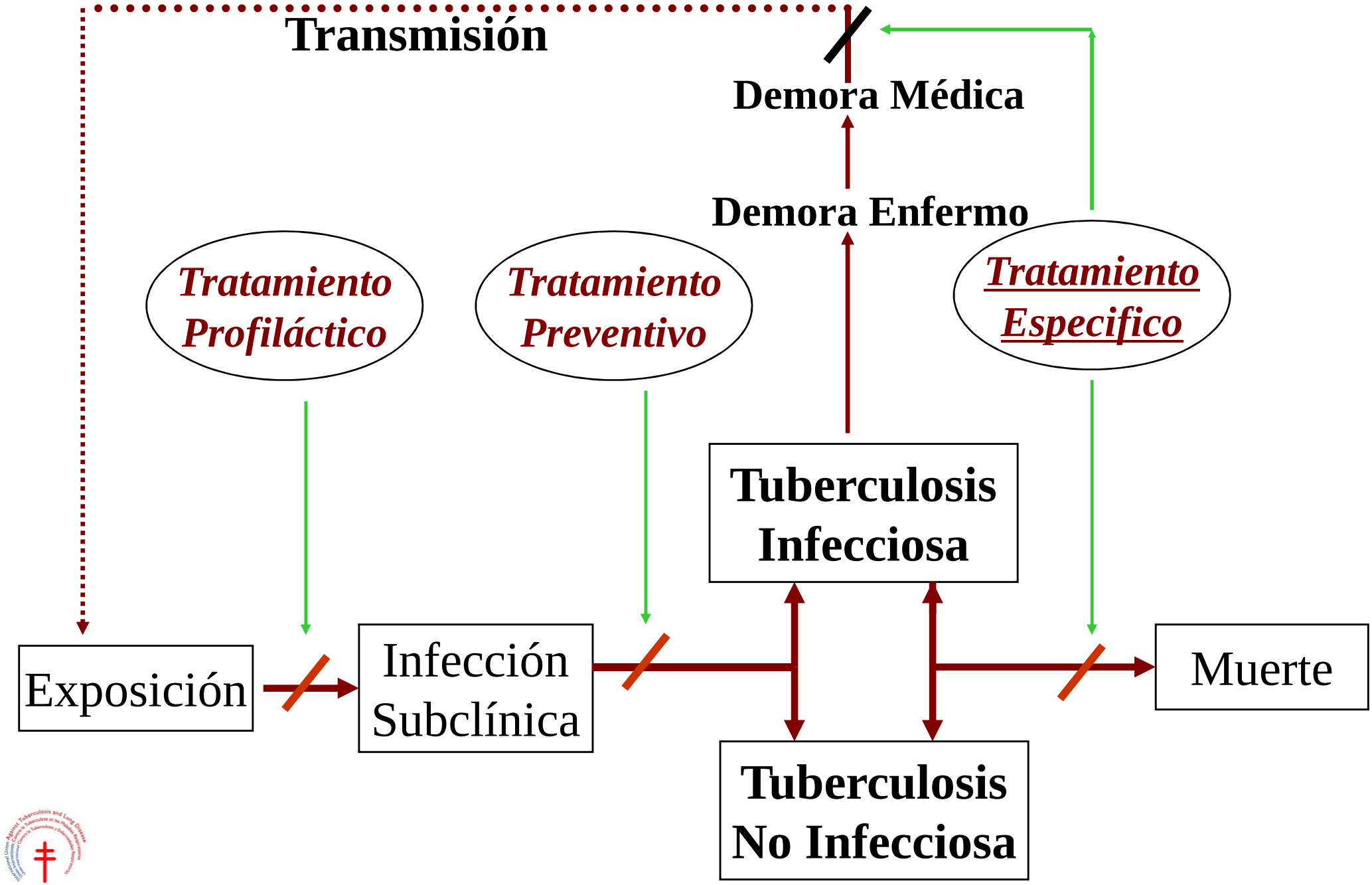
LXXIII Congreso Anual de la Sociedad Mexicana de Neumología y Cirugía de Tórax

Queretaro, Abril 2014

Tratamiento Preventivo de la Tuberculosis: Sirve para algo? Para quien?

Dra. Anna Scardigli MD, DHA

UNION INTERNACIONAL CONTRA LA TUBERCULOSIS Y ENFERMEDADES RESPIRATORIAS (La Union)


Transmisión
Demora Médica
Demora Enfermo
Tratamiento Profiláctico
Tratamiento Preventivo
Tratamiento Especifico
Tuberculosis Infecciosa
Exposición
Infección Subclínica
Muerte
Tuberculosis No Infecciosa

Quimioprofilaxis

- **Es la Quimioterapia empleada con fines PREVENTIVOS**

- **Dirigida a:**

- **Evitar la Infección en No Infectados: Quimioprofilaxis Primaria**

  -se indica especialmente a recién nacidos y lactantes PPD negativos, no vacunados, que conviven con madres contagiosas.

- **Evitar la Enfermedad en Infectados: Quimioprofilaxis Secundaria**

  - ***Prevenir la reactivacion de la infeccion latente***

  - ***Prevenir la rapida progresion de las nuevas infecciones***

A quien dar el tratamiento profilactico?

Balance entre:

Beneficios:

-para el individuo: No enfermar

-para la comunidad: Evitar Nuevos casos

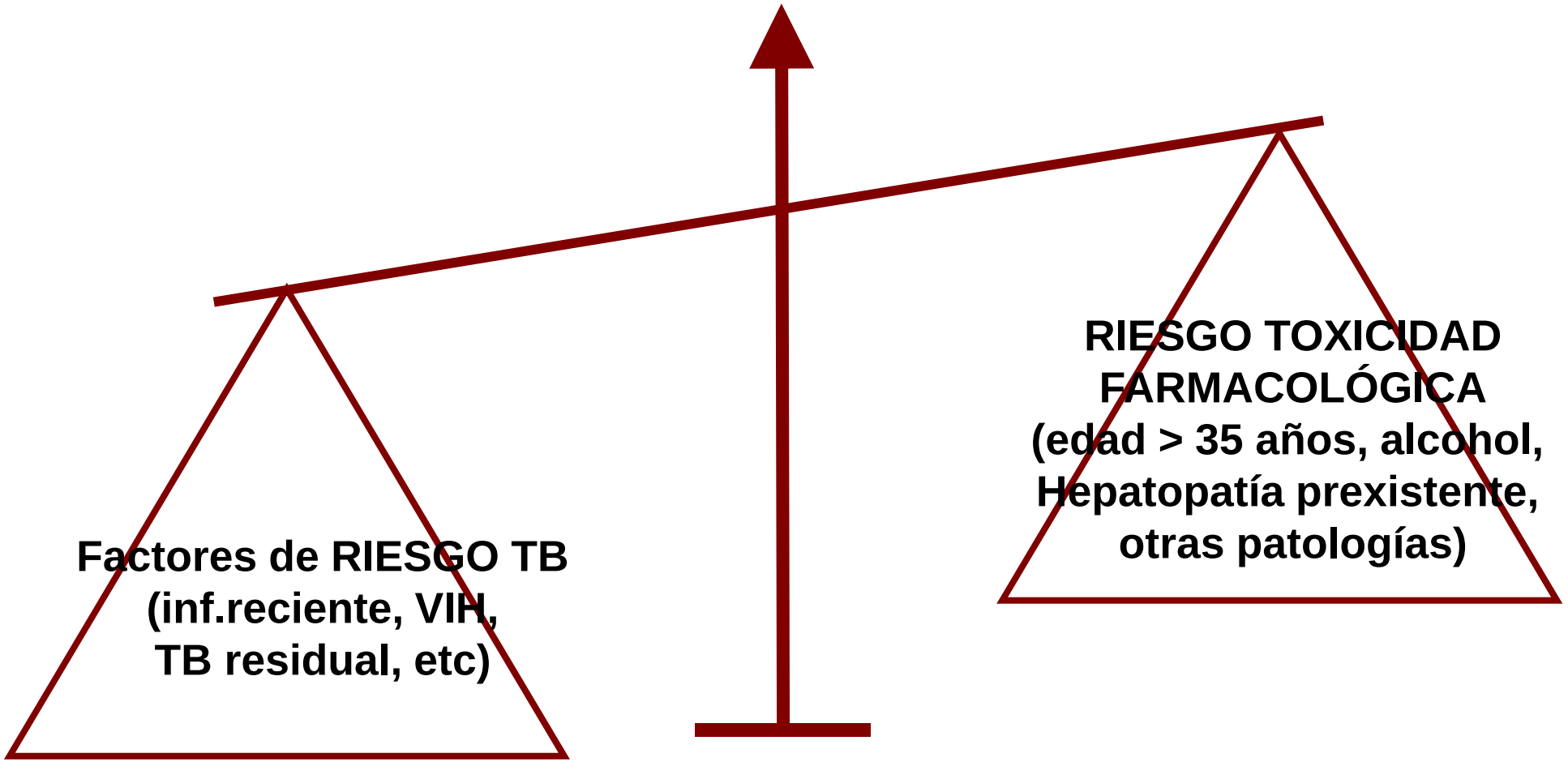
Incovenientes:

-Toxicidad (hepática…)

-Costo (medicamentos, seguimiento de los pacientes)

¿La Quimioprofilaxis antituberculosa como Indicación Individualizada o como intervencion comunitaria?

Evaluación Individualizada:
Seleccionar los pacs.con mayor riesgo de enfermar y menor riesgo de toxicidad



La Quimioprofilaxis antituberculosa como Indicación Individualizada

Para fundamentar su Indicación, son necesarias 3 Condiciones:

1. **Demostrar que la Persona a la que se va a dar la quimioprofilaxis pertenece a un Grupo de Riesgo aumentado para TB**
2. **Haber demostrado que interviniendo sobre este grupo se reduce claramente el riesgo de TB.**
3. **Demostrar que este beneficio supera el riesgo de la toxicidad farmacológica**

Quimioprofilaxis

Indicaciones NO discutidas

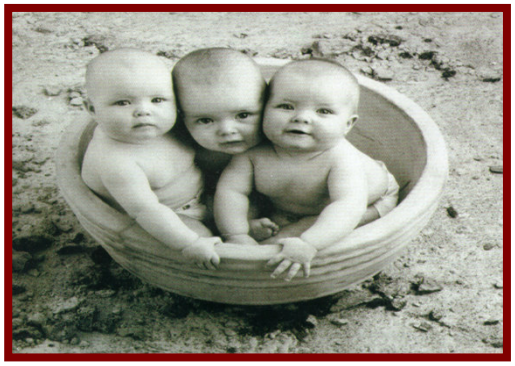
Personas infectadas por M. tuberculosis

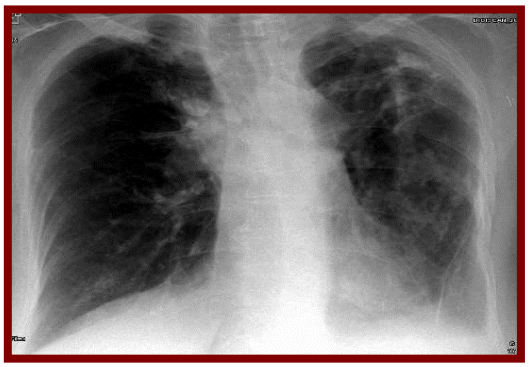
con mayores factores de riesgo:

1.Contactos de enfermos bacilíferos y convertores recientes del PPD

2.Infectados antiguos, con fact. de riesgo de reactivación endógena

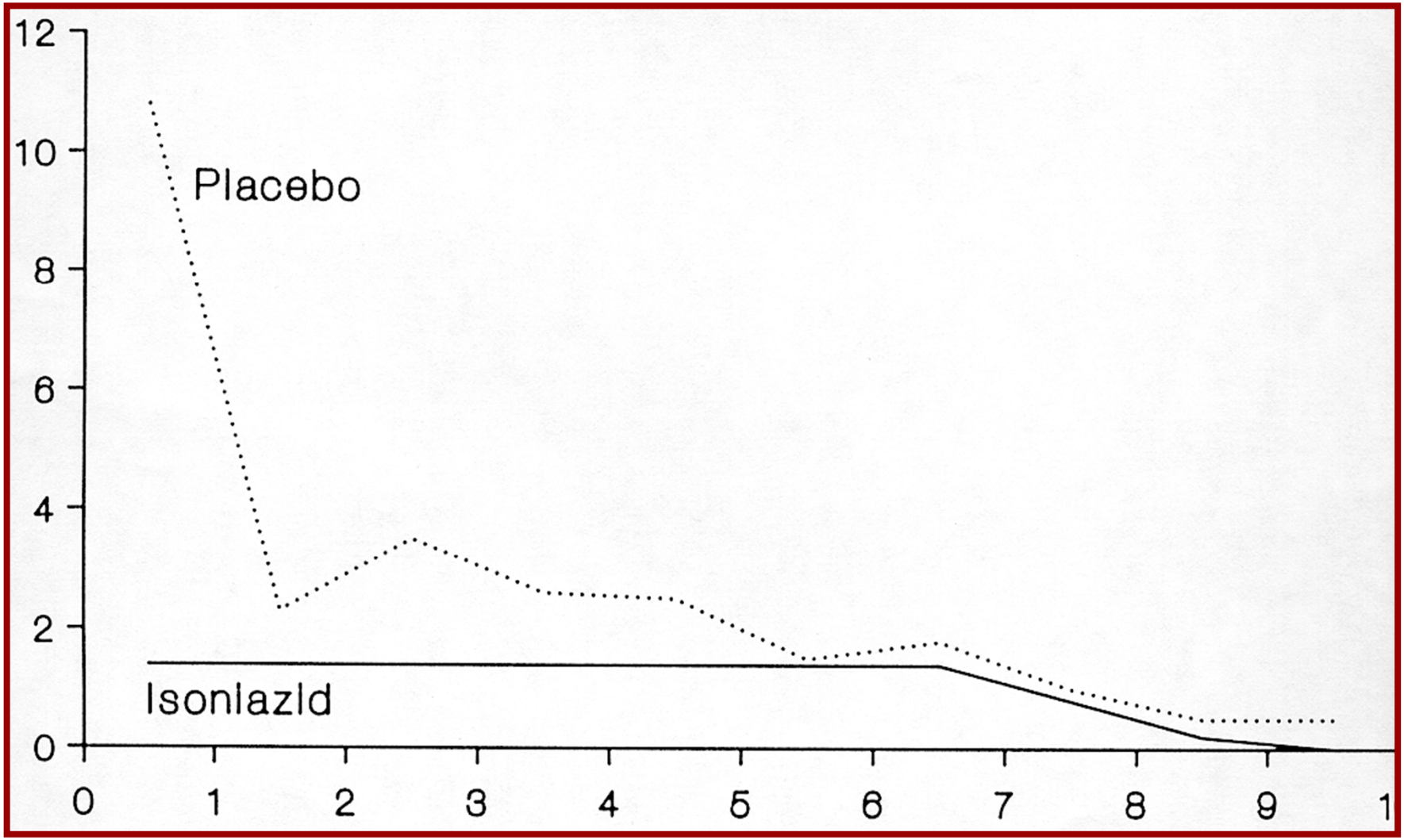
3.Enfermos VIH/SIDA





1. Quimioprofilaxis en Contactos

USPHS. Riesgo de Enfermedad siguiendo a Infección.



Ferebee SH. Adv Tuberc Res 1969; 17: 28-106

1. Contactos de enfermos bacilíferos y convertores recientes del PPD

- Aunque hayan sido vacunados con BCG, por el **riesgo debido a infecc. reciente**.
- **Los límites de edad dependerán de la situación epidemiológica** (por lo menos todos los contactos PPD+ < 5 años).
- Esta indicación puede ampliarse a los contactos positivos hasta los 10 y luego hasta los 15 años (y en algunos paises tambien jovens adultos), a medida que mejoren las condiciones epidemiológicas y los PNT de cada país. Pues los contactos recientes de un enfermo contagioso, tienen tasas de TB que pueden ser cien veces mayores que las de la población general.
- **Convertores recientes del PPD** (sujetos sanos que han virado de negativos a positivos dentro de un período de dos años)

Farga V. y Caminero J.A.
Tuberculosis, 2011

2. TB Residual (Lesiones Fibróticas)

Ensayo UICTER QP 1969-1977

27,830 participantes de 7 paises (Europa Este)

Incidencia TB a 5 años (% Reducción)

Grupo	Placebo	3H	6H	9H
Todos (27.830)	14,3	11,3 (21)	5 (65)	3,6 (75)
Adherentes (21.635)	15	9,4 (31)	4,7 (69)	1,1 (93)
Lesiones <2 cm^2 (18.663)	11,6	9,2 (20)	4 (66)	4,2 (64)
Lesiones >2 cm (8.428)	21,3	16,2 (24)	7 (67)	2,4 (89)

IUAT. Bull WHO 1982; 60: 555-564

2. Infectados antiguos, con fact. de riesgo de reactivación endógena

(indicacion sobre base individual)

-Portadores de sombras radiológicas residuales de origen tuberculoso

-Tratamientos con anti-TNF α (infliximab)

- Silicosis
- Insuficiencia renal, trasplante renal
- Diabéticos, especialmente juveniles
- Resecciones gastro-intestinales
- Enfermedades malignas, especialmente del sistema linfático
- Carcinomas de cabeza y cuello

-Tratamientos prolongados con dosis elevadas de corticoesteroides

-Tratamientos inmunosupresores

- En toda condición con severa depresión de la inmunidad celular

Farga V. y Caminero J.A.
Tuberculosis, 2011

Eur Respir J 2010; 36: 1185–1206
DOI: 10.1183/09031936.00028510

SERIES "UPDATE ON TUBERCULOSIS"
Edited by C. Lange, M. Raviglione, W.W. Yew and G.B. Migliori
Number 2 in this Series

The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement

I. Solovic, M. Sester, J.J. Gomez-Reino, H.L. Rieder, S. Ehlers, H.J. Milburn, B. Kampmann, B. Hellmich, R. Groves, S. Schreiber, R.S. Wallis, G. Sotgiu, E.H. Schölvinck, D. Goletti, J.P. Zellweger, R. Diel, L. Carmona, F. Bartalesi, P. Ravn, A. Bossink, R. Duarte, C. Erkens, J. Clark, G.B. Migliori and C. Lange

ABSTRACT: **Anti-tumour necrosis factor (TNF) monoclonal antibodies or soluble TNF receptors have become an invaluable treatment against chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease and psoriasis. Individuals who are treated with TNF antagonists are at an increased risk of reactivating latent infections, especially tuberculosis (TB).**

Following TNF antagonist therapy, the relative risk for TB is increased up to 25 times, depending on the clinical setting and the TNF antagonist used. Interferon-γ release assays or, as an alternative in individuals without a history of bacille Calmette–Guérin vaccination, tuberculin skin testing is recommended to screen all adult candidates for TNF antagonist treatment for the presence of latent infection with *Mycobacterium tuberculosis*.

Moreover, paediatric practice suggests concomitant use of both the tuberculin skin test and an interferon-γ release assay, as there are insufficient data in children to recommend one test over the other. Consequently, targeted preventive chemotherapy is highly recommended for all individuals with persistent *M. tuberculosis*-specific immune responses undergoing TNF antagonist therapy as it significantly reduces the risk of progression to TB.

This TBNET consensus statement summarises current knowledge and expert opinions and provides evidence-based recommendations to reduce the TB risk among candidates for TNF antagonist therapy.

AFFILIATIONS
For a full list of affiliations refer to the Acknowledgements section.

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TBNET is a Clinical Research

¿Son los Trasplantados de Organos Sólidos (TOS) un Factor de Riesgo de Padecer Tuberculosis?

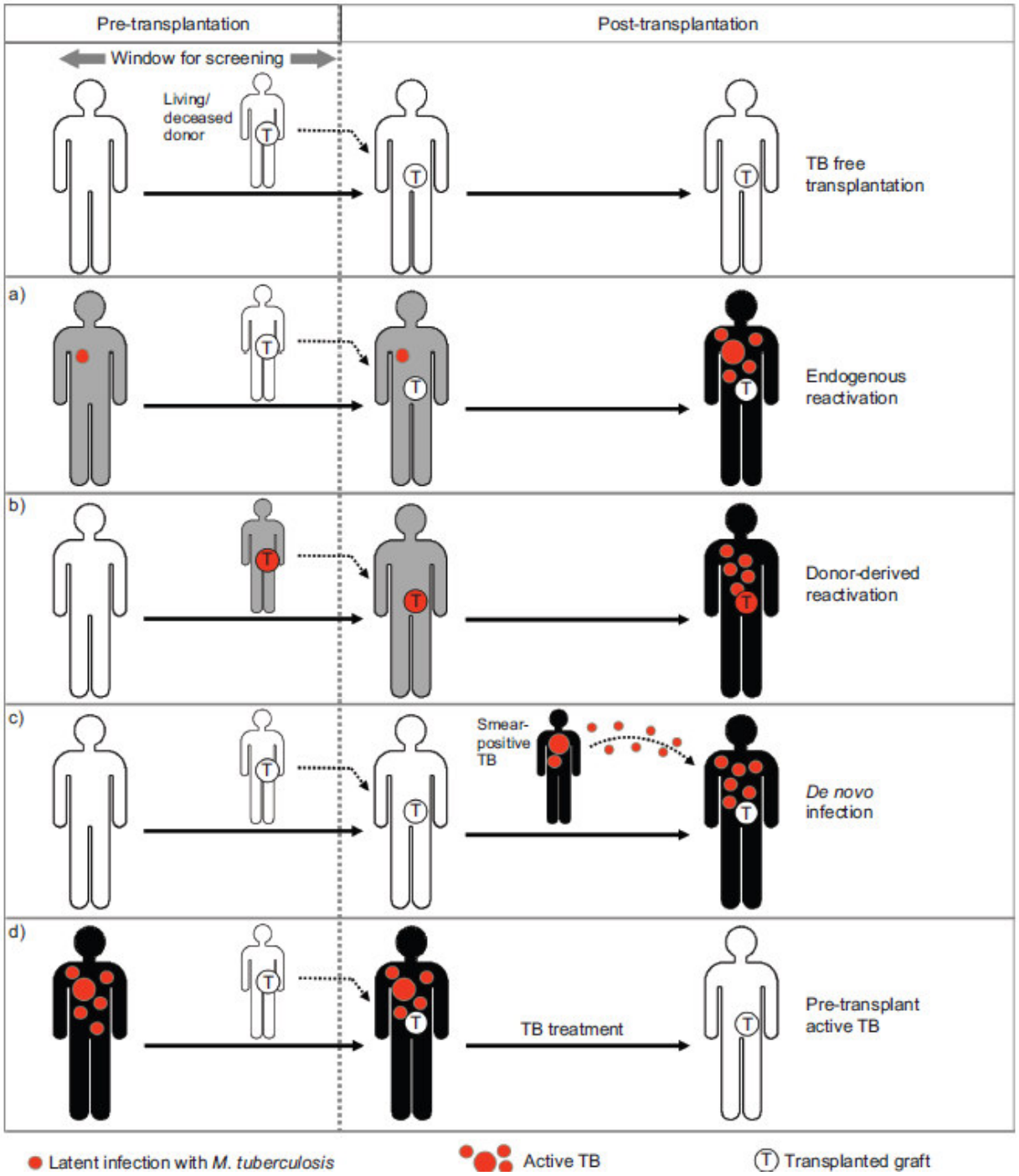
Eur Respir J 2012; 40: 990–1013
DOI: 10.1183/09031936.00000712

Bumbacea D. ERJ 2012, 40: 990-101

REVIEW

The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement

Dragos Bumbacea, Sandra M. Arend, Fusun Eyuboglu, Jay A. Fishman, Delia Goletti, Michael G. Ison, Christine E. Jones, Beate Kampmann, Camille N. Kotton, Christoph Lange, Per Ljungman, Heather Milburn, Michele I. Morris, Elmi Muller, Patricia Muñoz, Anoma Nellore, Hans L. Rieder, Urban Sester, Nicole Theodoropoulos, Dirk Wagner and Martina Sester



Bumbacea D. ERJ 2012, 40: 990-1013

¿Son los Trasplantados de Organos Sólidos (TOS) un Factor de Riesgo de Padecer Tuberculosis? (1)

- *La Frecuencia de TB Activa entre TOS se estima 20-74 veces el de la Población General*

- *La Prevalencia de TB en TOS se estima:*

  - *1,2-6,4% en Países Desarr. (1200-6400 / 100.000 hab.)*
    (Tasa TB en España 20 / 100.000)

  - *< 15% en Areas de Alta Endemia*

¿Son los Trasplantados de Organos Sólidos (TOS) un Factor de Riesgo de Padecer Tuberculosis? (2)

- *La Frecuencia de TB Activa en TOS varía dependiendo del Organo Transplantado → Mayor Frecuencia en Pulmón (2-6%) → Riñón (0,15-15%)*

- *2/3 de los Casos de TB en TOS ocurren en el Primer Año Post-Trasplante (Media 9 Meses)*

Mecanismos por las que los Trasplantados de Organos Sólidos (TOS) padecen Tuberculosis?

- *La Mayoría de Casos son por Reactivaciòn Endógena de Lesiones previas*

- *Casos aislados de Infección Primaria han sido descritos (más vulnerables después del Trasplante) → Han sido descritos Brotes Nosocomiales*

- *Adquirida del Organo Donado (< 5% de las TB)*

Factores de Riesgo de Padecer TB en TOS (1)

Aguado JM. CID 2009, 48: 1276-84

1. ***Tratamiento Inmunosupresor***

1. ***Historia de Exposición a M. tuberculosis***

2. ***Condiciones Clínicas***

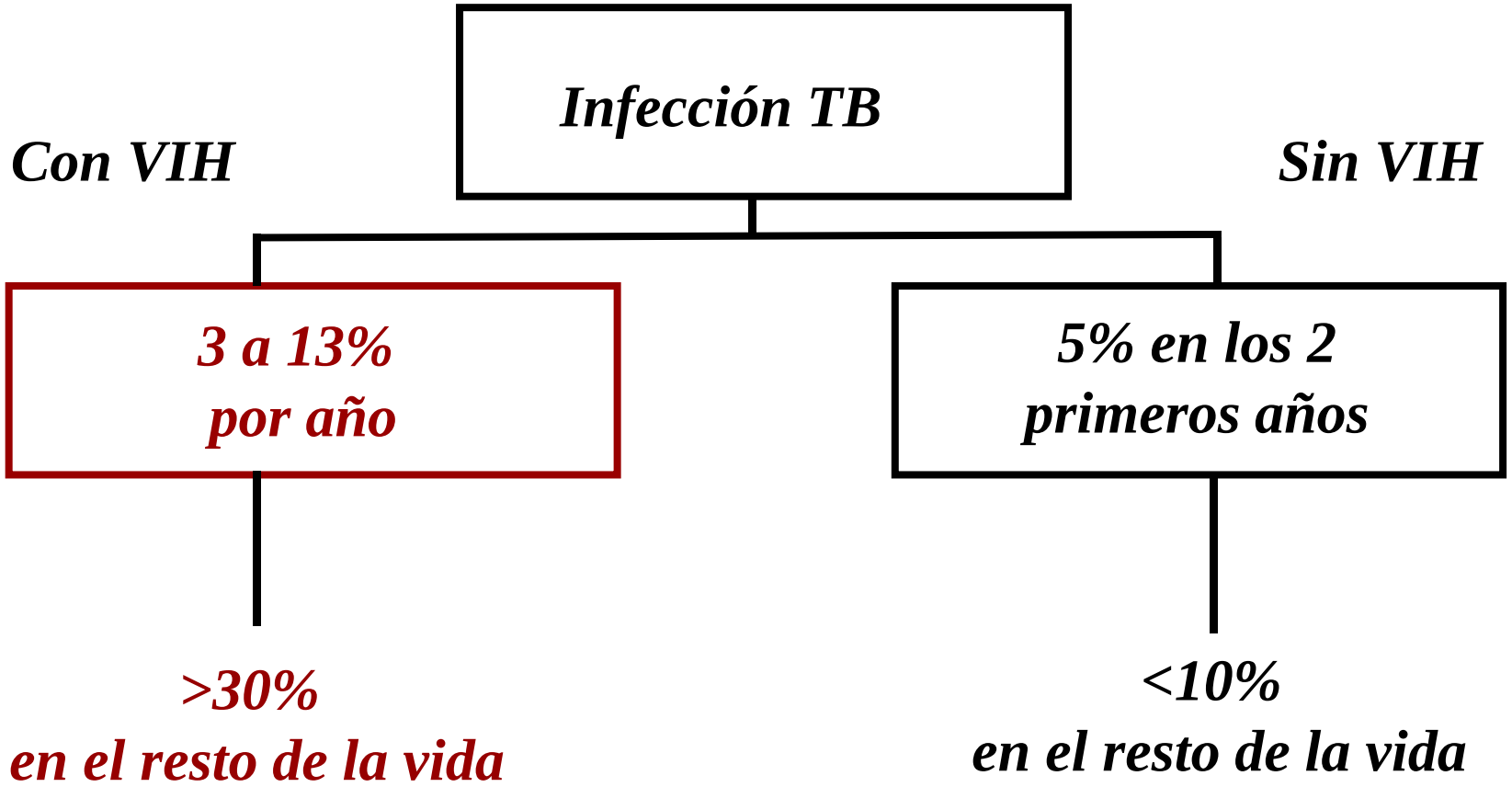
Factores de Riesgo de Padecer TB en TOS (3)

Aguado JM. CID 2009, 48: 1276-84

1. Tratamiento Inmunosupresor
2. Diabetes Mellitus
3. Infección Hepatitis C
4. Enfermedad Hepática Crónica
5. Otras: CMB, Neumonia Nocardia, etc

Sorprendentemente, sólo el 20-25% de los Casos de TB Activa que ocurren después del Trasplante son en Pacientes con PPD+ antes del Trasplante (Anergia?)

3. Enfermos VIH/SIDA



Probabilidad de desarrollar TB en pacientes con y sin infección por VIH

Riesgo de TB activa en personas con infeccion por M.tuberculosis

• SIDA (sin tratamiento)	110-170
• HIV (sin tratamiento)	50-110
• Transplante (inmuno-terapia)	20-74
• Silicosis	30
• Fracaso renal cronico (con hemodialisis)	10-25
• Carcinoma cabeza/cuello	16
• Infeccion reciente (<2aa)	15
• Lesiones fibro-nodulares loubulo sup.	6-19
• Inhibidores TNF	2-9
• Diabetes mellitus	2-4
• Tabaco	2-5

Adaptado de: Vernon A. Seminars in Respiratory and Critical Care Medicine, Vol.34, N.1/2013

3. Enfermos VIH/SIDA

Los adultos y adolescentes con VIH deben ser evaluados sobre la base de un algoritmo clínico; aquellos que no notifiquen síntomas de tos actual, fiebre, pérdida de peso o sudoración nocturna probablemente no tengan TB activa y se les debe ofrecer terapia preventiva con INH.

(recomendación fuerte, evidencia de calidad moderada)

OMS – ICF and IPT Guidelines – 2010

OMS – Actividades de Colaboracion TB/HIV – 2012

Quimioprofilaxis en VIH

Eficacia de H para Prevenir TB en VIH+ con PPD+. Haití.

	B_6 sólo	12H + B_6
Nº Estudiado	25	38
Nº (%) de Casos	6 (24)	2
Personas/ año de seguim.	61	118
Tasa/100 personas/año	10	1,7
RR (95% IC)	5,8 (1,2-28,7)	1
Tiempo para TB (meses)	28,9	37,6

Pape JW, et al. Lancet 1993; 342: 268-72

Efficacia de la Terapia Preventiva de la TB en reducir la Incidencia de TB en PVHS

Akolo, Cochrane Review 2010

PPD (Mantoux)	RR (95% CI)
Positivo	**0.38 (0.25, 0.57)**
Negativo	0.89 (0.64, 1.24)
TOTAL	**0.68 (0.54, 0.85)**

8,578 participantes randomizados, reduccion del 32% de TB con cualquier regimen profilactico (reduccion 62% en PPD Pos.y solo 11% en VIH neg.)

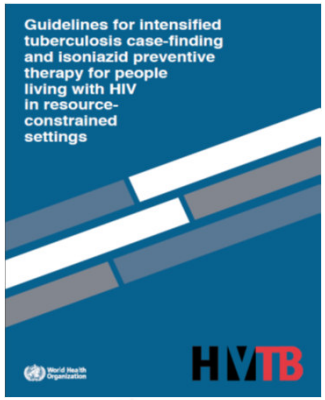
- TPI reduce mucho el riesgo de TB en PVVIH con PPD +, pero no tiene mucho efecto sobre las PVVIH con PPD -

- PPD – es dificil de hacer, problemas con la interpretación, falsos positivo/negativos (esp.en VIH), hay stock outs y necesita nevera

- IGRAs – no son mejores que el PPD en determinar TB activa vs. latente en VIH positivos, falsos negativos, alto coste y necesita una muestra sanguinea

¿Es correcto dar TPI a PVVIH con PPD negativo o a los que no se realiza PPD?

2.2.7 Figure 1. Algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



FOOTNOTES TO ALGORITHM FOR ADULTS

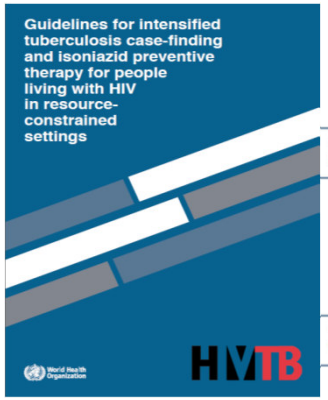
* Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce *M. tuberculosis* transmission in all settings that provide care.

** Chest radiography can be done if available, but is not required to classify patients into TB and non-TB groups. In high HIV-prevalence settings with a high TB prevalence among people living with HIV (e.g. greater than 10%), strong consideration must be given to adding other sensitive investigations.

*** Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption, and symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for starting IPT. Although not a requirement for initiating IPT, TST may be done as a part of eligibility screening in some settings.

**** Investigations for TB should be done in accordance with existing national guidelines.

Key recommendations



1. Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

   Strong recommendation, moderate quality of evidence[1]

2. Adults and adolescents living with HIV and screened with a clinical algorithm for TB, and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

   Strong recommendation, moderate quality of evidence

3. Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

   Strong recommendation, high quality of evidence

4. Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT.[2] IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

   Conditional recommendation, moderate quality of evidence[3]

5. TST is not a requirement for initiating IPT in people living with HIV.

   Strong recommendation, moderate quality of evidence

6. People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.

   Strong recommendation, high quality of evidence

ident that the desirable effects of adherence to a recommendation

l context such as the epidemiology of TB and HIV, and settings with people living with HIV.

cludes that the desirable effects of adherence to a recommendation he recommendation are scant. Therefore, the recommendation ew evidence may result in changing the balance of risk to uirements in all settings.

No hay síntomas: TPI

Sí hay sintomas: NO TPI investigar TB

No hay síntomas: TPI 6 meses

No hay síntomas: TPI 36 meses (donde es posible)

PPD no es necesario pero si está disponible, adelante

Actuales reomendaciones de la OMS (2010) para TB screening & TPI en personas viviendo con VIH

6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

TPI en VIH
6 meses vs.36 meses

Taraz Samandari, Tefera B Agizew, Samba Nyirenda, Zegabriel Tedla, Thabisa Sibanda, Nong Shang, Barudi Mosimaneotsile, Oaitse I Motsamai, Lorna Bozeman, Margarett K Davis, Elizabeth A Talbot, Themba L Moeti, Howard J Moffat, Peter H Kilmarx, Kenneth G Castro, Charles D Wells

www.thelancet.com **Published online April 13, 2011 DOI:10.1016/S0140-6736(11)60204-3**

Summary

Background In accordance with WHO guidelines, people with HIV infection in Botswana receive daily isoniazid preventive therapy against tuberculosis without obtaining a tuberculin skin test, but duration of prophylaxis is restricted to 6 months. We aimed to assess effectiveness of extended isoniazid therapy.

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April 13, 2011
DOI:10.1016/S0140-6736(11)60204-3
See Online/Comment
DOI:10.1016/S0140-6736(11)60434-0

Botswana–USA Partnership (BOTUSA), Gaborone and Francistown, Botswana (T Samandari MD, T B Agizew MD, S Nyirenda MD, Z Tedla MD, T Sibanda MBChB, B Mosimaneotsile RN, M K Davis MD, E A Talbot MD); **Ministry of Health, National Tuberculosis Programme, Gaborone, Botswana** (O I Motsamai RN); **Ministry of Health, Gaborone, Botswana** (T L Moeti MBBS, H J Moffat FRCP); **and Division of Tuberculosis Elimination** (T Samandari, N Shang PhD, L Bozeman RN, E A Talbot, K G Castro MD, C D Wells MD) **and Division of HIV/AIDS Prevention** (P H Kilmarx MD), **Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA**

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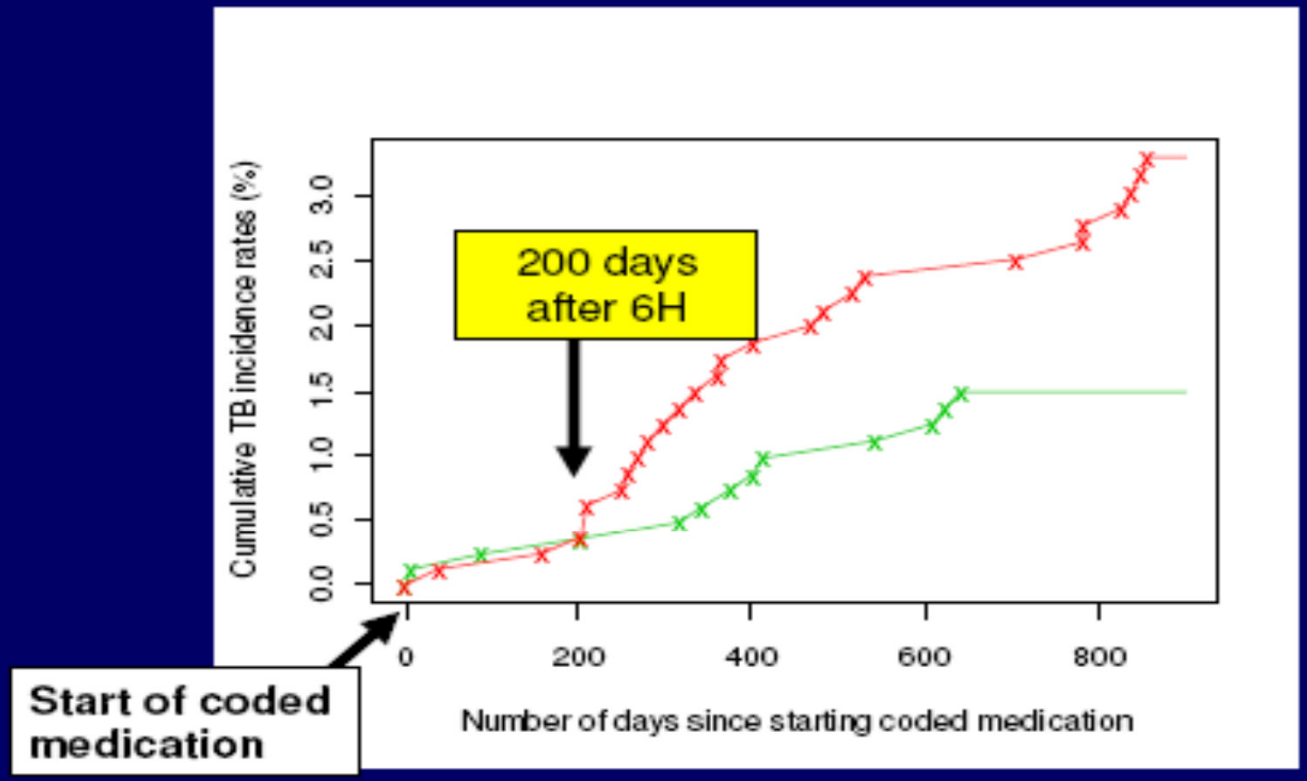
- **Incidencia de TB: 3.4% vs 2% en los 6 meses de TPI vs vs 36 meses (pero sin beneficios significativos en los PPD-).**
- **Diminucion de 43% en la Incidencia de TB con 36 meses de TPI (74% en los PPD+)**
- **No differencias en mortalidad entre 6 y 36 meses (pero mortalidad menor en los PPD+)**
- **Mejor adherencia en los con PPD+**
- **TARGA no fue randomizado y puede tener influenciado los resultados**

www.thelancet.com Published online April 13, 2011 DOI:10.1016/S0140-6736(11)60204-3

What was the duration of the benefit of six months IPT?



All participants analyzed in this graph received 6 months of IPT prior to day 0 in this graph

La incidencia de TB entre los dos grupos diverge a 200 dias despues de los 6 meses de profilaxis con H: el beneficio se pierde con el tiempo

Tratamiento Preventivo con H (TPI) + TARGA mejor

The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil

Jonathan E. Golub[a], Valeria Saraceni[b], Solange C. Cavalcante[b,c], Antonio G. Pacheco[b,c], Lawrence H. Moulton[a], Bonnie S. King[a], Anne Efron[a], Richard D. Moore[a], Richard E. Chaisson[a] and Betina Durovni[b,c]

AIDS 2007, **21**:1441–1448

- ***11,026 enfermos VIH+***
- ***Incidencia de TB en general : 2.28 casos/100 personas-ano (pa)***
- ***Sin TARV ni TPI, incidencia de TB: 4.01/100 pa***
- ***Solo en TARV, incidencia de TB: 1.90/100 pa***
- ***Solo en TPI: 1.27/100 pa***
- ***Con TARV+TPI, incidencia: 0.80/100 PY***

¿Tratamento Preventivo de la TB como intervencion de masa en areas de alta prevalencia de TB/VIH?

TPI como intervencion de masa en areas de alta prevalencia TB/VIH?

The Consortium to Respond Effectively to the AIDS-TB Epidemic (CREATE)

Study	Intervention(s)	Design (N)
THIBELA Team up against TB	Mass TB preventive therapy for S.A. gold miners	Cluster randomized trial (~80,000)
ZAMSTAR	Enhanced TB case finding, contact evaluations in Zambia and S.A.	Community randomized trial (~1 million)
TB Rio TB/HIV NO RIO	Preventive therapy and ARVs for HIV patients in Rio de Janeiro	Phased implementation trial (18,000)

CREATE Consortium to Respond Effectively to the AIDS TB Epidemic

A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control

Gavin J. Churchyard, M.B., B.Ch., Ph.D., Katherine L. Fielding, Ph.D., James J. Lewis, Ph.D., Leonie Coetzee, D.Soc.Sc., Elizabeth L. Corbett, M.B., B.Chir., Ph.D., Peter Godfrey-Faussett, F.R.C.P., Richard J. Hayes, D.Sc., Richard E. Chaisson, M.D., and Alison D. Grant, M.B., B.S., Ph.D., for the Thibela TB Study Team

ABSTRACT

BACKGROUND

Tuberculosis is epidemic among workers in South African gold mines. We evaluated an intervention to interrupt tuberculosis transmission by means of mass screening that was linked to treatment for active disease or latent infection.

METHODS

In a cluster-randomized study, we designated 15 clusters with 78,744 miners as either intervention clusters (40,981 miners in 8 clusters) or control clusters (37,763 miners in

From the Aurum Institute (G.J.C., L.C.) and the School of Public Health, University of the Witwatersrand (G.J.C.) — both in Johannesburg; the London School of Hygiene and Tropical Medicine, London (G.J.C., K.L.F., J.J.L., E.L.C., P.G.-F., R.J.H., A.D.G.); and the Center for Tuberculosis Research, Johns Hopkins University

- **78,744 miners**
- **IPT for 6-9 month did not change the Incidence (3/100pers/yr vs 2.95/100pers/yr) and the Prevalence (2.35 vs 2.14) of TB compared to the control clusters (P=0.90) during 1 year after the intervention.**
- **Some protection during the intervention (1.10 vs 2.91 cases/100pers/yr), but rapid loss of protection.**
- **High HIV infection, silicosis and ongoing TB transmission, may be responsible of the limited results in TB control.**
- **Need of shorter regimens and social interventions to increase compliance.**

Controlled Trials number, ISRCTN63327174.)

ADHERENCIA A LA TERAPIA PREVENTIVA

La Tasa de CUMPLIMIENTO de una Pauta de 6 Meses de T.I.T. oscila del 3-60%, con porcentajes del 20-30% en la mayoría de los trabajos

- ATS/CDC. Am J Respir Crit Care Med 2000; 161: S221-S247
- Tulsky et al. Am J Public Helath 1998; 88: 223-6
- Bock NN, et al. Am J Respir Crit Care Med 1999; 295-300
- Gilroy SA, et al. Clin Infect Dis 2000; 31: 826-9
- Nolan CM et al. Am J Respir Crit Care Med 1997; 155: 583-6
- Kohn MR, et al. Arch Pediatr Adolesc Med 1996; 150: 727-9

Tratamento Preventivo de la TB
Indicación Comunitaria

Eficiencia Operacional

1.- RIESGO de TB del Grupo seleccionado

2.- EFICACIA de la Pauta Terapéutica

3.- CUMPLIMIENTO (adherencia)

1.- Riesgo de TB del Grupo seleccionado

- Coinfectados VIH-TB
- Contactos y Convertores Recientes
- TB Residual. Manejo **Individual**.
- Tto Infliximab etc.. Manejo **Individual**.

¡ NO JUSTIFICADA INTERVENCION MASIVA EN EL RESTO !

Tratamento Preventivo de la TB
Indicación Comunitaria

Eficiencia Operacional

1.- Riesgo de TB del Grupo seleccionado

2.- Eficacia de la Pauta Terapéutica (duracion/regimen)

3.- CUMPLIMIENTO (adherencia)

Tratamento Preventivo de la TB
Indicación Comunitaria

Eficiencia Operacional

***Eficacia** de la Pauta Terapéutica:*

- ***Duracion***
- ***Regimen***

Ensayo UICTER QP 1969-1977

en un grande numero (27,830 participantes de 7 paises del Europa Este) de enfermos con TB Residual (Lesiones Fibróticas)

Incidencia TB a 5 años (% Reducción)

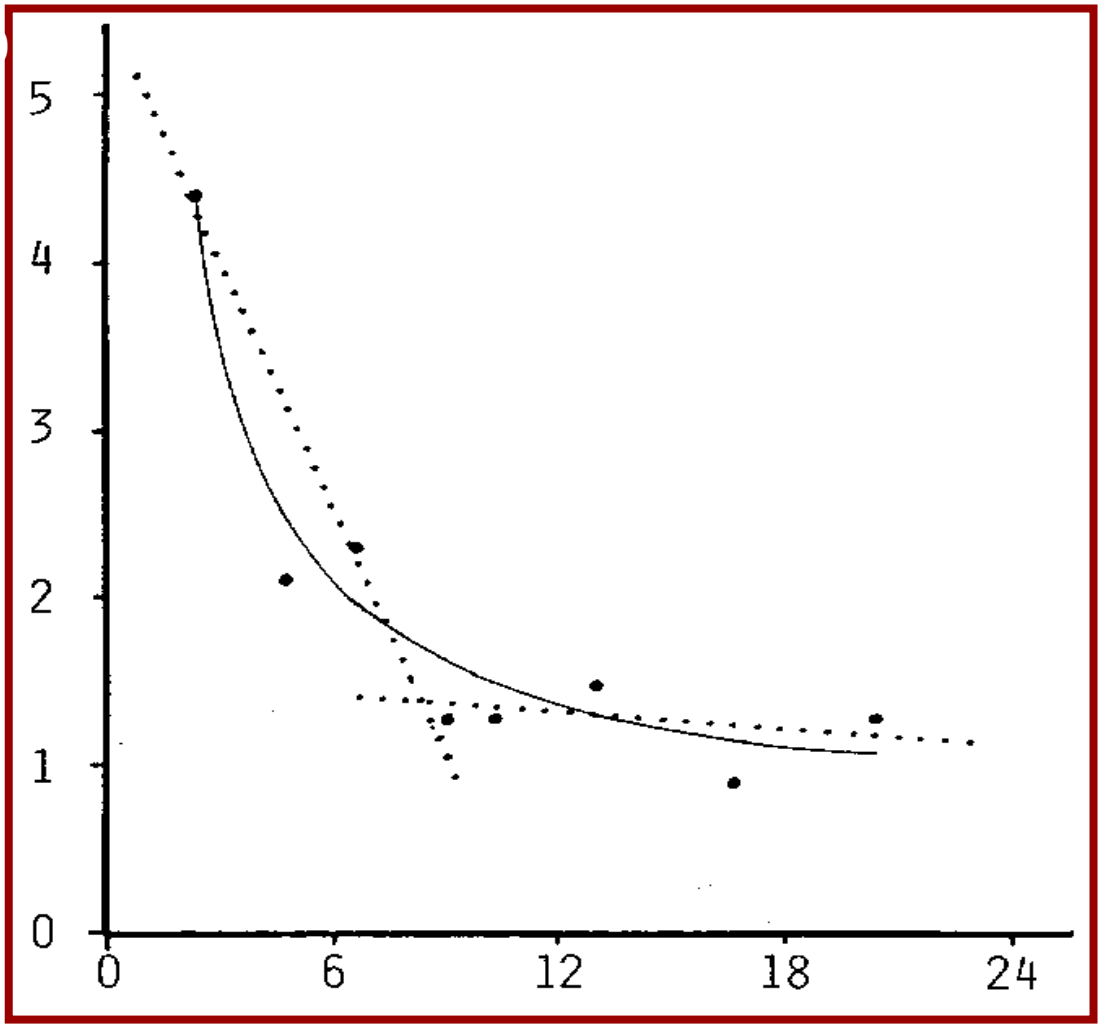
Grupo	*Placebo*	*3H*	*6H*	*9H*
Todos (27.830)	*14,3*	*11,3 (21)*	*5 (65)*	*3,6 (75)*
Adherentes (21.635)	*15*	*9,4 (31)*	*4,7 (69)*	*1,1 (93)*
Lesiones <2 cm² *(18.663)*	*11,6*	*9,2 (20)*	*4 (66)*	*4,2 (64)*
Lesiones >2 cm *(8.428)*	*21,3*	*16,2 (24)*	*7 (67)*	*2,4 (89)*

Efficacia mayor en los que se tomaron mas tiempo INH, y eficacia mayor en los mas aderentes (que se tomaron al menos el 80% de las doses)

Estudios de Comstock

Eficacia según la Duración de INH:

mayor efficacia cuando INH 9-12 meses



Comstock G, et al. Am Rev Respir Dis 1979; 119; 827-830

Comstock GW, et al. Am Rev Respir Dis 1967; 95: 935-43

Quimioprofilaxis
Eficacia según la Duración de INH

- **6 Meses de Tratamiento no otorgan protección óptima.**

- **Más de 12 Meses No otorgan ventajas adicionales.**

- **Quizás la duración más óptima se 9-12 Meses**

Comstock GW. Int J Tuberc Lung Dis 1999; 3: 847-850

Tratamento Preventivo de la TB
Indicación Comunitaria

Eficiencia Operacional

***Eficacia* de la Pauta Terapéutica:**

- ***Duracion***
- ***Regimen***

British Medical Research Council

primer ensayo randomizado con Rifampicina en silicoticos, Hong Kong-Madras

Grupo	3R	3HR	6H	Placebo
N.Partecipantes	165	161	167	159
%PPD pos	96%	91%	95%	95%
TB en 5 aa	17%	22%	20%	34%
Epatotox	1%	4%	5%	2%

- No diferencia significativa entre los 3 grupos.
- Placebo = mas TB
- RIF sola mejor performance (y menos tox)

AmRevRespDis 1992

Posible utilidad de combinanciones con Pirazinamida para acortar la duracion de la quemioprofilaxis?

- Estudios de Grosset: RIF sola o + INH y/o PZA = mejores resultados con RIF sola (3 meses) o RIF+PZA (2 meses).

  >>> miedo de desarrollar res a RIF en monoterapia

- Varios ensayos (USA, Brasil, Haiti y Mexico) evaluaron 2-3 meses RIF+PZA y confirmaron misma eficacia de 6 meses INH

  >>> aumentada epatotoxicidad con RIF+PZA

Posible utilidad de otras rifamicinas (Rifapentina) con larga vida media?

New Regimens to Prevent Tuberculosis in Adults with HIV Infection

Neil A. Martinson, M.B., B.Ch., M.P.H., Grace L. Barnes, B.S.N., M.P.H., Lawrence H. Moulton, Ph.D., Reginah Msandiwa, R.N., Harry Hausler, M.D., Ph.D., Malathi Ram, Ph.D., James A. McIntyre, M.B., B.Ch., Glenda E. Gray, M.B., B.Ch., and Richard E. Chaisson, M.D.

July 2011

ABSTRACT

BACKGROUND

Treatment of latent tuberculosis in pa
ciency virus (HIV) is efficacious, but fe
ment. We evaluated three new regime
potent and durable than standard iso

METHODS

We randomly assigned South African
berculin skin test who were not takin
(900 mg) plus isoniazid (900 mg) wee
niazid (900 mg) twice weekly for 12 we
(continuous isoniazid), or isoniazid (30
primary end point was tuberculosis-fr

RESULTS

The 1148 patients had a median age
484 per cubic millimeter. Incidence rat
100 person-years in the rifapentine–is
rifampin–isoniazid group, and 2.7 per
group, as compared with 3.6 per 100
all comparisons). Serious adverse reac
isoniazid group (18.4 per 100 person-y
to 15.4 per 100 person-years). Two of
were found to have multidrug resistan

CONCLUSIONS

On the basis of the expected rates of t
adults, all secondary prophylactic regi
of intermittent rifapentine or rifampin
superior to 6 months of isoniazid. (Fu
Infectious Diseases and others; ClinicalTrials.gov number, NCT00057122.)

Rifapentin+INH weekly (3mths), or

Rifampin+INH twice week (3mths.), or

INH (till 6yrs.) vs

INH 6 months.

No differencia de superioridad entre los 3 regimenes comparados con INH 6 meses

Tratamientos mas cortos=mejor adherencia

Tx mas extensos eficaces durante el Tx, pero pierden los beneficios terminando el Tx y por los efectos adversos

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

ABSTRACT

BACKGROUND

Treatment of latent *Mycobacterium tuberculosis* infection is an essential component of tuberculosis control and elimination. The current standard regimen of isoniazid for 9 months is efficacious but is limited by toxicity and low rates of treatment completion.

METHODS

We conducted an open-label, randomized noninferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) (combination-therapy group) with 9 months of self-administered daily isoniazid (300 mg) (isoniazid-only group) in subjects at high risk for tuberculosis. Subjects were enrolled from the United States, Canada, Brazil, and Spain and followed for 33 months. The primary end point was confirmed tuberculosis, and the noninferiority margin was 0.75%.

RESULTS

In the modified intention-to-treat analysis, tuberculosis developed in 7 of 3986 subjects in the combination-therapy group (cumulative rate, 0.19%) and in 15 of 3745 subjects in the isoniazid-only group (cumulative rate, 0.43%), for a difference of 0.24 percentage points. Rates of treatment completion were 82.1% in the combination-therapy group and 69.0% in the isoniazid-only group (P<0.001). Rates of permanent drug discontinuation owing to an adverse event were 4.9% in the com-

From the Vanderbilt University School of Medicine, Nashville (T.R.S., A.K.); the Centers for Disease Control and Prevention, Atlanta (M.E.V., A.S.B., N.S., E.B.-S., L.B.); the Washington DC Veterans Affairs Medical Center and George Washington University — both in Washington, DC (F.G.); the Johns Hopkins University School of Medicine, Baltimore (J.H., R.E.C.); Family Health International and Duke University — both in Durham, NC (C.D.H.); Montreal Chest Institute, McGill University, Montreal (D.M.); the University of North Texas Health Science Center at Fort Worth, Fort Worth (S.E.W.); the South Texas Veterans Health Care System and University of Texas Health Science Center at San Antonio — both in San Antonio (M.W.); and the South Texas Consortium, Harlingen (D.W.); the Federal University of Rio de Janeiro, Rio de Janeiro (M.B.C.); and Boston University School of Medicine, Boston (C.R.H.). Address reprint requests to Dr. Sterling at A2209 Medical Center North, 1161 21st Ave. S., Nashville, TN 37232, or at timothy.sterling@vanderbilt

- ***12 dosis de Rifapentina +INH, dadas semanalmente (3 meses) bajo TAES, efectivo como 9 meses de INH autoadministrada***
- ***Completaron el tratamiento más (82%) en INH+RPT que en INH solo (69%)***
- ***Hubo que suspender más el Tratamiento en INH+RPT (4.9%) que en INH (3.7%)***

Tratamento Preventivo (Quemioprofilaxis) de la TB Indicación Comunitaria

Eficiencia Operacional

1.- Riesgo de TB del Grupo seleccionado

2.- Eficacia de la Pauta Terapéutica

3.- CUMPLIMIENTO (adherencia)

Tratamento Preventivo (QP) de la TB
Indicación Comunitaria
Eficiencia Operacional

Riesgo TB (%)	Eficacia Régimen (%)	Cumplim. (%)	Eficiencia Global (%)	Prevenir 1 caso
5	80	30	1	100
10	80	30	2	50
10	80	60	5	20
30	80	30	7	14
30	80	50	12	8
30	90	70	19	5

Tratamento Preventivo (QP) de la TB
Indicación Comunitaria
Eficiencia Operacional - Ejemplo

- **Grupo BAJO Riesgo (<5%): Dializados, Diabéticos, etc**
  - **Sin QP menos del 5% harán TB**
  - **Luego, de cada 100 QP sólo se beneficiarían, como mucho, 5**
- **Eficacia Pauta Terapéutica:**
  - **6H: 70% ---> Ya sólo se Beneficiarán 3,5 de las 100 QP (70% de 5)**
- **Adherencia:**
  - **30% ---> Sólo se Beneficiaría 1 por cada 100 QP**

No es Rentable

Tratamento Preventivo de la TB
Indicación Comunitaria
Eficiencia Operacional - Ejemplo

- **Grupo BAJO Riesgo (<5%): Dializados, Diabéticos, etc**
  - *Sin QP menos del 5% harán TB*
  - *Luego, de cada 100 QP sólo se beneficiarían, como mucho, 5*
- **Eficacia Pauta Terapéutica:**
  - *9H: 95% ---> Se Beneficiarán 4,75 de las 100 QP (95% de 5)*
- **Adherencia:**
  - *60% ---> Se Beneficiarían 3 por cada 100 QP--> 1 por 30 QP*

No es muy Rentable

Tratamento Preventivo (QP) de la TB
Indicación Comunitaria
Eficiencia Operacional - Ejemplo

- ***Grupo ALTO Riesgo (30%): Contactos, VIH, Convert.***
  - ***Sin QP harán TB el 30% de los Infectados***
  - ***Luego, de cada 100 QP beneficiarán 30***
- ***Eficacia Pauta Terapéutica:***
  - ***6H: 70% ---> Se Beneficiarán 21 de las 100 QP (70% de 30)***
- ***Adherencia:***
  - ***30% ---> Sólo se Beneficiaría 6,3 por cada 100 QP --> 1 por 15 QP***

Mucho más Rentable

Tratamento Preventivo (QP) de la TB
Indicación Comunitaria
Eficiencia Operacional - Ejemplo

- ***Grupo ALTO Riesgo (30%): Contactos, VIH, Convert.***
  - ***Sin QP harán TB el 30% de los Infectados***
  - ***Luego, de cada 100 QP beneficiarán 30***
- ***Eficacia Pauta Terapéutica:***
  - ***9H: 95% ---> Se Beneficiarán 28,5 de las 100 QP (95% de 30)***
- ***Adherencia:***
  - ***60% ---> Se Beneficiarían 17 por cada 100 QP --> 1 por 5 QP***

Claramente Rentable

Tratamento Preventivo (QP) de la TB
Indicación Comunitaria
Eficiencia Operacional - Ejemplo

- ***Grupo ALTO Riesgo (30%): Contactos, VIH, Convert.***
  - ***Sin QP harán TB el 30% de los Infectados***
  - ***Luego, de cada 100 QP beneficiarán 30***
- ***Eficacia Pauta Terapéutica:***
  - ***6H: 70% ---> Se Beneficiarán 21 de las 100 QP (70% de 30)***
- ***Adherencia:***
  - ***60% ---> Se Beneficiarían 13 por cada 100 QP --> 1 por 8 QP***

Rentable. Realidad Aceptable

Eur Respir J 2011; 37: 690–711
DOI: 10.1183/09031936.00079310

SERIES "UPDATE ON TUBERCULOSIS"
Edited by C. Lange, M. Raviglione, W.W. Yew and G.B. Migliori
Number 5 in this Series

Treatment of latent infection with *Mycobacterium tuberculosis*: update 2010

C.C. Leung*, H.L. Rieder[#,¶], C. Lange[+] and W.W. Yew[§]

ABSTRACT: Much remains unknown about latent infection with *Mycobacterium tuberculosis*. Existing immunodiagnostic tools for this condition have various limitations, most importantly in their ability to predict disease. Randomised controlled trials have established protective efficacy of isoniazid therapy for 6–12 months among non-HIV-infected and HIV-infected subjects. While efficacy may reach 90%, acceptance and adherence to prolonged therapy are less than desired. Rifampicin plus pyrazinamide for 2 months, though efficacious, has been associated with excess hepatotoxicity in non-HIV-infected persons. Isoniazid plus rifampicin for 3 months has proven efficacy, but adverse effects may be more frequent than isoniazid or rifampicin monotherapy. Rifampicin monotherapy for 3–4 months is well tolerated, but efficacy data are currently limited, and concerns remain over possible selection of rifampicin-resistant mutants. For contacts of patients with multidrug-resistant tuberculosis, expert opinions differ on whether to treat with at least two drugs or just a fluoroquinolone, and for how long. With the existing diagnostic and treatment tools, efficacy of preventive therapy does not necessarily translate into field effectiveness. A targeted approach is required to maximise cost-effectiveness. Each geographic region needs to set its own priority after taking into account available scientific data and local circumstances.

Eur Respir J 2011; 37: 690–711

TABLE 6 Randomised controlled latent tuberculosis (TB) infection treatment trials comparing efficacy of isoniazid *versus* other regimens

Lead author [ref.]	Site (year)	TST	Cases/number treated[#]				RR (95% CI)[¶]		
			H	HR	RZ(H)	R	HR	RZ(H)	R
WHALEN [99]	Uganda (1997)	Positive	7/536[§]	9/556	10/462[f]		0.81 (0.30–2.15)	0.60 (0.23–1.57)	
MWINGA [102]	Zambia (1998)	Positive	4/52[##]		2/49[¶¶]			1.88 (0.36–9.83)	
		Negative	14/178[##]		13/173[¶¶]			1.05 (0.51–2.16)	
		Unknown	9/122[##]		10/129[¶¶]			0.95 (0.40–2.26)	
HALSEY [111]	Haiti (1998)	Positive	14/370[##]		19/380[§§]			0.76 (0.39–1.49)	
MARTINEZ [112]	Spain (2000)	Positive	3/21[++]	1/26			3.71 (0.42–33.15)		
		Negative	1/43[++]	1/43			1.00 (0.06–15.48)		
GORDIN [113]	International (2000)	Positive	29/792[++]		28/791[ff]			1.03 (0.62–1.72)	
RIVERO [104]	Spain (2003)	Anergic	3/83[§]	3/82	1/77[ff]		0.99 (0.21–4.75)	0.70 (0.16–3.05)	
RIVERO [114]	Spain (2007)	Positive	4/108[§]	5/103	2/105[ff]		0.76 (0.21–2.76)	1.94 (0.36–10.39)	
GIRLING [73][+]	Hong Kong (1992)	Positive[###]	20/100[§]	19/87		17/103	0.92 (0.52–1.60)		1.21 (0.68–2.18)

TST: tuberculin skin test; RR: risk ratio; H: isoniazid for 6–12 months; HR: isoniazid and rifampicin daily for 3 months; RZ(H): rifampicin plus pyrazinamide or rifampicin plus pyrazinamide plus isoniazid for 2–3 months; R: rifampicin daily for 3 months. [#]: active TB cases within 1–5 yrs of follow-up (variable and with considerable attrition); [¶]: isoniazid *versus* regimen; [+]: non-HIV; [§]: isoniazid daily for 6 months; [f]: isoniazid plus rifampicin plus pyrazinamide daily for 3 months; [##]: isoniazid twice weekly for 6 months; [¶¶]: rifampicin plus pyrazinamide twice weekly for 3 months; [++]: isoniazid daily for 12 months; [§§]: rifampicin plus pyrazinamide twice weekly for 2 months; [ff]: rifampicin plus pyrazinamide daily for 2 months; [###]: mainly TST-positive.

TABLE 8 Comparison of serious adverse effects between isoniazid and alternative regimens in randomised trials reported after 1990

Lead author [ref.]	Site (year)	Cases/number treated[#]				RR (95% CI)[¶]		
		H	HR	RZ(H)	R	HR	RZ(H)	R
HIV-infected								
Whalen [99]	Uganda (1997)	3/536[§]	13/556[f]	26/462[##]		0.24 (0.07–0.84)	0.10 (0.03–0.33)	
Mwinga [102]	Zambia (1998)	12/352[¶¶]		14/351[++]			0.85 (0.40–1.82)	
Rivero [104]	Spain (2003)	6/83[§]	15/82[f]	13/77[§§]		0.40 (0.16–0.97)	0.43 (0.17–1.07)	
Halsey [111]	Haiti (1998)	0/370[¶¶]		0/380[ff]			0.0 (0.0–0.0)	
Martinez [112]	Spain (2000)	15/64[###]	5/69[f]				3.23 (1.25–8.39)	
Gordin [113]	International (2000)	48/792[###]		75/791[§§]			0.64 (0.45–0.91)	
Rivero [114]	Spain (2007)	7/108[§]	7/103[f]	12/105[§§]		0.95 (0.35–2.62)	0.57 (0.23–1.38)	
Non-HIV infected								
Girling [73]	Hong Kong (1992)	13/173[§]	11/167[f]		7/172[¶¶¶]	1.14 (0.51–2.55)		1.85 (0.74–4.63)
Jasmer [115][+]	USA (2002)	8/282[§]		28/307[§§]			0.31 (0.14–0.68)	
Leung [116]	Hong Kong (2003)	2/36[§]		14/40[§§]			0.16 (0.04–0.70)	
Tortajada [117]	Spain (2005)	8/159[§]		19/133[§§]			0.35 (0.15–0.80)	
Spyridis [118] (children)	Greece (2007)	0/232[+++]	0/694[§§§]					0.0 (0.0–0.00)
Geijo [119]	Spain (2007)	4/45[§]	2/51[f]					2.27 (0.42–12.38)
Menzies [120]	Canada (2004)	8/58[+++]			2/58[fff]			4.00 (0.85–18.64)
Menzies [121]	International (2008)	16/427[+++]			7/420[fff]			2.25 (0.92–5.46)

RR: relative risk; H: isoniazid for 6–12 months; HR: isoniazid plus rifampicin daily for 3–4 months; RZ(H): rifampicin plus pyrazinamide or rifampicin plus pyrazinamide plus isoniazid for 2–3 months; R: rifampicin daily for 3–4 months. [#]: adverse events leading to termination of treatment; [¶]: isoniazid *versus* regimen; [+]: systematic, rather than randomised, allocation of subjects (by alternate week); [§]: isoniazid daily for 6 months; [f]: isoniazid plus rifampicin daily for 3 months; [##]: isoniazid plus rifampicin plus pyrazinamide daily for 3 months; [¶¶]: isoniazid twice weekly for 6 months; [++]: rifampicin plus pyrazinamide twice weekly for 3 months; [§§]: rifampicin plus pyrazinamide daily for 2 months; [ff]: rifampicin plus pyrazinamide twice weekly for 2 months; [###]: isoniazid daily for 12 months; [¶¶¶]: rifampicin daily for 3 months; [+++]: isoniazid daily for 9 months; [§§§]: isoniazid plus rifampicin daily for 3–4 months; [fff]: rifampicin daily for 4 months.

Tratamiento Preventivo de la TB
Conclusiones

- ***Importante la adecuada selección de los casos***

- ***INDICACIONES:***
  - ***Contactos y Convertores Recientes***
  - ***VIH (especialmente PPD+)***
  - ***TB Residual, tto.con Infliximab…(individualizada)***
- ***PAUTA TERAPÉUTICA:***
  - ***Preferible: 9H***
  - ***Al menos 6H***
- ***ADHERENCIA:***
  - ***Garantizar un Mínimo del 60%***

Quedan Retos en la implementación y questiones abiertas

A. ¿Cómo **descartar con certeza TB activa (y prevenir resistencias) especialmente en VIH**?

B. ¿que hacer despues, vista la breve **duración de la protección** de la QP en VIH?

C. ¿Como **garantizar la adherencia** a la QP y el **seguimiento** de lo enfermos?

D. ¿ Que QP en los contactos de **TB-MDR?**

Gracias!

Agradecimientos al Pr.José Caminero (La Union)

Contactos TB con Resistencia a H+R

Quien es la fuente de la infección (Susceptible o MDR ?)

1. Infección con M. TB resistente a INH y RIF?
2. Infección con M. TB de otra fuente hace mucho tiempo?
3. Infección con M. TB de otra fuente después del contacto con pacientes con TB MDR?
4. La infección con M. TB viene del contacto, pero durante el tiempo en el cual los bacilos aun no eran resistentes?
5. Probabilidad de re-infección?

Tasas de TB-MDR en los contactos con enfermos con TB-MDR

Study	*Country*	*Number of contacts*	*Percentage of patients with MDR-TB (# of TB case/total # with active TB)*
Kritski et al. (1996)	*Brazil*	*218*	***62%*** *(8/13)*
Schaaf et al. (2000)	*South Africa*	*149*	***83%*** *(5/6)*
Texeira et al. (2001)	*Brazil*	*133*	***83%*** *(5/6)*
Schaaf et al. (2002)	*South Africa*	*119*	***75%*** *(3/4)*
Bayona et al (2003)	*Peru*	*945*	***84%*** *(35/42)*

Contactos TB con Resistencia a H+R
Qué régimen quimioprofilactico?

- ***INH 6-9 meses?***
- ***INH + RIF 3 meses?***
- ***6 - 12 meses Z + E o Z + Quinolona (Ofl. ó Levof)***

(ATS/CDC. Am J Respir Crit Care Med 2000; 161).Pero poco tolerado:hepatotoxicidad (Horn,NEJM1994).

- **INH alta dose + Z + Eth / +-Ofx +- E**

(alguna experiencia en Sudafrica – Schaaf, 2002; regimenes individualizados eficaces)

Contactos TB con Resistencia a H+R

-NO HAY EVIDENCIAS PARA RECOMENDAR QUEMIOPROFILAXIS CON DROGAS DE SEGUNDA LINEA A LOS CONTACTOS CON TB-MDR; SOLO SUPERVISION ESTRECHA (por lo menos 2 anos)

-Sin embargo, hay experiencias positivas con quemioprofilaxis con FQ + Eth o Ethio o PZA en ninos

WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008

BOX 5. Factors affecting treatment decisions during the medical and diagnostic evaluation, by tuberculin skin test (TST) result

TST result ≥5 mm is positive	TST result ≥10 mm is positive	TST result ≥15 mm is positive*
• Persons infected with HIV†	• Recent immigrants (i.e., within the previous 5 years) from countries with a high incidence of TB disease	• Persons with no known risk factors for TB disease
• Recent contacts of a person with tuberculosis (TB) disease	• Persons who inject illicit drugs	• HCWs who are otherwise at low risk for TB disease and who received baseline testing at the beginning of employment as part of a TB screening program**
• Persons with fibrotic changes on chest radiograph consistent with previous TB disease	• Residents and employees (including health-care workers [HCWs])** of the following congregate settings — hospitals and other health-care facilities — long-term–care facilities (e.g., hospices and skilled nursing facilities) — residential facilities for patients with AIDS†† or other immunocompromising conditions — correctional facilities — homeless shelters	
• Organ transplant recipients and other immunosuppressed persons (e.g., persons receiving ≥15 mg/day of prednisone for ≥1 month)§	• Mycobacteriology laboratory personnel	
• TB suspects¶	• Persons with any of the following clinical conditions or immunocompromising conditions that place them at high risk for TB disease — diabetes mellitus — silicosis — chronic renal failure — certain hematologic disorders (e.g., leukemias and lymphomas) — other specific malignancies (e.g., carcinoma of the head, neck, or lung) — unexplained weight loss of ≥10% of ideal body weight — gastrectomy — jejunoileal bypass	
	• Persons living in areas with high incidence of TB disease	
	• Children aged <4 years	
	• Infants, children, and adolescents exposed to adults at high risk for developing TB disease	
	• Locally identified groups at high risk	

* TST results ≥15 mm is positive in anyone. These persons should receive a symptom screen and do not need be tested again. They should be evaluated for TB disease, and if disease is excluded, they should be offered treatment for latent TB infection (LTBI) if they have no contraindication to treatment.
† Human immunodeficiency virus.
§ The risk for TB disease in persons treated with corticosteroids increases with higher doses and longer duration of corticosteroid use.
¶ Persons with suspected TB disease can be treated based on the medical and diagnostic evaluation, regardless of the TST results.
** For HCWs who are otherwise at low risk for LTBI and progression to TB disease if infected and who received baseline testing at the beginning of employment as part of a TB infection-control screening program, a TST result of ≥15 mm (instead of ≥10 m
on baseline or follow-up testing is considered a positive result for HCWs for the purposes of refe
10–14 mm on baseline or follow-up testing, the referring clinician might not recommend treatm
Utility of dual skin tests to evaluate tuberculin skin test reactions of 10 to 14 mm in health-car
†† Acquired immunodeficiency syndrome.

Centers for Disease Control and Prevention. Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005. MMWR 2005;54(No. RR-17):

Table A1.1 Causes of false-negative and false-positive tuberculin skin tests (TSTs)

Causes of false-negative TST	Causes of false-positive TST
Incorrect administration or interpretation of test	Incorrect interpretation of test
HIV infection	BCG vaccination
Improper storage of tuberculin	Infection with nontuberculous mycobacteria
Viral infections (e.g. measles, varicella)	
Vaccinated with live viral vaccines (within 6 weeks)	
Malnutrition	
Bacterial infections (e.g. typhoid, leprosy, pertussis)	
Immunosuppressive medications (e.g. corticosteroids)	
Neonatal patient	
Primary immunodeficiencies	
Diseases of lymphoid tissue (e.g. Hodgkin disease, lymphoma, leukaemia, sarcoidosis)	
Low protein states	
Severe TB	