible y su capacidad para prevenir TB-MDR. A pesar del amplio uso de los MCFs, no existía en el momento ninguna revisión extensa de la materia. Los MCFs presentan importantes ventajas logísticas y operativas respecto al uso de medicamentos sueltos (80): se evita monoterapia o selección de fármacos por el paciente, facilitan el cálculo de dosis por peso evitando así fallos en la prescripción, reducen considerablemente el número de pastillas que ha de tomar el paciente, son sensiblemente más baratas, fáciles de almacenar, de pedir y de distribuir previniendo así rupturas de stock. Los pocos estudios y ensayos clínicos que existen confieren un papel similar en cuanto a tasas de curación y recaídas. Sin embrago, no son muchos los países que los utilizan y a nivel mundial la compra de medicamentos anti-TB sueltos es similar o superior al de medicamentos combinados (82). Con similar efectividad terapéutica y presentando otros aspectos positivos (ver Tabla 7), los MCFs deberían ser usados a gran escala. Sin embargo muchos países y directores de programas nacionales argumentan falta de evidencias científicas que soporten el cambio en las políticas nacionales. Este estudio pretende demostrar, todo lo anteriormente referido y vincularlo además a la reducción de resistencias observados en países que por largo tiempo han usado MCFs.

De los 127 artículos seleccionados inicialmente, 15 estudios fueron incluidos en la revisión aunque solo 12 eran estudios originales y 3 eran re-evaluaciones de estudios previos en distintos puntos en el tiempo. Existieron problemas para la realización formal de un meta-análisis ya que solo 2 cumplían con criterios PRISMA (99). La metodología usada en los estudios fue muy heterogénea, el tipo de medicamentos incluidos como MCFs y las dosis fueron muy variables de unos estudios a otros limitando la comparación estricta para llevar a cabo un metanálisis.

La **eficacia** fue considerada como variable de interés en 11 de los 12 estudios originales**.** En el 100% se obtuvieron similares resultados en eficacia. ($p<0.05$ o no inferioridad). Solo 3 estudios compararon la asociación de 4 medicamentos (4MCFs) actual estándar de tratamiento anti-TB. A pesar de haber sido el principal argumento en contra de la

introducción masiva de los MCFs como políticas nacionales, este estudio muestra que toda la evidencia científica encontrada apoya que entre los MCFs y medicación suelta no existen diferencias estadísticamente significativas en términos de eficacia con similares tasas de curación. Sin embargo llama la atención que fuera de las condiciones de estudio los resultados de curación pueden variar enormemente. Por ejemplo en uno de los estudios incluidos en la revisión (109) la tasa de curación fue del 95% mientras que en condiciones de programa nacional la curación era del 74% ($p< 0.01$).

Relativo a la **aceptación, efectos adversos** y **adherencia** usando MCFs, fueron tratados en 9 estudios en los que el 100% obtuvieron similares o mejores resultados en los pacientes usando MCFs respecto a medicación suelta. De nuevo es una variable que en ensayos clínicos controlados puede no tener un gran valor pero que en situaciones reales en PVD donde el enfermo recibe un apoyo muy básico, la diferencia entre tomar de 12 a 18 pastillas o tomar solo 3 (calculado para paciente en torno a 50-60 kg) puede significar la diferencia entre curación o abandono de tratamiento e incluso resistencias por mala adherencia.

Por lo tanto en condiciones de terreno la efectividad del tratamiento puede aumentar mediante el uso de los MCFs debido a las mencionadas ventajas operacionales y de aceptación. Sírvase como ejemplo los resultados obtenidos en Taiwán donde las dosis de prescripción eran con frecuencia inadecuadas o no adaptadas al peso en un número considerable de enfermos usando medicaciones sueltas mientras que era correcto en la mayoría de enfermos usando MCFs (110). Posiblemente en condiciones reales donde el TDO es inadecuado o los sistemas de salud son débiles la simplificación mediante el uso MCFs favorece la curación de enfermos. Muy posiblemente a igual eficacia, debido a las ventajas operativas en condiciones reales, los MCFs presentan mayor efectividad que los medicamentos sueltos.

En cuanto a las **recaídas**, fueron consideradas solo en 7 estudios. De ellos, en 6 (85%) no se obtuvieron diferencias significativas o fueron no inferiores tras 6 meses, 24 meses, 30 meses y 4.3 años de seguimiento. Un estudio usando MCFs con 3 medicamentos, encontró diferencias significativas al nivel de $p=0.04$ (8 recaídas vs. 2 en medicamento sueltos) tras 18 meses de seguimiento (111). Las recaídas han sido el tema más controvertido en el uso de los MCFs. A pesar de los resultados en contra de este estudio, el tamaño poblacional fue muy reducido (310 enfermos), no se cuantifico el rol de la reinfección, ni infección por VIH u otras inmunodeficiencias y tan solo un paciente más en cualquiera de los grupos podría haber hecho cambiar la significación del estudio.

La capacidad de los MCFs para **prevenir la aparición de resistencias** solo fue explorado en un estudio (112). En él se obtuvieron menores niveles de adquisición de resistencias (0.47 vs. 1%) en pacientes tomando tratamiento auto-administrado con MCFs que incluían principalmente 2 medicamentos (2MCFs). Cuanto mayor el número de medicamentos combinados en una pastilla, menor fue el número de resistencias obtenido, de hecho los pacientes que solo usaron MCFs presentaron solo un 0.1% de resistencias. A pesar de lo reducido de las evidencias, se trata de un estudio realizado en condiciones reales en Estados Unidos que tiene un programa de control de la TB fuerte. Por lo tanto si en programa fuerte los MCFs han demostrado capacidad para reducir la incidencia de resistencias es de esperar que en países con menor capacidad los MCFs sean un factor protector aún mayor frente a la adquisición de resistencias. Uno de los ejemplos más claros esta en nuestro país o Brasil, que a pesar de no realizar TDO o no

tener en el pasado un programa nacional contra la TB fuerte, las resistencias permanecen bajas. Posiblemente el uso generalizado de MCFs desde hace décadas entre otros factores haya podido contribuir. El uso de MCFs en el sector privado de los países en vías de desarrollo donde no hay TDO y muchas veces no se usan los estándares o guías internacionales podría contribuir a la reducción de resistencias de forma muy considerable.

A pesar de que muchos países han adoptado políticas de introducción de MCFs en las últimas décadas, el uso no es generalizado. De acuerdo a datos del *Global Drug Facility* el uso de MCFs fue reportado solo por la mitad de los 136 países que reportan TB a la OMS en el año 2007. De forma más general solo el 15% de los enfermos con TB a nivel mundial son tratados con MCFs (82). Y no solo en países en vías de desarrollo, datos de Estados Unidos del año 2006 confirman que la tasa de dinero gastado en Rifampicina es de 1 a 10 a favor de medicación suelta y no combinada. Resulta curioso además que con datos del año 2000 el costo del tratamiento de la TB en MCFs era la mitad que comprando las medicaciones por separado (83). Con datos más actuales el costo aproximado de un tratamiento de primera línea comprado a través del *Global Drug Facility* en MCFs es de 22,4 dólares americanos (113).

Por lo tanto a pesar de las limitaciones que presentan los estudios de esta revisión sistemática, basándose en las evidencias sobre similar eficacia, uso más sencillo, menor coste y ventajas tanto logísticas como operacionales, el uso generalizado de los MCFs debe continuar siendo recomendado. Bajo condiciones de tratamiento sub-óptimo como es la realidad en muchos de los países de alta carga de TB, los MCFs pueden jugar un papel muy relevante a la hora de aumentar las tasas de curación, descender los abandonos y reducir la adquisición de resistencias.

Con todo lo aportado en cuanto a similar eficacia y una muy posible mayor efectividad añadido a un probable descenso en el número de resistencias, no deben existir impedimentos para hacer uso de los medicamentos combinados de forma sistemática.

Estudio 2

Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. Rodriguez M, Monedero I, Caminero JA, Encarnacion M, Dominguez Y, Acosta I, et al. Int J Tuberc Lung Dis. 2013 Apr;17(4):520-5.

De forma tradicional los tratamientos de la TB-MDR han sido manejados por neumólogos especialistas en centros de referencia en países desarrollados mediante tratamientos individualizados, es decir diseñados a la necesidad del enfermo en función su historia clínica y test de resistencia (30). De hecho las principales evidencias científicas en el manejo de la TB-MDR proceden de países ricos con tratamientos individualizados (88, 89). Los esquemas estandarizados para TB-MDR se han percibido con frecuencia como un régimen de inferior eficacia o inadecuado.

Por otro lado el manejo de la TB con resistencias es un suceso que ha empezado a generalizarse en países en vías de desarrollo en los últimos años dado el número considerablemente alto de enfermos (mucho mayor del inicialmente esperado) y su potencial transmisión primaria a la comunidad (1).

Este estudio científico analiza de forma retrospectiva una cohorte de 289 pacientes con TB-MDR en República Dominicana en condiciones reales de programa. La cohorte comprende todos los enfermos confirmados mediante cultivo y test de sensibilidad que entraron en tratamiento entre agosto de 2006 y Junio de 2010. Las características de la muestra poblacional son similares a la de otros países con incidencia alta de TB con resistencias. Se trata de pacientes jóvenes (mediana 31 años, rango 24.5- 40.0) del que 54% eran hombres. Gran parte de ellos (72,6%) procedían de fracasos a tratamientos de primera línea. La mediana del tiempo de conversión del cultivo sucedió fue a los 2 meses de tratamiento aunque para el cuarto mes de tratamiento la mayoría (78.6%) presentaron cultivos negativos. No hubo diferencias estadísticamente significativas en cuanto a la velocidad de conversión entre pacientes recibiendo diferentes regímenes, lo que habla de una adecuada tasa de conversión en los estandarizados.

Entre los 150 pacientes que habían terminado el tratamiento y presentaban al menos un año de seguimiento, los resultados favorables (curación y tratamiento completado) fueron del 72%. De ellos los 105 casos que recibieron un esquema estandarizado obtuvieron un resultado favorable en un 74% mientras que los 45 pacientes con regimenes individualizados lo obtuvieron con un 66%, sin diferencias estadísticamente significativas (p=0.211). Tampoco hubo diferencias significativas en función del uso previo de medicamentos de segunda línea ni año de entrada en tratamiento. Estas altas tasas de *éxito terapéutico* (72%) son similares a las obtenidas en países ricos mediante tratamientos individualizados (114-118) y mayores a la media de 60% obtenida en los programas del *Green Light Committee* (25). También fue mayor que la media de éxito obtenida en los 2 recientes meta-análisis sobre tratamientos de TB-MDR de los cuales las mayores tasas de éxito eran presentados en centros usando más de 18 meses y TDO (88, 89). Estas 2 condiciones son similares a nuestro estudio y apoyan los resultados obtenidos. La menor efectividad de los tratamientos individualizados presentada en nuestro estudio puede estar relacionada con un mayor patrón de resistencias de estos enfermos, menor uso de quinolonas, enfermedad más avanzada y escasa disponibilidad de medicamentos del grupo 5. De forma adicional, previamente al año 2010, los

pacientes con TB-MDR debían aguardar en una lista de espera para iniciar tratamiento. Muchos pacientes diagnosticados murieron durante ese tiempo y pudo condicionar un sesgo de supervivencia por el cual los pacientes de estas cohortes eran especialmente adherentes incluso con un número importante de efectos adversos.

La *eficacia* global de tratamientos estandarizados e individualizados fue 92.8 y 81% respectivamente (p=0.056), una de las mayores publicadas hasta ahora. Posiblemente la efectividad habría sido menor presentando menos muertes y abandonos de haber podido contar con unidad de cuidados intensivos y medidas de apoyo social.

En cuanto a los *efectos adversos*, cada paciente presentó aproximadamente 5 efectos adversos diferentes, que es mayor que en otros estudios sobre el tema (119, 120). No obstante solo fue necesario suspender 1 tratamiento y en ningún otro caso fue necesario retirar medicamentos. Es posible que el manejo agresivo de los efectos adversos y ajuste adecuado de las dosis haya colaborado a la mantener la efectividad de los tratamientos.

En el análisis multivariante, los *factores de riesgo* independientes encontrados para el desarrollo de un resultado desfavorable fueron más de 2 meses para negativizar el cultivo (Riesgo relativo (RR) =2.693 (1.254-5.784, intervalo de confianza del 95% (IC) y la presencia de cavitación bilateral en la radiografía de tórax (RR= 3.616 (1.122-11.647, IC). La presencia de cavidades se relacionó con un exceso de mortalidad (15%) y fracaso (10%). Estos factores de riesgo encontrados no han sido explorados en profundidad por otros estudios y establece una diferencia con anteriores publicaciones. En cambio, los niveles bajos de hemoglobina, conocido factor de mal pronostico, se relacionaron con peores resultados con una significación estadística limite (P=0.075).

En cuanto a las *recaídas*, de los 108 pacientes tratados con éxito terapéutico, tan solo un paciente VIH positivo fue confirmado como recaída en nuestro estudio. Los pacientes fueron reevaluados entre 6 y 34 meses tras el fin del tratamiento aunque 83.3% tenían más de un año de seguimiento. De ellos 100 estaban asintomáticos, cuatro murieron presentando cultivos negativos, dos sintomáticos también con cultivos negativos y otros dos en que no fue posible su localización. Los resultados correspondientes en cuanto a recaídas hablan de tasa de recaídas bastante baja y similar a la encontrada en tratamientos para TB sensible.

Las *principales limitaciones* que presenta este estudio fueron las propias del uso de información de rutina y escasez de recursos. Algunos datos importantes como número de medicamentos al que era resistente cada paciente y otros potenciales factores de riesgo eran desconocidos así como las causas específicas de muerte durante el tratamiento. También algunos factores de riesgo pudieron pasar inadvertidos durante el análisis debido al reducido número de la población. La evaluación de las recaídas se realizó con numerosas restricciones y la el papel de las re-infecciones no fue posible por falta de fondos aunque se realizo test de sensibilidad a medicamentos a todos los sospechosos de recaída.

Creemos que el uso de datos de rutina y las limitaciones propias del trabajo sobre el terreno no hacen perder el interés de los hallazgos. Es más los ponen en relación con la realidad de la TB-MDR de los países en desarrollo y por tanto son especialmente útiles y posiblemente extrapolables. Mostrar las experiencias y resultados exitosos de

Republica Dominicana en sus primeros años de implantación puede servir como ejemplo positivo a exportar a otros países también en circunstancias de escasos recursos. La buena marcha del programa ha permitido que actualmente los pacientes sean diagnosticados y tratados más tempranamente. Este es un dato importante ya que condiciona no solo un mejor pronóstico del enfermo sino también puede contribuir a mejorar la capacidad del programa para frenar la transmisión comunitaria. Este hecho tiene una correlación directa con datos que se extraen del propio estudio como la mejora en el perfil clínico de los enfermos y menor uso de medicamentos de segunda línea de forma descontrolada. De los pacientes tratados en 2010 muy pocos habían usado fármacos de segunda línea y esto a su vez puede estar ligado a un hecho interesante: si el programa funciona bien, los enfermos no van al privado reduciendo el riesgo de epidemias de TB-XDR.

De forma indirecta la realización de este estudio ha contribuido a la mejora del sistema de información en Republica Dominicana. La búsqueda de datos ha permitido que la calidad de la información haya mejorado tras ser cotejada múltiples veces. Adicionalmente, ha servido para la promoción de la investigación operativa. Actualmente el personal local recurre a su propia información para hacer políticas sanitarias. Y a su vez, ha permitido la identificación de nuevos problemas como la alta mortalidad en pacientes con TB/VIH en el país y la relevancia de actualizar el programa a las altas tasas de VIH que presenta. Sin duda también el reconocimiento a nivel internacional puede servir de estimulo para motivar al equipo y a su vez la atracción de fondos de financiación. Fruto de todo este esfuerzo y la nueva orientación hacia la investigación operativa van a salir a la luz al menos otros 3 estudios de los cuales el propio país y otros países se podrían beneficiar.

De forma general este estudio muestra que los tratamientos estandarizados para TB-MDR son eficaces y presenta un menor coste que los tratamientos individualizados. Por lo tanto, son especialmente útiles en situaciones de escasos recursos bajos. Con un manejo clínico y programático adecuado, es posible tratar con buenos resultados pacientes con TB-MDR en países pobres. El 72% de éxito terapéutico obtenido en Republica Dominicana es un buen ejemplo.

En conclusión, las lecciones aprendidas durante los primeros pasos de implementación del programa de TB-MDR de Republica Dominicana podrían ser aplicables a otros países en similares condiciones socioeconómicas.

Estudios 3 y 4

Estudio 3: Management of multidrug-resistant tuberculosis: an update. Ignacio Monedero, José A. Caminero. Ther Adv Respir Dis 2010 4: 117-127.

Estudio 4: A basis for the clinical management of complicated MDR–TB cases. Monedero I, Holkar S. Africa Health. 2010 Sept; Vol 32 No 6: 20-25

Estos dos artículos de revisión se crearon para llenar un hueco en la literatura científica manifestado por médicos de países en desarrollo. Actualmente la guía más utilizada de manejo de TB-MDR consta de 272 paginas (22). Aunque es un documento muy completo, con frecuencia los clínicos en países de desarrollo no tienen acceso a él o no es leído o solo partes concretas. De esta manera los clínicos aprenden unos de otros y en función de la propia experiencia. El manejo de la TB-MDR y XDR es lo suficientemente complicada como para no ser aprendida de forma empírica. Con frecuencia los errores en su manejo se traducen en muertes o en amplificación de resistencias. Por otro lado los cursos clínicos internacionales en TB-MDR como los llevados a cabo por la Unión ofrecen una formación de calidad. Pero el costo de los mismos es alto y la capacidad para formar médicos es insuficiente para la gran demanda y la necesidad existente en países en desarrollo. La creación de guías clínicas nacionales en el manejo de TB-MDR es un proceso aún incipiente en muchos países que a su vez corre a cargo de personal de programas nacionales o clínicos que no han recibido formación específica y de nuevo se recurre a documentos muy extensos o incluso a experiencias personales para sus recomendaciones.

La existencia de documentos sencillos que de una forma holística aborden la TB-MDR como un punto de partida por el que formar a los médicos atendiendo enfermos con TB-MDR en PVD era necesaria. Durante la experiencia profesional como asistente técnico en PVD del doctorando fue una necesidad identificada y mencionada múltiples veces.

Durante el proceso de esta tesis no se encontraron revisiones que de una forma breve sencilla y ordenada incluyeran todos los aspectos básicos del manejo de la TB-MDR orientado a países de escasos recursos. Mediante una aproximación en forma de requerimientos mínimos, los estudios 3 y 4 abordan el manejo de estas complicadas condiciones.

El ***Estudio 3*** condensa en tan solo 8 páginas las bases fundamentales y los mínimos conocimientos para asegurar la curación de enfermos con TB-MDR. El texto incluye tablas donde se esquematiza el manejo intentando simplificar al máximo los conocimientos necesarios para tratar esta complicada dolencia. Se afronta el manejo de la TB-MDR de una forma comprensiva desde la sospecha clínica, pasando por el diagnóstico y la construcción de regímenes terapéuticos curativos, efectos adversos y monitorización de estos enfermos. La simplicidad del texto crea una diferencia comparativa con la mayoría de textos y revisiones de MDR-TB donde se muestran aspectos muy específicos de forma muy amplia. Generalmente el conocimiento de esta enfermedad ha sido habitualmente orientado a super especialistas en el tema. Sin embargo, siendo un problema tan prevalente en países pobres y la existencia de especialistas tan escasa, la super especialización probablemente no es la respuesta para atajar esta enfermedad mortal. Con formación o sin ella los médicos van a intentar aportar soluciones por tanto cuanto mayor acceso a formación sencilla y de calidad,

mejor será el pronóstico de los pacientes. El estudio 3 pretende apoyar este hecho y divulgar los conocimientos mínimos para obtener buenos resultados.

Con similar orientación, el **Estudio 4** afronta el manejo de la TB-MDR pero desde un enfoque a países Africanos con altas tasas de coinfección TB-VIH. En África sub-sahariana el VIH está incrementando la epidemia de TB de una forma sin precedentes. En el momento actual la TB es la principal causa de muerte en el mundo en personas viviendo con VIH. Cada año mueren aproximadamente 350,000 personas por la coinfección TB-VIH (1). Y no solo eso la TB-MDR y también la XDR se está transmitiendo con rapidez en poblaciones con altas tasas de VIH dando lugar a formas de TB con una letalidad muy alta (por encima del 90%) y donde la enfermedad se presenta de forma muy agresiva con rápida progresión a muerte. Por lo tanto la TB con resistencias es una amenaza importante no solo para el control de la TB sino también para la efectividad de los programas de VIH. Recientes investigaciones han encontrado altas tasas de TB-MDR en la región de África del Sur altamente asociadas con la epidemia de VIH.

Esta situación es preocupante y desafortunadamente la tendencia se está incrementando (1). La TB-MDR es al menos 2 veces más frecuente en pacientes con TB que también tienen VIH frente a los no infectado por el VIH (121). La necesidad de un texto sencillo para la formación de clínicos en países de África subsahariana en el manejo de la TB-MDR en el paciente con VIH era necesaria. De igual manera en 6 páginas se condensa el conocimiento mínimo y necesario para construir tratamientos de TB-MDR con las precauciones necesarias en el caso de la existencia de VIH. En este caso se decidió publicar el artículo en una revista que a pesar de carecer de factor de impacto es de acceso gratuito a través de Internet y también en la base de datos de la región AFRO de la OMS.

Ambos artículos suponen herramientas sencillas para el autoaprendizaje de manejo de de la TB en circunstancias complejas de resistencias y aún más complicadas cuando se asocian resistencias en TB con infección por VIH.

Estudio 5

Tuberculosis Multidrogorresistente: una enfermedad, dos realidades diferentes. Monedero I, Caminero JA, Palomares FA, Alonso E, Mazario S. Enfermedades Emergentes. 2011; 13(2):68-73

En el estudio 5 se abordan de una forma global las diferencias encontradas en cuanto al manejo de casos con TB-MDR en países ricos y pobres así como el diferente impacto de la epidemia en ambos. El artículo de una forma sistemática analiza las principales diferencias existentes en la presentación de la TB con resistencias en países ricos o pobres. Se evalúa de forma comparativa epidemiología, etiopatogenia, clínica, diagnóstico, tratamiento, pronóstico e impacto poblacional de la TB con resistencias.
A pesar de que las citas a cuestiones de pobreza y desigualdad son frecuentes en la literatura en relación a la TB (4), este artículo científico trata de forma monográfica y específica el problema de la diferente capacidad de países ricos y pobres para el abordaje de la TB con resistencias.

El estudio surgió como una prolongación lógica de la metodología general de esta tesis doctoral. Los objetivos de esta tesis y parte de las barreras identificadas para la optimización del manejo de la TB-MDR en países de escasos recursos son analizados a lo largo del estudio. Siendo la misma enfermedad, las barreras tanto de diagnóstico y tratamiento como de *"know-how"* o conocimientos en el manejo, condicionan de forma determinante el pronóstico de los enfermos de unos y otros países. No solamente a nivel individual, las dificultades para el manejo de pacientes crean una respuesta inadecuada frente a la epidemia en países de mayor carga de enfermedad y menor capacidad para evitar la progresión sobre la comunidad.

La TB-MDR es una enfermedad emergente ligada a pobreza, muy mediada por la capacidad económica y sanitaria, tanto clínica como de salud pública de las naciones. De no ser contenida a tiempo la epidemia de TB-MDR puede suponer nuevos retos para el control global de la TB incluyendo países de altos recursos. Teniendo en cuenta la desigual presentación de la enfermedad y las diferentes posibilidades de diagnóstico y tratamiento en el terreno, la dinámica de la epidemia de TB-MDR en países pobres y ricos, es distinta.

A nivel clínico, los pacientes con TB-MDR son diagnosticados más tarde con una enfermedad más evolucionada y con una capacidad de tratamiento más limitada. Otro de los grandes problemas es que las evidencias científicas y en gran medida las líneas guía de tratamiento están orientadas hacia países con altos recursos, problema tratado en los estudios 2, 3 y 4. Por otro lado el diagnóstico de la TB con resistencias en muchos lugares permanece inaccesible, tema abordado en otro estudio disponible en el Anexo 1.

A nivel poblacional, todas las dificultades y limitaciones mencionadas contribuyen a que la capacidad de reacción ante la epidemia de TB-MDR sea más lenta y desorganizada en los países con menos recursos y además con más carga de enfermedad. Sin embargo el tratamiento y la contención de la TB-MDR son posibles incluso en países con grandes dificultades, como viene a confirmar el estudio 2 presentado en esta misma tesis. En cualquier caso, el número de pacientes en tratamiento en los países pobres es tan solo la punta del iceberg. Se cree que la mayoría fallece en la comunidad

tras varios años de enfermedad. Es por ello que el impacto de la enfermedad a nivel poblacional puede ser desmesuradamente mayor en países pobres que ricos.

Puede que las soluciones actualmente empleadas para la TB-MDR en países ricos y posteriormente usadas en países pobres no sean totalmente extrapolables. Nuevos esfuerzos y soluciones propias y adaptadas a cada escenario son necesarios.

7.2 Discusión general del estudio de doctorado

La presente tesis doctoral aporta desde los 5 artículos referidos un conjunto de medidas básicas de bajo coste que permiten aumentar la calidad de la atención de los enfermos con TB. Los artículos presentados suponen un respaldo científico a las estrategias de uso de medicamentos combinados para tratar TB sensible y las estrategias de tratamiento estandarizado para TB-MDR en países de escasos recursos obteniendo una alta tasa de éxito terapéutico. También en esta tesis se ha conseguido la elaboración de artículos que de forma sencilla, breve, actualizada y gratuita favorecen el acceso a conocimiento y autoaprendizaje en el manejo de la TB con resistencias en países en desarrollo.

La TB carece de un lobby o grupo de presión fuerte y lleva décadas de retraso en la investigación de nuevas formas de diagnóstico y tratamiento. Mientras aparecen nuevas soluciones, optimizar las herramientas actuales y difundir el conocimiento lo más posible para un manejo adecuado puede suponer una diferencia para un número considerable de enfermos y a su vez reducir el riesgo de resistencias. En consonancia con esta tesis, otros colectivos como, el Consorcio Alto a la Tuberculosis, RESIST TB, ONGs y grupos independientes también buscan hacer más con los medicamentos y medios diagnósticos actualmente disponibles. Uno de los mejores exponentes es el trabajo que Médicos Sin Fronteras lleva a cabo desde hace tiempo trabajando en aumentar el acceso a medicamentos de segunda línea contra la TB (122). La escasez de medicamentos y su alto precio es otra de las grandes barreras para llegar a un mejor control de la TB-MDR en países en desarrollo.

Optimizar los recursos científicos actuales es una de las respuestas más lógicas, aunque es claramente insuficiente. Sin embargo en el momento actual y de forma casi sin precedentes en los últimos 50 años, estamos siendo testigos de un nuevo empuje en la I+D+I en el campo de la TB. La amenaza de una TB resistente o virtualmente incurable tanto en países pobres como ricos y una especial afectación en las personas viviendo con VIH ha hecho que grupos como FIND, la *Global TB Alliance*, universidades como la *London School of Hygiene and Tropical Medicine* y laboratorios internacionales como Otsuka o Johnson & Johnson estén poniendo atención en la búsqueda de nuevas soluciones contra la TB. Los nuevos tests basados en PCR a tiempo real que aportan un diagnóstico de TB en 2 horas con el añadido del diagnóstico de resistencias a RIF, son probablemente el mayor avance en el campo del diagnóstico de la TB en los últimos 100 años. Sin embargo esta tecnología sigue siendo demasiado cara para la mayoría de países de alta carga de enfermedad (64). Por tanto están lejos de ser test diagnósticos sencillos, económicos y rápidos que se puedan hacer en el mismo lugar donde se atienden pacientes.

Por otro lado en diciembre de 2012 se ha aprobado por primera vez en 50 años un nuevo medicamento en la Agencia de la Alimentación y el Medicamento de Estados Unidos (FDA, en sus siglas en inglés). De forma acelerada se aprobó para uso en humanos la bedaquilina (Sirturo™, antes conocido como TMC207) como parte del tratamiento de TB-MDR (123). La aprobación de una nueva medicación sin duda habla de un renovado interés en esta enfermedad en la agenda internacional (124). Otros nuevos medicamentos están en camino y posiblemente serán aprobados en los próximos años. Los cambios que estamos viviendo ofrecen una nueva luz al viejo, grande y olvidado problema de la TB.

Potencial impacto internacional de esta tesis doctoral

Los presentes estudios de doctorado se plantearon como potenciales respuesta a problemas concretos para el manejo correcto de la TB-MDR. Los contenidos englobados en esta tesis doctoral son claramente insuficientes para atajar el problema global de las resistencias en países en desarrollo. Sin embargo, aporta nuevos conocimientos y herramientas con potencial para un mejor control de la TB-MDR en países en desarrollo.

El estudio 1 cierra una vieja pregunta en cuanto a la eficiencia de los MCFs. Desde su publicación a un nivel científico no se cuestiona la eficacia de su uso y actualmente el uso preferente de los MCFs es una estrategia básica asumida por las principales autoridades sanitarias internacionales. Tanto es así que los grupo de presión incluyen el uso de los MCFs como parte de las medidas básicas para el buen control y manejo de la TB a nivel nacional. De hecho el estudio 1 se encuentra mencionado en foros de debate y blogs de abogacía de pacientes con TB (125). Quizás una de las medidas del impacto de esta tesis que se han podido objetivar ha sido el uso del estudio 1 como justificación científica para la implantación de los MCFs en el programa Nacional de TB de Sudáfrica. Médicos Sin Fronteras y otros grupos de presión usaron el estudio en el año 2011 como argumento para la implantación inmediata de los MCFs en el país. Actualmente el programa de Sudáfrica trata a casi todos sus enfermos con medicamentos combinados (126).

El estudio 2 cierra también una polémica cuestión en cuanto a la eficacia y efectividad de los tratamientos estandarizados frente a individualizados para la TB-MDR. La experiencia en Republica Dominicana demuestra que con un menor costo se puede tratar casos previamente catalogados como incurables con esquemas estándar aún en situación de escasos recursos. Es un estudio a nivel nacional por lo tanto presenta efectividad en un país pobre y no eficacia como muestran los estudios realizados, a su vez casi siempre en países ricos. Presenta además altas tasas de éxito terapéutico. Por lo tanto, este estudio y otros que irán surgiendo, abren la puerta al tratamiento masivo de enfermos con TB-MDR en otros países. También es un estudio que complementa nuevas estrategias que a medio plazo puedan ser más importantes como el esquema acortado de Bangladesh donde también con un esquema estandarizado se trata TB-MDR en 9 meses.

Los estudios 3, 4 y 5 recogen también una necesidad sentida por una parte considerable de clínicos en países en desarrollo, que es la simplificación de conocimientos en el complejo manejo de la TB-MDR y el reconocimiento de que las estrategias seguidas en países ricos no siempre son extrapolables a los países pobres. El *estudio 3*, de hecho es

un documento donde hay constancia que se utiliza para la formación de médicos en lugares tan variados como la Facultad de Medicina de Islamabad (Pakistán), en unidades de TB-MDR del Líbano, Jordania, Indonesia, varios países de America Latina y África e incluso Nueva Zelanda.

Como medida de impacto del *estudio 4* mencionar que con la búsqueda del título en Google se accede al documento en formato PDF en el primer encuentro. También en la búsqueda por las palabras clave "*clinical management MDR–TB*" el artículo original aparece en la primera página de las búsquedas. Esto es un indicador indirecto de que la gente accede y busca el artículo. El acceso gratuito y de calidad marca una diferencia en el uso de la información científica en países en desarrollo donde muchos de los clínicos no tienen acceso a las revistas de impacto y mayor calidad, utilizadas y creadas en occidente. Difundir información de calidad, en las revista gratuitas leídas por los médicos de en países pobres, significa acercar el conocimiento y la capacidad de manejo o "*know-how"* a quien más lo necesita, uno de los objetivos específicos de esta tesis doctoral.

Así pues, los aportes de los artículos incluidos en esta tesis doctoral se considera que son de gran interés para mejorar el control de la TB-MDR en países en desarrollo.

Implicaciones en investigaciones futuras

El trabajo llevado a cabo en esta tesis doctoral no supone un fin en si mismo sino que marca el inicio de nuevas investigaciones científicas. En el caso de los tratamientos estandarizados para TB-MDR, se ha iniciado con el mismo grupo de República Dominicana un nuevo estudio que permitirá evaluar el uso de la Capreomicina (inyectable) 3 veces por semana en lugar de tratamiento diario. Los potenciales beneficios si se demuestra similar eficacia es una reducción en el costo de tratamientos y por lo tanto mayor acceso, una reducción de toxicidad tanto vestibular como ótica y renal. A su vez se reduce el número de pinchazos que en el caso de pacientes desnutridos con poca masa muscular son muy dolorosos. Los resultados preliminares son positivos y ofrecen una similar tasa de conversión del cultivo que los tratamientos inyectados diarios.

También con el mismo grupo de médicos se esta trabajando en una cuantificación de pacientes muertos esperando el tratamiento MDR durante los primeros años de implementación y el papel que el VIH está pudiendo tener en la epidemia de TB del país. Conjuntamente se va a trabajar en la caracterización de los pacientes que abandonan el tratamiento de la TB con resistencias para intentar orientar políticas sanitarias para reducir el impacto de este gran problema.

Por otro lado, de forma similar al planteamiento de esta tesis, se está trabajando en la identificación de barreras para la optimización de los actuales tratamientos de TB y VIH en países en desarrollo, del cual se esperan surjan nuevos estudios. También la aparición de nuevos medicamentos en TB abre la puerta a nuevas investigaciones y a la evaluación de nuevos esquemas para TB sensible usando quinolonas. Se exploraran las potenciales consecuencias e impacto de la perdida de eficacia de las quinolonas en países en desarrollo.

Producción científica adicional

Aparte de los otros 5 estudios que componen el cuerpo principal de esta tesis durante el tiempo de la tesis doctoral la TB-MDR en países en desarrollo ha sido tratada por el doctorando ampliamente en otros documentos añadidos como complemento. Los otros 7 documentos científicos que componen la producción adicional complementaria son explicados brevemente en esta sección y ampliados en la sección de anexos. Se trata de una publicación en una revista de segundo cuartil (64), dos artículos pendientes de revisión y 2 guías clínicas internacionales (76, 106). De forma adicional también se ha colaborado en otras dos guías internacionales (107) (108).

6. Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? *Trébucq A, Enarson D A, Chiang C Y, Van Deun A, Harries A D, Boillot F, Detjen A, Fujiwara P I, Graham S, Monedero I, Rusen I D, Rieder H L. Int J Tuberc Lung Dis 15(12):1567–1571. Factor de impacto: 2.73*
Se trata de un artículo original donde se exploran las ventajas y desventajas del uso del Genexpert como medio diagnóstico para la TB y la TB-MDR y su implantación masiva en países en vías de desarrollo. Ver artículo completo en *anexo 1* (64).

7. Common errors in MDR-TB management and how to avoid them. *I. Monedero, JA. Caminero. Sujeto a revisión.*
Este estudio pendiente de revisión, es un compendio de errores en el manejo de la TB-MDR recopilados durante el trabajo como asistente técnico del doctorando en distintos puntos del mundo. Se identificaron 7 errores altamente frecuentes en el manejo de pacientes que de forma repetitiva sucedían en países con contextos socio-económicos muy dispares. Con un objetivo similar al que guía los estudios 3, 4 y 5 de esta tesis, se busca acercar el conocimiento en manejo adecuado de pacientes con TB-MDR pero esta vez con una orientación diferente: se intenta que los errores altamente prevalentes no se repitan y puedan ser evitados. Ver artículo completo en *anexo 2*.

8. Treatment of patients with multidrug-resistant/extensively drug-resistant tuberculosis. Management of patients with M/XDR TB in Europe. A TBNET consensus statement. *Jose A. Caminero, Kwok-Chiu Chang, I. Monedero, A. Scardigli, Wing-Wai Yew. Sujeto a revisión.*
Este artículo sujeto a revisión es un documento de consenso para el manejo de la TB-MDR y XDR en contextos europeos. Comprende las mejores prácticas actualizadas en el manejo de la TB orientado a países de altos recursos. Ver artículo completo en *anexo 3*.

9. Guideline for the Clinical and Operational Management of Drug Resistant Tuberculosis. *JA Caminero, A van Deun, PI. Fujiwara, I Monedero, CY Chiang, HL Rieder, D Enarson, A Harries, E Heldal, A Trebucq, E Alarcón, R Armengol, C Macé, C Perrin, RA Dlodlo, NE. Billo Paris, France: Internacional Union Against Tuberculosis and Lung Diseases. En prensa 2013*
Este documento son las guías internacionales de la Unión Internacional contra la TB y Enfermedades Respiratorias en relación al manejo de la TB con resistencias (106). Suponen la primera edición de unas guías de TB-MDR orientadas a países en desarrollo. El doctorando contribuyó como autor de 3 capítulos de alta relevancia: TB con resistencias e VIH, control de infección y manejo de la TB con resistencias en casos

especiales. Los tres capítulos están disponibles en el *anexo 4.* La guía será publicada a mediados de 2013 y estará disponible on line con acceso gratuito desde: http://www.theunion.org/images/stories/resources/PUB/MDR-TBGuide_20Mar2013.pdf

10. Management of Tuberculosis: A Guide to the Essentials of Good Clinical Practice. *Authors: N. Aït-Khaled, E. Alarcón, R. Armengol et al. Publisher: International Union Against Tuberculosis and Lung Disease (The Union). Edition: 6th edition (English), 5th edition (Other languages) 2010.*
Se trata de las guías Internacionales de la Unión Internacional contra la TB y enfermedades respiratorias en relación al manejo general y programático de la TB en países en desarrollo. Es un documento de consenso donde el doctorando que aparece como co-autor (76). Está disponibles on line con acceso gratuito desde: http://www.theunion.org/index.php/en/resources/scientific-publications/tuberculosis

11. Implementing collaborative TB-HIV activities: a programmatic guide. *Fujiwara PI, Dlodlo RA, Ferrousier O, Nakanwagi-Mukwaya A, Cesari G, Boillot F. Paris, France: International Union Against Tuberculosis and Lung Diseases, 2012.*
Se trata de las guías Internacionales de la Union Internacional contra la TB y Enfermedades Respiratorias en relación al manejo programático de la TB y el HIV en países en desarrollo (107). El doctorando aparece como colaborador y trabajo en las revisiones iniciales y finales del texto. La guía está disponibles on line con acceso gratuito desde: http://www.theunion.org/index.php/en/resources/technical-publications

12. Manual on use of Routine Data Quality Audit (RDQA) tool for TB monitoring. *WHO 2011. WHO/HTM/TB/2011.1*
Este documento es un manual de la OMS donde de una forma breve se aborda el manejo de una herramienta sencilla para verificar la calidad de la información de los programas de salud de TB. El doctorando aparece como colaborador y trabajo en el diseño inicial del documento y las revisiones finales del mismo (108). Se puede acceder a él de forma gratuita desde la página:
http://whqlibdoc.who.int/publications/2011/9789241501248_eng.pdf

8. CONCLUSIONES

Las resistencias a medicamentos de primera y segunda línea están poniendo en peligro los progresos previos en TB, especialmente en países de escasos recursos y alta carga de VIH. Los nuevos medicamentos o vacunas pueden tardar décadas en ser utilizados de forma rutinaria en PVD. Por lo tanto se necesitan nuevas formas de enfrentarse a la TB con las herramientas que ahora disponemos. Basado en los objetivos planteados se han diseñado 5 estudios mediante los cuales podemos concluir:

1. Estudio 1

De acuerdo a los estudios revisados y teniendo en cuenta sus limitaciones los MCFs contra la TB tienen una similar eficacia respecto a los medicamentos sueltos en términos de conversión de esputo, curación y probablemente recaídas. El papel que pueden jugar los MCFs para prevenir monoterapia y amplificación de resistencias permanece sin esclarecer y está limitada a un estudio. Otras características como aceptabilidad, adherencia, ventajas logísticas y operacionales y costo hacen a los MCFs mejores opciones de tratamiento que los medicamentos sueltos. Sin embrago el uso de los MCFs sigue siendo muy reducido a nivel mundial.

2. Estudio 2

Basado en condiciones de programa, los tratamientos estandarizados para el manejo de TB-MDR son efectivos incluso en PVD. El 86.4% de conversión de esputo y el 74.3% de éxito terapéutico obtenido a nivel de programa en República Dominicana son buenos ejemplos. Además los tratamientos estandarizados son más sencillos de monitorizar, es más fácil formar al personal involucrado y presentan menor coste que los individualizados. En términos económicos y logísticos a igual efectividad los tratamientos estandarizados para tratar TB-MDR son convenientes especialmente en países con alta carga de enfermedad y escasos recursos.

3. Estudios 3, 4 y 5:

La formación en TB-MDR sigue siendo compleja y costosa para médicos en países en desarrollo que tienen una alta carga de enfermos. El acceso a la información y formación de calidad en cuanto al manejo de la TB-MDR es fundamental y puede ser clave para la obtención de buenos resultados terapéuticos. Se han creado herramientas sencillas para la formación rápida en manejo clínico de TB-MDR que actualmente están siendo usadas en programas nacionales y en distintas universidades del mundo.

Finalmente, los artículos incluidos en esta tesis doctoral se considera que aportan información científica relevante para una mejor prevención y control de la TB-MDR en países de escasos recursos, principal objetivo de esta tesis doctoral.

8. Conclusiones

9. RECOMENDACIONES

Basado en las conclusiones obtenidas de los artículos presentados como resultados de esta tesis y sus objetivos, se procede a hacer las siguientes recomendaciones:

1. Existe suficiente evidencia acumulada para afirmar que los MCFs tienen la misma eficacia y superior efectividad para curar TB que los medicamentos sueltos. Además probablemente reducen el riesgo de resistencias a nivel poblacional. En consecuencia, los MCFs deben ser parte de las estrategias nacionales e internacionales para tratar pacientes con TB sensible y evitar adquisición resistencias.

2. Los esquemas estandarizados para el tratamiento de la TB-MDR tienen una eficacia alta y elevada efectividad en PVD. Por lo tanto su uso debe ser expandido especialmente en programas de escasos recursos y alta carga de enfermedad que tengan capacidad para el manejo de pacientes con TB-MDR.

3. Es necesario simplificar y difundir de forma directa o indirecta y a ser posible de forma también gratuita las bases científicas del manejo de los casos con TB-MDR, sobre todo a los países más afectados por este problema que además suelen tener un menor acceso a formación científica y mayores dificultades económicas para financiar tanto formación como tratamientos y medidas preventivas.

9. Recomendaciones

10. REFERENCIAS

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11. ANEXOS

Anexo 1. Xpert MTB/RIF for national TB programmes in low income countries: when, where and how?

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Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how?

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SUMMARY

Xpert® MTB/RIF offers new and important possibilities for the diagnosis of sputum smear-negative tuberculosis (TB) and/or rifampicin (RMP) resistance, and many are encouraging rapid and widespread implementation. This simple test can be implemented almost everywhere, and it provides results within a few hours. In low-income countries (LICs), however, its cost, environmental limitations (stable and regular electricity, adequate room temperature) and difficulties involved in supply and maintenance are major obstacles. While it may be suitable for major reference hospitals, operational research is needed to evaluate the test and its additional yield above high-quality smear microscopy and clinical algorithms before its use at the peripheral level. In the meantime, direct microscopy should remain the initial diagnostic test for TB suspects. In most LICs, the prevalence of RMP resistance among new TB patients is very low; an Xpert MTB/RIF result indicating RMP resistance will thus always need confirmation by another test. In a population at high risk of RMP resistance (>15%), however, the positive predictive value for RMP resistance by Xpert MTB/RIF is high, and identification of RMP resistance is an excellent proxy for multidrug-resistant TB (MDR-TB). The assay should be widely used for this purpose if, and only if, excellent MDR-TB management is available, both for ethical reasons and to reduce the risk of extensively drug-resistant TB.

KEY WORDS: tuberculosis; diagnostics; GeneXpert; low-income countries; Xpert® MTB/RIF

RECENT YEARS have seen a heightened interest in and output of research into new tools for the diagnosis of tuberculosis (TB). An automated nucleic acid amplification test, the Xpert® MTB/RIF test (GeneXpert, Cepheid, Sunnyvale, CA, USA), has recently been developed, which seems very promising for use at the peripheral level of the health services for the diagnosis of TB and detection of rifampicin (RMP) resistance.[1,2] Since the approval of this test by the Strategic and Technical Advisory Group for TB (STAG-TB) in September 2010, the World Health Organization (WHO) has been strongly advocating its swift and large-scale implementation.[3]

The MTB/RIF test is a disposable cartridge-based assay that can operate in temperatures of 15–30°C, even in high-humidity environments. It is easy to train health workers in its use,[4] there is virtually no risk of sample cross-contamination and there is no need for a specific biological safety environment.[5] Examinations for diseases other than TB can be performed using the same GeneXpert platform, such as *Staphylococcus aureus* infection and enteroviral meningitis, and other applications are under development. The simplicity of the test allows its implementation almost anywhere; this is not the case for culture techniques, which require a specific and expensive laboratory environment. The test provides results within a few hours, a tremendous advantage compared to culture.

However, some characteristics of this tool can cause operational problems: the shelf-life of the cartridges is only 18 months, a very stable electricity supply is required, the instrument needs to be recalibrated annually, the temperature ceiling is critical, the subsidised cost of one test, including the cost of the equipment and recalibration, is about US$20,[3] and the safe disposal of large volumes of plastic cartridges may be problematic.[4]

Crucial questions need to be addressed to derive maximum benefit from this test for truly better TB and multidrug-resistant TB (MDR-TB) control. These questions are principally 'when, where and how should the MTB/RIF test be promoted for use in National Tuberculosis Programmes (NTPs), and specifically in low-income countries (LICs)?' A clear distinction based on the objective of the test is needed: diagnosis of TB, or diagnosis of RMP resistance.

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TB DIAGNOSIS WITH XPERT MTB/RIF

The specificity of the MTB/RIF test in the diagnosis of TB has been shown to be very high (97–100%) in demonstration studies coordinated by the Foundation for Innovative New Diagnostics (FIND).[6,7] The sensitivity differed between pulmonary TB patients whose sputum was positive on smear microscopy and culture and those who were positive on culture only. Taking culture as the gold standard, the sensitivity is >95% for direct sputum smear-positive samples, and varies between 65% and 77% if direct sputum smear microscopy is negative,[6–9] with an incremental gain in sensitivity when the number of tests is increased from one to three. While a negative MTB/RIF test result does not exclude a diagnosis of TB, the test is much more sensitive than smear microscopy in detecting bacteriologically positive pulmonary TB. This is particularly important among human immunodeficiency virus (HIV) infected patients.

The STAG-TB supported the WHO Expert Group findings,[10] stating that 'the MTB/RIF test should be used as the initial diagnostic test in individuals suspected of having (*MDR or*) HIV-associated TB' [our italics and parentheses].

Does this statement imply that in sub-Saharan Africa, where HIV infection among TB patients is particularly frequent and where two thirds of LICs are situated (Table), every TB suspect should have an MTB/RIF test? Although the WHO MTB/RIF implementation document states upfront that the microscopy network needs to be maintained,[3] smear microscopy is curiously assigned as a second choice after the MTB/RIF test, or even radiographic screening; it remains the first choice only for treatment follow-up tests. Nevertheless, even in LICs with high HIV prevalence, it would be unwise at this stage to try to replace smear microscopy in peripheral health facilities by the MTB/RIF test, for several reasons:

- The use of the assay is limited to laboratories where the temperature is constantly below 30°C. In most tropical countries, this makes permanent air-conditioning equipment a prerequisite, which is not currently the case in the majority of peripheral laboratories in LICs.
- US$20 for one MTB/RIF test[2] is far too expensive, and substantially (40-fold) greater than the US$0.5 for two sputum smear examinations (this corresponds to capital and running costs; it does not take into account labour and the gain in effectiveness, which are possibly in favour of GeneXpert). Governments or patients will face great difficulties in financing such an amount, and, thus, if external funding sources are no longer available, all laboratory TB diagnostics would stop.
- Even if funds were available (and for how long?), regular provision and uninterrupted availability will prove challenging for many peripheral health facilities due to the short shelf-life of the test cartridges (18 months). These consumables must be imported regularly, while microscopy staining solutions are easily prepared at the regional level.
- Sustaining its implementation may be challenging: electricity supplies are frequently interrupted and unstable in most LICs. It will be difficult to send the modules inside the machine for annual calibration, the cartridges are bulky and their maintenance at a maximal storage temperature of 28°C is unfeasible in most peripheral centres in tropical countries.

Table Estimated % of all new TB cases with MDR-TB per low-income country[11]

Low-income country*	MDR-TB %	Low-income country*	MDR-TB %
Afghanistan	2.8	Lao People's Democratic Republic	1.9
Bangladesh	2.2	Liberia	0.9
Benin	0.3	Madagascar	0.5
Burkina Faso	0.9	Malawi	1.8
Burundi	1.8	Mali	0.9
Cambodia	0.0	Mauritania	0.9
Central African Republic	1.1	Mozambique	3.5
Chad	0.9	Myanmar	4.2
Comoros	0.9	Nepal	2.9
Congo, Democratic Republic	1.8	Niger	0.9
Eritrea	0.9	Rwanda	3.9
Ethiopia	1.6	Sierra Leone	0.9
Gambia	0.5	Solomon Islands	1.9
Ghana	0.9	Somalia	0.9
Guinea	0.6	Tajikistan	16.5
Guinea-Bissau	0.9	Tanzania	1.1
Haiti	2.0	Togo	0.9
Kenya	0.0	Uganda	0.5
Korea, Democratic Republic	2.2	Zambia	1.8
Kyrgyz Republic	12.5	Zimbabwe	1.9

*Gross national income < US$995 per capita. World Bank, http://data.worldbank.org/about/country-classifications/country-and-lending-groups.
TB = tuberculosis; MDR-TB = multidrug-resistant TB.

While the widespread availability of the MTB/RIF test at peripheral health facility level may be challenging, it should be possible to offer the test fairly rapidly at the main provincial or regional referral hospitals, where more services can and should be offered to patients. Subsequent to a negative sputum smear result, the MTB/RIF test could be useful in the diagnostic process if patients under investigation are still strongly suspected of TB, based on clinical presentation and/or an abnormal chest radiograph. This is especially true of children, provided an appropriate sputum sample can be obtained.[12] The molecular technology also makes it easier to transport sputum from one peripheral health facility to a reference centre.

Always beginning with smear microscopy examination in referral hospitals will keep laboratory technicians trained to recognise acid-fast bacilli on smears, which is essential for the identification of failure cases (for which the MTB/RIF test cannot be used). The use of the test at a more peripheral level, i.e., a district hospital serving a population of 50000 to 150000,

will require carefully conducted operational research to evaluate the feasibility and effectiveness of this new technology compared with the combination of routine and optimised smear microscopy and a clinical algorithm as the first-line diagnosis. The recently developed Impact Assessment Framework (IAF) which, for new diagnostic tools, looks at effectiveness, equity, health systems, scale-up and policy analysis, could guide such research.[13] It will also be important to convince donors, and particularly the Global Fund to Fight AIDS, Tuberculosis and Malaria, to assist in scaling up the use of this tool.[14]

IDENTIFICATION OF RIFAMPICIN RESISTANCE WITH XPERT MTB/RIF

From a technical point of view, the MTB/RIF test lends itself to decentralisation of the identification of RMP-resistant TB, a sufficient indication for initiating MDR-TB treatment (isoniazid should always be added to such a regimen, unless resistance is proven to be due to mutations in the *kat*G gene).[15] This represents important progress, as the centralised system for MDR-TB diagnosis has been an important impediment in scaling up the fight against MDR-TB. STAG-TB supports the WHO Expert Group findings[10] that 'the MTB/RIF test should be used as the initial diagnostic test in individuals suspected of having MDR-TB (*or HIV-associated TB*)' [our italics and parentheses].

The phrase 'individuals suspected of having MDR-TB' needs to be scrutinised and precisely defined. Any test result needs to be interpreted according to the prevalence of MDR-TB. Given the 95% sensitivity and 98% specificity of the MTB/RIF test in the detection of RMP resistance,[7] the positive predictive value of the test is >90% if the prevalence of RMP resistance is >15%, but only 32% if the prevalence is 1%, and 49% if it is 2%. In all LICs, the prevalence of RMP resistance is less than 5% among patients who have never previously been treated for TB (with two exceptions: Kyrgyz Republic and Tajikistan) and, for the most part, even less than 2% (Table).[11] For these 'naïve' TB patients, any MTB/RIF test result requires an alternative confirmatory test for a definitive diagnosis of RMP resistance. Among patients previously treated for TB, such as relapses or those returning after default, the prevalence of resistance is often around 10%. Whether or not a positive RMP resistance result will need confirmation will depend on the level of RMP resistance in the country for these specific groups. On the other hand, among patients with treatment failure or with disease after contact with MDR-TB, the prevalence of RMP resistance commonly exceeds 15%, and the MTB/RIF test result alone should usually suffice to decide to treat for MDR-TB.

Sub-Saharan African countries have the highest prevalence of HIV infection in the world; the situation is gravest in southern Africa. Throughout the continent, the prevalence of RMP resistance among never previously treated TB cases is less than 4%, whatever the income level.[11] Evidence supporting an association between MDR-TB and HIV is conflicting at best,[16] barring some dramatic institutional outbreaks.[17] The precautions required for interpreting a result for RMP resistance therefore remain the same, irrespective of whether the TB patient is HIV-infected or non-infected.

Confirmation of an RMP-resistant result will thus often be necessary. The categories of patients for whom an MTB/RIF test result indicating RMP resistance requires confirmation and the technique for obtaining it must be clearly defined and accurately described. The algorithms will depend both on the distribution of the risk groups and existing reference laboratory possibilities in each country. If a sputum specimen must be sent to a reference laboratory, an important advantage of the test is lost, unless research demonstrates that confirmation obtained by repeating the MTB/RIF test in the same laboratory on another sputum specimen enhances its accuracy.

Another factor should be considered before extending the use of the MTB/RIF test, and consequently the identification of MDR-TB cases: according to current logic, NTPs should ensure that they achieve high cure rates before focusing on expanding case detection, to avoid a potential worsening of the situation.[18] This is also appropriately reflected in the WHO's stated priority listing, where the first objective is to cure 85% of sputum smear-positive cases and the second objective is to detect 70% of such cases.[19] If we detect more MDR-TB cases, it is an ethical obligation to build capacity for good treatment from the start; moreover, as stated in recent WHO guidelines, 'individuals should not be given diagnostic testing in the absence of treatment unless they have provided specific informed consent'.[20]

This is a very real challenge; programmatic management of MDR-TB is hard to implement, and scaling up of good MDR-TB treatment is very difficult, for the following reasons.

- Access to quality-assured second-line drugs (SLDs) is a huge challenge. Shortages of SLDs in NTPs are common. These constraints are not solely attributable to management problems at the national level: the problem is much more fundamentally linked to the fact that SLDs are not currently produced in sufficient quantities to meet market needs. This dire situation could become even worse if there is a sudden rise in demand due to increased case detection related to the availability of new tests. Intensified advocacy is needed to maintain pressure on manufacturers to invest in development and/or increase their production capacity.

- The prices of SLDs are increasing, resulting in constraints on NTP budgets, and institutional arrangements such as the Global Fund Board's Market Dynamics and Commodities Ad-Hoc Committee need to become involved.
- Delay in the development of new, effective drugs for MDR-TB patients: despite the efforts of the Global Alliance for TB Drug Development, too little funding is available for drug development. New potential compounds such as TMC-207, PA-824, and OPC-67683 are unlikely to be available for general use in the near future.[21]
- Success with the current WHO-recommended MDR-TB regimens rarely exceeds 60%; default, failure and death are all too frequent adverse treatment outcomes.[15] This is true even in settings where considerable efforts have been made to handle MDR-TB treatments seriously. New, shorter regimens with better efficacy are needed.

As a result of these serious constraints and the severe limitations in providing curative treatment for MDR-TB, more and more countries are reporting extensively drug-resistant TB (XDR-TB) cases, and the number of XDR-TB cases is increasing.[22] The clear imperative of scaling up MDR-TB diagnosis is simultaneously seriously challenged by inefficient case management. The situation can only worsen if there is no link between the diagnosis of MDR-TB and good management of those cases diagnosed. Poor management of MDR-TB is the direct precursor of XDR-TB, just as poor management of new TB cases leads to the development of MDR-TB.[23]

If we accept the premise that high-quality MDR-TB treatment is a non-negotiable prerequisite,[24] we must then identify those settings where the NTP is able to treat these patients correctly; only then should we ask for the best methods of performing drug susceptibility testing.

The answer to this question will vary between countries, depending on the capacity of the NTP and on the country's possibilities of providing quality-assured MDR-TB treatment. The situation must then be analysed separately and specifically for each country, and indeed for each intermediate level; decisions should be taken according to the result of the analysis in the perspective of scaling up quality services. Extension of MDR-TB treatment sites should always be planned very carefully, and very gradually.[25]

CONCLUSION

To scale up MDR-TB control, we must focus, as a priority, on avoiding the creation of further MDR-TB cases. A well-performing NTP must be the first rule, and this prerequisite should be repeated constantly. Treatment of MDR-TB cases should not divert the NTPs from their main focus, which is to cure TB patients, thus preventing the development of RMP resistance.[26]

In LICs, case detection based on sputum smear microscopy and a clinical algorithm must remain the cornerstone for TB diagnosis at all levels. In most settings, the MTB/RIF test must be considered as a follow-up test to microscopy at this stage, and its use should be particularly encouraged in settings where HIV is highly prevalent, for a better diagnosis of TB among sputum smear-negative cases. While the assay could be implemented rapidly in major referral hospitals in LICs, given its limitations, its cost (even if this decreases as expected), the supply difficulties, and the problems of maintenance, for now the obstacles outweigh the advantages in implementing the test at a more peripheral level. Operational research with the MTB/RIF test is urgently needed to carefully measure the pros and cons of more decentralised use at the district level.

Although a positive result for *Mycobacterium tuberculosis* is sufficient for the diagnosis of TB, for the diagnosis of RMP resistance the results must be carefully interpreted taking into account the expected prevalence, including a thorough assessment of individual and population risk for RMP resistance. It should then be confirmed by another test if the patient does not belong to a high-risk group for MDR-TB. Extension of the diagnosis of RMP resistance must be linked to the implementation of high-quality MDR-TB treatment services, for ethical reasons and to prevent the development of XDR-TB. This is a crucial point for efficient TB control.

Progress made in molecular technology with tests such as Xpert MTB/RIF, which do not need a sophisticated environment, brings huge expectations for improvements in TB diagnostics and the identification of MDR-TB. We can hope that, in the not too distant future, the limitations of the test described here will be overcome, and that it will be possible to use this new technology everywhere, even in the most remote areas of LICs where the main burden of disease occurs.

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RÉSUMÉ

Le test Xpert® MTB/RIF offre de nouvelles et importantes possibilités pour le diagnostic des tuberculoses (TB) pulmonaires à microscopie négative et/ou pour l'identification de la résistance à la rifampicine (RMP). Beaucoup de personnes et d'institutions plaident en faveur de sa rapide dissémination et de sa large utilisation. Ce test simple peut être installé pratiquement n'importe où et donne un résultat en quelques heures. Cependant, dans les pays à faibles revenus (LIC), son coût, ses limitations environnementales (électricité régulière et stable, température correcte), les difficultés liées à l'approvisionnement en tests et à la maintenance de l'appareil sont des obstacles majeurs. Tandis qu'il semble être une possible technologie adaptée aux hôpitaux majeurs de référence, des recherches opérationnelles restent nécessaires pour évaluer ce test et mesurer ce qu'il apporte de plus qu'une microscopie de qualité en utilisant différents algorithmes, avant de considérer sa diffusion à un niveau périphérique. En attendant, l'examen microscopique direct devrait rester le test diagnostic initial pour tout patient suspect de tuberculose. Dans la plupart des LIC, la prévalence de la résistance à la RMP parmi les nouveaux cas est très faible ; un test Xpert MTB/RIF indiquant une résistance devra toujours être confirmé par un autre test. Cependant, dans une population à haut risque de résistance (>15%), la valeur prédictive positive d'un résultat indiquant une résistance à la RMP est élevée, et est une très bonne approximation pour détecter la TB multirésistante (TB-MDR). Ce test devrait être largement utilisé pour ce diagnostic si, et seulement si, une excellente prise en charge du patient TB-MDR est disponible, à la fois pour des raisons éthiques et pour limiter le développement d'une TB ultrarésistante.

RESUMEN

La prueba Xpert® MTB/RIF ofrece nuevas e interesantes posibilidades al diagnóstico de la tuberculosis (TB) con baciloscopia negativa y la TB resistente a rifampicina (RMP) y muchas de ellas favorecen su pronta y amplia aplicación. Esta prueba sencilla se puede ejecutar casi en todas partes y sus resultados se obtienen en un lapso de pocas horas. Sin embargo, en los países de bajos ingresos (LIC), el costo, las limitaciones del medio ambiente (la estabilidad y continuidad de la corriente eléctrica y la adecuación de la temperatura ambiente) y las dificultades relacionadas con los suministros y el mantenimiento constituyen obstáculos mayores a su utilización. Si bien la prueba se considera apta en los principales hospitales de referencia, antes de utilizarla en el nivel periférico es preciso llevar a cabo nuevas investigaciones operativas con el fin de evaluar su procedimiento y el rendimiento adicional que aportaría, en comparación con un examen microscópico de gran calidad y los algoritmos clínicos. Entretanto, la microscopia directa debe seguir siendo la prueba diagnóstica inicial en todos los pacientes con presunción de TB. En la mayoría de los LIC, la prevalencia de resistencia a RMP en los casos nuevos de TB es muy baja; un resultado de la prueba Xpert MTB/RIF que indique resistencia a RMP exige una confirmación con otra prueba. No obstante, en una población con alto riesgo de resistencia a RMP (>15%) este método ofrece un alto valor pronóstico positivo y constituye un indicador óptimo de la TB multidrogorresistente (TB-MDR). La prueba Xpert MTB/RIF® se debería utilizar ampliamente con este fin, pero solo cuando se cuente con un excelente tratamiento de la TB-MDR, y esto por razones de carácter ético y con el fin de disminuir el riesgo de aparición de TB extremadamente drogorresistente.

Anexo 2. Common errors in MDR-TB management and how to avoid them.

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SUMMARY:

Background

Multi-drug resistant tuberculosis (MDR-TB) defined as resistant to Rifampicine and Isoniazid, has an increasing burden and threats TB control. Diagnose is limited and usually delayed while treatment is long-lasting, toxic and less effective. MDR-TB cure rates usually do not exceed 60%. MDR-TB management is something new for many TB programs. In this challenging scenario clinical and programmatic errors are prone to happen.

Methods

The present article is a compilation of archetypal errors repeatedly observed by the authors in a wide range of countries during technical assistant missions and trainings.

Findings

Clinical and programmatic errors are often intrinsically linked. Regarding error in diagnose, over diagnose of MDR based on clinical facts and conferring full credibility to drug susceptibility test by proportion methods was frequently found. Adding a single drug to a failing regimen and improvisation after a drug stock were sources of error in regimen designing. The most commonly observed errors were found at treatment delivery. Errors were mainly failure to apply direct observation of treatment, incorrect dosage of second line drugs, early injectable withdrawal and lack of attention to side effect management.

Conclusion

Curing MDR-TB patients will remain difficult in resource-constrain settings. Point of care test, new drugs and simplification of regimens are necessary to limit the MDR-TB epidemic. MDR-TB management in scarce-resource settings is challenging but feasible and necessary. Nonetheless frequent errors can be prevented with appropriate training. Avoiding or putting especial attention on the common errors may benefit patients and programs in scarce resource settings.

Background

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant to Isoniazid (INH) and Rifampicin (RIF). It is estimated that over half a million new cases emerge annually (1). Uprising in resistance is currently a major concern in global TB control (2). The most cost-effective strategy to control MDR-TB is to prevent its emergence achieving high cure rates on the susceptible cases. But once resistance exist, treatment of patients is necessary from an humanitarian point of view but also as a way to reduce primary resistance transmission. Other measures like infection control and antiretroviral therapy (ART) might be relevant to control MDR-TB in high HIV settings (3).

Resistance has put TB again in the international agenda with an unprecedented increase in research and development (R&D) and funding. Nonetheless, given the magnitude of the problem and the decades of delay in R&D current funding and efforts are insufficient (1). The number of clinical trials is reduced and there is not a clear consensus on the best way to treat these patients (4). As a result of it MDR-TB patients in low and middle income countries (LMICs) presents success rates rounding 60% (5).

The increasing visibility of the problem, success in advocacy and funds available for drugs has created an unprecedented increase in MDR-TB management (6). Second line drugs (SLDs) more toxic and less effective (3), is certainly something new in LMICs even for physicians with vast experience in TB (7). MDR-TB treatment is more complex and lengthy and learning by doing is a situations regularly found in LMICs. Apart from drugs, it requires a health systems able to monitor side effects and the daily intake of drug for 18 to 24 months. Certainly curing MDR-TB in LMICs is not easy.

Most often only one standardized SLD regimen is available and it represents the one and only chance for cure. In this challenging scenario, errors are bound to occur.

Clinical and programmatic complexities merge in untrained staff and novel MDR-TB programs. Not only the low efficacy regimens but also these circumstances play a significant role in the aforementioned low cure rates. In addition, the substandard use of SLD contributes to drug resistance amplification in the community, reducing future cure possibilities (8). Putting attention on frequent errors in MDR-TB management found in different settings might be a logical approach to avoid them others.

The aim of this article is to describe and warn against a number of archetypal mistakes found in MDR-TB clinical and programmatic management which have been repeatedly observed by the authors in a wide range of countries. The ultimate goal is to provide guidance to prevent avoidable errors even in the most resource-constrained settings.

Methodology

The authors expose in this article the most frequently observed erroneous practices (individual or countrywide) according to current scientific knowledge. The description of these errors is based on the gathered experience of the authors during technical assistances evaluations missions as MDR-TB consultants in the field between 2000 and December 2012 in more than 35 countries from Latin America, Africa, Middle East, Asia and Europe. All authors are being involved in MDR-TB trainings and technical assistance for more than 5 years. Instances of common mistakes in MDR-TB management were tallied but this article only includes those observed in at least five different MDR-TB settings.

Findings

Common errors found could be described in terms of clinical or programmatic level. Nonetheless, both are inherently related and consequences of mismanagement in one level affect the other. Therefore an exposition divided in errors at diagnose, regimen designing and treatment delivery was preferred. Surprisingly, main errors were the basically same in the different socio-economic countries visited.

11. Anexos

Common errors in diagnose

Two major errors are usually observed in MDR-TB diagnose. The first one is the *over diagnose of MDR based on clinical facts*. In that sense many clinicians label as MDR-TB all patients that are not cured at the standard time or are out of the normal presentation and are put under SLDs without resistance confirmation.

The second error at diagnose level was *conferring complete credibility to drug susceptibility test (DST)* to other drugs apart from RIF and INH in the detriment of patient history of drugs. This was particularly conflictive when designing MDR-TB or extensively drug resistant TB (XDR-TB) individual regimens.

Common errors in regimen designing

In this regard two errors had been frequently found. First one is the well known of *adding a single drug to a failing regimen*. This is in reality a monotherapy, masked by the presence of other drugs which may be ineffective due to previous resistance (9). Regimen designing is a purely clinical issue but it is influenced by programmatic weaknesses. Ordering SLDs is troublesome and quite frequently LMICs experience stock outs. When SLDs are scarce clinicians only have two options: stopping treatments or change the regimen according to the drugs available. *Improvisation after SLDs stock-outs* often results in weaker regimens that may end up with resistance amplification.

Common errors in treatment delivery.

Errors in treatment delivery were the most frequently found with severe implications in unfavourable results. Not infrequently there are long lasting backlogs due to unavailability of drugs or beds at the hospital or even dying while waiting for the results to come. Not all patients diagnosed are finally put on treatment. Moreover for those entering, *ancillary drugs for the treatment of SLDs side effects* usually do not exits. At a time the people delivering the treatment can be not used to side effects or simply do not know what to do. This error leads to probably the most common and deleterious error found at the clinical level that is *incorrect dosage of SLDs* according to international standards by weight. Similarly due to the painful daily injection or hearing loss, it was found *early interruptions of injectable* before smears or cultures were negative.

We also regularly found that during the continuation phase the patient *do not receive direct observation of treatment (DOT)* or the especial support received during the initial phase.

Discussion

For decades the management of resistant TB cases was only delivered in referral centers in rich countries by a few number of specialized clinicians (10). In LMICs these patients were classified as chronics or incurable. Waiting for the death was the only thing to do. Conversely no research in TB is being maid for decades (7). The consequences of this neglect in R&D are the lack of point of care tests, new drugs and simple and low toxicity regimens. The cost of this neglect is dragging us into complex solutions for MDR-TB from rich countries which are sometimes difficult to extrapolate in LMICs.

The fact is simply, with the current outdated tools, low trained staff and under weak health systems, cure MDR-TB is not that straightforward. Not surprising cure rates of MDR-TB in LMICs are low. To improve cure rates it is necessary new and simpler tools in addition to better access to SLDs and training. In this complex scenario errors being clinical or programmatic, are prone to happen at several levels.

Errors in diagnose

Drug resistance detection is difficult and usually delayed. MDR-TB diagnose rate is minimal compared to the expected numbers (1). Many patients start SLDs treatments while waiting for the results (11) and sometimes there are good reasons for that: lack of access to appropriate diagnose and/or delays in laboratory reporting system (sometimes 4-8 months (12). Reference laboratories are usually far from the patients and busy. Clinicians are forced to take empiric decisions that are might be life saving in circumstances like severe clinical conditions or TB/HIV. But it can happen all the way round, after 6-8 months of treatment a full susceptible DST arrives. Once started the MDR-TB treatment, it can be hard give a step back to first line drugs (FLDs). There are a number of reasons that may explain why a failure to FLDs may not be an MDR-TB patient (13) (8):

1. Late negatives and dead bacilli: patients with bilateral and extensive disease present greater bacillary load. In addition fibrotic lesions present worst drug biodisponibility and lower drug concentration levels. These cases usually need longer than 6 months treatments or more time is needed to clear the airways of dead bacilli (14).

2. *Poor adherence.* This is probably the most common condition in susceptible TB failures. It is also the most difficult to document. Poor adherence can be manifested as

inconstant intake (stopping medication from time to time) or constant intake but in a lower dose or only of certain drugs or only on selected days.

For these reasons WHO category II treatment, a bad treatment for MDR-TB, is able to cure a high proportion of failures. Conversely, if surveys show high proportion of MDR-TB among failures, starting SLDs treatment might be justified. The use of SLDs for non MDR-TB patients consumes necessary and scarce resources while expose patients to unnecessary toxicity and suffering. Whenever possible bacteriological confirmation of RIF and INH resistance and specie differentiation is always advisable (4, 15, 16). Accelerate the information systems between reference laboratories and clinicians through telephone or email is basic to avoid deaths on the back log.

To date the major predictor of anti-TB drug resistance is still considered the use of drugs in monotherapy for more than one month (4, 9, 15-17). The DST for TB by proportion methods was described more than four decades ago (18) and is still the most used technique though its interpretation is troublesome. Reliability to RIF and INH is high but is much limited for SLDs (16, 19-22). Routinely performing DST is only recommend by WHO for FLDs, FQ and injectables (22, 23). Unexpectedly, many national guidelines stipulate that MDR-TB treatment is to be adjusted after DST results. The authors observed multiple mistakes leading to resistance amplification when strictly using DST for designing individualized regimens. For example if a result was resistant to Cycloserine (Cs), the drugs was not used despite never been used by the patient or in the country. Knowing that reliability of DST for Cs is poor, this can be considered an error. Others findings like RIF resistance but INH susceptible on a high MDR-TB risk patient can be misleading. In such a case the probability of MDR-TB is high. INH false susceptible can occur in 15-20% of the cases. Hence, considering INH as an essential drug and providing a RIF monoresistant treatment, would risk FQ susceptibility and limit cure chances. Providing an MDR-TB adding INH is probably a better option for these patients. In other settings, several DSTs are performed for the same patient, showing discordant results driving to unnecessary therapy switches. DST might be performed only after assuming failure similarly that it is done in HIV contexts.

A recent error found in the use of Genexpert especially in the private sector is using the test for all TB suspects without phenotypic DST confirmation. The positive predictive

value for low MDR-TB risk groups is quite low (32.4%). Hence rounding 1 in 3 positive resistant tests when applied to a non high risk resistance group will be a false positive contributing again to over diagnosing MDR-TB. Calls for advances in gene-based technology are not motivated only to shorten delays but also to increase reliability (20, 21, 23). The understanding of mutations conferring resistance to TB is still exiguous.

Errors in regimen designing

With the advent of standard treatments for MDR-TB the likelihood of errors had decreased. But the accessibility to treatment is still reduced even for those already diagnosed. Backlogs for treatment are frequent especially in poor countries where treatment is only available in one centre. The indirect and emotional costs are high and can discourage patients to start in the formal sector and care is seek in the private sector. Not only, but in these conditions the classical error of *"adding a single drug to a falling regimen"* tends to happen. This approach is valid for other infectious diseases but for TB or HIV drives to resistance amplification (24, 25). This practice seems to thrive in under trained clinicians. In addition, variants of this error where found for compassionate reasons. Often the same previously unsuccessful treatment (RHZE) is prescribed with the only one or two newly available drugs (E.g. Ofloxacin + Ethionamide). Resistance may emerge in months. When the rest of the treatment arrives in the country (e.g. Kanamycin + Cs), these drugs are added to the previous regimen to which the bacilli population is already resistant. After all these sequential monotherapies or weak combinations, patients end up developing resistance to all drugs given. In many countries in the past, quinolones and Amikacin were the only SLDs available. These practices might be among the causes of the current XDR-TB epidemic (3). MDR-TB treatment should be based on *at least four effective drugs* which are new drugs or drugs with susceptibility confirmed by DST (3). All drugs should be given *at the same time*. Sequential addition of drugs over the course of several months will result in opportunities for resistance amplification. Avoid whenever possible to start treatment if 3 or 4 effective drugs are not available. In any case a new generation quinolone (preferentially high dose) and an injectable should be the core of the regimen (26).

Availability of SLDs is a neglected issue. Once stock-outs occur, clinicians must manage the best they can to offer a solution sometimes leading to inappropriate drug

regimens and switches (4). Stock outs are unfortunately frequent even for FLDs (27). Well-organized MDR-TB programmes often have to struggle to procure SLDs. Expiration dates are reduced and shipment delays high. Reliable information systems are critically needed for meticulous forecasting. SLDs supply chain is highly complex, new for most programs and sometimes overlooked. Innovative strategies, such as the creation of regional SLD banks or formal inter-country procurement and distribution networks, would help.

Errors in treatment delivery

Treatment delivery in LMICs usually relays in already overburden and low trained physicians or nurses. According to our observations, errors in treatment delivery seem to be increasing and might be a key factor for the high default, failure and death rates among MDR-TB patients. The close follow up during the 20-24 months of treatment is difficult to maintain, especially in resource constrained health systems.

Not only the length but side effects are another major cause of default (28). Currently, side effects are always to be expected when treating MDR-TB. Fortunately, most are easily treatable and rarely life-threatening (3). Prescribe ancillary treatment (mostly proton pump inhibitors or anti-H2), provide drugs with light meals, and drug ramping are suitable approaches (29). In many MDR-TB sites visited, ancillary drugs simply do not exist or patient can not afford them. In these situations the approach to reduce side effects is to reduce drug dosage especially group 4 drugs (see Table 1). Definitely side effects are reduced but treatment efficacy is reduced too. Decreasing dosage even by just one third, dramatically reduces effectiveness (3). Sub-therapeutic dosage of companion drugs end up creating masked monotherapies of quinolones in the continuation phase. Failure with quinolone resistance was observed under these circumstances.

In some programmes, clinicians were reluctant to use injectables. Certainly, irreversible hearing loss is a real and frequent limitation. Additionally, intramuscular injections in malnourished patients can be very painful. Renal insufficiency and electrolyte abnormalities can be dangerous on the HIV patients. However, not using or very early injectable withdrawal without culture conversion dramatically reduces cure chances (3, 30). We have observed withdrawals after 1 or 2 moths from initiation due to patient complain. In many instances these practices led to quinolones and other drugs resistance

amplification during the continuation phase. To avoid toxicity and reduce cost, injectables can be use three times per week instead of daily (3). Though, whether effectiveness is fully comparable remains controversial (31, 32). Capreomycin, less ototoxic and not teratogenic, can be used in patients with personal or family history of hearing loss (3). To avoid painful shots, intravenous application through peripheral catheter is safely and effectively used in many programmes. The current recommended length of injectable varies from 4 to 8 months (3, 30). More studies are needed to ascertain the earliest moment to stop the injectable.

Generally, clinicians have to make a pragmatic decision whether to prioritize side effects or MDR-TB management: if the patient is not correctly treated from TB most likely will die by TB. More attention has to be put in side effect management.

Another issue deserving more attention is adherence during the continuation phase. It was recurrently observed poor or no DOT for MDR-TB cases. Another variation of this error is having DOT on the continuation phase but keep drug delivery split as it was when the patient was in the hospital (e.g. drugs every 8 hours) ending up with DOT only for a part of the regimen. In some settings, MDR-TB cases were referred to untrained units with just a short letter and a box of pills. Health centre staff was afraid of these patients and unable to manage their side effects. Careful communication between hospital, peripheral centres and social workers are strong pre-requisites for a successful MDR-TB programme. Side-effects management and training for the staff delivering the continuation phase is rarely included in budgets. There is no sense in starting an expensive and toxic MDR-TB treatment if the continuation phase can not be assured.

Infection control conditions in peripheral centres tend to be poor or inexistent. A strong impulse in prevention through infection control is as well need especially in setting with high HIV or DM prevalence. Drug-drug interaction is something that may require major awareness in HIV-MDR-TB coinfected patients as communication between the different experts.

Overall, there is a great need for less toxic and shorter treatments for MDR-TB. Experiences with 9 months MDR-TB regimens are encouraging. With high efficacy and

being more simple and shorter, would probably reduce delivery errors and may increase the final effectiveness (28).

Conclusions

MDR-TB management in LMICs is challenging but feasible and necessary. Throughout visits to programmes both clinical and programmatic errors were often detected. MDR-TB management is something new for most TB programs and is demanding for countries with scarce economic and human resources. Nonetheless, the starting point of many of these errors is a lack of training. To avoid preventable deaths, drug resistance amplification and primary resistance spread into the community, comprehensive understanding of TB disease is needed. Several mistakes are linked to misconceptions in diagnose, regimen design and especially treatment delivery. Rising awareness on the common errors observed may benefit patients and programs in scarce resource settings. Nonetheless, until MDR-TB diagnosed and treatments are much more simplified similar errors will continue be observed in field technical assistance visits.

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Box and Table

Box 1. Common errors in MDR-TB management and potential ways solved them

ERROR	PROBLEM / REASONING	WHAT TO DO
Errors in diagnose		
1. Over-diagnose of MDR based on clinical facts	• Chronic cases and failures to category II treatment are the main risk groups for MDR-TB. • Frequently, complicated cases are labelled as MDR-TB, and SLDs treatment is started without resistance confirmation.	• Before starting MDR-TB treatment, perform a good clinical history including adherence and drugs used in the past. • Whenever possible, perform smear, culture, DST and specie identification to rule out all differential diagnosis possibilities • In severe clinical conditions and HIV infection on a high risk MDR-TB patient staring SLDs treatment while waiting the results might be life-saving
2. Complete credibility to DST	• Regular DST is most reliable for R and H and acceptable for FQ and injectables. • It is currently not recommended for group 4 and 5 drugs.	• DST interpretation should be done according to patient history of drugs taken in past, searching for real or covered monotherapies. • New genotypic DST are an advance in terms of rapidity and probably reliability at least for RIF resistance • Perform DST only ones when assuming failure
Errors in regimen designing		
3.Adding a single drug a failing regimen	To create resistance, two conditions are necessary: 1. High bacillary load (e.g. cavitary lesions, bilateral disease). 2. Monotherapy. At ambient pressure, natural mutant resistant bacilli are selected among the bacillary load. Often, over a non-curative treatment, a single drug is added resulting in a masked monotherapy.	• Start treatment with at least 3-4 effective drugs (always including a new generation quinolone and an injectable) • Avoid sequential introduction of drugs
4. stock out and further improvisation	SLDs shortages are frequent. Sometimes clinicians are forced to change treatments based on drug availability. Treatment shifts and improvisations are not always adequate and in many instances lead to amplification of the resistance pattern.	• Careful planning and drug provision may be done by pharmacologists or specialist. • Avoid treatment improvisations as possible. The drug selection should follow a rational order.
Errors in treatment delivery		
5. Lack adequate management of SLDs side effects	Lack of ancillary drugs or training in side effects recognition especially during the intensive phase	• Intensive use of ancillary drugs • Provide treatment with light meals • Drug ramping
6. Suboptimal dosage	Due to side effects, sometimes dosage is reduced especially for group 4 drugs. When dosages are sub-therapeutic become ineffective, leading to masked monotherapy	• Maintain drugs all drugs at recommended dosage unless there are life-threatening side effects • Take into account drug-drug interaction especial in TB/HIV coinfected patients
7. Early injectable withdrawal	When the injectable is withdrawn too early, the bacillary load could remain high which is one of the premises to resistance amplification. Without injectablea and with high bacillary burden treatment turns less effective and eventually resulting in further resistances and failure.	• Maintain injectable for 4-6 months or until culture conversion. • In conditions like hearing loss or pregnancy capreomycin use is preferred. • If shot are painful, intravenous infusion can be used. • In case of toxicity injectable 3 times per weak instead of weekly

		may offer similar effectiveness
8. No DOT	DOT, adherence and side effect management tend to be acceptable during hospitalisation. Conversely, all can be suboptimal during the ambulatory phase, leading to default.	• Train the staff managing the continuation phase and provide ancillary treatment and socio-economic support during continuation phase. • Strengthen the communication between hospital and health care centres.

DST: drug susceptibility test; FLDs: first line drugs; FQ: fluoroquinolones; H: isoniazid; R: rifampicin; SLDs: second line drugs; Sm: streptomycin

Table 1. Rational classification of anti-tuberculosis drugs. Adapted from: (3, 4, 7)

GROUPING	DRUGS
Group 1: First line oral agents	isoniazid; rifampicin; ethambutol; pyrazinamide
Group 2: Fluoroquinolones	levofloxacin; moxifloxacin; gatifloxacin; ofloxacin
Group 3: Injectable agents	Capreomycin; kanamycin; amikacin streptomycin
Group 4: Oral bacteriostatic second-line agents	ethionamide; protionamide; cycloserine; terizidone; p-aminosalicylic acid (PAS)
Group 5: Agents with unclear efficacy	clofazimine; amoxicillin/clavulanate; linezolid; imipenem/cilastatin; thioacetazone; clarithromycin; high-dose isoniazid
New agents	bedaquiline, delamanid

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Anexo 3. Treatment of patients with M/XDR-TB. Management of patients with M/XDR TB in Europe. A TBNET consensus statement.

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Introduction

Drug-resistant tuberculosis (DR-TB), especially rifampicin-resistant TB, has become a major challenge of TB control worldwide. With high bactericidal and sterilizing activities, rifampicin is by far the least toxic and most active TB drug that also plays an important role in preventing drug resistance. When it is not possible to use rifampicin, the treatment duration should be prolonged to 12-18 months, and the prognosis may be less favorable. Owing to the importance of rifampicin, bacillary resistance to rifampicin is included in the definition of multidrug-resistant TB (MDR-TB), which denotes bacillary resistance to both isoniazid and rifampicin. As rifampicin monoresistance is rare except in HIV-infected patients, rifampicin resistance generally serves as a surrogate marker of MDR-TB (1). Among second-line drugs (SLD), newer-generation fluoroquinolones (FQs) have demonstrated prominent bactericidal (2) and sterilizing activities (3). Bacillary resistance to FQs clearly influences the prognosis in extensively drug-resistant-TB (XDR-TB) (4;5), which is MDR-TB with additional resistance to any FQ and at least one second-line injectable drug (SLID).

Regardless of the drug resistance pattern, all TB forms should be treated with a combination of drugs (to avoid drug resistance) for a sufficient duration (to avoid

treatment failure or relapse). The number of drugs in a multidrug regimen and the total treatment duration depend on the bactericidal and sterilizing activities of the TB drugs included (4). Availability of drugs that are likely to be effective decreases as drug resistance becomes more extensive.

In this chapter we will provide some principles in the treatment of MDR-TB/XDR-TB.

Number of Drugs for Treating MDR-TB/XDR-TB

If *M.tuberculosis* is fully susceptible to all the TB drugs used in a regimen, two active drugs (core drugs), such as isoniazid and rifampin or FQ and SLID, are probably adequate for cure (4). In the treatment of MDR-TB, it is advisable to give at least four drugs that are known or likely to be effective against the drug-resistant *M. tuberculosis* strain harboured by the patient. If possible, at least two of these should be core drugs (FQ and SLID), with the rest being accompanying drugs that may help protect the core drugs in the initial phase when bacillary load is high (5).

What Drugs to Treat MDR-TB/XDR-TB

Drugs not previously used by the patient or those with *in vitro* activity based on drug susceptibility testing (DST) results are more likely to be effective. For this reason, a detailed drug history is important for formulating the MDR-TB regimen (6). It is very important to highlight that the clinical reliability of DST (concordance between *in vitro* and *in vivo*" activity) is very good for isoniazid and rifampicin, good for FQs and SLID, and low or uncertain for the other drugs (6-8). Drugs that are likely to be effective are then included in the MDR-TB treatment regimen according to the hierarchy described in Table 1**.** It is not necessary to choose more than one drug from each of Group 2 (newer-generation fluoroquinolones) and Group 3 (SLID) (1;11).

In case of FQ-resistant MDR-TB and XDR-TB, Group 5 drugs, notably high-dose isoniazid and linezolid, are likely required. High-dose isoniazid (16-20 mg/kg) is likely effective when isoniazid minimal inhibitory concentration (MIC) < 1 mg/L, and probably beneficial when isoniazid MIC < 5 mg/L. Linezolid is a oxazolidinone that has been used off-label in the treatment of FQ-resistant MDR-TB and XDR-TB (Table 1) (11-14). Despite high costs and substantial toxicity (especially neurotoxicity after prolonged use) (14;15), a recent meta-analysis demonstrated that 81.8% among 121

MDR/XDR-TB patients given linezolid-containing regimens were successfully treated (9). Price is a practical problem that may be partly resolved by using a non-proprietary source (10), provided that drug quality can be assured. Neurotoxicity may be ameliorated by reducing the dosage (11), although the best dosing schedule of linezolid in the treatment of MDR-TB is still uncertain(17;18).

Treatment duration of an MDR-TB Treatment Regimen

In the treatment of MDR-TB, the initial phase is defined by the duration of treatment with a SLID, which has lately been recommended by the World Health Organization (WHO) to be at least 8 months on the basis of very low level of evidence (19;20). In practice, the duration may also vary according to the potency of other drugs in the regimen, the bacteriological status of the disease, and tolerance by the patient. If a regimen also contains three effective drugs from Groups 1, 2 and 4 (Table 1), respectively, the SLID may be stopped after confirming sputum culture conversion (2 consecutive negative cultures with a month of difference) , especially when there are signs of otovestibular or renal toxicity. In case of delayed culture conversion (> 3 months), the IP may be prolonged up to 6 months after culture conversion.

WHO has recommended that the total treatment duration be at least 20 months (12;13). This is consistent with giving treatment in the continuation phase for 12-18 months after culture conversion.

The possibility of shortening the total treatment duration to a minimum of nine months has been suggested by a recent publication from Bangladesh, which showed high relapse-free cure rates approaching 88% by a gatifloxacin-based regimen (14). However, these patients were predominantly SLD naïve.

Ideal treatment regimen for MDR-TB/XDR-TB

Due to the complexity of the decisions, the choice of a MDR-TB treatment regimen is preferably formulated under the guidance of experienced clinicians with due reference to internationally accepted guidelines (1;12;13). In several countries, secure websites have been established and hosted by experienced health care professionals to discuss treatment decisions and clinical course of MDR-TB/XDR-TB patients with “consilia” via emails (15).

Treatment of MDR-TB/XDR-TB can be standardized with individualization according to contact history, drug history and DST. Based on clinical evidence from non-XDR MDR-TB patients, WHO has recommended a standardized MDR-TB treatment regimen that consists of pyrazinamide plus four drugs, namely, a FQ (such as moxifloxacin or high-dose levofloxacin), a SLID, a thioamide (ethionamide or prothionamide), and one more oral bacteriostatic drug (preferably cycloserine) (1;7;11;19;20). WHO has recommended use of pyrazinamide (conditional recommendation, very low quality evidence) without pyrazinamide susceptibility testing, which is technically difficult and often not performed.

To facilitate formulation of second-line treatment regimens, DR-TB patients can be classified into three subgroups: (A) new patients with a contact history of DR-TB, (B) new patients with no contact history or previously treated patients with exposure to only first-line drugs (FLD), and (C) previously treated patients with exposure to both FLD and SLD.

(A) New patients with a contact history of DR-TB

With a contact history of DR-TB, new DR-TB patients should initially receive the same regimen as the putative index case (5;16;17), with possible individualization according to the patient's DST results.

(B) New patients with no contact history or previously treated patients with exposure to only FLD

These patients should receive the WHO MDR-TB standardized regimen, which can be individualized according to the patient's DST results. However, in MDR-TB high-prevalence settings, it may be necessary to modify the WHO MDR-TB standardized regimen according to the local drug resistance pattern, especially when the prevalence of bacillary resistance to FQ/ SLID is high.

(C) Previously treated patients with exposure to both FLD and SLD

Treatment should always be individualized with reference to the drug history and the patient's DST. Drugs from Group 5, notably linezolid and high-dose isoniazid, and perhaps clofazimine, should be duly considered in the treatment of XDR-TB/ FQ-resistant MDR-TB.

All TB patients including those with XDR-TB have a chance to be cured (18). The chance of cure increases with rapid diagnosis and prompt treatment using effective multidrug regimens in a well-functioning TB program that is built on the DOTS strategy and drug-resistance programmes (1;19).

New drugs

New drugs that have been evaluated for the treatment against TB in clinical phase II-III include linezolid, bedaquiline (TMC207), delamanid (OPC-67683) and PA-824 (20). Of the new compounds, delamanid and PA-824 are two nitroimidazopyrans with encouraging trial results to date (25-27). Delamanid is promising with a good early bactericidal activity in the phase 1 studies (21). It also demonstrated efficacy as an add-on to a MDR-TB backbone treatment regimen in one recently published randomized placebo controlled phase IIb study(22). Another very promising compound in clinical phase IIb is the diarylquinoline bedaquiline, which inhibits the proton pump ATP synthase of *M. tuberculosis.* Bedaquiline and is active against drug-sensitive and drug-resistant strains of *M. tuberculosis* in pre-clinical evaluations. The published results of a phase IIb clinical trial with bedaquiline as add-on to a MDR-TB backbone treatment regimen showed significant improvement in the rate of culture conversion by 2 months (29).

Surgery in the treatment of MDR-TB/XDR-TB

In the great majority of patients with pulmonary TB, surgery is not indicated. Adjunctive lung resection should be considered when these critera are all met: (1) a fairly localized lesion with an adequate postoperative respiratory reserve; (2) drug therapy per se cannot ensure cure, and (3) effective drugs are available to facilitate postoperative healing of the bronchial stump (23). Thus adjunctive surgery may be justifiable in carefully selected patients with XDR-TB/ FQ-resistant MDR-TB. It cannot be overemphasized that surgery should be performed by experts with support by intensive care units to reduce perioperative morbidity and mortailty (5;16).

Conclusions

The majority of patients with MDR-TB can be cured. With the emergence of FQ-resistant MDR-TB and XDR-TB, treatment has become more difficult and costly with favorable outcomes rarely exceeding 50-60%. Early diagnosis and appropriate treatment are urgently needed to improve the treatment of MDR-TB/XDR-TB.

Bullet point statements

1. All TB patients including XDR-TB have a chance to be cured. The chance of cure increases with rapid diagnosis and prompt treatment using effective multidrug regimens in a well-functioning TB program that is built on the DOTS strategy and drug-resistance programs.
2. Treatment of MDR-TB/XDR-TB can be standardized with individualization according to contact history, drug history and DST.
3. At least four TB drugs that are known or likely to be effective should be given. Drugs not previously used by the patient or those with *in vitro* activity based on reliable DST results are more likely to be effective.
4. The selection of effective TB drugs to be included in a DR-TB regimen should follow a hierarchy of drug groups (Table 1).
5. In MDR-TB high-prevalence settings, it may be necessary to modify the WHO MDR-TB treatment regimen according to the local drug resistance pattern, especially when the prevalence of bacillary resistance to FQ/ SLID is high.

Table 1. Rational and sequential categorisation of drugs used in the treatment of DR-TB

Daily dosage unless specified otherwise

1. First-line oral antituberculosis drugs *

** Use all possible drugs.*

- Ethambutol (E) 15-25 mg/kg
- Pyrazinamide (Z) 25-35 mg/kg

2. Newer-generationFluoroquinolones **

*** Use only one, since they share genetic targets.*

- Levofloxacin (Lfx) 15 mg/kg (750-1000 mg)
- Moxifloxacin (Mfx) 7.5-10 mg/kg (400 mg)

3. Second-line Injectable drugs (SLID) ***

**** Use only one, since they share very similar genetic targets.*

- Amikacin (Am) 15 mg/kg
- Capreomycin (Cm) 15 mg/kg
- Kanamycin (Km) 15 mg/kg

4. Oral bacteriostatic second-line agents ****

***** Use all possible drugs when necessary.*

- Ethionamide (Eto)/Prothionamide (Pto) 15 mg/kg
- Cycloserine (Cs)/Terizidone(Trd) 15 mg/kg
- para-aminosalicylic acid (PAS) 200 mg/kg (split into 2-3 doses per day)

5. Other less effective drugs or drugs with limited clinical experience *****

****** Use all possible drugs if necessary, especially linezolid, clofazimine and consider high-dose isoniazid.*

- Linezolid (Lzd) 600 mg
- Clofazimine (Cfz) 100 mg
- High-dose isoniazid (hdH) 16-20 mg/kg
- Amoxicillin (Amx)/Clavulanate (Clv) 875/125 mg BD
- Meropenem/Clavulanante 500-1000 mg TID
- Clarithromycin (Clr) 500 mg BD
- Thioacetazone (Thz) 150 mg

& adapted from Caminero JA, Sotgiu G, Zumla A, Migliori GB.Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis 2010;10:621-9

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11. Anexos

Anexo 4. Guideline for the Clinical and Operational Management of Drug Resistant Tuberculosis.

Chapter 7. TB infection control - minimal requirements given limited resources

Ignacio Monedero, Paula I. Fujiwara, Riitta A. Dlodlo

Abstract

Infection control is a package of measures focused on stopping the transmission of TB in hospital or other congregating settings. It comprises 3 key measures: administrative, environmental and protective measures. Administrative measures the most important and preventive ones, covers a variety of public health activities like accurate and timely TB diagnosis, isolation of TB patients or suspects, prompt initiation of anti-TB treatment and development of risk assessment and infection control plans and staff and patient education. Usually this measures yield great benefit in TB infection prevention at a much reduced cost and able to be done even in the most difficult scenarios. Environmental measures tend to reduce the concentration of infective particles in the facilities where TB patients or suspect are. Protective measures are aimed to reduce the likelihood of infection in settings where the other two packages of measures can not reduce infection risk. Usually seen as the most important by health care workers, protective measures presents several caveats that turn down their effectiveness in the field. Prevention of TB through infection control should be prioritized, especially in health facilities where HIV-positive, children or patients with other immumodeficiencies are attended. Considering the suffering and prices of MDR-TB treatments just avoiding 1 MDR-TB case turns infection control into extraordinary cost effective (especially administrative measures).

Introduction

TB infection control is a combination of measures aimed at minimizing the risk of transmission of TB bacilli within populations. Despite having wide evidence of the important role of transmission of TB especially in hospitals it wasn't after the deathly outbreaks of XDR-TB in HIV populations in South Africa that this aspect achieved the relevance that have nowadays. Infection control is currently one of the crucial points in the package of measures to prevent MDR-TB and is as well included among the

measures to reduce the burden of TB among the HIV patients. Transmission of TB bacilli is a frequent problem in congested health facilities with poor infection control measures and it is a big concern in settings with a high TB prevalence. TB infection control has become a major challenge in the era of multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB that are serious conditions with limited treatment options. It was previously though that resistant strains presented a much reduced capacity of transmission. However, many studies alert of similar risk of transmission on MDR-TB and even XDR-TB strains on immune competent but especially in immune-comprise population. But, the recent outbreaks of XDR-TB among HIV infected patients with high death rates have highlighted the relevance of primary resistance transmission on resistant strains and the importance of these non-purely clinical preventive measures. Not only among the HIV-infected but also other immune-compromised patients, such as individuals with Diabetes Mellitus (DM) seem to present higher likelihood of becoming infected during a contact with a TB patients and have as well greater risk of developing an active TB disease after being infected with *M. tb* .

The key activities for TB infection control are: administrative, environmental and respiratory protection. This is the hierarchy of the control measures and indicate the activities to be carried out in their order of priority.

- **Administrative controls** are managerial and work practices aimed at reducing the risk of exposure of TB bacilli to patients and health care workers. These include putting in place policies and plans for infection control; changing the manner in which tasks are performed at health facilities e.g. screening patients for TB and triaging them for fast tracking or separation; screening and protecting health care workers from TB and monitoring and evaluation of TB infection control interventions.
- **Environmental controls** aim at reducing the concentration of infectious particles in the air space shared by patients and health workers. These include natural ventilation, use of fans, ultra-violent germicidal irradiation (UVGI) and the use of filters.
- **Respiratory protection/personal protection** means personal protective equipment used to protect health workers working in high risk areas for transmission of TB bacilli. These include use of respirators that have the

capacity to block entry by particles of the size of aerosolized *Mycobacterium tuberculosis*.

Prevention of TB through infection control should be prioritized, especially in health facilities for HIV-positive patients and persons with diabetes mellitus (DM) and other immumodeficiencies, congregate settings (places where people are brought together, for example, for health services or incarceration). This chapter focuses on TB infection control within health care facilities but many of the measures are applicable to other congregated settings. Considering the suffering and prices of MDR-TB treatments just avoiding 1 MDR-TB case turns these activities into extraordinary cost effective (specially administrative measures).

Basic concepts regarding propagation of Mycobacterium tuberculosis

TB propagation is not solely a pathogenic issue, but is widely influenced by other factors. Same basic knowledge on how infection happens is valuable to understand how it can be controlled.

- **Virulence**: the capacity of the pathogen to cause disease from infection. This depends mainly on a pathogen's ability to escape the human immune system.
- **Transmissibility**: the capacity for an index case to infect other persons. It depends on patient's behaviour and contact opportunities, disease presentations (a person with a cavitary TB disease is more likely to transmit TB bacilli to another person than a person without a cavitary TB) and environmental conditions
- **Fitness:** These concepts merge the concepts of virulence and transmissibility and try to reflect the infectiousness of a determinate TB strain. Similar to the basic reproductive number, fitness measures the number of secondary cases caused by an individual infected soon after disease introduction into a population with no pre-existing immunity to the disease in the absence of interventions to control the infection.

Based on laboratory experiences, previously it was thought that MDR-TB strains, being a mutant sub-selection of bacillary poppulation, had a much reduced fitness compared to drug susceptible strains. However, according to recent studies, it appears that fitness of MDR-TB strains are at least similar to susceptible ones. In fact, similar fitness was

found among susceptible and MDR-TB strains in settings were MDR-TB was common. At the same time, highly virulent strains like Beijing are associated with MDR-TB in many areas.

In addition patients with MDR-TB in many parts of the world receive inappropriate treatment regimens that do not cure the patient but prolong their lives and amplify the resistant pattern in the community.

To appreciate the prevention of TB, of which TB infection control is one of the measures, the basics of the c**ycle of transmission of TB bacilli** needs to be understood:
1. The source of TB bacilli is a coughing person. Individuals with the most frequent and strongest cough are the ones with the highest capacity to infect others. In addition, those who have smear-positive tuberculosis especially with cavitary disease and are not on effective anti-TB treatment have an increased chance to spread TB bacilli.

- To reduce the opportunity for transmission of *M. tuberculosis,* a mask or handkerchief should be offered to patients, who should be educated to cover their mouths and noses when coughing. This is called 'cough hygiene' or 'cough etiquette' and it is one of the simplest, cheapest and most effective measures to limit the number of droplet nuclei in the environment. Also, coughing patients should be quickly identified and separated from others. Rapid diagnosis and early and correct treatment lead to a quick decrease in the bacillary burden and limit the patient's infectious capacity and thus the number of contacts that may get infected.

2. After being released into the air in tiny droplets, TB bacilli remain infectious for 2-8 hours depending on the environmental conditions, such as ventilation and availability of sun light. In conditions with poor ventilation and insufficient sun light, the bacilli may remain in the air for many hours.

- It is therefore necessary to create environmental conditions that are conducive for removal or destruction of infectious particles. These conditions include improved ventilation, natural light or ultra violet, UV light exposure and filters.

3. Once in the environment, the infectious particles and the potential host get in contact through breathing.

- It is necessary to limit the opportunities for contact between infectious particles and the potential hosts. Separation of coughing individuals from others is one

way to achieve this. Personal protection with respirators can also be used by the health care workers in high risk areas.

4. Once after TB bacilli and potential host have had contact, depending on the virulence of the strain and potential host immune system, there are two possibilities. i) The contact may have been effective one and the host infected with TB bacilli or ii) the contact may have been ineffective and the infection avoided. The risk of infection in each contact with the TB bacilli depends mainly on host factors that include his/her immune competence (mainly through the macrophage capacity) and his/her nutritional status.

- Ideally, persons at risk, such as PLHs and individuals with DM or other inmunodeficiencies should maintain an adequate nutrition, blood glucose balance and immune responses due early and effective antidiabetic and antiretroviral treatment.

5. From the time of infection with *M. Tuberculosis*, approximately 10% develop TB disease in their life time though the half of them develop TB disease during the first 2 years after infection. Again immune sy*stem status play an important role to keep the infection on a latent state.*

- As an individual health measure, TB preventive therapies can be used to prevent development of active TB disease in persons who have been infected, also said to have a latent TB infection (LTBI). Whenever possible, optimize nutritional status, immune status and adequately manage other co-morbidities. In many instances, like that of recent converters, HIV +ve and children, they may benefit from treatment for latent TB infection (LTBI). Most current evidence on treatment of LTBI is based on the use of isoniazid (INH) or INH-rifampicin (RIF). However, it should be noted that persons infected with MDR-TB strains, these treatment modalities are unlikely to provide good results.

Infection control measures discussed below play a fundamental role in prevention at different stages of the transmission cycle of TB.

1. ADMINISTRATIVE CONTROL MEASURES

Administrative measures are the first priority in TB infection control. They are:

1.1 Accurate and timely TB diagnosis

Identification of suspected TB patients should begin as soon as the patient enters the clinic or an out-patient clinic in a hospital. Clerks registering patients should be trained to ask simple questions that identify a TB suspect. These questions include whether the person has a cough of any duration. Patients with symptoms and signs of TB should immediately be referred to the nurse overseeing these patients in the clinic. They should also have access to a designated, well ventilated waiting area. In high HIV burden countries and settings, apart from cough fever, weight loss and night sweats should be asked in initial screening for TB. The nurse responsible for triaging may use a written questionnaire with more detailed questions to identify patients suspected or confirmed to have TB and the investigations or treatments given to them. The nurse should ask patients with a cough to cover their mouths and noses with a handkerchief or tissue paper while coughing and take them to another part of the health facility to separate them from other patients.

To reduce as much as possible the exposure to others from a potential TB source, the first thing to do is to identify the potential TB patient with capacity to infect others. In this way, diagnosing TB as early as possible avoids further risk to the community and better outcomes for the patient. A fast-tracking system should be put in place to ensure that TB suspects in need of a medical test or procedure are accompanied to other departments and not made to wait in the occupied waiting rooms. The receiving department should be informed in time to minimize delays having the procedures performed. Whenever possible, tests or procedures that can be done in the isolation rooms should be done there to minimize the risk of transmission to other patients and staff.

One of the tests the TB suspects will need is sputum smear microscopy. Patients should be guided on how to produce the specimen and taken to a ventilated or open air space to produce the sputum. The specimen should be taken to the laboratory for microscopy. A system should be put in place to ensure that results are promptly received and acted on. The patients found to have one or more sputum smear microscopy results positive should be started on correct anti-TB treatment without delay. The patients should be provided with a health education session on why this is

necessary and how it should be done. Frequently patients will indoors mingle with others during leisure activities (eg watching Television). Ensure they wear a mask during these times while being smear +ve.

1.2 Separation/isolation of TB patients and persons suspected to have TB

Persons suspected of having TB should be separated / isolated whenever possible and a designated waiting area should be arranged, for example, in health facilities. This is one of the most effective measures to reduce the risk of infection and propagation of TB in health care facilities. The role of undiagnosed patient in TB transmission, especially in the emergency services has been largely underestimated.

For patients diagnosed at the community and not treated at the hospital, the same measures of infection control should be observed at home, especially when babys, children, elder or HIV infected people is living in the same house hold. Isolation of the patient in a well ventilated room should be promoted and the use of mask or handkerchief whenever possible during the two first week of treatment.

1.3 Prompt start of anti-TB treatment

Starting appropriate anti-TB treatment quickly reduces infectiousness. Normally when the bacilloscopy is negative the transmission is considerably reduced and in this way, early treatment is one of the most effective ways to reduce the risk of infection in others. Currently it is thought that in less than 15 days from the start of an effective treatment transmissibility reduces considerably even when the smear is still positive.

Nonetheless, TB patients should cover their mouths and noses using a surgical mask or handkerchief when visiting health and other congregate settings for a period of 2 weeks if no drug-resistant TB is suspected. On a practical way, problem arrives when primary MDR-TB patients receive first-line anti-TB medications. They do not cure their condition and thus do not stop the transmission of M. tb. In this situation, the smears and culture will remain positive. Molecular based technology for the diagnosis of TB and resistance may eventually reduce the time for appropriate treatment initiation.

1.4 Health facility risk assessment

A risk assessment should be performed in each TB facility and especially in those managing MDR or XDR-TB patients. This assessment should include the TB epidemiological indicators (district and health centre) to determine the level of risk. Also time the actions and procedures that affect risk of infection (time need to perform and deliver results from sputa time that the patients wait in the waiting areas, etc) while evaluating the areas of major risk which are usually the diagnostic areas (sputum collection, sputum induction, bronchoscope, CXR, etc). Perform a sketch of the facility to analyse how the air, the TB patients and their samples flow helps to identify the risky areas where infection control has to be improved.

1.5 Development of a TB infection control plan

It is recommended that health facilities have an infection control committee and a person responsible for infection control, a so called IC focal point or person. This could be an experienced nurse. Based on the intra-hospital risk transmission evaluation (previous point) the committee elaborates an action plan that the infection control responsible has to turn into reality. In each facility, previous to the creation of the infection control plan, the current practices on each facility should be evaluated to know what and how practices should be changed.

A proficient infection plan includes a realistic package of specific infection control activities (starting from administrative control measures) necessary to each particular setting, while indicate when the activities have to be done and by whom. Basic contents of an infection plan should comprise:

- How suspected or confirmed infectious TB cases are identified and isolated from other clients.
- Triaging TB suspects/cases for expedited care.
- How TB suspects will receive TB diagnosis, either at site or through referral
- How the facility minimizes employee exposure to TB.
- How staff are trained and educated on TB symptoms and signs, TB control and TB infection control.
- The environmental controls that reduce the likelihood of TB exposure and how they are maintained.
- How employees are protected from TB during high-risk procedures.

- How employees are screened for TB and how often this is done.
- How follow-ups for employees exposed to TB are conducted.
- How monitoring will be done for TB infection control interventions (include indicators of process and impact of the activities)

The infection control plan should be written and each health care worker should know and understand it. For all actions to be performed, a staff person should be assigned the responsibility to follow up and the staff person's name should be included next to each action or set of actions within the TB infection control plan.

1.6 Staff, patient and visitors education

Upon entering a facility with a high risk of TB and especially X/MDR-TB, patients, staff and visitors should understand the risks involved. Both verbal and written information should be made available to visitors at every visit. Posters depicting basic TB infection control measures should be displayed in the waiting areas and wards.

Administrative infection control measures should be followed also in emergency services, medical and other wards where PLHs and patients with DM may be admitted.

2. ENVIRONMENTAL CONTROL MEASURES

Environmental measures are aimed at reducing the number of infectious particles in the environment where patients or others are. The basic measures to achieve this include ventilation (natural or mechanical), in full (UVGI) radiation (whether natural or artificial) and the use of filters. Despite the benefit of environmental measures, they are not likely to be useful if the fundamental administrative measures are not followed.

2.1 Ventilation

Ventilation, whether natural or mechanical, allows fresh air to enter a room, which dilutes the concentration of airborne infectious particles. Thus, ventilation reduces the likelihood that a person in a room will breathe in air that contains infectious droplet nuclei. In any ventilated area, the fresh air that enters the room mixes with the air already in the room. The more effective the mixing of the air, the better the dilution of airborne pollutants and the higher the reduction in the risk of airborne pathogen transmission.

NATURAL VENTILATION: Natural ventilation can be ensured by keeping the doors and windows open. Since the doors for consultation rooms of health facilities are usually closed to observe privacy, the windows should be considered for this purpose. To ensure adequate natural ventilation, the total area of the windows that are opened to let in or out air should represent the equivalent of 20% of the floor area. Managers of health facilities should make an assessment of the adequacy of natural ventilation. Renovations to improve natural ventilation may also be considered if resources allow.

If natural ventilation is not adequate, propeller fans can be used to increase its effectiveness. Propeller fans mix the air in the room, causing a dilution of infectious particles by spreading them throughout the room. However, this dilution effect needs to be combined with a mechanism that continuously allows fresh air to enter the room and the existing air to leave the room. Replacing room air with fresh air can be adequately done by keeping windows or doors open. The overall effect is fewer infectious particles within the room and therefore much reduced risk of TB transmission. A room with an open window and a fan provides a much safer environment for both the health workers and the patients. Because propeller fans can be used to encourage air movement in and out of the room, their positioning is important to maximize their benefit. To determine the direction of the air movement a smoke test could be done. A smoke test consist in the use of visible smoke as a monitoring tool to observe the air flow. It can be done for example burning a bar of incense on an indoor setting. Wherever the smoke goes is where the air flow and where the potential infective particles go. The clinic staff should be trained on how to do and interpret a smoke test.

MECHANICAL VENTILATION AND AIR FILTERS: Fans and other devices can be used to enhance ventilation in settings where natural ventilation is inadequate. Fans should facilitate quick movement of contaminated air to the outside and the entrance or fresh air in the facility. The staff and the patients that need to be protected from TB should be placed in the area of the room where air enters. The patients who are coughing and likely to spread TB should be placed in the area the air is exhausting by natural ventilation airstreams or fans. High technology and negative pressure devices are expensive and need regular maintenance. Hence in developing countries are only indicated in especial settings like National reference laboratories. Air filters are fixed or

mobile devices that can clean the air of small settings. HEPA (High-Efficiency Particulate Air) filters satisfy the main international quality standards and are the ones recommended in TB settings. Nonetheless, their application in low and middle income countries offer similar problems as Ultraviolet germicidal irradiation and high-tech mechanical ventilation as they tend to be expensive, delicate and needing regular and expensive maintenance by specialist technicians.

2.2 Ultraviolet germicidal irradiation (UVGI)

Ultraviolet radiation being from natural sun light and created by special UV lamps, inactivates M. tuberculosis containing droplet nuclei in the air. Good natural lighting of rooms that are visited by patients suspected and confirmed to have TB is desirable. UVGI devices are special lamps that emit this specific wave length of radiation. UVGI may be used in a return or exhaust air duct to kill the TB germs so that the recirculated air is cleaned of infectious organisms. The lamps must be installed at a height of about 7 feet from the floor to the ceiling. Room fans or a ventilation system are recommended to mix the disinfected air in the upper portion of the room with the contaminated air below. When installing UVGI equipment, there should be strict compliance with the guidelines on the use of UVGI as UVGI may cause temporary harm to the eyes and the skin. Facility staff should also receive adequate education on the benefits and risks of UVGI and maintenance of the equipment. Facility staff should observe strict maintenance of the equipment to minimize the dangers of UVGI and to ensure that the UVGI is working properly all the time. Although upper air UVGI helps to dilute the overall room concentration of TB germs, it has little benefit to the health worker who is in close proximity with the patient, especially in high-ceiling rooms.

Despite being effective the usefulness of these devices in low and middle income countries is limited as the cost of it is high and the maintenance complicated. In many countries observed, the maintenance was poor (expired lamps, inappropriate allocation, dirty…) leading to ineffective germicidal capacity and false sense of security among the staff.

2.3 Architectural design of new health facilities renovated for DR-TB

To date the best architectural design for DR-TB wards still being the classical sanatoria model with high roofs, big windows and room for less than 4 patients. This classical design has demonstrate to present extraordinary for ventilation and bacilli inactivation by natural and no extra cost measures. In many settings visited, funds were

allocated for MDR-TB new wards. Conversely, these wards were low ventilated and enclosed places with a small UV lamp where TB transmission for health care workers and visitors was higher than in regular TB patient's wards in old sanatoria style ward.

3. RESPIRATORY PROTECTION/PERSONAL PROTECTION MEASURES

Personal protective equipment is used in situations where administrative and environmental control measures are not sufficient to prevent transmission of TB bacilli to the staff. Staff working in health facilities with low risk of TB transmission do not need to use personal protective equipment because administrative and environmental controls are sufficient to protect them.

The correct personal protective equipment for prevention of TB transmission to health workers is respirators, which are capable of filtering particles of 3 microns (similar to *M. tuberculosis* size) with at least a 95% of efficiency. These are the most commonly used respirators are denominated N95.

Respirators should be used by health workers who are in contact with infectious TB patients. There are many different types and sizes of respirators. It is important to do a fit test for the health workers before issuing the respirator. Surgical masks should not be worn by health workers because they do not protect them from inhaling aerosolized droplet nuclei.

At the same time, respirators are often bend, crush or simple improperly fit reducing their effectiveness. Working during hours with a respirator is very uncomfortable especially when it turns wet and health care workers tend to stop using it. As not all faces are the same but all users need a respirator that seals with the face different sizes an models of respirators exist. Use of respirators need to test the face-seal capacity. It is commonly known as fit-test where the air leakage should be less than 10%. However in the field hardly any MDR-TB workers have ever under come a fit –test and usually only one size of respirators exist if it really exists. Overall respiratory protection is often perceived by the staff as the most important infection control measure but present important limitations and in the absence of administrative and environmental control measures, its benefits are limited. As an example in one country visited, all staff used a respirator when entering the MDR-TB wards, but the wards were connected to other wards and the medical student's lecture room by two usually widely opened doors. In

addition, patients freely moved in the hospital without using a mask. Hence, the infectious areas were not restricted to the TB wards where clinicians use respirators.

Monitoring and evaluation of Infection control activities

The TB infection control plan is the basis for monitoring and evaluating TB infection control interventions. Implementation of the infection control plan should be monitored on a daily basis to ensure that activities written in the plan are implemented. Each activity within the infection control plan should have a staff assigned to monitor its implementation.

Implementation of the planned activities should be evaluated and a reassessment of the level of risk of the health facility should be conducted to determine if the activities are appropriate or if there is a need to revise the plan in order to reduce the risk of transmission of TB. The effectiveness of the infection control plan should be evaluated annually and a responsible of the task named.

Monitoring latent TB infection and TB disease among health care workers

It is important to monitor the incidence of latent TB infection and active TB disease among health professional and other staff who work in health facilities. Latent TB infection can be detected using tuberculin skin test (TST) or PPD (Mantoux test) or IGRAs if the country have enough economic resources. Comparing the number of persons with positive reactions over several years gives an overview of nosocomial TB infection. However, there are limitations to this measurement in that i) its accuracy is reduced by the fact that staff working in high TB burden countries tend to have positive TST/ PPDs test results. On the other hand, PPD –ve health care workers should be especially cautious while working on MDR-TB wards for the risk it involves.

All health workers should be screened for TB symptoms at the time of recruitment and at least annually. In high-burden settings, all health workers should be educated about TB symptoms and be encouraged to come forward for evaluation if they experience any of the symptoms. Health workers that have symptoms of TB should be investigated without delay. Sputum microscopy examination should be carried out followed by molecular diagnostic test (if available), chest X-ray and other tests, as necessary. Health workers diagnosed with TB disease should be started on TB treatment according to the national guidelines and should be supported to adhere to the treatment. Knowing one's HIV status facilitates i) health worker requests to be transferred to less

risky working areas and ii) health workers to IPT, if found to be HIV-positive. HIV-positive health workers should also be supported to access antiretroviral treatment. In addition, clinicians caring for patients with DM should ensure that their patients' glucose levels are well controlled.

Another useful measure is to calculate the TB rate among health care workers and the compare it with national TB or MDR-TB rates. If the rate in the hospital is higher than the national one, it usually means that working in the facility is a risk factor for TB. This can be easily calculated multiplying the number of patients by 100.000 and dividing them by the total number of health care workers. From a real example, in a facility visited from a country with a TB rate less than 80 TB cases per 100,000 population?? 10^5 cases, 2 TB cases (1 susceptible TB and 1 MDR) appeared during the year. The hospital had an approximate staff of 86 workers. Although two cases per year do not look like a high number, if calculated as a rate, the hospital had a TB case rate of 2,325 cases per 10^5 TB, which was 29 times the country's rate. The MDR-TB rate was 1,163 cases per 10^5 which was probably more 100 times the country's rate.

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11. Anexos

Chapter 11. Drug-resistant tuberculosis and human immunodeficiency virus: update and management

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Chapter outline

Summary

Tuberculosis (TB) and human immunodeficiency virus (HIV) infection are conditions that may cause challenges in diagnosis and treatment. TB can present in HIV-infected individuals with a range of atypical symptoms. In addition, diagnosis with front-line tests, such as sputum smear microscopy and chest X-rays, is not always reliable when the immune system is compromised. Without treatment, TB may evolve rapidly in people living with HIV (PLH) due to immunosuppression and may frequently result in meningeal, milliary or disseminated TB. These types of TB are associated with poor prognosis. Additionally, HIV-infected patients are more likely to be affected by MDR or XDR-TB outbreaks. DR-TB treatment in PLH and in HIV-negative individuals is, in principle, the same. Certain challenges could arise though when managing PLH with DR-TB. They include high pill burden, TB-Immune Reconstitution Inflammatory Syndrome (TB-IRIS), drug-drug interactions and overlapping toxicities and other opportunistic infections or conditions. DR-TB-HIV patients need prompt diagnosis and prompt commencement of anti-TB treatment, co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART).

Drug-resistant tuberculosis and HIV: reasons for and consequences of association of the two diseases

HIV infection leads progressively to extensive destruction of the immune defence mechanisms of the body. HIV grows mainly in certain cells called CD4+ T lymphocytes, or CD4 cells. These cells are an important part of the immune defence mechanisms responsible for protecting individuals against various infections and cancers. As a result,

PLH become ill with severe and often deadly infections to which HIV-negative persons are not usually vulnerable. These are called opportunistic infections. When the immune system weakens, *M. tuberculosis* (either from a new infection or previously dormant state of infection) may begin to multiply causing TB disease. TB is the most common opportunistic infection in PLH in countries with a high TB prevalence, and also the leading cause of death among PLH in these communities. It follows, that in these settings, PLHs should be regularly screened for TB. All patients who do not know their current HIV status should be routinely offered HIV testing and counselling.

Although HIV infection is the strongest known risk factor for TB to develop in persons with latent TB infection, HIV is not currently considered as a risk factor for developing DR-TB. Nonetheless, PLH are prone to infection *by M. tuberculosis* and development of active TB disease, whether drug-susceptible or resistant. There is also evidence that PLH may have decreased anti-TB drug absorption, especially for rifampicin (R). Low drug levels in the blood may eventually lead to the acquisition of drug-resistant strains of *M. tuberculosis*. In fact, there are many documented examples of MDR and XDR-TB thriving among PLH. It follows that preventing the spread of TB bacilli in health, congregate and other settings that may be frequented by PLHs is an essential step towards preventing DR-TB. There is no doubt that the combination of DR-TB and HIV puts patients at a great risk: not only are their lives threatened, but TB control also faces severe challenges in high HIV burden countries.

Drug-resistant tuberculosis and HIV: typical and atypical clinical presentation

Symptoms and signs suggestive of TB do not differ among patients with drug-susceptible or –resistant-TB. However, the clinical presentation of TB in PLH depends largely on the degree of immunosuppression. In early HIV infection, when the immune defence mechanisms of the body are almost normal, TB presents with symptoms and signs similar to those in HIV-negative persons, with a high proportion of adult cases being smear-positive. When the body's immune defence mechanisms weaken, clinical presentation of TB becomes atypical. Patients with pulmonary disease may present with no respiratory complaints and may have extreme fatigue, fevers, night sweats, loss of appetite and weight and anaemia. Extra-pulmonary forms of TB occur more frequently in PLHs. TB should be suspected whenever a PLH with any of the following symptoms: cough of any duration, fever, weight loss or night sweats.

Diagnosing tuberculosis and drug-resistant tuberculosis in PLH

All TB patients should be offered testing for HIV unless they already know their recent HIV status. As explained above, diagnosis of TB is more difficult in persons with severe immunosuppression when sputum microscopy and chest X-rays are less sensitive. The steps for early diagnosis of TB in PLHs include:

- **Step 1: Clinical presentation.** The first step in the diagnosis of TB or DR-TB is to suspect the presence of TB. Clinical staff should always maintain a high degree of clinical suspicion and conduct symptomatic TB screening at every contact with a PLH. The best symptom screening to date includes evaluation for presence of the aforementioned four clinical symptoms (cough of any duration, fever of any duration, weight loss and night sweats). The presence of any one of

these four symptoms has TB diagnostic sensitivity of more than 90% and specificity of almost 35%. If a patient does not have any of these symptoms, a TB diagnosis can be not completely but reasonably rule out.

- **Step 2: Sputum smear examination.** This step plays a vital role in the diagnosis of infectious TB cases, even in countries where HIV infection is prevalent. For known HIV-positive patients, induced sputum, sputum concentration methods and LED microscopy may increase the sensitivity of microscopy. Note that many TB-HIV patients will be AFB smear-positive if their immune and nutritional statuses are satisfactory.
- **Step 3: Chest X-ray (CXR).**The CXR remains very relevant in PLH because its sensitivity is greater than that of sputum microscopy. Unfortunately, specificity is much reduced with atypical radiological patterns and possible presence of several other conditions. As CD4 count declines, also the diagnostic value of CXR is reduced.
- **Step 4**: **Detection of TB LAMs**. Lipoarabinomannans or LAMs are very specific membrane glycolipids from the cellular wall of M. tuberculosis. TB LAMs can be detected in urine of patients with highly disseminated TB disease. The novel test for detecting TB LAMs consist on a strip (similar to rapid HIV test) that react with the patient urine (no need for sample process) in less than 30 minutes. No laboratory of highly train technician so it is probably the first rapid point of care test for TB. The sensibility is thought to be about 56% while the specificity rounds 91-95%. Nevertheless, these low sensibility increases when CD4 decrease and in that way is able to quick diagnose at a very affordable price those patients who are at greatest risk of dying if do not receive treatment. At the same time LAM positive patients seems to be linked to TB-IRIS and worst prognosis. The use of TB LAMs detection being a low price and point of care test may help to increase the access to TB/HIV diagnose while reducing the cost by rationalizing the techniques and resources.
- **Step 5**: **Molecular technologies.** The introduction of molecular technologies may lead to improvement of diagnosis of both drug-susceptible and –resistant-TB in PLH. These techniques are highly specific and sensitive diagnostic tests for detection of *M.tb*, especially in smear-negative persons. They can also provide results rapidly. If resources allowed, molecular techniques could become first-line investigations for TB in PLH. Results indicating rifampicin resistance are proxy measures for MDR-TB diagnosis.
- **Step 6: Bacteriological tests.** Culture and drug susceptibility testing (DST) is the next step to assess the possibility of DR-TB. Unfortunately, these tests are not routinely available in many resource-limited countries. The results may also take several weeks and, since rapid clinical decisions may be vital in TB HIV patients, their role is frequently limited. However, culture and DST are essential in confirming the diagnosis of DR-TB.

Management of drug-resistant tuberculosis in PLH

HIV-infected TB patients (with drug-susceptible or -resistant strains) may face an accelerated course of HIV infection and even die without appropriate early treatment. Presence of TB in an HIV-positive patient indicates the need to start treatment with antiretroviral (ARV) medicines. Pulmonary TB in a PLH leads to the WHO clinical stage 3 and extra-pulmonary TB is indicative of presence of a WHO clinical stage 4. This classification is also applicable to patients with DR-TB. A severely immune compromised patient may have other concomitant conditions, both infectious and non-infectious, making their management complicated.

The following steps are recommended:

1. *Immediate initiation of anti-TB treatment:* regardless of whether TB is of a susceptible or resistant strain, the patient needs anti-TB treatment as soon as possible to prevent death.
2. *Co-trimoxazole preventive therapy should be offered for at least the duration of the anti-TB treatment*: co-trimoxazole is a well tolerated and inexpensive fixed-drug combination consisting of trimethoprim and sulfamethoxazole. It has been shown to considerably reduce morbidity and mortality among symptomatic PLHs.
3. *Consideration of diagnosis and treatment of any other opportunistic diseases, especially those affecting the central nervous system (CNS), prior to the start of ART.* In patients with neurological symptoms, it is important to carry out investigations for an opportunistic CNS infection, such as TB meningitis, cryptococcal meningitis and toxoplasmosis, and defer ART until the condition has been treated. The rational behind is treating all that conditions that if ARVs are introduce may evolved into a potentially deadly IRIS.
4. *Start ART as soon as the patient tolerates the anti-TB treatment and at the latest, at completion of the intensive phase of anti-TB treatment.* New evidence demonstrates the need for early treatment (ART within two weeks of anti-TB treatment start), especially in persons with CD4<50/ml. For those with >50cel/ml CD4 counts benefits from starting within the first 2 weeks are not that clear, but starting during the first 8 week after TB treatment initiation offers great survival benefit. Not only the CD4 count is important but the disease location. Whenever any opportunistic disease is affecting CNS or in the event of of IRIS it may turn into a life-threatening situation ARVs introduction might be delayed.

Treatment of MDR-TB is more complex, more toxic and less effective than treatment of drug-susceptible TB. Treatment interruptions can occur due to a high pill burden, drug-drug interactions and toxicities in patients who receive concomitant treatment for both HIV infection and MDR-TB. Patients must be counselled, and they and their families should be offered information and support regarding importance of taking medications as scheduled, possible adverse medication effects, and how to take the medication. Patients must also be informed about the possibility of TB-IRIS (see below) to prevent treatment interruption.

Management of DR-TB in PLH

Initiation of anti-TB treatment is a priority when TB has been diagnosed. If DR- or MDR-TB is suspected, empiric MDR-TB treatment may be a suitable option due to possible long delays in receiving definitive results (2-6 months in many settings) and the risk of death in immunosuppressed patients. The anti-TB treatment regimens are in principle the same for patients with and without HIV infection and the recommendations made in the previous chapters should be followed. It is important to include rifampicin throughout the entire treatment in patients with a rifampicin-susceptible *M. tuberculosis* strain, especially in PLH.

Antiretroviral treatment in DR-TBpatient

The WHO MDR-TB guidelines state: 'Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first eight weeks, see above) following initiation of anti-tuberculosis treatment.' Evidence confirms the beneficial effects, even though mortality remains high. Recent evidence indicates that the earlier ARVs are introduced in PLH with TB, especially in severely immune compromised patients, the better the survival is. ART is a life-long treatment is all PLH.

ART, called also 'highly active antiretroviral treatment (HAART)', is a combination of at least three medicines administered with the goal of restoring and maintaining immune defence mechanisms by restoring the immunity and slowing the replication of HIV in the body, thereby decreasing occurrence of opportunistic infections and cancers. As in anti-TB treatment, ART regimens consisting of at least three ARV medicines decrease the risk of development of drug resistance. ARV medicines improve anti-TB treatment outcomes and also enhance quality of life in PLH. Lastly, by decreasing the HIV load in plasma and other body fluids, efficacious ART can decrease the risk of HIV transmission to a sexual partner and from an infected mother to baby during pregnancy, delivery and breastfeeding. At the same time by treating and eliminating the persistent inflammatory process created by the virus, long term cardiovascular risk is reduced.

Good ART adherence is most important and it is advisable to use fixed-dose combinations where possible to simplify the dosing of medicines and lighten the pill burden.

Issues and challenges of concomitant anti-TB and HIV treatment

Several issues and challenges can arise when treating TB HIV patients. The following may complicate TB HIV patient management:

TB Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is an exaggerated immune response against living or dead pathogens, and occurs when the immune system returns to normal after having been depressed. IRIS is one of the most frequent complications in TB HIV patients. They may develop IRIS after commencement of anti-TB treatment and/or ART, especially when ART follows soon after the start of anti-TB treatment. HIV-infected patients whose immune status is very low are at a higher risk of developing this syndrome than those with better immune status. A short interval between the start of anti-TB treatment and initiation of ART

increases the risk of IRIS, though this must be weighed against delaying ART which increases the risk of death. Additionally, patients with disseminated TB disease are prone to develop IRIS. Patients with secondary or acquired MDR-TB are more likely to develop IRIS after the introduction of ART because they have had the disease for a longer period and have widely dispersed bacilli in their bodies.

There are two main types of TB-IRIS:

- **Paradoxical TB-IRIS** develops mainly in PLH with TB and who are already receiving anti-TB treatment and sometime later receive ART. They improve initially but after two to four weeks of ART, paradoxical worsening of previous lesions (of TB or other opportunistic disease) occurs. Patients develop fever, enlarged lymph nodes, pulmonary infiltrates, meningitis and other symptoms. In other words, a previously sub-clinical/latent opportunistic infection became very symptomatic mediated by the immune system now recovered. In addition, the immune system reacts with inflammation not only against living pathogens but also against antigens of unviable pathogens. Paradoxical TB-IRIS is thought to happen in at least 10% of PLHs starting ARVs and especially among those with severe immune suppression.
- **Unmasking TB-IRIS** occurs in patients who have been started on ART with undiagnosed TB. Patients may be initially symptom-free or pauci-symptomatic and then reproduce strong TB symptoms at an abnormally quick evolution. The recovered immune system suddenly unmask a previous TB. Patients need anti-TB treatment as soon as the condition is suspected, if not patients may die of TB.

TB-IRIS is a clinical diagnosis. The differential diagnosis consists of:

1. Recent history of irregular intake of anti-TB or ARV medicines
2. Progression of TB, HIV infection or a new opportunistic infection/ disease.
3. Drug-resistant TB: this is a frequently condition in certain southern African countries
4. Adverse drug effects of anti-TB and/ or ARV medicines.

Management of TB-IRIS

The current standard management of TB-IRIS includes NSAIDs and other support measures, such as an abscess aspiration. A short course of oral corticosteroids is also recommended for patients with severe IRIS. Prednisone at a dose of 1.5mg/kg/day for two weeks followed by 0.75mg/kg/dayfor two weeks is recommended for adults. Anti-TB treatment and ART should be continued. ARVs can be discontinued in life-threatening situations, especially if severe neurological symptoms appear. Anti-TB treatment should not be stopped.

TB-IRIS may lead to multiple visits to emergency departments, hospital admissions and frequent treatment default.

Drug-drug interactions and toxicities

Concomitant management of TB and HIV infection requires multiple medicines. This frequently leads to occurrence of adverse drug effects and overlapping toxicities, especially when second-line anti-TB medicines are used. Vigilant monitoring is recommended and careful informing of patients are recommended so that treatment interruption can be prevented. Several other conditions, such as malnutrition, dehydration and advanced HIV wasting or opportunistic infections, may complicate management further.

The classical drug-drug interaction occurs between rifampicin (R) and several ARVs. R induces the cytochrome P450 enzymes and reduces the serum concentration of protease inhibitors, nevirapine, efavirenz and others. This is a lesser problem in patients with MDR-TB because, by definition, the strains are resistant to rifampicin and it is not included into the treatment regimen. However, for all drug-susceptible cases, daily treatment with R remains the cornerstone of TB treatment, and therefore the ART regimen should consist of ARV medicines with lesser or no interaction with R. New medicines, such as TMC207, may be also metabolized by cytochrome P450. Clarithromycin, sometimes used in XDR-TB patients, can also produce cytochrome induction.

Unfortunately, limited information on drug-drug interactions between second-line anti-TB drugs (SLDs) and ARVs is available though some evidence has recently started to emerge (see Table 11.2). The vast majority of toxicities and side effects of SLDs in the immune competent patient are disturbing but not life-threatening (see Chapter 10). Currently used ARVs combinations and new ARVs present considerably less side effects compared to those commonly use only 5 years ago.

Problems arise whenever there are major side effects, such as hypersensitivity or severe skin reactions, severe hepatitis or severe neurological reactions. In these situations, it is difficult to determine the medicine(s) that is/are responsible for interactions and adverse reactions. At the same time, clinical diagnosis is complicated with the added possibility of TB-IRIS, non-response to anti-TB or ARV medicines, or presentation of an unsuspected opportunistic infection or disease. Prompt and focused evaluation of adverse drug events and other conditions mentioned here should be given priority to prevent adverse treatment outcomes.

The following typical and life-threatening circumstances in TB HIV patients due to SLDs should be noted:

- Hypokalaemia and electrolyte wasting can occur in severely immune compromised PLH who are dehydrated due to diarrhoea or vomiting when ethionamide or capreomycin is used with tenofovir. Patients may present with muscle pain and are at risk of lethal arrhythmia. Potassium and sometimes magnesium levels must be replenished intravenously in the most severe cases. A component of renal insufficiency might also be present in these patients.
- Peripheral neuropathy, which may be disabling, in a malnourished PLH who takes stavudine and cycloserine or H in high doses. High doses of vitamin B6 and switching stavudine to, for example, zidovudine or tenofovir, is frequently indicated. Treating with carbamazepine, amitriptyline or gabapentin might be also necessary.

- Commonly, the presence of a psychiatric disorder may be exacerbated by efavirenz or cycloserine, or both. Again, vitamin B6 is recommended in addition to the treatment of the psychiatric disease. Depression is very common and apart from medical treatment, the use of social measures to alleviate difficult circumstances can help to prevent treatment interruptions.
- PLH have frequently chronic hepatitis B or C infection. In these patients, Z or H at high doses and an hepatotoxic ARV medicine, such as efavirenz or nevirapine, increase significantly the risk drug-induced hepatitis, especially in patients who also consume large quantities of alcohol. Tenofovir and emtricitabine can be helpful in treating chronic hepatitis B infection. It is also advisable to consider the hepatotoxic profile of the anti-TB drugs use. Patients should receive support to stop or reduce alcohol intake.

Other: presence of other opportunistic infections, treatment adherence and high pill burden

In TB HIV patients, mortality during the early months of treatment is considerable, even in drug-susceptible TB. Anti-TB treatment might not be fully effective if other frequents conditions, such as malnutrition, are not properly addressed. Extraordinarily high pill burden that MDR-TB-HIV patients may face also need attention. Some patients may be taking Lfx+Km+Eth+Cs+Zfor MDR-TB, EFV-3TC-TDF for HIV infection, and co-trimoxazole and possibly fluconazole preventive treatments. Even if they wish to adhere the treatment regimens well, it may be difficult to understand when and how to take the various medicines. Depending on the formulation, patients may have to take more than 30 pills and one injection per day. Directly observed treatment (DOT) is essential to ensure proper ingestion of medicines. The use of fixed-dose combinations (FDCs) and treatment simplification is highly recommended.

During follow up visits, active screening of possible adverse drug events and provision of constant support are crucial to avoid defaulting and dying. Role of health care workers and importance of psycho-social support of patients by their families and communities' throughout treatment is indispensable. Many of these patients might be facing not only the two diseases but loss of employment, low income, stigma, discrimination, gender violence, family separation etc. This means that additional resources may be required, especially in settings with a high burden of both HIV infection and DR-TB, to achieve good DR-TB-HIV treatment results.

Special points in management of MDR-TB in PLH

Special care must be taken of MDR-TB-HIV patients:

- ✓ During DR-TB treatment, most patients will receive an injectable medication daily. Strict observation of the principles of the universal precautions for HIV infection control is essential. These include: use of a sterile needle and syringe for each injection in each individual patient, followed by destruction of the syringe and needle, and appropriate management of clinical waste.
- ✓ Among all in-patients, there is a high risk of nosocomial transmission and MDR-TB outbreaks. This is especially true for HIV-infected patients. Avoid placing

HIV-positive patients in MDR-TB wards after cure, as they may become re-infected (see infection control chapter for more information).

- ✓ After TB cure, patients on ARVs should be screened regularly for the presence of any symptoms suggestive of TB because of the risk of TB relapse and reinfection may be greater in PLHs than in the immune competent persons.
- ✓ Considering the higher risk of non-tuberculous mycobacteria (NTM) in HIV-positive populations, all TB suspects should undergo species identification or at least species differentiation. For countries with low-resource laboratories, Runyon's classification is sufficient to differentiate TB from NTM for the purposes of treatment. New molecular techniques are able to differentiate and identify NTM, marking a great advance in early identification and proper treatment.

Collaborative TB-HIV activities and Implementing Collaborative TB-HIV Activities, a Programmatic Guide of The Union

Given the complexity of managing TB HIV patients, and particularly PLHs with DR-TB, clinical activities on their own are likely to fail if not guided by national policies and guidelines, and supported by national TB and AIDS control programmes. Strong political commitment is also required.

The WHO recommendations on collaborative TB-HIV activities provide a well-established framework to guide national programmes in their response to HIV-related TB. The objectives of collaborative TB-HIV activities outlined in the 2012WHOguidelines on collaborative TB-HIV activities are to:

- Establish mechanisms between AIDS and tuberculosis programmes for the delivery of integrated TB and HIV services at the same place and time whenever possible.
- Decrease the burden of TB for PLHs, their families and communities by ensuring the delivery of the Three I's (Intensified case finding, Infection control, Isoniazid Preventive Therapy) to HIV/TB patients and through earlier initiation of ART.
- Decrease the burden of HIV in presumptive and confirmed TB patients, their families and communities through the provision of HIV prevention, diagnosis and treatment.

With the exception of isoniazid preventive therapy, all HIV-positive MDR-TB patients and their contacts benefit from the implementation of the above measures (see Annex X). The Union has published a TB-HIV programmatic guide based on its country-level experiences on the best ways to make these policies operational in the field.

Table 11.1 Potential overlapping toxicity from ARVs and anti-TB medicines (adapted from WHO Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update)

Potential toxicity	Antiretroviral therapy	Anti-tuberculosis therapy
Peripheral neuropathy	stavudine, didanosine	cycloserine, isoniazid, ethambutol, fluoroquinolones, streptomycin, kanamycin, amikacin, capreomycin, viomycin, ethionamide/prothionamide, linezolid
Psychiatric symptoms	efavirenz	cycloserine, isoniazid, fluoroquinolones, ethionamide/prothionamide
Hepatitis	nevirapine, ritonavir-boosted protease inhibitors, efavirenz etravirine, maraviroc	pyrazinamide,isoniazid, rifampicin/rifabutin,p-aminosalicylic acid, ethionamide/prothionamide, fluoroquinolones
Gastrointestinal intolerance	zidovudine, protease inhibitors, didanosine	ethionamide/prothionamide, p-aminosalicylic acid, pyrazinamide, isoniazid, rifampicin, ethambutol, clofazimine
Renal toxicity	tenofovir, indinavir, capreomycin	streptomycin, kanamycin amikacin, viomycin, rifampicin
Bone marrow toxicity	zidovudine	linezolid, rifampicin/rifabutin
Lactic acidosis	stavudine, didanosine zidovudine	linezolid
Stevens-Johnson syndrome	nevirapine, efavirenz, etravirine	thiacetazone, cycloserine, linezolid, ethambutol streptomycin
Arrhythmias / QT prolongation	atazanavir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir	fluoroquinolones
Rash / pruritus	Nevirapine, efavirenz,etravirine,abacavir	rifampicin/rifabutin, pyrazinamide

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Chapter 12. Management of the DR-TB in special situations

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Summary

In the following chapter, a wide variety of DR-TB cases with special situations are going to be presented. Despite being patients out of the standard, special cases are certainly frequent nowadays that DR-TB treatment is getting more available for those who need it. Usually especial groups need a slightly different approach from clinical or social perspective to achieve positive outcomes. The chapter comprises the management of DR-TB in pregnancy and children where most of the management rules follows the same rational than adults. The appearance of DR-TB in patients with frequent comorbidities like diabetes mellitus is increasingly recognized. Indeed, diabetes induce a relative immunedeficiency status that makes TB appear in an atypical way that make diagnosis and sometimes treatment harder. Renal failure on the other hand, require changes and adjustments in anti-TB drugs dosages. The management of DR contacts is one of the most open to discussion matters. Nonetheless, the number of potential DR contacts can be extraordinary high and the appropriate care may be key in the future. Finally the chapter will address with examples how best approach DR-TB patients from vulnerable groups. Often excluded, vulnerable groups represent a considerable proportion of the DR-TB patients. Not only increased access to prompt diagnosis and correct TB treatment but also follow-up of outreach or excluded populations is essential to prevent and cope with the ongoing DR-TB epidemic.
If drug resistance TB management presents in occasions more controversies than evidence, this is especially true for especial cases. An exercise of flexilibility and extra care is need for them.

1. DR-TB management during pregnancy

Introduction

Being TB a disease affecting mainly young people, it is not infrequent finding DR-TB on childbearing age women. Managing DR-TB during pregnancy creates anxiety not only among the patients but also among clinicians especially considering the toxicity of the drugs used. Nonetheless, aggressive management of gestational DR-TB may benefit both mother and child.

All women in childbearing age who are diagnosed of DR-TB, should be tested for pregnancy (and HIV) previous to treatment. If the test is negative, it is highly recommend family planning during the length of treatment and should be inform about the potential problems of pregnancy while receiving DR-TB treatment.

If the test is positive all the regular prenatal care used in the country should be followed. Pregnancy is not a contraindication for DR-TB management. Moreover, not treating DR or susceptible TB during pregnancy put in risk the mother and the foetus. The clinical presentation of TB during pregnancy does not differ. On the other hand, pregnancy does not increase the likelihood of resistance or worst results. Nonetheless, if TB remains untreated, maternal mortality increases as do low birth weight, premature birth, foetal

loss, and transmission to child. When DR-TB is adequately treated, these maternal-child risk are much reduced.

Fundaments of DR-TB treatment during pregnancy

After revealed the DR-TB condition in a pregnant woman, treatment strategy must weigh risks and benefits for mother and foetus. There is a large experience in the use of firsts line drugs (FLDs) during pregnancy but it is limited on safety of second line drugs (SLDs).

Ideally, it is preferred starting DR-TB treatment within the second pregnancy trimester in the HIV -ve patient and if the clinical conditions are stable. Deferring the treatment, reduces the risks of teratogenesis or toxicity which are is greater during the first trimester of pregnancy and allows enough time during the 2nd and 3rd for the mother to achieve sputum or culture negativisation previous to the delivery. Thus, the risk of transmission mother to child is reduced.

In life-threatening situations (respiratory failure, advanced disease, HIV+, etc) it is recommended TB treatment straight away even being in the 1st trimester provided the risk that exist for both (mother and child) (3). The patient should be informed and understand the risks and benefits of treatment or absence of it. She should understand and be involved on the clinical decisions.

Pregnancy and anti-TB drugs

There is vast evidence on the secure use of FLDs during pregnancy being all but streptomycin permitted and recommended. Indeed most of SLDs are quite secure during pregnancy as well with exception of aminoglicosydes.

Aminoglycosides namely streptomycin (Sm), kanamycin (Km) and amikacin (Am) are potentially teratogenic drugs and care is need to be put on the use of them. These drugs are pregnancy safety class D according to FDA (US Food and Drug Administration) classification (*see table n 1*) and are not recommended during the pregnancy especially during the first 20 weeks. It is thought that around 10% of the cases Sm can induce ototoxicity and malformation on the foetus. Km and Ak could very probably induce similar teratogenic effects than Sm and Km.
If there is no other option they can be used, but preferably after the 20th week and always balancing with the patient risks and benefits. It use should be limited to patients whose poor clinical state and resistance pattern justify it use.
Capreomycin (Cm) is an injectable drug that belongs to the family of polipetides and has a similar action but no teratogenic effect. Capreomycin is a positive alternative to aminoglicosydes as the toxic profiles is much reduced in terms of ototoxicity and present safety class C (equal to most of the SLDs used). Capreomycin has no document teratogenic effect for the foetus and is commonly used in pregnant DR-TB women all around the world.

Fluoroquinolones (FQ), are considered Safety class C. No documented teratogenicity in human studies, although average treatment duration was 2-4 weeks. Data on prolonged use in pregnancy is limited but is currently used in all GLC approved DR-TB

programs. Being the best drugs for DR-TB given their high bactericidal activity, benefits are likely to exceed risk.

All drugs from group 4 (Ethionamide (Eto), Cycloserine (CS), PAS) are safety class C with no evidence of foetal toxicity. Nonetheless, Ethionamide creating greater vomiting and can exacerbate the usual nausea and vomiting presented on pregnancy.

Group 5 drugs are all considered safe with no documented foetal toxicity but yet again with limited evidence.

DR-TB treatment in pregnancy

Pregnant DR-TB women should received a similar regimen than other patients, receiving at least 4 effective drugs with one fluoroquinolon as the core drugs in the treatment. The main difference relays in the use of ***capreomycin*** as the injectable of election. If this is not possible or available use Km but preferably starting during the second trimester. Consider the use of Km 3 times weekly instead of daily during the first trimester.

Overall, it would be a great mistake not adding an injectable even during pregnancy. Not doing it can compromise the effectiveness of the treatment and increase the likelihood of DR amplification making virtually impossible a curative treatment.

Vitamin B6 (pyridoxine) should be used in all pregnant women with TB in dose not higher than 150 mg. Higher dosages may interact with FQ absorption and after birth the child can experiment Vitamin B6 deprivation with seizures and other neurological presentations.

Table 1. FDA classification on drug safety during pregnancy

CATEGORY	INTERPRETATION
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities to the fetus in any trimester of pregnancy.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. **OR** Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. **OR** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs canno be used or are ineffective.

X	Adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of the product is contraindicated in women who are or may become pregnant.

Box 1. Pregnancy drugs safety of the current anti-TB according to FDA classification:

- ***Safety class A***: --
- ***Safety class B***: E, Amx/Cla
- ***Safety class C***: RIF, INH, Z, FQs, Cm, Cs, PAS, Eth/Pto, Clf, Clr, Lzd
- ***Safety class D***: Sm, Am, Km
- ***Safety class X***:--

Box 2. Recommendations for management of DR-TB and Pregnancy

Initial screening to all childbearing age women
- Encourage family planning if not pregnant

IF PREGNANT:
- Close follow up of the pregnancy with at least regular care
- Involve patient in therapeutic decisions
- Individualized management
  - Ideally avoid treatment during first-trimester If life-threatening symptoms, consider treatment regardless of trimester
  - During first 20 weeks, avoid injectables if possible or use preferentially Capreomicyn
  - Initiate DR-TB therapy during second or third trimester to achieve smear conversion prior to delivery
  - Consider risks & benefits to mother and foetus
- Use Pyridoxine (<150mg) in all patients on ETH and/or Cs or INH

Especial care to be taken after birth and during breastfeed

Afterbirth one of the most important issue to be considered is the risk of TB transmission from the mother to the child. Unlike HIV, transmission mother to child congenital TB may exist via haematogenous contagion or during the partum is extraordinarily rare. Infection due to breast milk is extraordinarily rare as well. The source of contagion is by far airborne transmission. If the mother is not under an appropriate treatment or still culture positive the contacts among them should be limited for the wellbeing of the child. Contact might be in an open air space if possible and the mother using surgical mask or N95 respirator.

Breastfeeding is permitted especially when the mother is smear negative (and ideally culture-negative). If the mother is smear positive, separate mother from child (different

bedrooms) and use preferably formula feeds or extracted breast milk to avoid the close contact. Breast milk will present certain levels of anti-TB drugs but currently are not though to be deleterious for the child but also not enough to protect children against TB infection. All children born from a TB mother should be closely followed up and monitored to assure no TB symptoms or in case of them provide early TB treatment (see section on DR-TB contacts).

2. DR-TB management in children

Introduction

DR-TB in children is most often a primary DR-TB, in that sense is usually a resistant TB transmitted from an adult. Generally (>90%of the cases) TB in children is developed within the first 12 months of infection. As with susceptible TB, children tend to have pauci-bacillary forms of TB. The pauci-bacillary forms of TB in the children makes diagnose more difficult given the higher number of pauci-symptomatic disease and the atypical presentations. Even culture can be negative in 50% of the children with active TB.

Hence, even if children can develop and increase the pattern of resistance the same way adults do, it is less likely due to reduced number of TB bacilli even in the management is not completely correct. DR amplification only happens in grown children with cavitary forms (high number of bacilli) and failing to previous treatment. In that sense the number of children with DR-TB indirectly reflects the transmission of DR in the community. Infection control at family level turns crucial for children but it is even more important in families in high HIV settings. Despite having reduced evidences prognosis in DR children might be similar or better than in adults when treatment is adequate and completely taken

Main differences in diagnose of DR-TB children

Several issues make the confirmation of TB more difficult in the children: lower bacillary load, less forceful cough and more extra pulmonary cases especially in children younger than 5 years. Considering that DR-TB is mainly a bacteriological diagnose through culture and DST the complete diagnose is sometimes unavailable. In children other less specific but more sensitive diagnose tools achieve greater relevance. In that sense, the chest X ray CT scan may support. Medical image tests just inform about the likelihood of presenting TB but can not discriminate whether this TB is resistant or susceptible. In that sense, clinical symptoms added to the existence of a close contact having TB or DR-TB turns highly significant. New tools like Genexpert may in a near future support the diagnosis of TB and DR-TB even in extrapulmonary samples.

According to current evidences in a high proportion of cases, child contacts of known DR-TB index case are often presenting DR-TB. On line with it, if the children do not improve with regular TB treatment and is a contact of a high risk group (failure to category II or I or other conditions) DR-TB should be always considered.

Initial management of children suspect or presenting DR-TB

Despite the difficulties, try to confirm DR-TB whenever is possible but this should not represent a delay in treatment for the child. The management should preferentially be at a specialized DR TB clinic and parents should understand the risk of the disease and the importance of the complete DR-TB treatment. Parents are going to grant the treatment of the children, hence should be involved in all clinical decisions and support should be offered to them. In that sense DOT and parents involvement is fundamental.

DR-TB regimen for children

With little evidences, the same principals for adult DR-TB treatment should be applied than for adults with some minor differences:

- Given the lower bacillary load and the reduce risk of drug resistance acquisition probably with 3 effective drugs may be enough
- Use the adult index case's isolate DST pattern if no isolate from child is available. Most often the treatment that is curing the index case will work well with the children.
- Use as many first line drugs that they child might be susceptible.
- Injectables and quinolones should remain as the core drugs for DR-TB treatment. Fluroquinolones despite presenting teratogenic effect in the murine model has not demonstrate being toxic for creating defects in the development of children and is currently used for long period in presenting DR-TB and cystic fibrosis.
- Add 1 or 2 drugs from group 4 (Eth, Cs). Be aware of different drug groups and cross-resistance.

The treatment can be given for 6 days per week for 12-18 months. The optimal duration of treatment in children is still uncertain, for cavitary or extensive pulmonary TB the proposed length is similar than for adults. For primary, non-cavitary DR-TB probably 12 months or less treatment is sufficient. Currently there are no evidence regarding the effectiveness of "Bangladesh regimen" with 9 months of treatment in children but may appear soon and from a bacteriological point of view there is no reason way it can work in adults but not in children. It has been frequently observed reluctances on the use of FQ, injectables and ethambutol in DR children. Nonetheless all have proved to be secure and necessary of the cure of adults and children.

Monitoring and follow up of children with DR-TB

For the patient monitoring use clinical symptoms and chest X ray plus cultures and sputum and the regular blood test whenever possible. Children should be very closely monitored. Monthly visit during the intensive phase are recommended to check for side effects, counsel parents about possible adverse events recognition and the importance of adherence and to weight the children. As the child gains weight, the doses will have to be adjusted. Treatment adverse reactions appear to be less frequent than in the adult but also might be more difficult to perceive.

Table 2. Recommended dosages for anti-TB drugs in children

Drug	Daily dose(mg/kg)	F requency	Ma ximum da ily dose
streptomycin	20–40	Once daily	1 g
kanamycin	15–30	Once daily	1 g
amikacin	15–22.5	Once daily	1 g
capreomycin	15–30	Once daily	1 g
ofloxacin	15–20	Twice daily	800 mg
levofloxacin	7.5–10	Once daily	750 mg
moxifloxacin	7.5–10	Once daily	400 mg
ethionamide	15–20	Twice daily	1 g
protionamide	15–20	Twice daily	1 g
cycloserine	10–20	Once or twice daily	1 g
p-aminosalicylic acid	150	Twice or thrice daily	12 g

Ethambutol: Recent comprehensive review showed ocular complications to be rare in children in doses up to 25 mg/kg/d. the currently recommended dosage for children is 15mg/Kg/d

3. DR-TB management in DM

Introduction

DM which is a disease leading to high levels in blood sugar creates as well a state of relatively impairment of immune system. To some extent and with many similarities DM and TB interact in milder but similar way than HIV and TB. The precise mechanisms by which DM predisposes to TB are still not clear but it is though that the high blood sugar levels interact with the activation of macrophages, monocytes and lymphocytes which play a pivotal role in combating the TB pathogen. In fact DM patients present a risk of TB development from two to three times higher than in persons without DM. DM patients with poorer glycaemic control appear to be at higher risk for TB, demonstrating a dose-response relationship between the degree and duration of hyperglycaemia and vulnerability to TB, rather similar to that observed with HIV and TB.

The combination of these two diseases turns highly relevant and will be even more in the future as the burden of DM in the world is continuously increasing not only

developed but in developing countries. The much larger, and rapidly growing, pool of DM patients makes the global and population attributable fraction of TB due to DM very similar to that seen with HIV. Currently there are not enough evidence to affirm that DM present more risk of pharmacological failures and thus greater creation of DR-TB. But in the same way HIV patients do, are probably more prone to present primary DR-TB even with strains will lower fitness . In fact the proportion of patient with DM among the DR-TB cohorts is higher than the regular populations in many middle income countries.

Not many precise studies on the DR-TB/DM outcomes exist so far. However for susceptible TB there is an increased risk not only for poor outcomes but also for present almost 4 times more risk of relapse or TB recurrence.

Main differences in diagnose of DR-TB in the diabetic patient

As happening with HIV infected and children, the relatively immune impairment existing on DM patient creates a lesser inflammatory response to TB bacilli. Hence, the typical symptoms of TB might be milder or even none existing. Classical existing screening diagnose test like smears can be less sensitive and this lead to a delayed diagnosis. Prompt diagnosis and initiation of adequate therapy are key in immune-compromised patients. In fact, the poor the glycaemia control is, the more likely the presentation with atypical symptoms (smear-negative, atypical chest x ray findings and extra-pulmonary disseminated). It is relevant to mention that most of the diabetic patients in developing countries do not know their disease status and thus it is likely that their glycaemia controls might be poor.

Probably cough for more than 2 weeks and smear test might be not enough to diagnose TB in the diabetic as it not enough in the HIV patient. A similar approach searching for cough of any duration, fever, weight loss and night sweats might be more sensitive. Investigation with smears, chest x ray and culture or new technologies might be an ideal approach when presenting the symptoms above. Regarding DR-TB, DM might be considered as an additional risk factor when presenting an DR-TB contact or the patient is not responding correctly to the standard therapy. The profit of culture and DST probably do not differ than the non-DM patients.

Management of DR-TB with DM

For susceptible TB some authors argument and increase in the length of treatment to 8 or 10 months to reduce the risk of relapses. Nonetheless, there is still no evidence in this regard and The Union and WHO still recommend 6 months of treatment until sound evidences appear.

Initially the DR-TB management does not differ from the non-DM patient and the same principles exposed along these Guidelines are valid. Regarding if the optimal length of DR-TB treatment should be similar or not than the non-DM is still uncertain and more evidences are needed to establish the most appropriate DR-TB treatment for the DM.

On the other hand the management of these DR-TB/DM can be challenging and more complicated provided the increased risk of toxicities from anti-TB drug added to typical

DM conditions. Neuropathy, renal failure and older age are conditions frequently found in advanced DM patients that can complicate TB treatment.

At the same time, glycaemia control may become an important issue to increase the immune system capacities and avoid further complications. Some author support the interest of DOT not only for anti-TB medication but also for anti-diabetic medication (oral or injectable) to improve the patient's outcome.

Close monitoring for adverse effects, especially renal failure and glycaemia, are highly recommended. Whenever possible, creatinine and potassium levels should be monitored weekly for the first month and then at least monthly thereafter.

4. DR-TB management in other frequent co-morbidities

DR-TB management in renal dysfunction

Renal dysfunction may lead as well to worst immunity and likewise the previous conditions lead to TB with atypical presentation. As mentioned, renal dysfunction is extraordinarily linked to DM and the aforementioned complications may overlap.

Nonetheless, the main problem related to renal failure relays in the fact that the levels on drugs might remain high in blood being the kidneys unable to filter them. Drugs levels may increase into toxic levels creating worsening of the renal condition and the likelihood of other toxicities. In addition aminoglicosydes have a toxic profile badly affecting the kidneys. At the same time tenofovir (TDF) an ARV commonly used, can create renal toxicity especially in the much deteriorated HIV patient. In case of acute renal failure consider stopping nephrotoxic medication. At the same time, the combination of TDF and Cm can lead in the advanced HIV patient into an electrolyte wasting syndrome breaking with a highly mortal hypokalemia. Drugs should be stopped until patient recovery and potassium should be replaced.

In many occasions most of the anti-TB drugs dosages have to be adjusted and whenever possible the opinion of a nephrologist is recommended. However, the integrity of the SLDs regimen should be maintained as much as possible to avoid compromising the efficacy of the anti-TB treatment and dying by TB. In the absence of an specialist one of the approaches recommended is shifting the daily treatment into a three times weekly while monitoring renal function and potassium.

DR-TB management in liver dysfunction

Hepatotoxicity is one of the main issues regarding toxicity to first line drugs. Isoniazid, rifampicin and pyrazinamide are all associated with hepatotoxicity. Of the three, Pyrazinamide is the most hepatotoxic (associated with liver destruction) and rifampicin the less (associated with cholestatic jaundice).

From the SLDs the most hepatotoxic might be Eto/Pro due the fact of being a molecule similar to Isoniazid. As well PAS and fluoroquinolones could be hepatotoxic but much less than FLDs. As in the example of renal failure DR-TB patients presenting liver dysfunction should received anti-TB treatment but with closer monitoring of liver enzymes and other liver function test and active searching of the classical liver

dysfunction clinical presentations: nausea, vomiting, fever, jaundice, dark urine, abdominal pain, increase of liver size and confusion.

The source of the potential previous liver disorder should be treated or address (virus, alcohol consumption, others) to avoid further complications during treatment. As well, whenever presenting severe chronic liver disease or acute viral hepatitis especially on the HIV patient the consultation of a liver expert or screening for hepatitis B and C is recommended.

Special care is to the drugs use is to be taken when the patient breaks with acute liver failure or have a pre-existing liver dysfunction. In severe hepatitis or dysfunction and if the clinical condition allow it remove the most suspicious responsible drug and give time for the liver function to restore or improve before anti-TB treatment re-initiation. Defer antituberculosis treatment until the acute hepatitis has been resolved. The combination of four non-hepatotoxic drugs is the safest option but whenever possible in the DR-TB try to include a fluoroquinolon to assure the efficacy of the regimen (10).

5. Management DR-TB contacts

The management of DR-TB contacts is one of the most controversial issues in DR-TB management as more uncertainties that evidences exist. Nonetheless this issue is fundamental given the potentially large number of DR-TB infected people. Several uncertainties not only in DR-TB infection diagnose but also in management exist.

A. Has the Contact been Infected?

Currently we lack of full reliable diagnose tools. IGRAs and PPD present many false positives and false negatives and so far non complete superiority has been proven by IGRAs. Moreover these diagnosis test only detect TB infection but not if the strain is a resistant or susceptible one. In addition, not all contacts have necessarily to be infected. The likelihood of an infective contact depends especially on transmissibility and the immune status of the potential host.

B. Who is the Source of the Infection? Susceptible or DR?

At the same time, knowing precisely who was the source of infection is difficult to ascertain. Was it the suppose contact or it was any other?
In the case of secondary DR-TB, the susceptibility pattern depends on the moment of the infection. For example, when the index case infect the contact was the index case still susceptible or was already resistant? Usually, secondary DR-TB patient start being susceptible and after several cycles of inappropriate treatment or other conditions, that can take months or years, the patient develop resistances. In that sense, the precise moment of the infective contact turns crucial. Nevertheless according to studies, especially done in children contacts, most of the DR-TB contacts have indeed DR-TB strains.

C. Which is the Ideal Chemoprophylaxis for the infected cases?

On susceptible infection, more and more evidences are arising on the profit of preventive therapy and treatment of latent TB infection (TLTI) especially over highly susceptible population like HIV patients. Nonetheless, many uncertainties remain regarding the most appropriate drug, for whole long and also policies have to be adapted to local infection transmission rates and risks.

For DR-TB the uncertainties are even greater. Several attempts have been done to ascertain an appropriate drug regimen for resistance infection. The combination of Ofx-Z was tried by a CDC study that had to be stopped due to high hepatotoxicity rates. As well INH was tried resulting in no protection. Other complex combinations were used in children resulting in protection but were almost true DR-TB treatment for infection. Currently there is under study in murine models the potential use of TM207 and Rifapentine for DR and XDR-TB contacts. Given the absence of evidence on which drugs and how long to use them, the current recommendation is close monitoring of the contact cases.

D. If the Contact Develop TB Disease, which is the Ideal Treatment?

After the previous statement, the secondary case will present TB but whether it is resistant or susceptible will not completely be known after DST. According to the reduced number of studies the likelihood of presenting a TB disease is greater. This is especially important for children with TB for whom culture and DST might be difficult to obtain or might delay too much the treatment start. According to this reduce evidence and on a patient orientated approach probably the best to do is give the patient the same treatment that is curing the index case while waiting for the DST result.

6. Management DR-TB in vulnerable and marginalized populations

If TB is a disease of the poor, certainly DR-TB tends to be a disease of the poor among the poorest and the most marginalized or discriminated. The creation of DR-TB is intrinsically linked to difficulties in accessing an appropriate susceptible TB treatment or ensuring proper follow up. This is probably the reason why DR-TB thrives among the most vulnerable and discriminated groups.

Socially neglected or excluded populations present higher rates of TB and worst access to treatment and health care assistance for several reasons. With an adequate approach in increasing access to susceptible TB treatment probably many of these DR-TB cases can be prevented. Considering the bulk of patients in a high burden country, the absolute numbers of TB cases in the marginalized groups may appear reduced (excluding regions where girls and women are discriminated with regard to access to health care). But the proportion of DR-TB in these groups tends to be much higher than in other groups. These untreated or badly treated patients act as remaining pockets of disease. If there is no political will to treat correctly these susceptible TB patients, surely DR-TB will emerge among them and will be later transmitted to others. As the recommendations from WHO are to pursue Intensified Case Finding (ICF) to increase the Case Detection Rate, these marginalized populations cannot be left aside.

Migrants (internal, legal, undocumented, refugees), indigenous and outcast populations usually face difficulties in accessing TB treatment and care. When they manage to access TB treatment and care, it is often in an inconsistent way given their high mobility.

On the other hand, other vulnerable patients who try to access to treatment and care through established channels are denied the care they need and deserve. When men who have sex with men, transgender persons, ethnic minorities, sex workers, drug users, PLWHIV and in some settings women and children are diagnosed, they may be treated with rude manners or discriminated in other ways by the health care workers or others. Hence, they present an increased risk of default and DR-TB development. In these cases,

disease stigma is added to social stigma and makes treatment completion even more complicated. Beside, after experiencing such discrimination the patients may return to their community and discourage others to get diagnosed when sick. This results in individuals remaining infectious at the community level instead of seeking appropriate care. So not only the default rate and DR-TB increase, but also the Case Detection Rate decreases (we lose those potential cases) and TB incidence overall may increase.

The usual argument for not reaching these populations is logistical and difficulties in accessing them. If NTPs wish to reach those patients, their structures, guidelines and procedures need to be more flexible in order to properly address these more complicated cases. On the other hand, lack of human resources is a real limitation in NTPs in developing countries. Nonetheless, the cost of neglecting these groups is economically and socially higher in the end. And discrimination and stigma are amplifying the DR-TB epidemic.

TB and DR-TB diagnostic and treatment for vulnerable groups do not differ from regular population. The key issue is how to make these patients come to the health centers when they are sick and take their medication on the long run. Obviously this varies widely from population to population and from country to country depending on their socio-economic circumstances and depending on the level of stigma and discrimination these groups encounter. Taking that into account, sometimes access to this vulnerable population it is just an issue of negotiation, flexibility and health care workers education.

A positive example in how thinking out of the "one fits all strategy" can increase access to vulnerable groups was recently presented in Namibia (Southern African country) (Uukunde, et al., 2011; (Ruswa, Uukunde, Platt, & Mavhunga, 2011)). The country was presenting high rates of DR-TB among the indigenous San population who are a nomadic group practising a hunter-gatherer lifestyle in the wilderness with a very traditional and unique social structure. Many DR-TB patients were put on treatment and hospitalised according to the national guidelines in the district TB ward situated in a town more than 300 kilometres from their conservancy. There were very high defaulter rates among the San when this treatment approach was being used. The reason was that according to their culture being separated from the family entity was considered a form of punishment. Once this was acknowledged, the NTP negotiated with the group representatives and trained the local community members in DOT and treatment delivery. Adherence improved remarkably and cure rates increased considerably.

For bacteriological, ethical and public health reasons, susceptible and multidrug resistant treatment should be available for ALL vulnerable populations even if this requires more flexibility from the NTPs. Increased access to a correct TB treatment and care and follow-up of outreach or excluded populations is essential to prevent and cope with the ongoing DR-TB epidemic.

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