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International Union Against Tuberculosis and Lung Disease

Health solutions for the poor

La tuberculosis que no tose y mata.

Retos en el diagnóstico y manejo de la TB diseminada en el paciente infectado por VIH en el trópico

TUBERCULOSIS responsable de un tercio de las muertes en la PVVIH

Ignacio Monedero MD, MPH, PhD

MDR-TB Unit / TB-HIV department

Unión Internacional contra la Tuberculosis y enfermedades respiratorias

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H, PhD

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MSF.UK

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Indice

1. Patogénesis y la presentación clínica de la tuberculosis diseminada
2. Diagnóstico
3. Tratamiento
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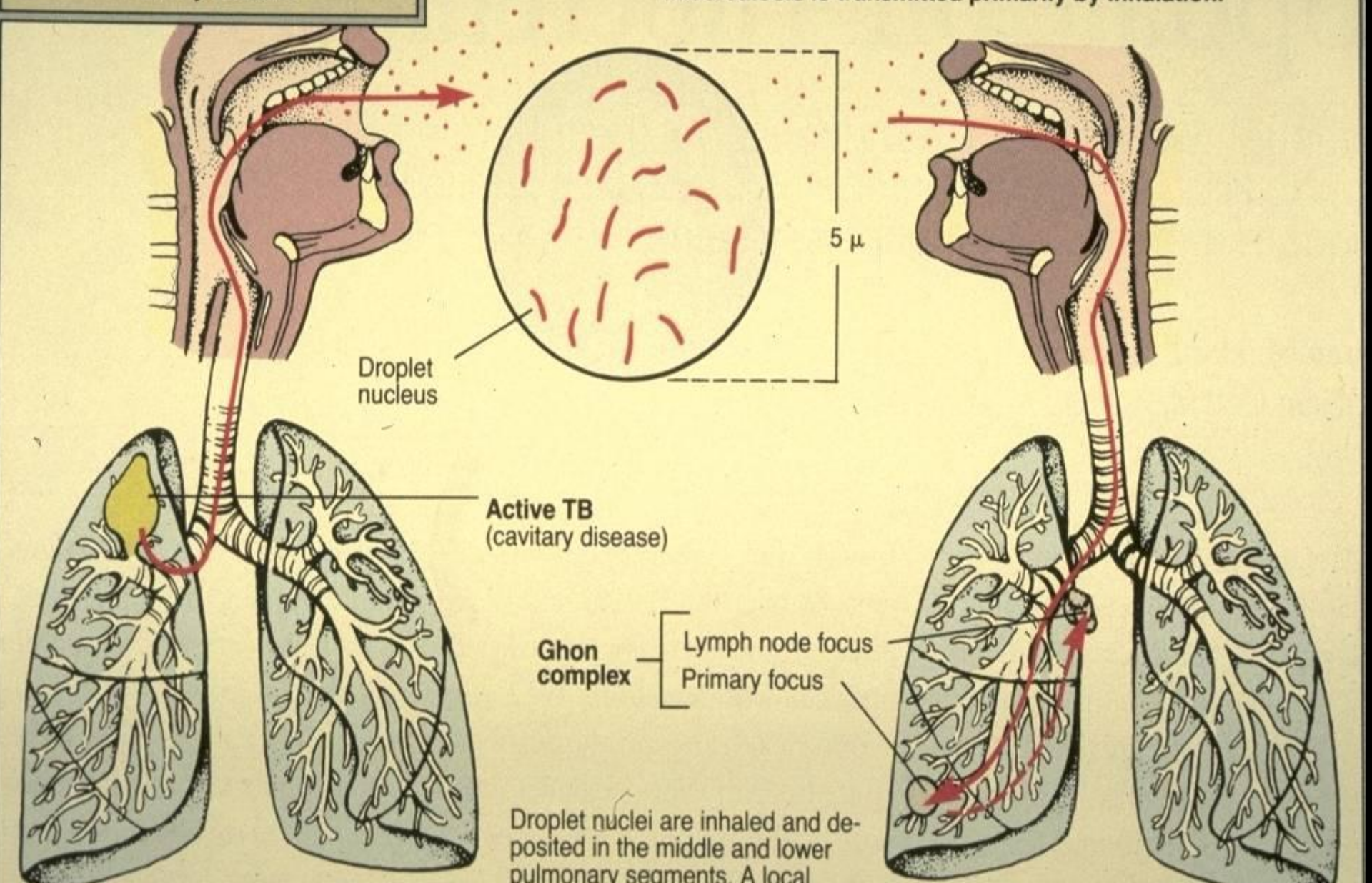
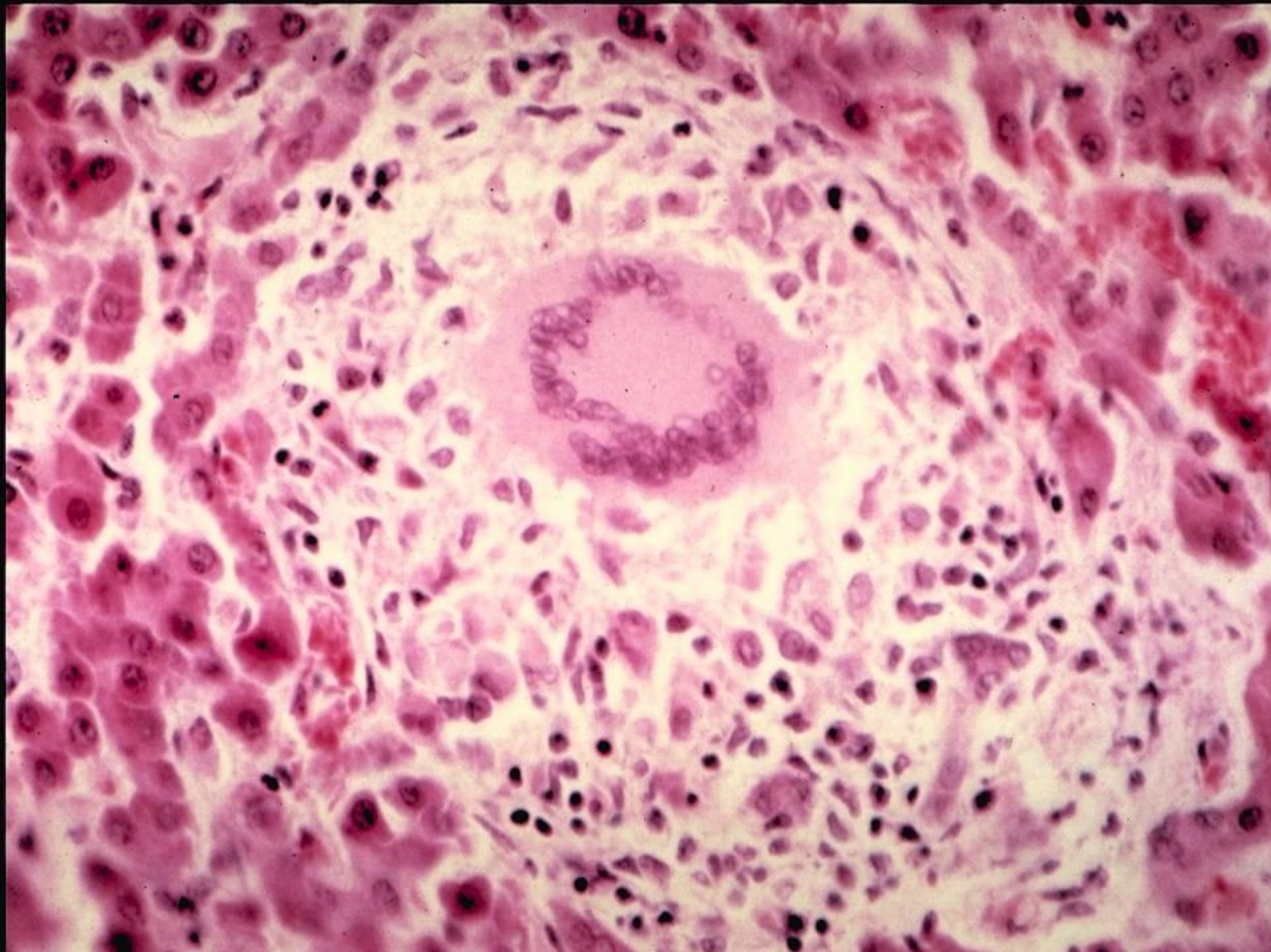
PATHOGENESIS OF TUBERCULOSIS

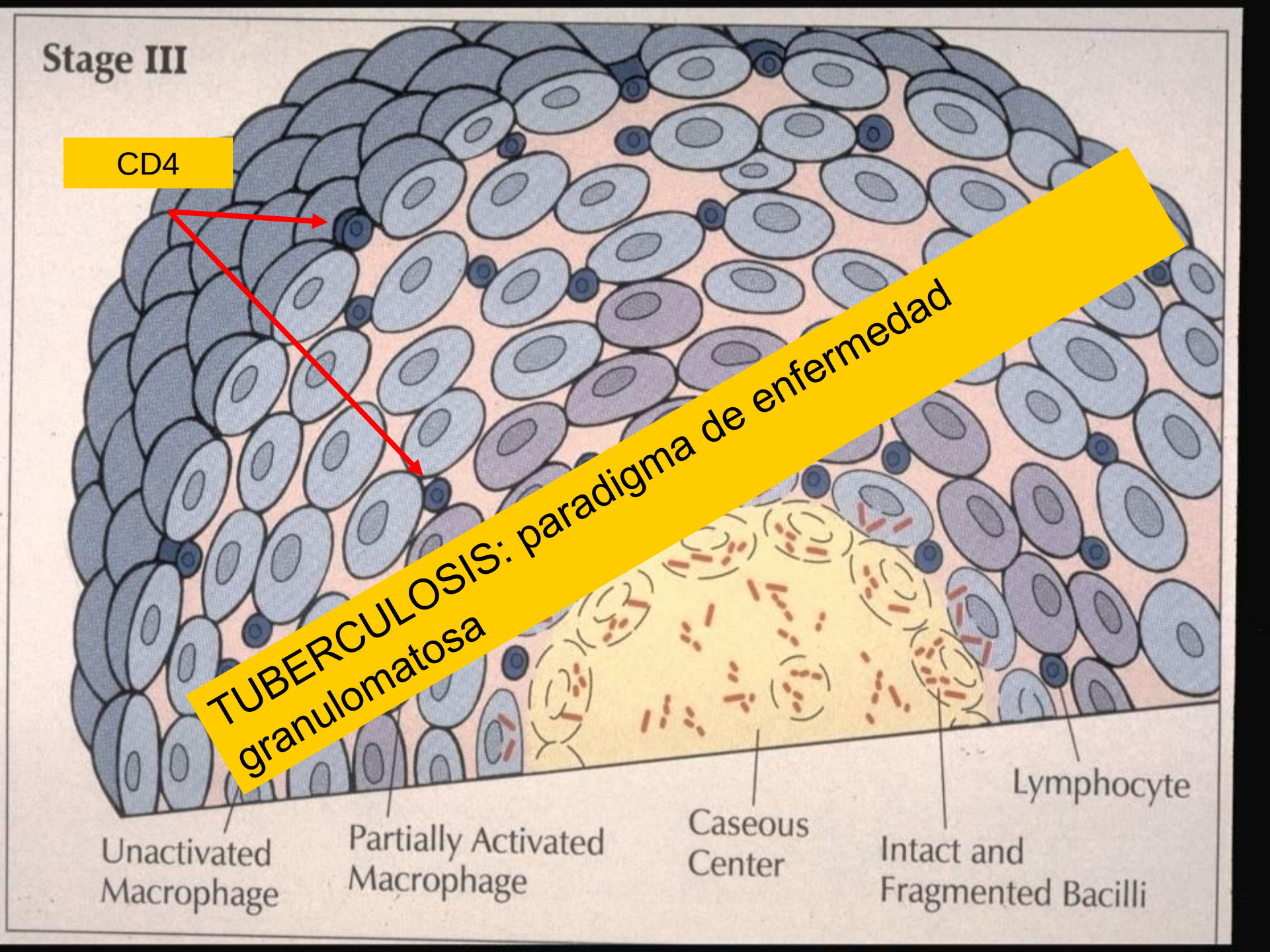
Primary disease

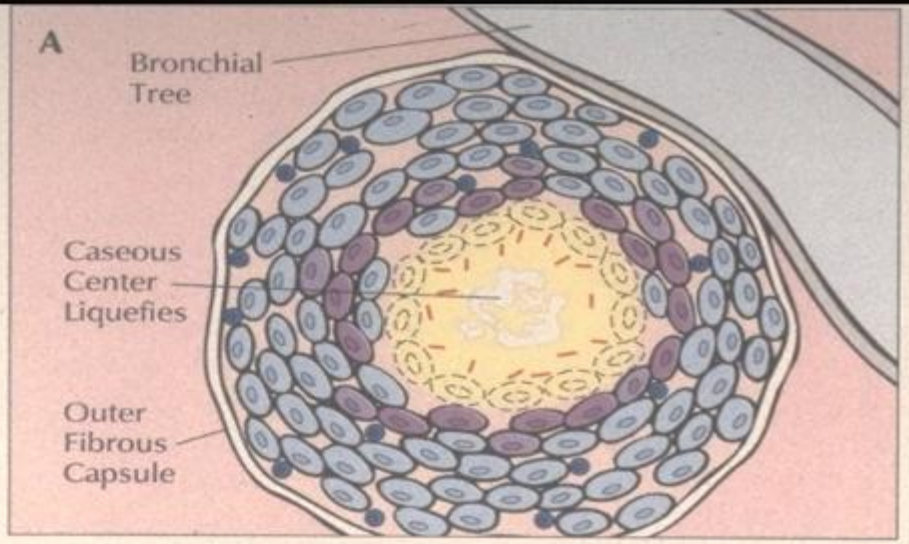
Tuberculosis is transmitted primarily by inhalation.

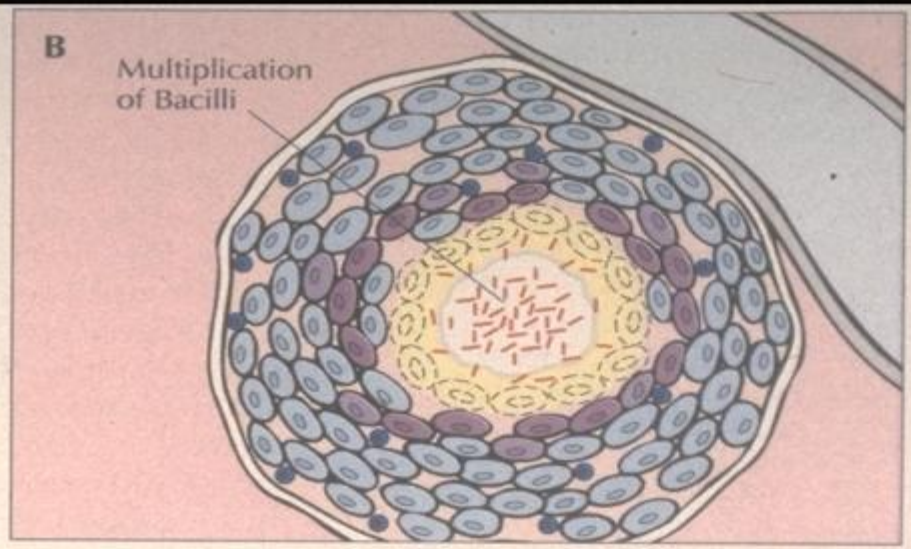


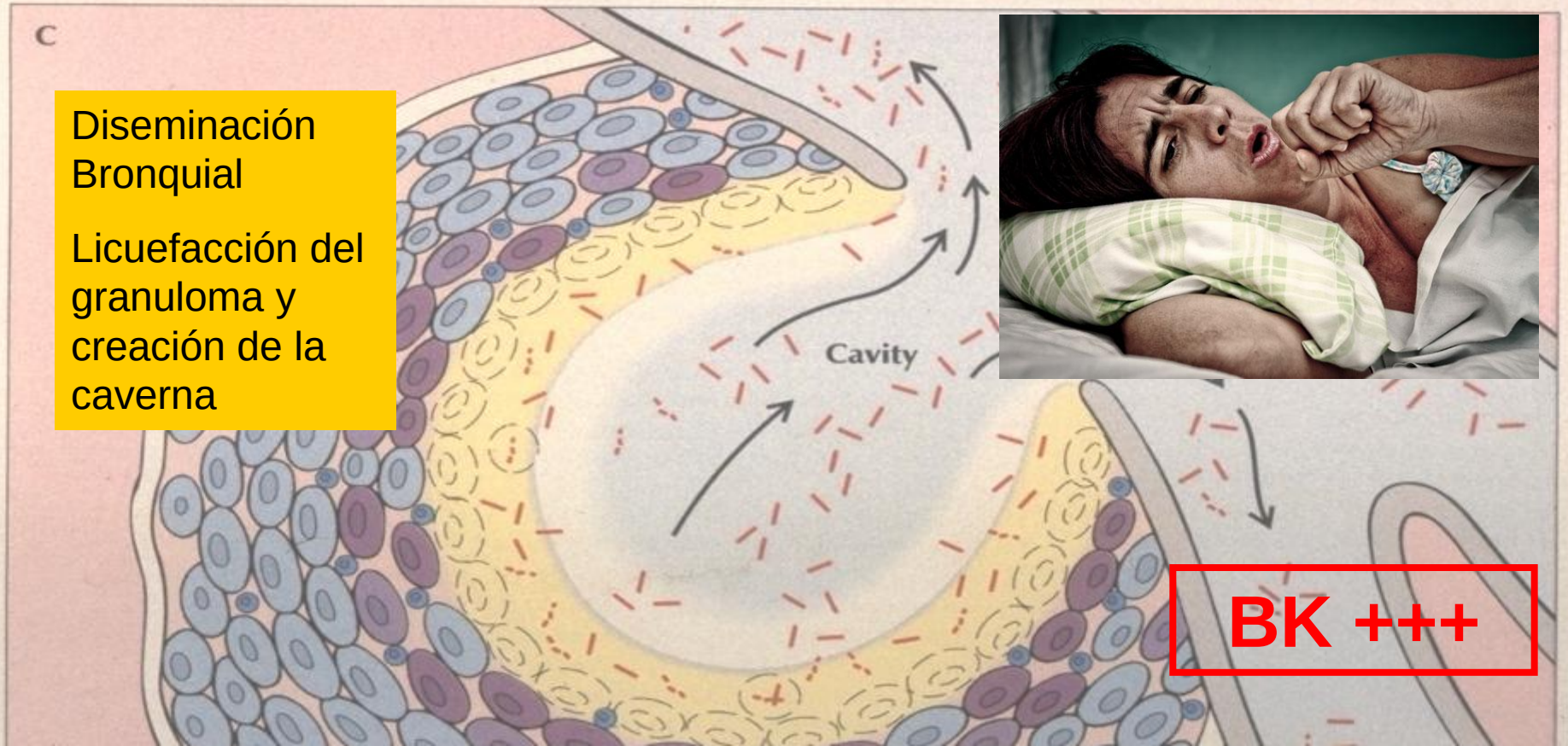
Droplet nuclei are inhaled and deposited in the middle and lower pulmonary segments. A local




Stage III
CD4
TUBERCULOSIS: paradigma de enfermedad granulomatosa
Unactivated Macrophage
Partially Activated Macrophage
Caseous Center
Intact and Fragmented Bacilli
Lymphocyte



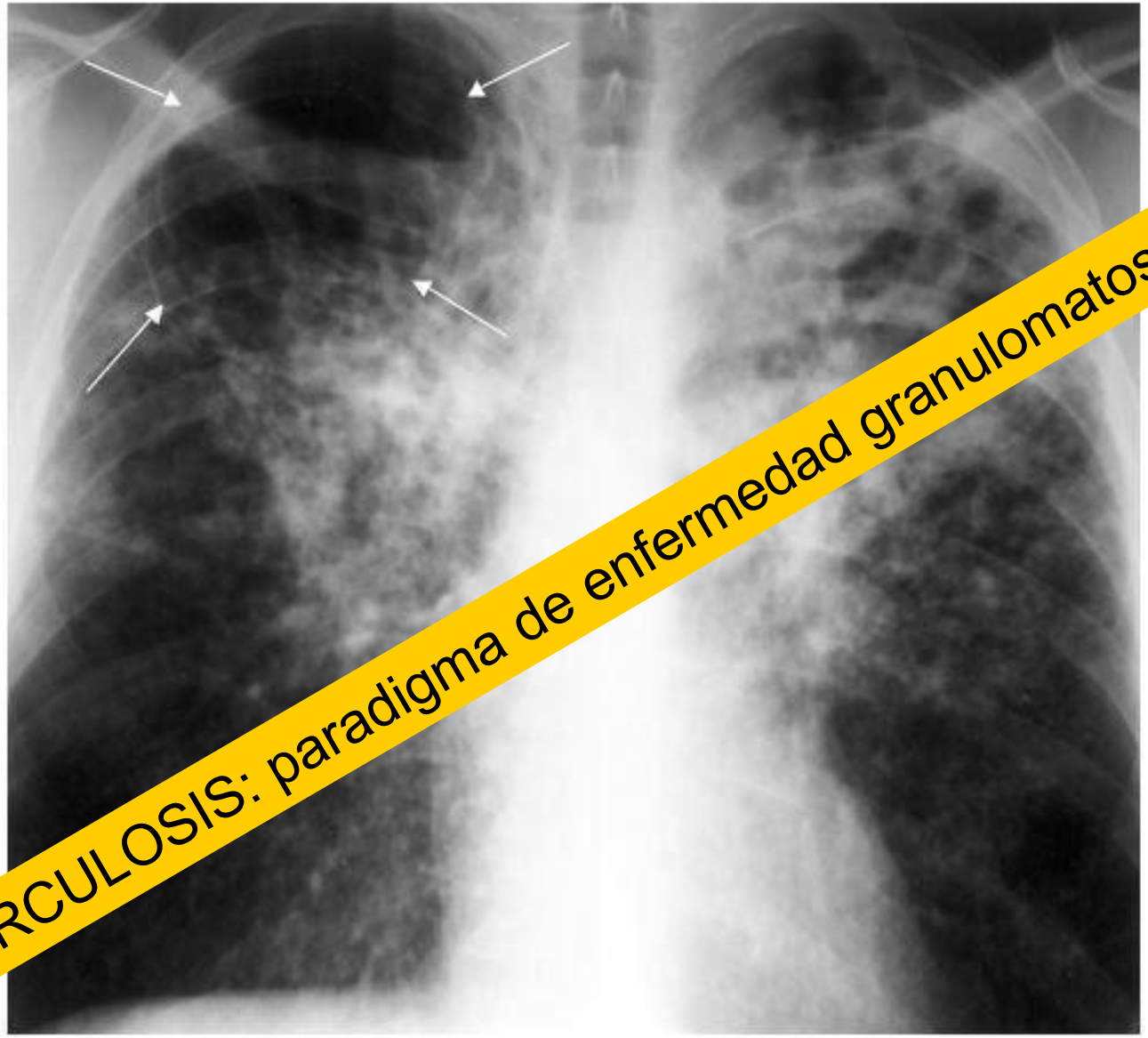




Diseminación Bronquial

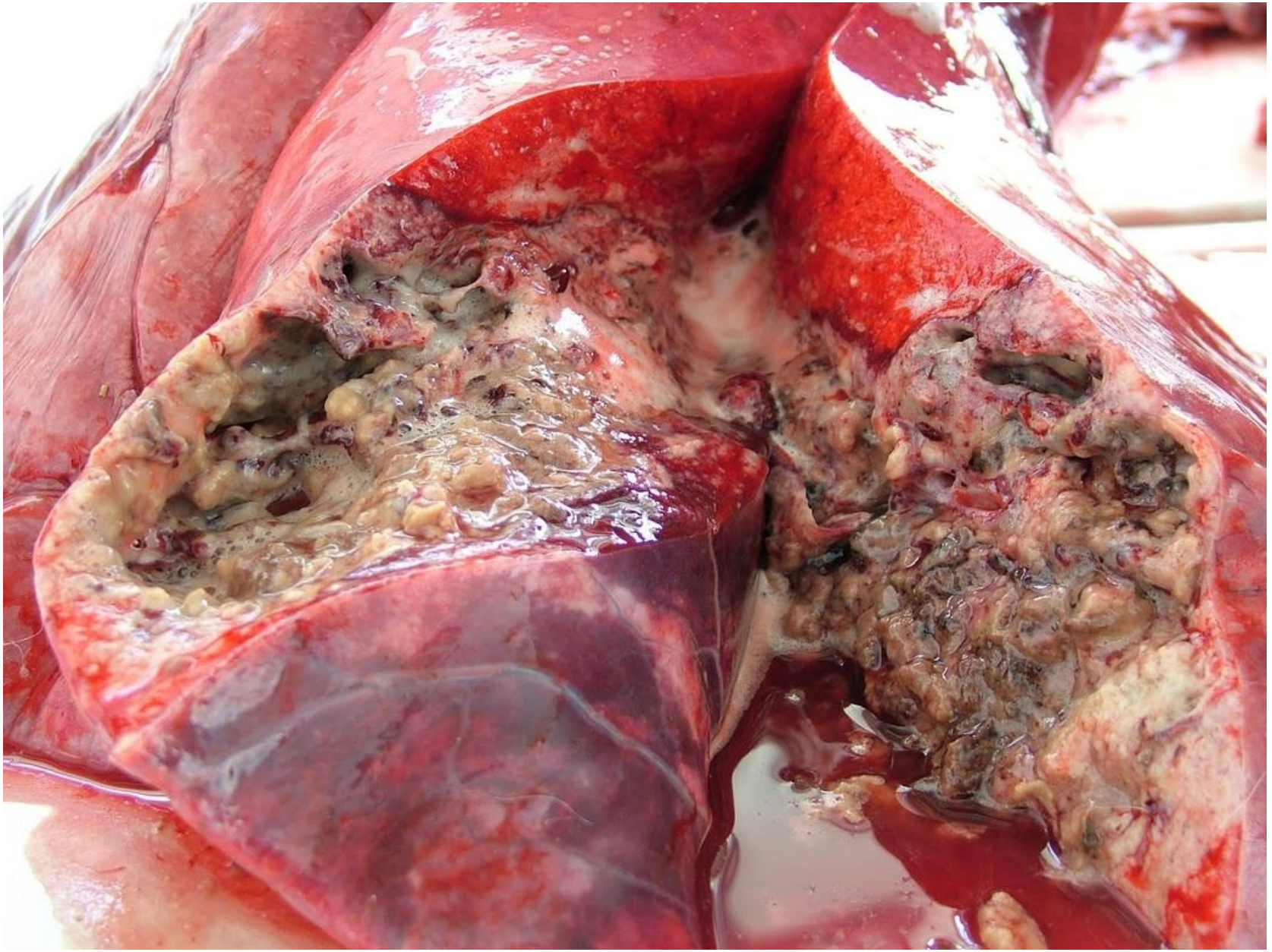
Licuefacción del granuloma y creación de la caverna

BK +++



TUBERCULOSIS: paradigma de enfermedad granulomatosa

Figure 8. Chest x-ray with bilateral upper lobe opacities (white areas) with multiple cavities including a very large cavity in the right upper lobe (arrows).



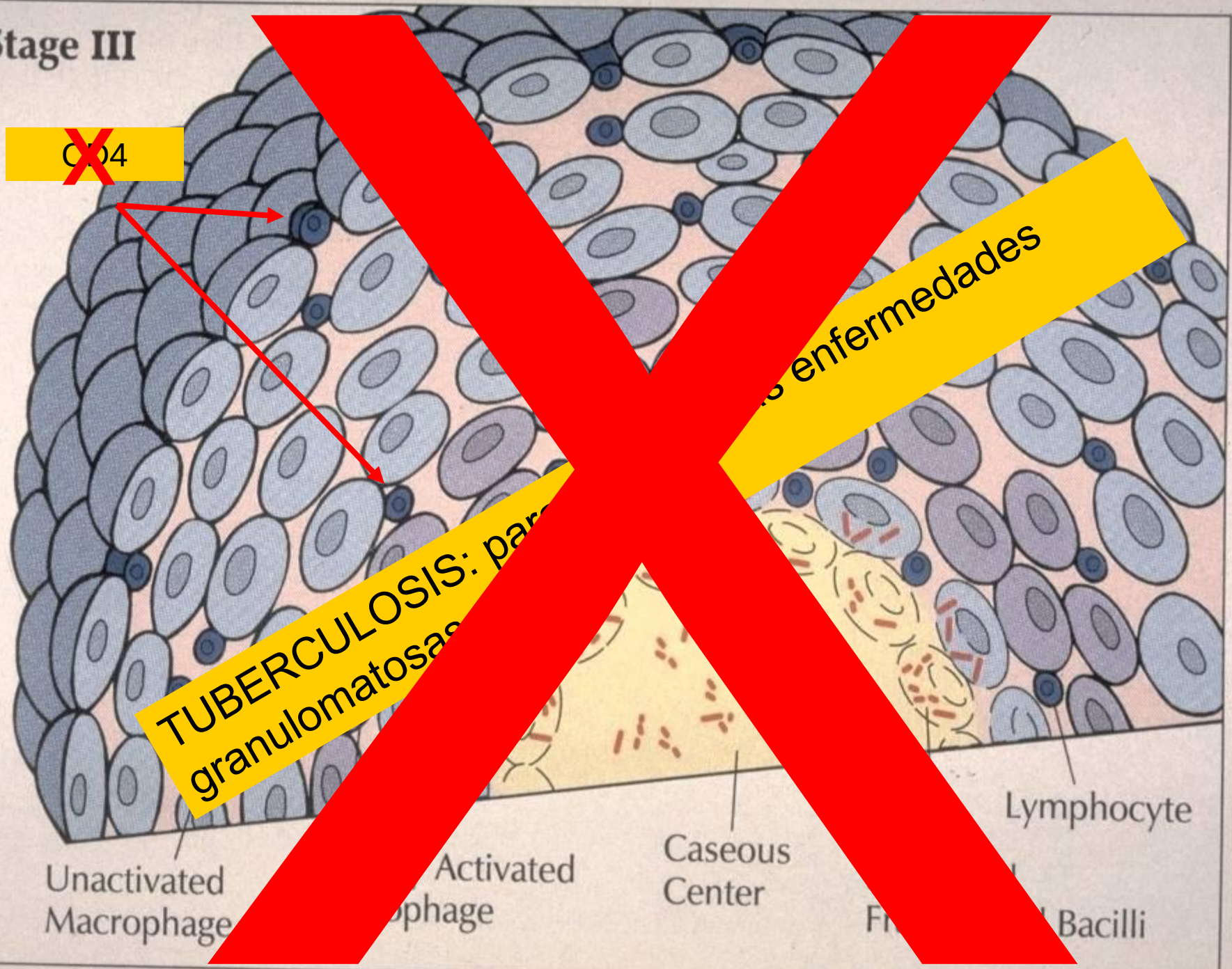
Acción del VIH sobre la inmunidad

- Diana de unión es el receptor CD4
- Parasita y destruye al Linfocito T CD4
- Por lo tanto no
  - Activación del macrófago y del LT CD8
  - Activación del Linfo B: Ig
  - Activación al NK
  - No libera citokinas: activa el complemento
  - No se activan otros sistemas

- Parasita y destruye macrófago
  - Primera línea de defensa contra enfermedades comunes

Cuando la inmunidad cae por debajo de 350 CD4…

- Margen de riesgo de TB
  - Nueva infección,
  - reinfección
  - o reactivación infección previa
- VIH mayor factor de riesgo de TB hasta la actualidad
- Progresión de la TB más rápida y más mortal
- TB primera causa de muerte en el paciente VIH
  - **Muertes por TB no percividas**


Stage III
CD4
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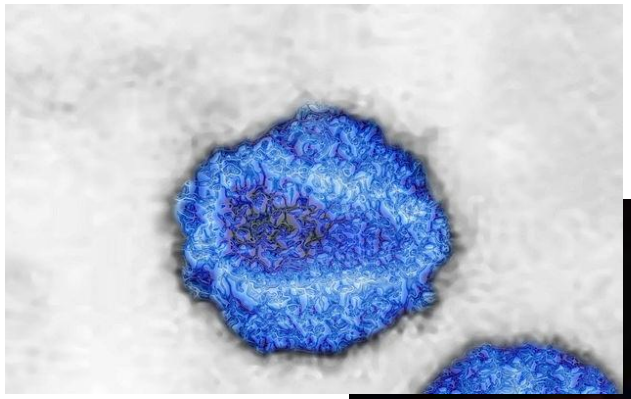
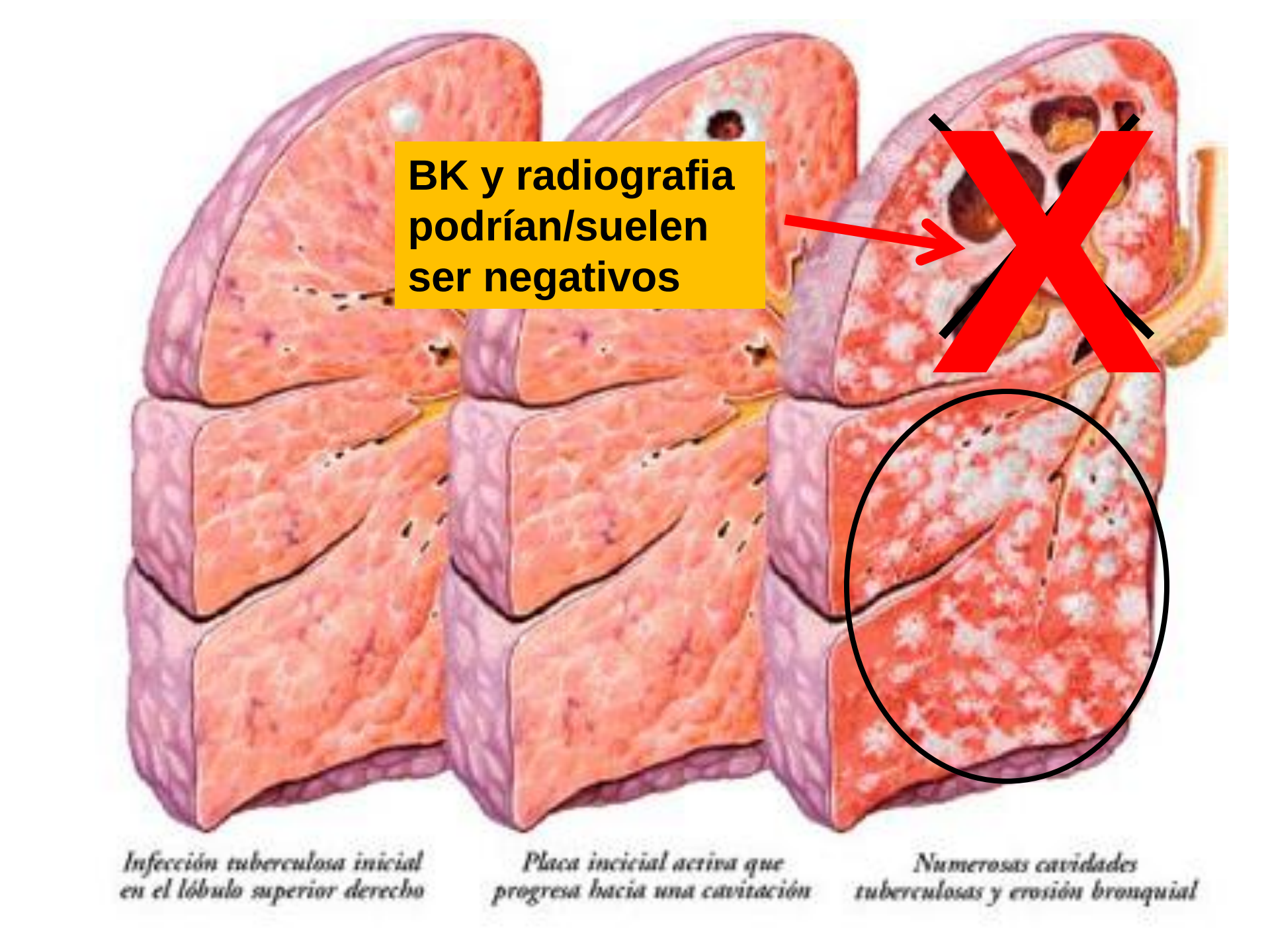
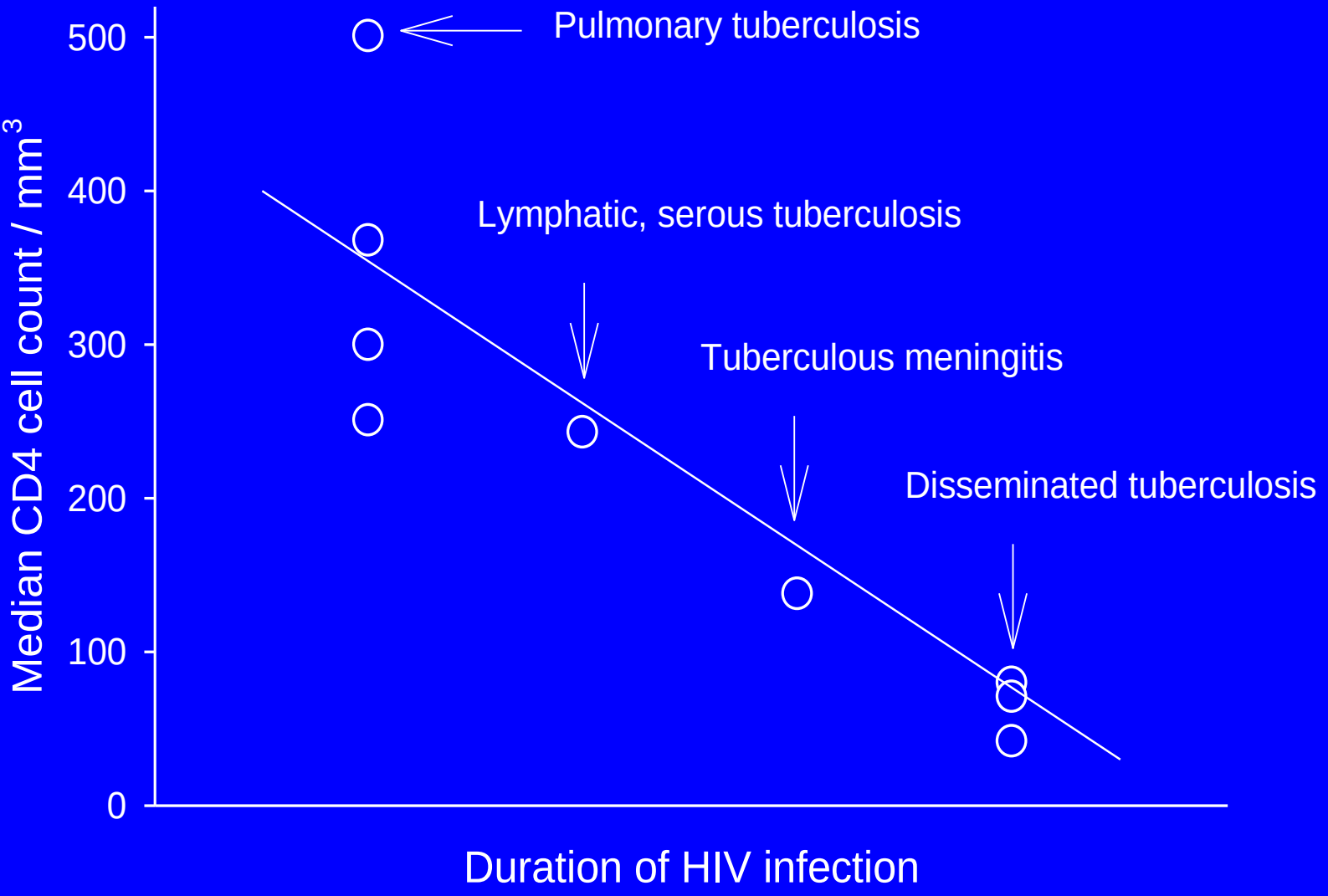
TUBERCULOSIS: par
granulomatosas
Unactivated
Macrophage
Activated
phage
Caseous
Center
Lymphocyte
Bacilli



¿ADÓNDE ESTÁ LOS BKs?


BK y radiografia podrían/suelen ser negativos
Infección tuberculosa inicial en el lóbulo superior derecho
Placa incicial activa que progresa hacia una cavitación
Numerosas cavidades tuberculosas y erosión bronquial

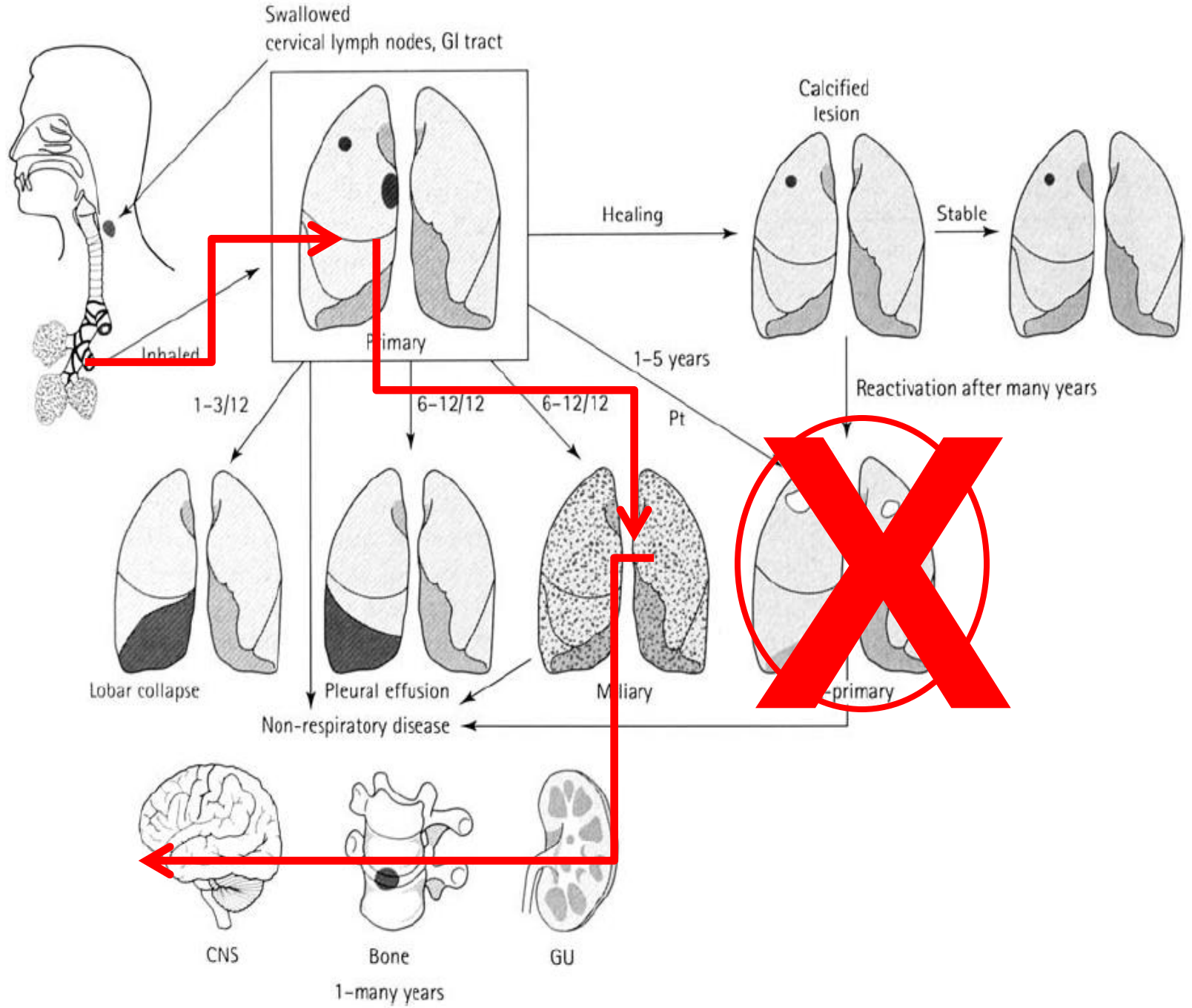
Correlation Between Extent of HIV-Induced Immuno-Suppression and Clinical Manifestation of Tuberculosis



De Cock KM, et al. J Am Med Assoc 1992;268:1581-7

Tuberculosis Post primaria

- Reactivación
  - Escape de bacilos desde el granuloma
  - Granuloma se convierte en una cavidad
- Difusión bronquial
  - Presentación TB Clásica: cavidades multiples y siembra broncogena
- **Difusión Hematógena (TB atípica)**
  - TB miliar, derrame pleural
  - TB extrapulmonar:, hepatitis, meníngea, la ocupación de la médula ósea renal
  - TB diseminada o Septicemia TB: cuadros fulminantes, asociada al VIH


Swallowed
cervical lymph nodes, GI tract
Calcified
lesion
Healing
Stable
Inhaled
Primary
1–5 years
Reactivation after many years
1–3/12
6–12/12
6–12/12
Pt
Lobar collapse
Pleural effusion
Miliary
-primary
Non-respiratory disease
CNS
Bone
GU
1–many years

	<50 CD4	>500 CD4
CULTIVO	+	+
ESPUTO	-	+
RADIOGRAFIA DE TORAX	-	+

Radiografia de torax y esputo son muy poco sensibles para descartar TB pulmonar en el enfermo con avanzada inmunodepresión

Varios estudios post mortem de África Subsahariana han demostrado que el 50% de los pacientes VIH fallecidos presentaban TB

Una consideración impo... en la TB extrapulm...

La enfermedad se ... era leve debido a la b... ga bacilar

hay a... nes en el estado inmune?

...ia común, extrapulmonar es igual a menos grave

A menudo, diagnóstico es más difícil, se retrasa, la enfermedad más avanzada ...

Guinea Ecuatorial 2005

Del diagnóstico de la TB en el VIH → a la probabilidad de TB/VIH

- Los casos más severo de TB/VIH y con mayor probabilidad de morir a corto plazo son:
  - Radiografía de tórax negativo
  - Esputo negativo
  - Síntomas atípicos
  - Cultivo no disponible

- Lo siento
  - Creo que usted tiene TB
  - Pero todos los resultados son negativos, no tiene TB
- El paciente no vuelve nunca
  - Muerto? Frecuente según los estudios post-morten
  - TB pulmonar activa asintomática
  - Screening: síntomas + esputo inducido o concentrado

INT J TUBERC LUNG DIS 15(4):459–464
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doi:10.5588/ijtld.10.0353

Enhanced tuberculosis identification through 1-month follow-up of smear-negative tuberculosis suspects

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SUMMARY

SETTING: Bandim Health Project, Bissau, Guinea-Bissau.

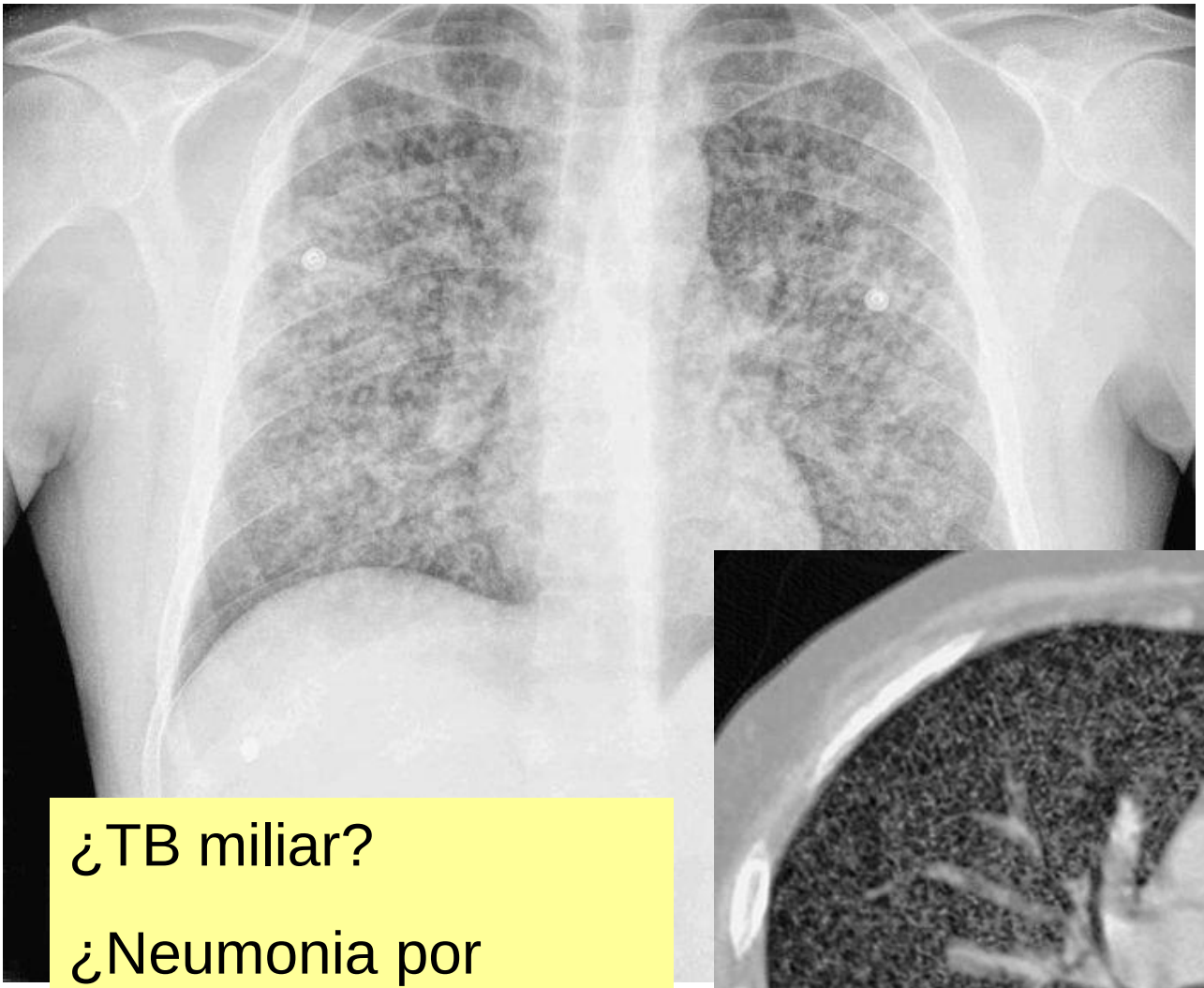
OBJECTIVE: To conduct tuberculosis (TB) screening among former TB suspects in whom TB had been ruled out on initial consultation and therefore assumed to be TB-negative (aTBneg).

DESIGN: In a cohort follow-up study, 'aTBneg suspects' were screened for symptoms from 1 month after the initial negative sputum smear examination. Symptomatic individuals were referred for clinical re-examination and human immunodeficiency virus (HIV) testing.

RESULTS: Among 428 TB suspects presenting over a 10-month period in 2007, 80% (343) were smear-negative. Of these, 21 were subsequently diagnosed with smear-negative TB. Of the remaining 322 aTBneg patients, 212 were followed up and symptoms were examined ⩾1 month after initial examination. Among followed up patients, 89 (42%) were still symptomatic: five were diagnosed with TB on the basis of repeated sputum smears and chest X-ray. Of 44 symptomatic patients, 39% (n = 17) were HIV-infected. Thirteen (4%) of the 322 aTBneg suspects died before follow-up.

CONCLUSION: A large proportion of aTBneg patients remained symptomatic after 1 month. Several TB cases had initially not been diagnosed, and HIV infection was highly prevalent. aTBneg suspects have a high mortality rate and need increased attention from both TB and HIV programmes.

KEY WORDS: tuberculosis suspects; active case finding; HIV; Guinea-Bissau



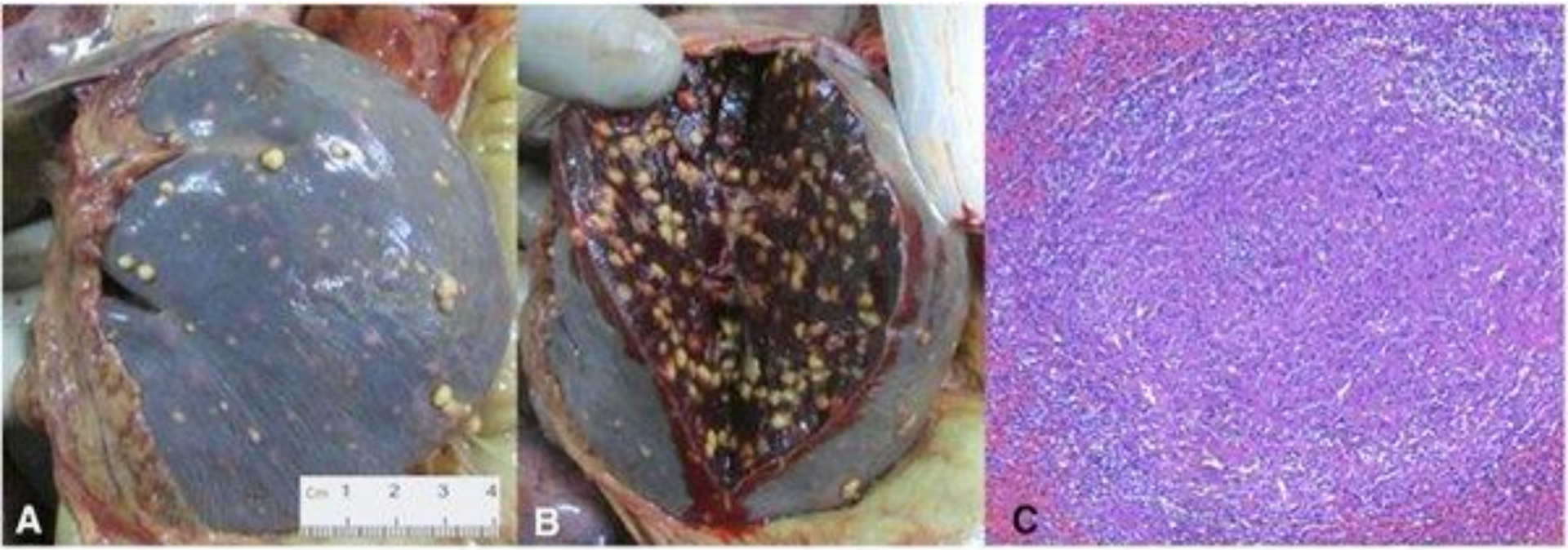
¿TB miliar?

¿Neumonia por Pneumocistis?

¿Neumonia atípica?

¿Otro?

Bazo en granada



TB diseminada

- Todo a la vez
  - Tuberculosis miliar: insuficiencia respiratoria
  - TB hepática: colestasis hepática / toxicidades!
  - Médula ósea TB: pancitopenia
  - TB neurológica: confusión, etc
- Alta carga bacilar?
  - Todo el cuerpo es invadido
  - Probabilidad de amplificación de la resistencia?
  - Alto riesgo de recaídas si el tratamiento es corto?
- Alto riesgo de muerte si no se diagnostica y no se trata a tiempo

Diagnóstico TB diseminada

Retos diagnósticos en paises de escasos recuros

- Síntomas clínicos
  - Tos, perdida de peso, sudoración nocturna, fiebre
  - Síntomas de TB de otra localización
- Esputo, cultivo
- Rx de torax
- Xpert
- TB-LAM
- En un futuro proximo
  - TB-LAMP: un nuevo tipo de “PCR”
  - Whole genome sequencing
  - Omnic science

Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

Timothy E Sweeney, Lindsay Braviak, Cristina M Tato, Purvesh Khatri

Summary

Background Active pulmonary tuberculosis is difficult to diagnose and treatment response is difficult to effectively monitor. A WHO consensus statement has called for new non-sputum diagnostics. The aim of this study was to use an integrated multicohort analysis of samples from publically available datasets to derive a diagnostic gene set in the peripheral blood of patients with active tuberculosis.

Methods We searched two public gene expression microarray repositories and retained datasets that examined clinical cohorts of active pulmonary tuberculosis infection in whole blood. We compared gene expression in patients with either latent tuberculosis or other diseases versus patients with active tuberculosis using our validated multicohort analysis framework. Three datasets were used as discovery datasets and meta-analytical methods were used to assess gene effects in these cohorts. We then validated the diagnostic capacity of the three gene set in the remaining 11 datasets.

Findings A total of 14 datasets containing 2572 samples from 10 countries from both adult and paediatric patients were included in the analysis. Of these, three datasets (N=1023) were used to discover a set of three genes (*GBP5*, *DUSP3*, and *KLF2*) that are highly diagnostic for active tuberculosis. We validated the diagnostic power of the three gene set to separate active tuberculosis from healthy controls (global area under the ROC curve (AUC) 0·90), latent tuberculosis (global AUC 0·88), and other diseases (global AUC 0·84) in eight independent datasets composed of both children and adults from ten countries. Expression of the three-gene set was not confounded by HIV infection status, bacterial drug resistance, or BCG vaccination. Furthermore, in four additional cohorts, we showed that the tuberculosis score declined during treatment of patients with active tuberculosis.

Interpretation Overall, our integrated multicohort analysis yielded a three-gene set in whole blood that is robustly diagnostic for active tuberculosis, that was validated in multiple independent cohorts, and that has potential clinical application for diagnosis and monitoring treatment response. Prospective laboratory validation will be required before it can be used in a clinical setting.

Lancet Respir Med 2016

Published Online
February 19, 2016
http://dx.doi.org/10.1016/S2213-2600(16)00048-5

See Online/Comment
http://dx.doi.org/10.1016/PII

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Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

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Abstract

Background: The World Health Organization recommends the screening of all people living with HIV fo disease, followed by TB treatment, or isoniazid preventive therapy (IPT) when TB is excluded. Howeve reliably excluding TB disease has severely limited TB screening and IPT uptake in resource-limited settings. individual participant data meta-analysis of primary studies, aiming to identify a sensitive TB screening

Methods and Findings: We identified 12 studies that had systematically collected sputum specimens reg symptoms, at least one mycobacterial culture, clinical symptoms, and HIV and TB disease status. Bivaria meta-analysis and the hierarchical summary relative operating characteristic curves were used to evalu performance of all combinations of variables of interest. TB disease was diagnosed in 557 (5.8%) of 9,626 HIV. The primary analysis included 8,148 people living with HIV who could be evaluated on five symptom 12 studies. The median age was 34 years. The best performing rule was the presence of any one of: c duration), fever, night sweats, or weight loss. The overall sensitivity of this rule was 78.9% (95% confi 58.3%–90.9%) and specificity was 49.6% (95% CI 29.2%–70.1%). Its sensitivity increased to 90.1% (95% among participants selected from clinical settings and to 88.0% (95% CI 76.1%–94.4%) among tho previously screened for TB. Negative predictive value was 97.7% (95% CI 97.4%–98.0%) and 90.0% (95% C 5% and 20% prevalence of TB among people living with HIV, respectively. Abnormal chest radiographic the sensitivity of the rule by 11.7% (90.6% versus 78.9%) with a reduction of specificity by 10.7% (49.6%

Conclusions: Absence of all of current cough, fever, night sweats, and weight loss can identify a subset of HIV who have a very low probability of having TB disease. A simplified screening rule using any one of th be used in resource-constrained settings to identify people living with HIV in need of further diagnostic Use of this algorithm should result in earlier TB diagnosis and treatment, and should allow for substant

Please see later in the article for the Editors' Summary.

- Tos de cualquier duración
- Fiebre
- Sudores nocturnos
- Perdida de peso

Con uno de los síntomas busque TB

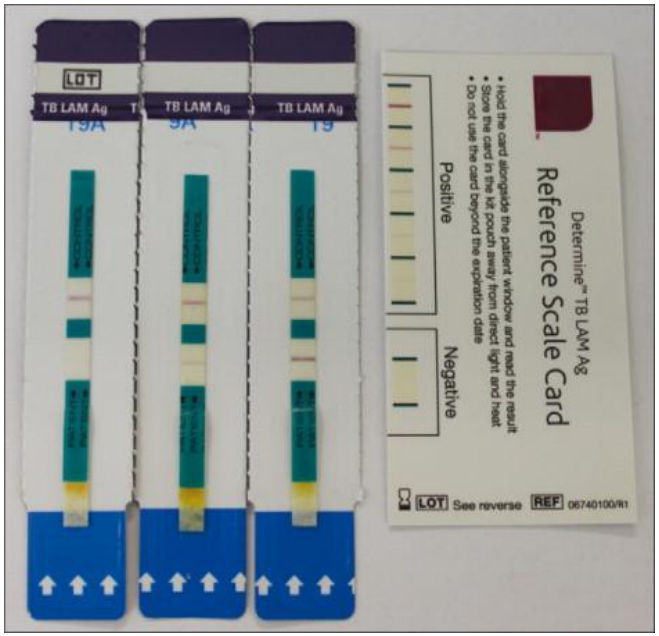
En ausencia de los 4 no es TB con el 97% de probabilidad

Genexpert utilidad en la Co-infección

- Mayor sensibilidad que el esputo, cercano al cultivo
  - Evita perder enfermos
  - Sensibilidad del 71.7% en BK-
  - Uso en muestras extrapulmonares
- Permite además
  - Diferenciar entre M.TB o MOTTs
  - Resistencia a RIF
- Rápido (2 horas)
- Caro…
  - 40 veces más que el esputo

Alternativa más accesible en camino:

Determine TB-LAM assay



tira parecida al determine de VIH “point of care” test 2.5 a 3 USS.

Mejor rentabilidad cuanto menores los CD4.

Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial

Jonny G Peter, Lynn S Zijenah*, Duncan Chanda*, Petra Clowes*, Maia Lesosky, Phindile Gina, Nirja Mehta, Greg Calligaro, Carl J Lombard, Gerard Kadzirange, Tsitsi Bandason, Abidan Chansa, Namakando Liusha, Chacha Mangu, Bariki Mtafya, Henry Msila, Andrea Rachow, Michael Hoelscher, Peter Mwaba, Grant Theron, Keertan Dheda*

Summary

Background HIV-associated tuberculosis is difficult to diagnose and results in high mortality. Frequent extra-pulmonary presentation, inability to obtain sputum, and paucibacillary samples limits the usefulness of nucleic-acid amplification tests and smear microscopy. We therefore assessed a urine-based, lateral flow, point-of-care, lipoarabinomannan assay (LAM) and the effect of a LAM-guided anti-tuberculosis treatment initiation strategy on mortality.

Methods We did a pragmatic, randomised, parallel-group, multicentre trial in ten hospitals in Africa—four in South Africa, two in Tanzania, two in Zambia, and two in Zimbabwe. Eligible patients were HIV-positive adults aged at least 18 years with at least one of the following symptoms of tuberculosis (fever, cough, night sweats, or self-reported weightloss) and illness severity necessitating admission to hospital. Exclusion criteria included receipt of any anti-tuberculosis medicine in the 60 days before enrolment. We randomly assigned patients (1:1) to either LAM plus routine diagnostic tests for tuberculosis (smear microscopy, Xpert-MTB/RIF, and culture; LAM group) or routine diagnostic tests alone (no LAM group) using computer-generated allocation lists in blocks of ten. All patients were asked to provide a urine sample of at least 30 mL at enrolment, and trained research nurses did the LAM test in patients allocated to this group using the Alere Determine tuberculosis LAM Ag lateral flow strip test (Alere, USA) at the bedside on enrolment. On the basis of a positive test result, the nurses made a recommendation for initiating anti-tuberculosis treatment. The attending physician made an independent decision about whether to start treatment or not. Neither patients nor health-care workers were masked to group allocation and test results. The primary endpoint was 8-week all-cause mortality assessed in the modified intention-to-treat population (those who received their allocated intervention). This trial is registered with ClinicalTrials.gov, number NCT01770730.

Findings Between Jan 1, 2013, and Oct 2, 2014, we screened 8728 patients and randomly assigned 2659 to treatment (1336 to LAM, 1323 to no LAM). 108 patients did not receive their allocated treatment, mainly because they did not meet the inclusion criteria, and 23 were excluded from analysis, leaving 2528 in the final modified intention-to-treat analysis (1257 in the LAM group, 1271 in the no LAM group). Overall all-cause 8-week mortality occurred in 578 (23%) patients, 261 (21%) in LAM and 317 (25%) in no LAM, an absolute reduction of 4% (95% CI 1–7). The risk ratio adjusted for country was 0·83 (95% CI 0·73–0·96), p=0·012, with a relative risk reduction of 17% (95% CI 4–28). With the time-to-event analysis, there were 159 deaths per 100 person-years in LAM and 196 per 100 person-years in no LAM (hazard ratio adjusted for country 0·82 [95% CI 0·70–0·96], p=0·015). No adverse events were associated with LAM testing.

Interpretation Bedside LAM-guided initiation of anti-tuberculosis treatment in HIV-positive hospital inpatients with suspected tuberculosis was associated with reduced 8-week mortality. The implementation of LAM testing is likely to offer the greatest benefit in hospitals where diagnostic resources are most scarce and where patients present with severe illness, advanced immunosuppression, and an inability to self-expectorate sputum.

Lancet 2016; 387: 1187–97

Published Online March 9, 2016 http://dx.doi.org/10.1016/S0140-6736(15)01092-2

See Editorial page 1134

See Comment page 1139

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.. outer lipids: cord factor
2. mycolic acid
3. polysaccharides (arabinogalactan)
4. peptidoglycan
5. plasma membrane
6. lipoarabinomannan (LAM)
7. phosphatidylinositol mannoside
8. cell wall skeleton

Tratamiento

TB raramente es una emergencia clínica excepto:

- TB Miliar
- Meningitis
- Pericarditis, constrictiva
- TB en gland supra
- TB en pacien con gran inmunod ion
  - **Diseminada: probablemente el asesino n.1 enfermos TB-VIH**

Todos necesitan corticosteroides!!!

Cosas q salvan la vida o te dan un tiempo

Cosas q salvan la vida o te dan un tiempo

1. Transfusión
2. Oxigeno
3. Corticoides
4. Antibióticos de amplio espectro
5. Medicación anti TB
6. Tratar a ciegas cualquier patógeno prevalente o con sospecha…

Para acabar con la TB diseminada, tratar el VIH precoz e independiente del número de CD4. Estudio *TEMPRANO y START*

Gran mortalidad en los primeros 3 meses de inicio del TARGA

- ¿Progresión de enfermedad subyacente? (**TB no diagnosticada, IRIS desenmascarado**)
- ¿IRIS cuando el sistema nervioso central esta inflamado?
- ¿Hepatitis fulminates? ¿oportunistas diseminadas?

TB desenmascarada: Puede ocurrir en 1 de cada 3 casos que inician ARVs en los primeros 4 meses en países en desarrollo

Pensar en TB! incluso en casos con presentación totalmente atípica: fiebre, anemia

Muerte por TB pulmonar activa y asíntomática

REMEMBER study: no es concluyente

Screening de VIH a todos los tuberculosos (una de las actividades de colaboración TB/VIH)

Busqueda intensiva de casos (una de las 3Is)

La clave del éxito en la **tuberculosis** extrapulmonar:

1. Alto nivel de **sospecha**: diagnóstico precoz
2. Iniciación **rápida** de un tratamiento oportuno
3. **Régimen correcto** y suficientemente largo
4. El uso de **corticosteroides** en las formas graves

The Union

International Union Against Tuberculosis and Lung Disease

Health solutions for the poor

¡¡Muchas gracias por vuestra atención!!

Ignacio Monedero MD, MPH, PhD

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Unión Internacional contra la Tuberculosis y enfermedades respiratorias

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El supernotición…
Ayer: 12 de mayo de 2016!!!

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Rapid diagnostic test and shorter, cheaper treatment signal new hope for multidrug-resistant tuberculosis patients

News release

12 MAY 2016 | GENEVA - New WHO recommendations aim to speed up detection and improve treatment outcomes for multidrug resistant tuberculosis (MDR-TB) through use of a novel rapid diagnostic test and a shorter, cheaper treatment regimen.

"This is a critical step forward in tackling the MDR-TB public health crisis," said Dr Mario Raviglione, Director of WHO's Global TB Programme. "The new WHO recommendations offer hope to hundreds of thousands of MDR-TB patients who can now benefit from a test that quickly identifies eligibility for the shorter regimen, and then complete treatment in half the time and at nearly half the cost."

Shorter treatment with better outcomes

At less than US$ 1000 per patient, the new treatment regimen can be completed in 9–12 months. Not only is it less expensive than current regimens, but it is also expected to improve outcomes and potentially decrease deaths due to better adherence to treatment and reduced loss to follow-up

Share Print

MDR-TB Regimen

Fact sheet on the shorter MDR-TB Regimen
pdf, 497kb

Molecular line-probe assay for the detection of resistance to second-line anti-TB drugs (SL-LPA)
pdf, 448kb

WHO End TB Strategy

Global strategy and targets for tuberculosis prevention, care and control after 2015