LA TUBERCOLOSI NEL SOGGETTO IMMUNOCOMPROMESSO

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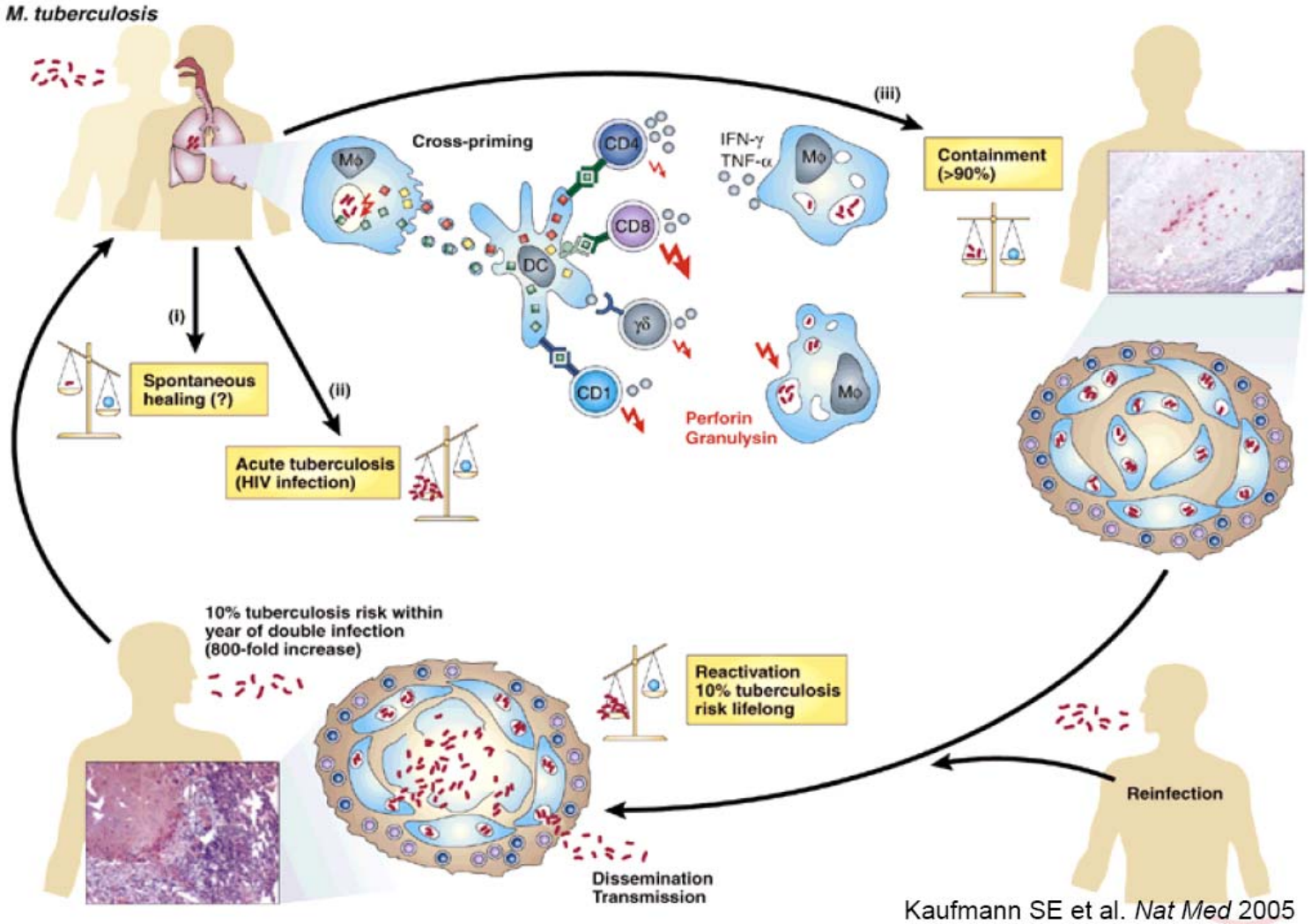
Scandiano (Reggio Emilia), 19 dicembre 2008

Evoluzione dell'infezione tubercolare



Kaufmann SE et al. *Nat Med* 2005

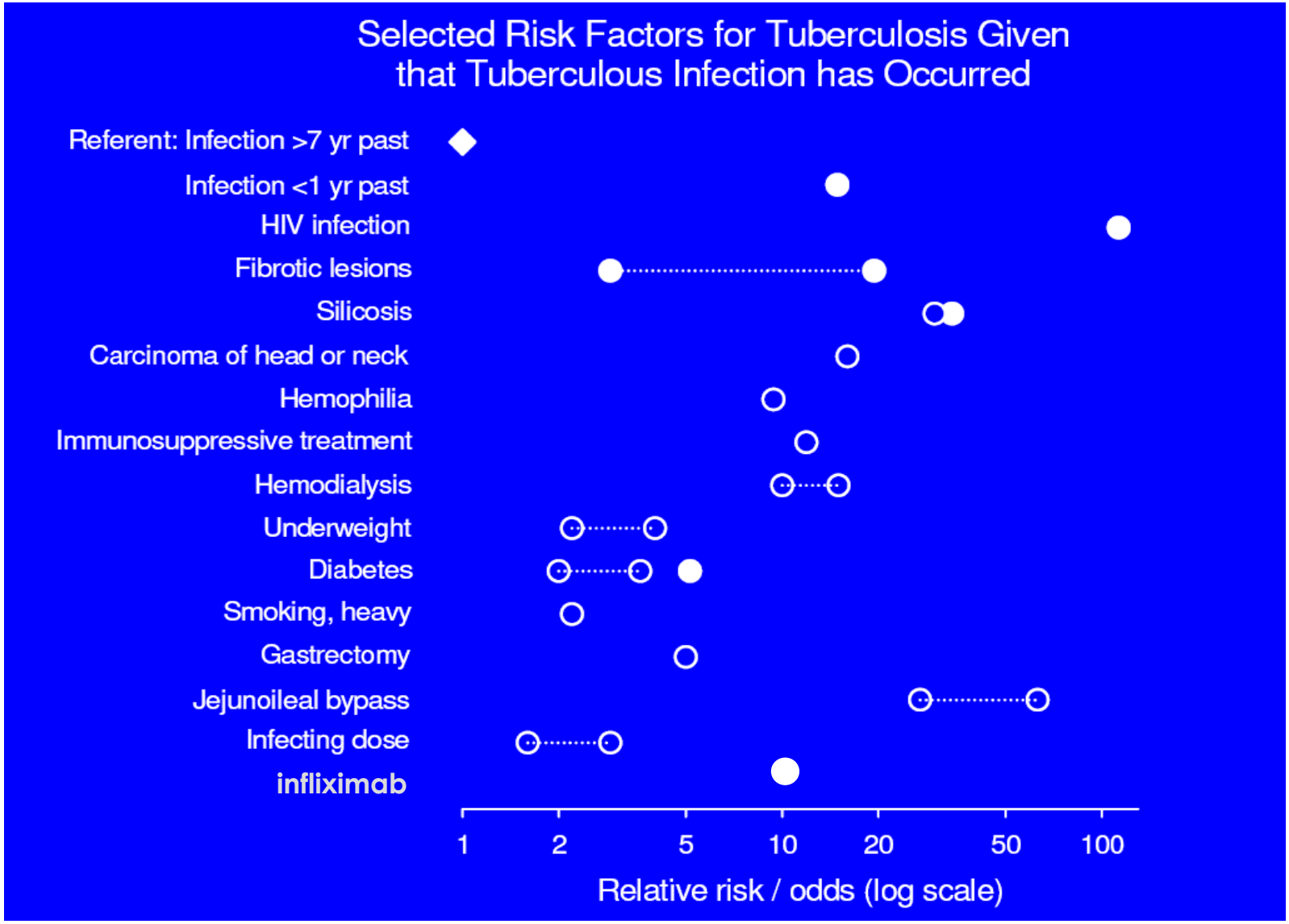
Persons More Likely to Progress From LTBI to TB Disease

- HIV-infected persons
- Those with a history of prior, untreated TB or fibrotic lesions on chest RX
- Underweight or malnourished persons
- Those receiving TNF-α antagonists for treatment of RA or Crohn's disease

Persons More Likely to Progress From LTBI to TB Disease

Persons with following medical conditions:

- Silicosis
- Diabetes mellitus
- Chronic renal failure or on hemodialysis
- Solid organ transplantation (e.g., heart, kidney)
- Carcinoma of head or neck
- Gastrectomy or jejunoilial bypass


Selected Risk Factors for Tuberculosis Given that Tuberculous Infection has Occurred
Referent: Infection >7 yr past
Infection <1 yr past
HIV infection
Fibrotic lesions
Silicosis
Carcinoma of head or neck
Hemophilia
Immunosuppressive treatment
Hemodialysis
Underweight
Diabetes
Smoking, heavy
Gastrectomy
Jejunoileal bypass
Infecting dose
infliximab
1
2
5
10
20
50
100
Relative risk / odds (log scale)

TB/HIV

Global TB/HIV Epidemiology
2006

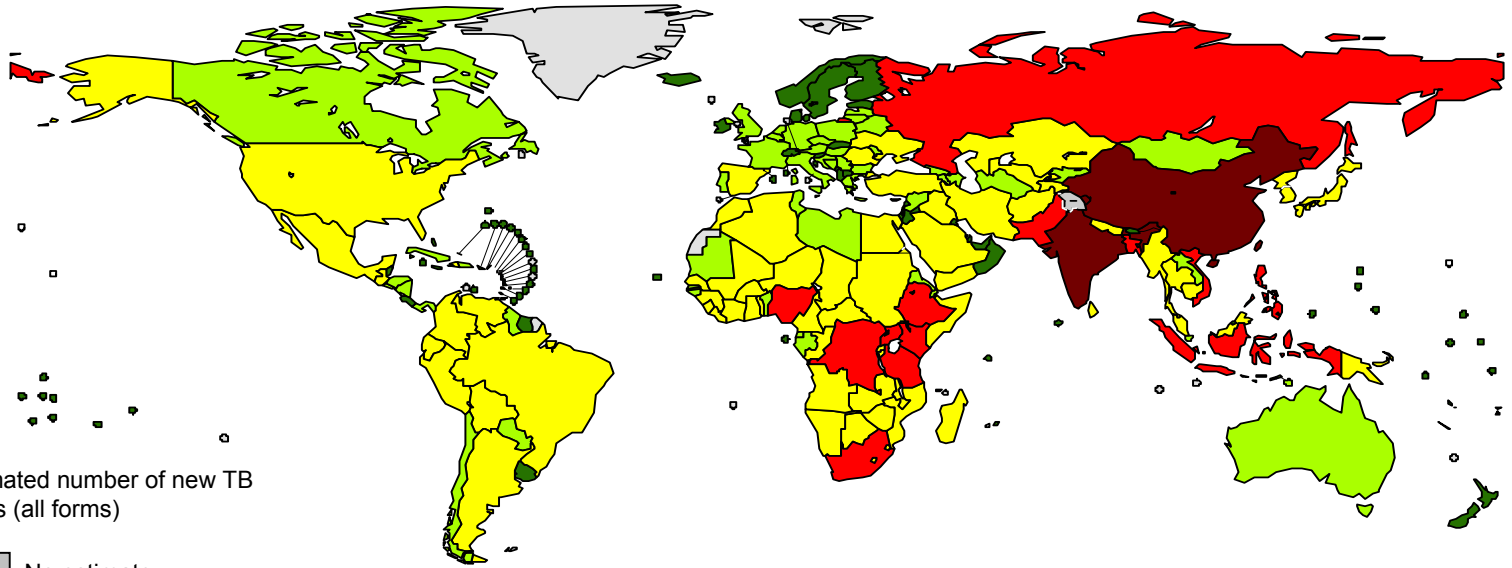
- Estimated # new TB cases: 9.2 million
  - HIV-infected TB cases 700,000
- Estimated # prevalent cases: 14.4 million
- Estimated # deaths: 1.7 million
  - HIV-infected TB deaths 195,000
- Estimated # infections: 2 billion
  - 33% of population

WHO Report 2008. WHO/HTM/TB/2008.393

HIV/AIDS and TB: a Coepidemic

- At the end of 2007
  - Approximately 2 billion people infected with *Mycobacterium tuberculosis*
  - Approximately 33 million people infected with HIV
  - 10-15 million people coinfected with HIV and TB
  - Approximately 2 million HIV-related deaths
    - Up to 50% of those were HIV/TB-coinfected individuals

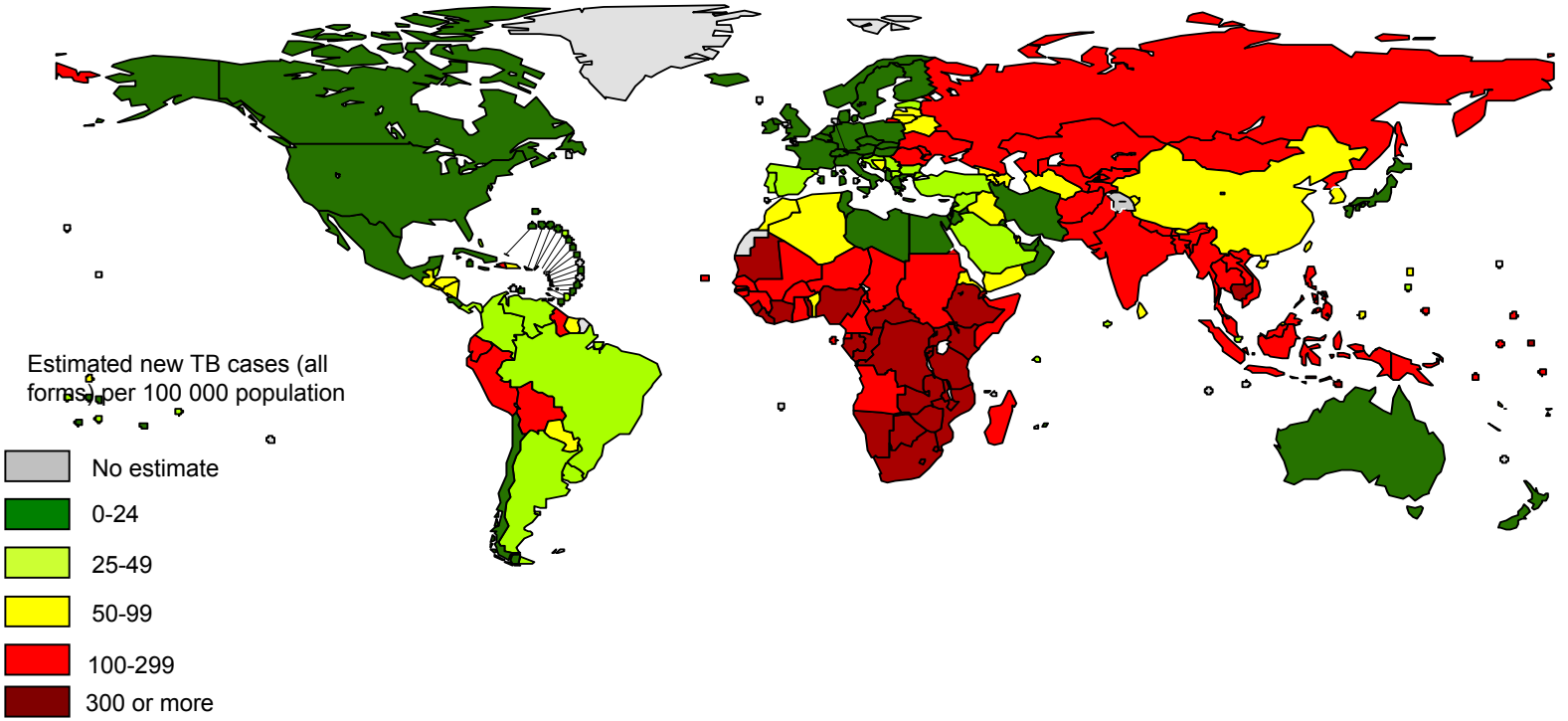
Estimated Numbers Of New TB Cases 2006



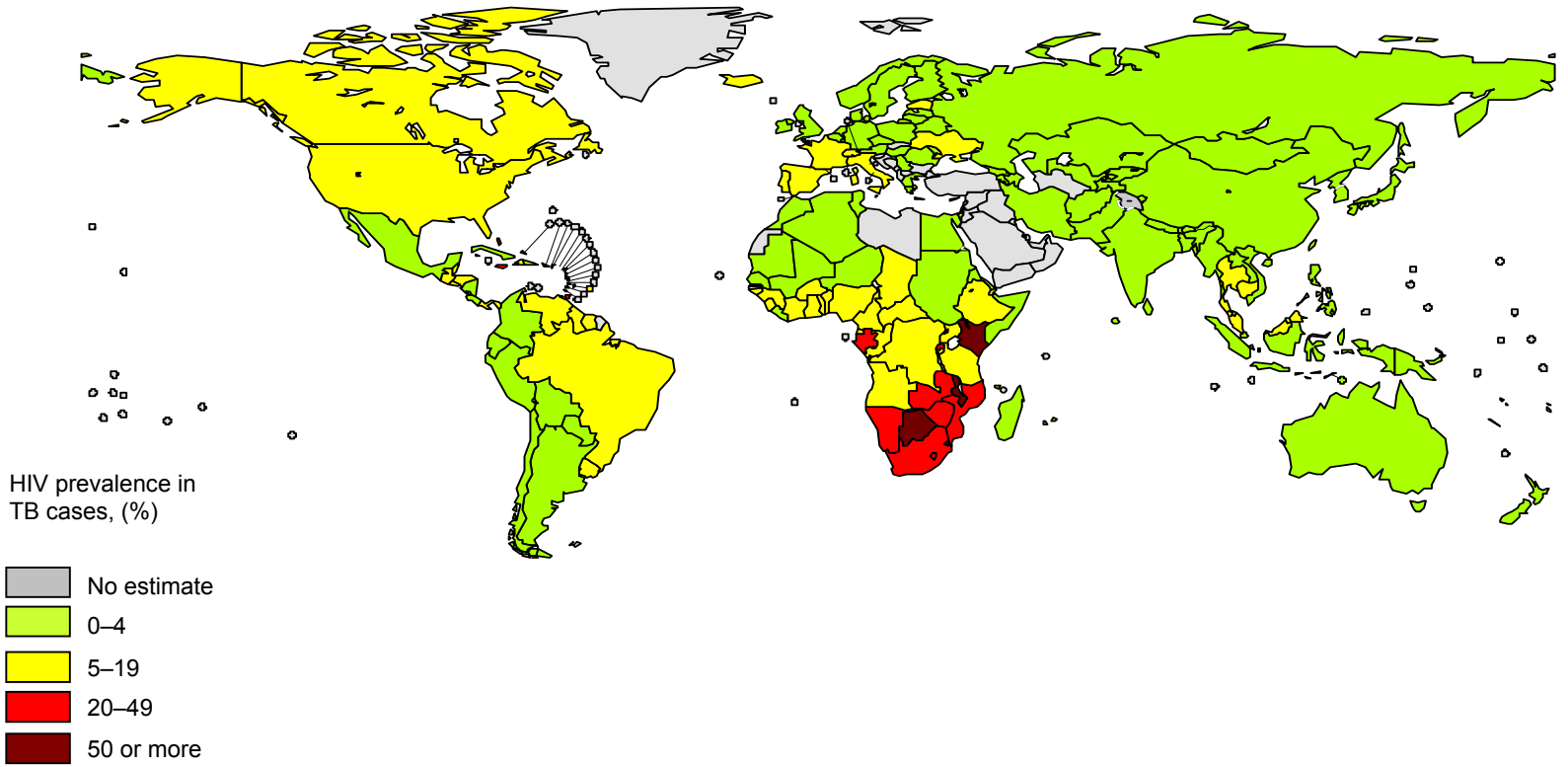
Estimated number of new TB cases (all forms)

- No estimate
- 0–999
- 1000–9999
- 10 000–99 999
- 100 000–999 999
- 1 000 000 or more

Estimated TB Incidence Rates 2006



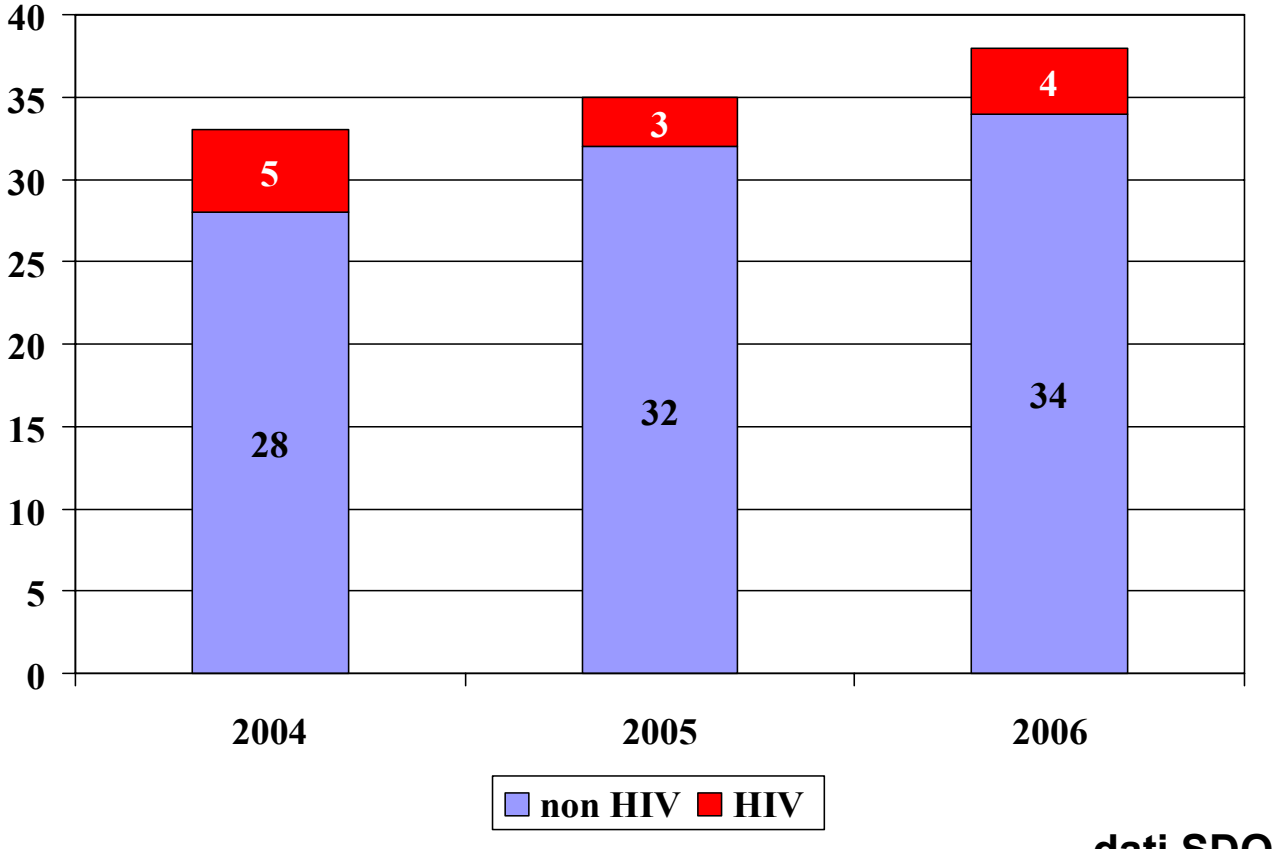
Estimated HIV Prevalence In New TB cases 2006



Studio GISTA-SIMIT : Studio Prospettico, Multicentrico, Condotto in Italia nel 1999-2000 in Pazienti HIV con TB

Età (media)	37 (21-36)
Sesso (M)	271 (81,3%)
Nazionalità italiana	178 (65,4%)
Fattore rischio HIV • IVDU • Rapporti eterosessuali • MSM • Altro	 130 (47.8%) 76 (27,9%) 39 (14,4%) 27 (9,9%)
CD4 cell x 10^5/l (media)	120 (0-1111)
Localizzazione TB • polmonare • Polmonare + extra-polmonare • Extra-polmonare	 151 (55,5%) 69 (25,4%) 52 (19,1%)
Precedente episodio di TB	44 (16,2%)
Precedente trattamento con INH per LTIB	4 (1,5%)

Ricoveri per TB polmonare presso UO Malattie Infettive di Reggio Emilia



dati SDO

Interactions Between HIV and TB

- HIV has a negative impact on TB disease:
  - increased risk for active TB from exogenous infection
  - increased risk for latent TB reactivation
  - accelerated progression of active TB
- TB infection has a negative impact on HIV disease:
  - significant increase in plasma HIV viremia
    - generalized immune activation
    - ↑ expression of the HIV CCR5/CXCR4 coreceptors

Important Issues in HIV/TB

- Impact of HAART
- Clinical manifestations
- Treatment
- IRIS

Important Issues in TB/HIV
Impact of HAART

- HAART reduces, but not eliminate the risk of developing TB.
- The greatest risk factor for the development of TB on HAART is the pretreatment level of baseline CD4 cell count , and those at 6 months after HAART initiation.
- Patients on HAART tend to have classic radiographic findings compared with patients who have not received HAART, who may have a more unusual presentation.
- HAART increases the frequency of PPD conversion rates.
- HAART decreases TB related mortality.
- Functional restoration of CD4+ T cells can lead to immune reconstitution syndromes with a wide spectrum of clinical manifestations.

HAART Decreases Overall TB Risk

TB risk in 1st 3 months of HAART is high

Months HAART	TB/100 p-y[1]	TB/100 p-y[2]	TB/100 p-y[3]	
0-3	1.3	23.0	10.7	1.7
4-6	0.8	10.7	7.5	1.0
7-12	0.5	7.0	5.2	0.6

1.Girardi E. CID 2005. Europe, North America
2.Lawn SD. AIDS 2006. South Africa
3.Brinkhof MW. CID 2007. Developing countries + developed countries

Incidence of Tuberculosis after HAART

Table 2. Incidence of tuberculosis per 1000 person-years of follow-up (PYFU) during the first 3 years after HAART initiation according to baseline characteristics, Antiretroviral Therapy Cohort Collaboration, 1996–2003. (Europe, Nord America)

Baseline characteristic	No. of cases of tuberculosis	No. of PYFU	Incidence rate of tuberculosis, cases per 1000 PYFU (95% CI)
Duration of HAART, months			
0–3	55	4208	13.1 (9.6–1.7)
4–6	30	3852	7.8 (5.0–10.6)
7–12	34	7322	4.6 (3.1–6.2)
13–24	40	12,210	3.3 (2.3–4.3)
25–36	14	9314	1.5 (0.8–2.5)

Girardi, E. et al. Clin Infect Dis 2005; 41:1772.

Incidence of Tuberculosis after HAART Stratified By CD4+ Cell

Table 4. Incidence of tuberculosis (TB) occurring ≥6 months after HAART initiation, stratified by CD4⁺ cell count and HIV RNA level as measured at HAART initiation and at 6 months after HAART initiation, Antiretroviral Therapy Cohort Collaboration, 1996–2003.

Variable	No. of cases of TB	No. of PYFU	No. of cases of TB per 1000 PYFU (95% CI)
CD4⁺ cell count, cells/μL			
At HAART initiation			
<50	18	1961	9.2 (5.4–14.5)
50–199	24	6792	3.5 (2.1–5.0)
200–349	27	8771	3.1 (1.9–4.2)
350–499	11	6552	1.7 (0.8–3.0)
≥500	8	4770	1.7 (0.7–3.3)
At 6 months after HAART initiation			
<50	6	303	19.8 (7.3–43.2)
50–199	25	3668	6.8 (4.1–9.5)
200–349	19	6108	3.1 (1.9–4.9)
350–499	16	6613	2.4 (1.4–3.9)
≥500	12	9551	1.3 (0.7–2.2)

Girardi, E, et al. Clin Infect Dis 2005; 41:1772

Important Issues in TB/HIV

Clinical Manifestations

- The symptoms seen in HIV patients with TB are usually similar to those in other patients with TB.
- The diagnosis should be suspected not only in patients with pulmonary symptoms, but also in those with weight loss, fever of unknown origin, or malaise.

Extrapulmonary Disease

- HIV patients with TB have a higher incidence of extrapulmonary and pleural disease.
- The risk of extrapulmonary TB is greater in patients with advanced immunosuppression.
- The most common sites of extrapulmonary involvement are blood, extrathoracic lymph nodes, bone marrow, genitourinary tract and the central nervous system.

Frequency of Various Clinical, Laboratory, and Radiographic Features of HIV-Associated Tuberculosis (TB) in Patients Whose CD4+ Cell Counts were < 200 And > 201/ml

97 HIV-infected patients with tuberculosis

Feature	CD4+ cell counts		p
	<200/µl	>201/µl	
Extrapulmonary TB, %	63	35	<0.01
Mycobacteremia, %	40	4	<0.01
Positive acid-fast smear, %	75	53	=0.03
Positive skin test, %	31	65	<0.02
Mediastinal adenopathy, %	36	13	=0.02
Pleural effusion, %	10	27	=0.05

Data modified from Jones et al. Am Rev Respir Dis 1993; 148:1292

Tuberculous Pleurisy is More Common in AIDS Than in Non-AIDS Patients with Tuberculosis

A case-control study of approximately 3000 patients with tuberculosis with pleural involvement performed in South Carolina from 1988 through 1994.

- **Main results**:
  - **11%** (22/202**) of the AIDS patients** with tuberculosis had pleural involvement v.s. **6%** (169/2,817) **in non-AIDS patients (p=0.01).**
  - Associated features of AIDS tuberculous pleurisy:
    - substantial weight loss (7.65 ±1.35 kg)
    - lower lobe infiltrates (12/22; 55%).

Frye, MD, et al. Chest 1997; 112:393

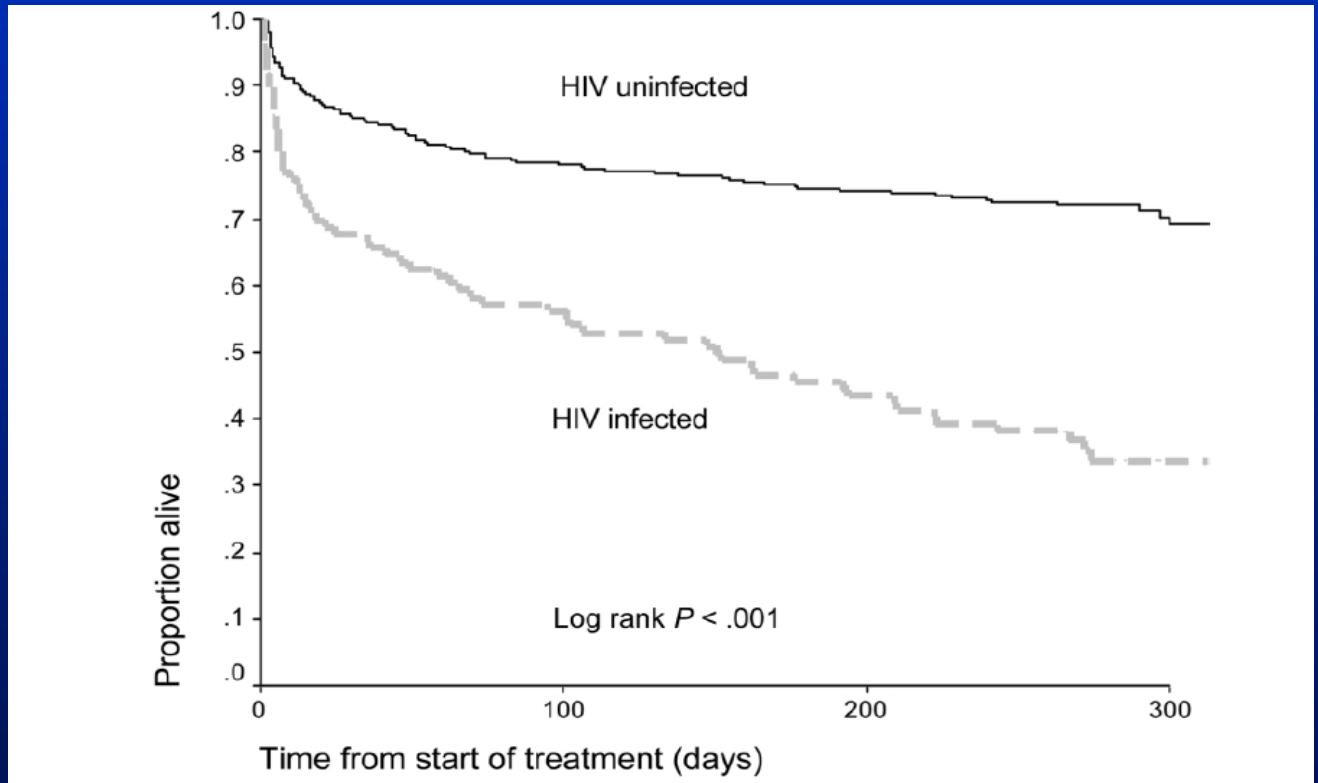
Tuberculous Meningitis is Associated with Decreased Survival in HIV Patients

Prospective study in 528 adults (96 HIV, 432 non HIV) with tuberculous meningitis

- **Main results:**
  - Similar neurological presentation between HIV and non HIV patients
  - Extrapulmonary TB manifestation more frequent in HIV patients
  - The 9-month survival rate significantly decreased in HIV patients: RR of death = 2,91 (95% CI 2.14–3.96)

Thwaites, GE, et al J Infect Dis 2005; 192:2134

Survival Estimates in 96 HIV-Infected and 432 HIV-Uninfected Patients with Tuberculous Meningitis



No. at risk				
HIV uninfected	432	330	312	71
HIV infected	96	53	41	9

Thwaites, GE, et al J Infect Dis 2005; 192:2134

Active Pulmonary Tuberculosis in Patients with AIDS: Spectrum of Radiographic Findings

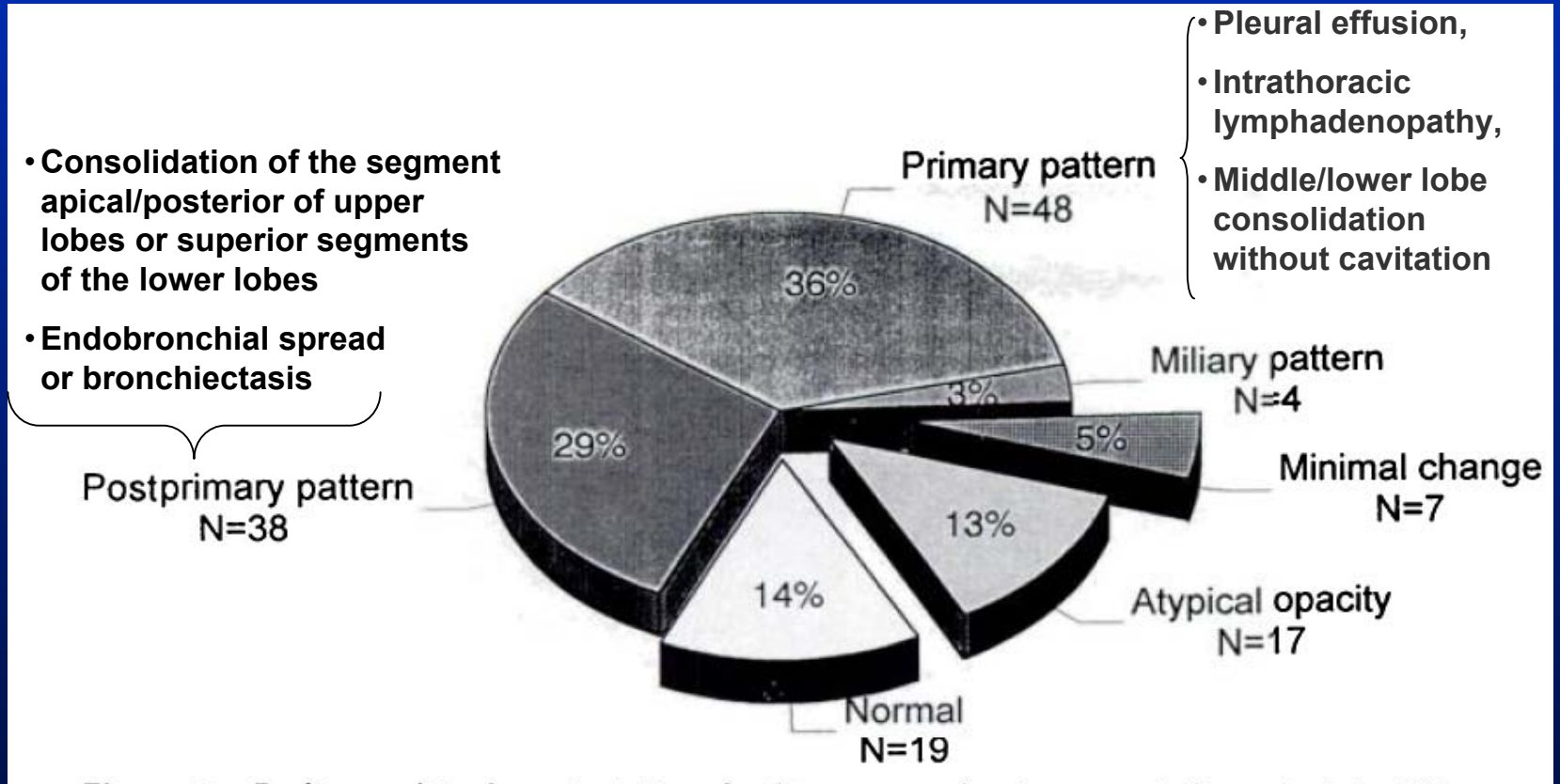


Figure 6. Radiographic characteristics of culture-proved pulmonary tuberculosis in 133 patients with AIDS.

Greenberg SD, et al.Radiology 1994; 193:115

Active Pulmonary Tuberculosis In Patients With AIDS: Spectrum Of Radiographic Findings.

Table 2

Correlation in AIDS Patients with Pulmonary Tuberculosis Based on CD4 T-cell Counts

A. Normal and Abnormal Radiographic Findings

CD4 T-cell Count (cells per microliter)	Total No. of Patients	Radiographic Findings*	
		Normal	Abnormal
< 200	48	10 (21)†	38 (79)
> 200	20	1 (5)†	19 (95)

B. Postprimary and Other Radiographic Patterns

CD4 T-cell Count (cells per microliter)	Total No. of Patients	Radiographic Pattern*	
		Postprimary	Other
< 200	48	11 (23)‡	37 (77)
> 200	20	11 (55)‡	9 (45)

* Numbers in parentheses are percentages.
† $P < .05$.
‡ $P < .001$.

Greenberg SD, et al.Radiology 1994; 193:115

HIV Status is the Most Significant Predictor of an Abnormal Radiographic Appearance

Retrospective analysis of 456 TB patients (191 HIV seropositive) treated at a New York City hospital between 1990 and 1999.

Table 3. Association Between Radiographic Features and HIV Status Across Strata of Cluster Status

Characteristic	No. (%) of Unique Isolates (n = 159)				No. (%) of Clustered Isolates (n = 193)				*P* Value for Breslow-Day Test for Heterogeneity Across Strata of Cluster Status
	No.	HIV Negative	HIV Positive	OR (95% CI)*	No.	HIV Negative	HIV Positive	OR (95% CI)†	
Cavitary lesion	47	34 (40.0)	13 (17.6)	0.32 (0.15-0.67)	47	31 (40.8)	16 (13.7)	0.23 (0.11-0.46)	.53
Upper lobe infiltrate	99	63 (74.1)	36 (48.7)	0.33 (0.17-0.64)	100	59 (77.6)	41 (35.0)	0.22 (0.14-0.36)	.11
Lymphadenopathy	37	13 (15.3)	24 (32.4)	2.66 (1.24-5.71)	55	14 (18.4)	41 (35.0)	2.39 (1.19-4.78)	.84
Effusion	34	20 (23.5)	14 (18.9)	0.76 (0.35-1.63)	32	8 (10.5)	24 (20.51)	2.19 (0.92-5.1)	.07
Effusion only	7	3 (3.61)	4 (6.45)	1.83 (0.40-8.53)‡	10	1 (1.41)	9 (11.25)	8.87 (1.09-71.9)§	.21
Lower or middle lung infiltrate	68	39 (45.9)	29 (39.2)	0.76 (0.40-1.43)	74	27 (35.5)	47 (40.2)	1.21 (0.67-2.22)	.29
Miliary	9	3 (1.89)	6 (8.1)	2.41 (0.58-10.0)‡	10	5 (6.58)	5 (4.27)	0.63 (0.18-20.27)‡	.16
Multilobar	71	41 (48.2)	30 (41.1)	0.75 (0.40-1.40)	82	38 (50.0)	44 (37.6)	0.60 (0.34-1.08)	.62
Typical	99	63 (74.1)	36 (48.7)	0.33 (0.17-0.94)	100	59 (77.6)	41 (35.0)	0.16 (0.08-0.30)	.11

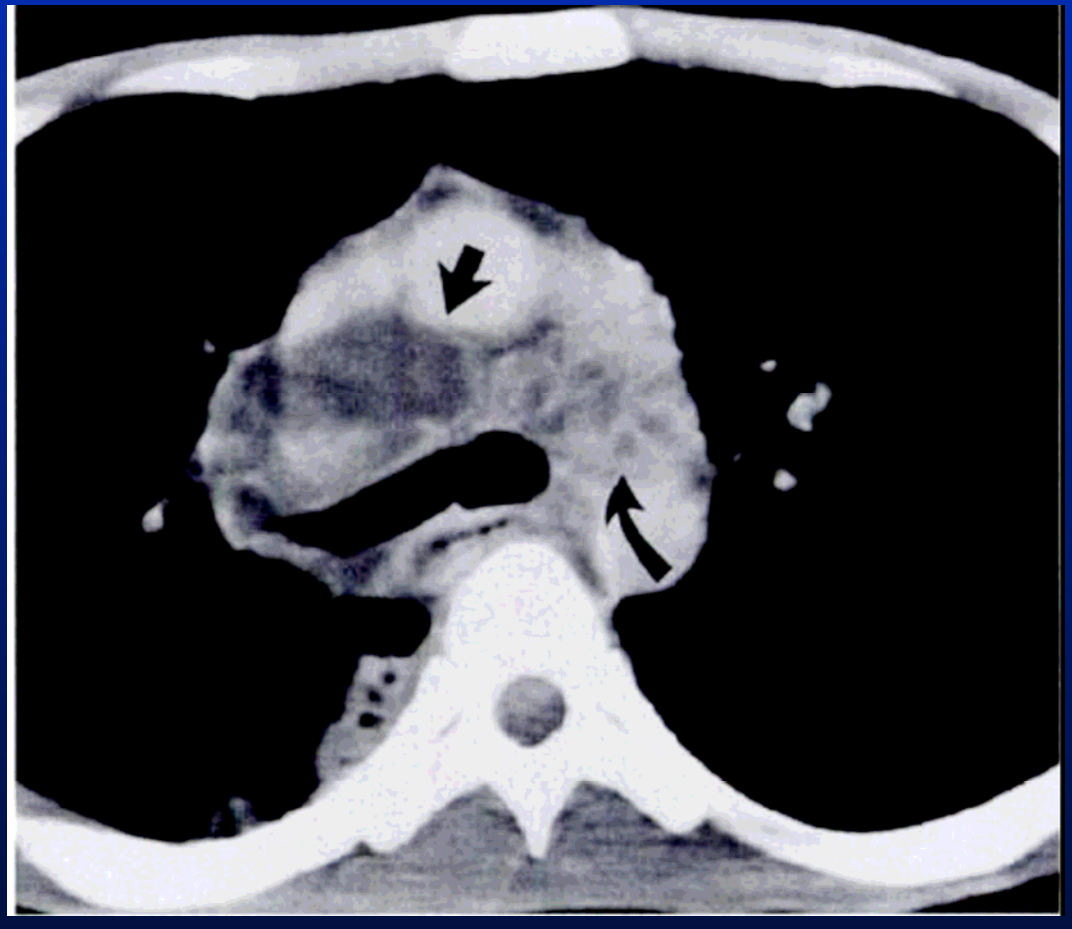
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.
*Compares the association between radiographic variables and HIV status among persons with unique isolate.
†Association between radiographic variable and HIV status among persons with clustered isolate.
‡$P > .05$ by Fisher exact test.
§$P < .05$ by Fisher exact test.

Geng E, et al. JAMA 2005; 293:2740

Intrathoracic Adenopathy Associated with TB/AIDS

- Characteristic appearance on CT: the lymph nodes appear hypodense relative to soft tissue, and the rim is enhanced with contrast.
- This finding is not pathognomonic of TB (occasionally seen in Kaposi's sarcoma and lymphomas), but it is sufficiently characteristic that empiric therapy should be started pending results of cultures.

Intrathoracic Adenopathy Associated with TB/AIDS



Pastores SM, et al. Chest 1993; 103:1433.

Important Issues in TB/HIV Treatment

- When to start HAART in TB/HIV patients
- Drug interactions
  - Rifampin +
  - Protease inhibitors (PI)
    - > 90% ↓ in PI levels generally precludes use of PIs
  - NNRTI
    - Efavirenz, nevirapine
  - Newer agents
    - Raltegravir, Maraviroc: no data
    - http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm
    - Updated May 18, 2008
- Integration of TB and HIV care
    - Havlir D. JAMA 2008;300:423-30.
- Optimal duration of TB treatment

THRio Cohort
HAART Initiation after TB Diagnosis Improves Survival

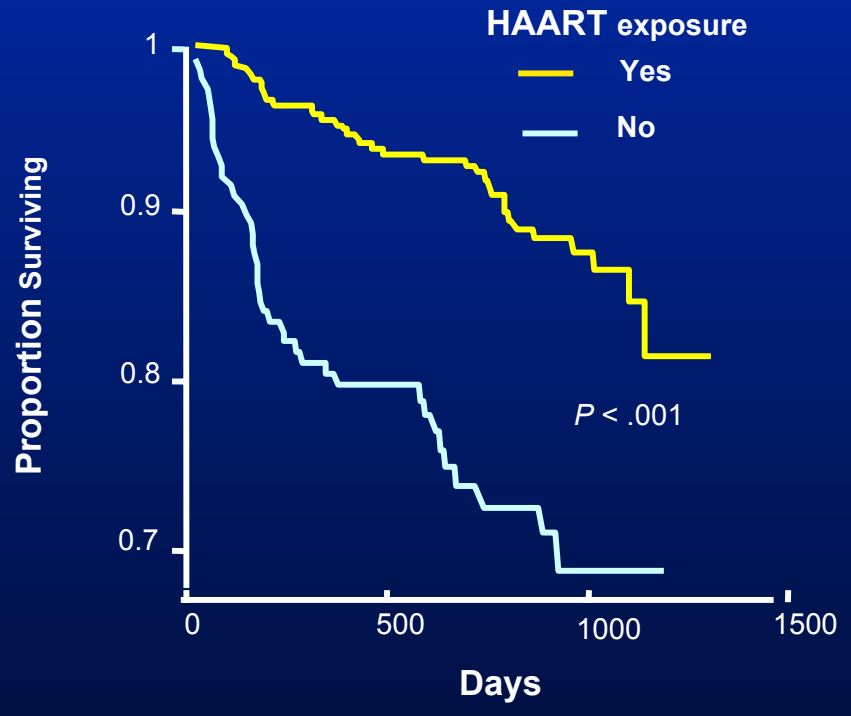
- **THRio Cohort**

  No significant difference in survival rate between patients starting HAART

  ≤ 60 days

  61-180 days

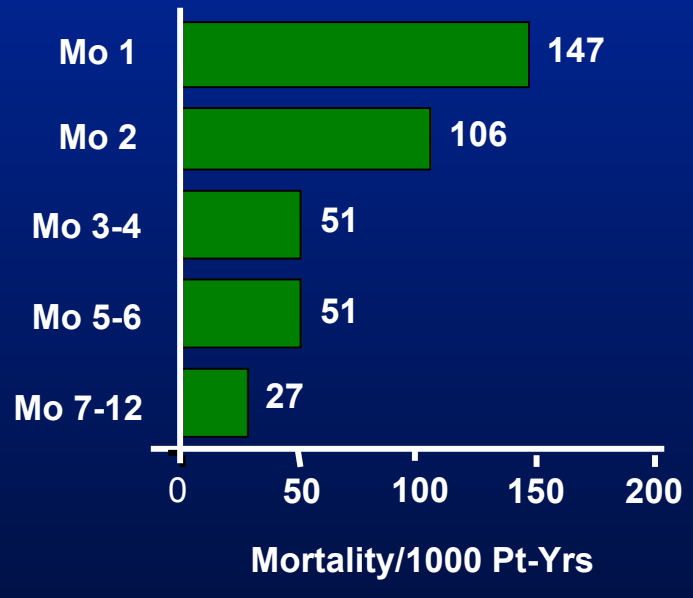
  > 180 days



Saraceni V, et al. IAC 2008. Abstract MOAB0305. Reprinted with permission.

Reduced Mortality after First 3 Mos of ART in Developing Countries

- ART-LINC dataset[1] (N = 2725 with active follow-up)



- Botswana National HIV Treatment Program[2] (N = 53,423 with adequate follow-up data)
- 47.8% of patients who died received HAART for < 3 mos
- If patients survived > 3 mos, 94.3% likelihood of survival for > 5 yrs

1. Braitstein P, et al. Lancet. 2006;367:817- 824
2. Puvimanasinghe JP, et al. IAC 2008. Abstract MOAB0204

Conflicting Data on Timing of HAART Initiation after Starting TB Therapy

- Iran study (N = 69)[1]: HAART initiated early (at 2 weeks of TB therapy if CD4+ count ≤ 100, at 8 weeks if CD4+ count 101-200) vs late (at 8 weeks if CD4+ count > 200)
  - Significantly higher TB cure rate with early HAART (*P* = .002)
  - Significantly lower death rate within 12 mos with early HAART (*P* = .028)
- Argentina study (N = 142)[2]: HAART initiation early (within 8 weeks of starting TB therapy) vs late (after 8 weeks)
  - Significantly higher TB cure/treatment completion rate with late HAART (71% vs 88%; *P* = .035)
  - Significantly lower death rate with late HAART (14% vs 7%; *P* = .013)

1. Tabarsi P, et al. IAC 2008. Abstract MOPDB205
2. Toibaro JJ, et al. IAC 2008. Abstract MOPDB206

HIV/TB HAART Mortality: Malnutrition & Advanced HIV Disease, not Timing

Mortality With HAART, TB vs Non-TB	Crude Incidence Rate Ratio	Adjusted Incidence Rate Ratio*
All patients	**1.69**	**0.94**
Stratified by Time Between TB Treatment and HAART Initiation		
• **≤ 30 days (n = 331)**	**2.04**	**0.97**
• **30-60 days (n = 286)**	**1.64**	**0.80**
• **60-120 days (n = 311)**	**1.36**	**0.93**
• **> 120 days (n = 274)**	**1.71**	**1.11**

*Adjusted for advanced HIV disease, malnutrition, low hemoglobin.

- **Nearly 6-fold higher risk for mortality among HIV/TB-coinfected patients with *both* lower BMI and short duration between TB treatment initiation and HAART initiation**

Westreich D, et al. CROI 2008. Abstract 145

Therapy for Susceptible Active TB

- Although most HIV-infected patients can be successfully treated with standard six-month treatment regimens, longer courses of treatment are indicated for some patients:
  - patients with cavitary disease who remain smear-positive after two months of induction therapy,
  - patients with CNS or skeletal involvement
- TB therapy are the same as in patients without HIV, including four-drug therapy in most cases
- Issues related to drug interactions, immune status, and prevention of resistance must also be considered before initiating therapy

Treatment Regimens for Tuberculosis

TABLE 1. TREATMENT REGIMENS FOR PATIENTS WITH TUBERCULOSIS, ACCORDING TO HIV STATUS.*

DRUG RESISTANCE	PATIENTS WITHOUT HIV INFECTION	PATIENTS WITH HIV INFECTION	ANTIRETROVIRAL THERAPY
None	IRPE for 2 mo, IR for 4 mo†	IRPE for 2 mo, IR for 4–7 mo‡	No protease inhibitors or NNRTIs can be used with rifampin§
		or	
		IPE plus rifabutin for 2 mo, I plus rifabutin for 4–7 mo	Rifabutin can be used with indinavir or nelfinavir but not with saquinavir, ritonavir, or NNRTIs
Isoniazid	RPE for 6 mo	RPE for 6–9 mo¶	No protease inhibitors or NNRTIs can be used with rifampin
		or	
		rifabutin plus PE for 6–9 mo	Rifabutin can be used with indinavir or nelfinavir but not with saquinavir, ritonavir, or NNRTIs
Rifampin	IPE for 18–24 mo	IPE for 18–24 mo	All antiretroviral drugs can be used
		or	
		IPSE for 2 mo, IPS for 7–10 mo	All antiretroviral drugs can be used

*Recommendations are based on those of the American Thoracic Society,[30] the Centers for Disease Control and Prevention,[31] and expert opinion. I denotes isoniazid, R rifampin, P pyrazinamide, E ethambutol, NNRTI non-nucleoside reverse-transcriptase inhibitor, and S streptomycin.

Recommendations for Regimens for the Concomitant Treatment of Tuberculosis and HIV Infection

Combined regimen for treatment of HIV and tuberculosis	PK effect of the rifamycin	Tolerability / toxicity	Antiviral activity when used with rifampin	Recommendation(comments)
Efavirenz-based antiretroviral therapy* with rifampin-based TB treatment	Well-characterized, modest effect	Low rates of discontinuation	Excellent	Preferred (efavirenz should not be used during the first trimester of pregnancy)
PI-based antiretroviral therapy* with rifabutin-based TB treatment	Little effect of rifabutin on PI concentrations, but marked increases in rifabutin concentrations	Low rates of discontinuation (if rifabutin is appropriately dose-reduced)	Favorable, though published clinical experience is not extensive	Preferred for patients unable to take efavirenz †
Nevirapine-based antiretroviral therapy with rifampin-based TB treatment	Moderate effect	Concern about hepatotoxicity when used with isoniazid, rifampin and pyrazinamide	Favorable	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / abacavir / tenofovir with rifampin-based TB treatment[10]	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	No published clinical experience	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / tenofovir with rifampin-based TB treatment	50% decrease in zidovudine, no other effects predicted	Anemia	Favorable, but not evaluated in a randomized trial	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / abacavir with rifampin-based TB treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	Early favorable experience, but this combination is less effective than efavirenz-based regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz and if rifabutin not available
Super-boosted lopinavir-based ART with rifampin-based TB treatment	Little effect	Hepatitis among healthy adults, but favorable experience, among young children (< 3 years)	Good, among young children (< 3 years)	Alternative if rifabutin not available; preferred for young children when rifabutin not available

ART=antiretrovirol therapy
* with 2 nucleoside analogues
† includes patients with NNRTI-resistant HIV, those unable to tolerate efavirenz, women during the first 1-2 trimesters of pregnancy

Drug Interactions

Table 1. Pharmacokinetic drug interactions between rifampin (RIF), rifabutin (RIB), protease inhibitors (PIs), and nonnucleoside reverse-transcriptase inhibitors (NNRTIs).

Drug	Interaction with RIF	Recommendation for concurrent ARV use with RIF[a]	Interaction with RIB	Recommendation for concurrent ARV use with RIB	RIB dose adjustment
PIs					
RTV	RTV ↓ 35%	No dose adjustment	RIB ↑ 435%	No dose adjustment	150 mg 3× per week
IDV	IDV ↓ 89%	Avoid	IDV ↓ 32%; RIB ↑ 204%	IDV 1000 mg t.i.d.	150 mg daily or 300 mg 3× per week
SQV	SQV ↓ 84%	Avoid SQV (400 mg) + RTV (400 mg) b.i.d.; may be effective but is hepatotoxic in healthy volunteers; monitor liver function closely	SQV ↓ 40%	Avoid unboosted SQV	
NFV	NFV ↓ 82%	Avoid	NFV (1250 mg b.i.d.[b]) ↔; RIB ↑ 207%	NFV 1250 mg b.i.d.	150 mg daily or 300 mg 3× per week
APV, f-APV	APV ↓ 82%	Avoid	APV ↓ 15%; RIB ↑ 193%	No dose adjustment	150 mg daily or 300 mg 3× per week
ATV	Predicted significant ATV ↓	Avoid	RIB ↑ 250%	No dose adjustment	150 mg daily or 150 mg 3× per week
RTV-boosted[c]		Avoid		No dose adjustment	150 mg 3× per week
RTV-boosted LPV (Kaletra)	LPV ↓ 75%	Avoid LPV/rtv + RTV (300 mg b.i.d.): monitor liver function closely	RIB ↑ 303%	No dose adjustment	150 mg 3× per week
NNRTIs					
NVP	NVP ↓ 20%–55%	No dose adjustment; safety and efficacy not established; monitor liver function closely	NVP ↓ 16%	No dose adjustment	No dose adjustment
EFV	EFV ↓ 25%	Consider EFV ↑ to 800 mg daily in patients >60 kg	EFV ↔; RIB ↓ 35%	No dose adjustment	450–600 mg daily or 600 mg 3× per wee
DLV	DLV ↓ 96%	Avoid	DLV ↓ 80%; RIB ↑ 100%	Avoid	

NOTE. Adapted from [10]. Percentage values are changes in area under the concentration-time curve: ↑, increase; ↓, decrease; ↔, no change. APV, amprenavir; ARV, antiretroviral; ATV, atazanavir; b.i.d., twice daily; DLV, delavirdine; EFV, efavirenz; f-APV, fosamprenavir; IDV, indinavir; LPV, lopinavir; LPV/rtv, ritonavir-boosted LPV; NFV, nelfinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir, t.i.d., 3 times daily.

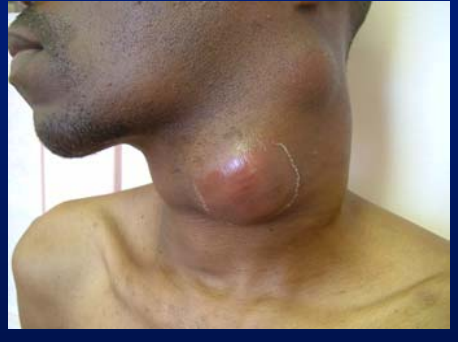
[a] Rifampin levels are not significantly affected by PI or NNRTI coadministration; therefore, no rifampin dose adjustment is required.

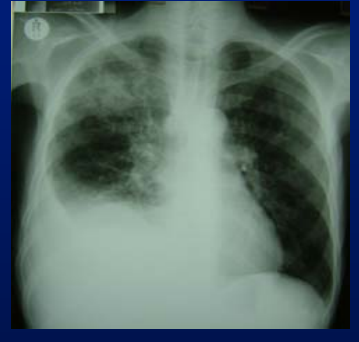
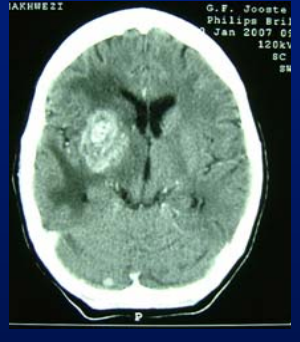
[b] NFV (750 mg t.i.d.) should not be used with RIB.

[c] SQV, APV/f-APV, IDV, or ATV.

Important Issues in TB/HIV
TB-IRIS

- Paradoxical deterioration on TB treatment
- "Unmasking" of untreated TB



PARADOXICAL TB-IRIS

TB-IRIS Paradoxical Reactions

- Incidence: 8-45%
- Median 2 - 4 weeks after ART initiation
- Risk factors
  - Shorter interval between TB treatment and ART initiation
  - Disseminated TB
  - Low baseline CD4 and high baseline VL
  - Vigorous CD4/VL response to ART
- Life threatening complications described but mortality rare

Lawn 2005, Shelburne 2005, Breton 2004, Narita 1998, Michailidis 2005
Ollala 2002, Breen 2004, Kumarasamy 2004, Lawn 2007

Complications of Antiretroviral Therapy in Patients with Tuberculosis: Drug Interactions, Toxicity, and Immune Reconstitution Inflammatory Syndrome

Table 3. Tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS) paradoxical responses: clinical case series that have reported on ⩾8 patients.

Study	IRIS incidence, no. of cases/ total patients (%)	Interval between HAART and IRIS, median or mean (range), days	Duration of IRIS, median (range), days	Significant association(s)
Breen et al. [84][a]	8/28 (29)	11 (8–18)	NR	Starting HAART within 6 weeks of TB diagnosis
Breton et al. [75]	16/37 (43)	12 (2–114)	NR	Increase in CD4 cell %; increase in CD4/CD8 cell count ratio; disseminated TB
Burman et al. [85]	25/137 (18)	NR	64 (IQR, 44–99)	Extrapulmonary TB; early initiation of HAART
Kumarasamy et al. [86]	11/144 (8)	42 (10–89)	NR	NR
Michailidis et al. [87][b]	14/55 (26)	15[c]	76 (0.53–14.97)	Low baseline CD4 cell count; disseminated TB; CD4 cell count increase while receiving HAART
Narita et al. [81]	12/33 (36)	15	20[d]	PPD conversion
Olalla et al. [88][e]	9/33 (27)	18 (3–210)	57 (19 to >395)	Greater decrease in VL; lower CD4 cell count at 6 months
Shelburne et al. [89][f]	26/86 (30)	46 (3–658)	NR	Shorter interval for starting HAART; more rapid initial decrease in VL

NOTE. HAART, highly active antiretroviral therapy; IQR, interquartile range; NR, not reported; PPD, purified protein derivative; VL, viral load.

McIlleron, H, Meintjes, G, Burman, WJ, Maartens, G. J Infect Dis 2007; 196 Suppl1:S63

Challenges In Diagnosis

No Diagnostic Test; Diagnosis Of Exclusion

DRUG RESISTANCE

13/141 in Cape Town cohort of
TB-IRIS suspects had
MDR
or Rifampicin monoresistant

ADDITIONAL DIAGNOSIS

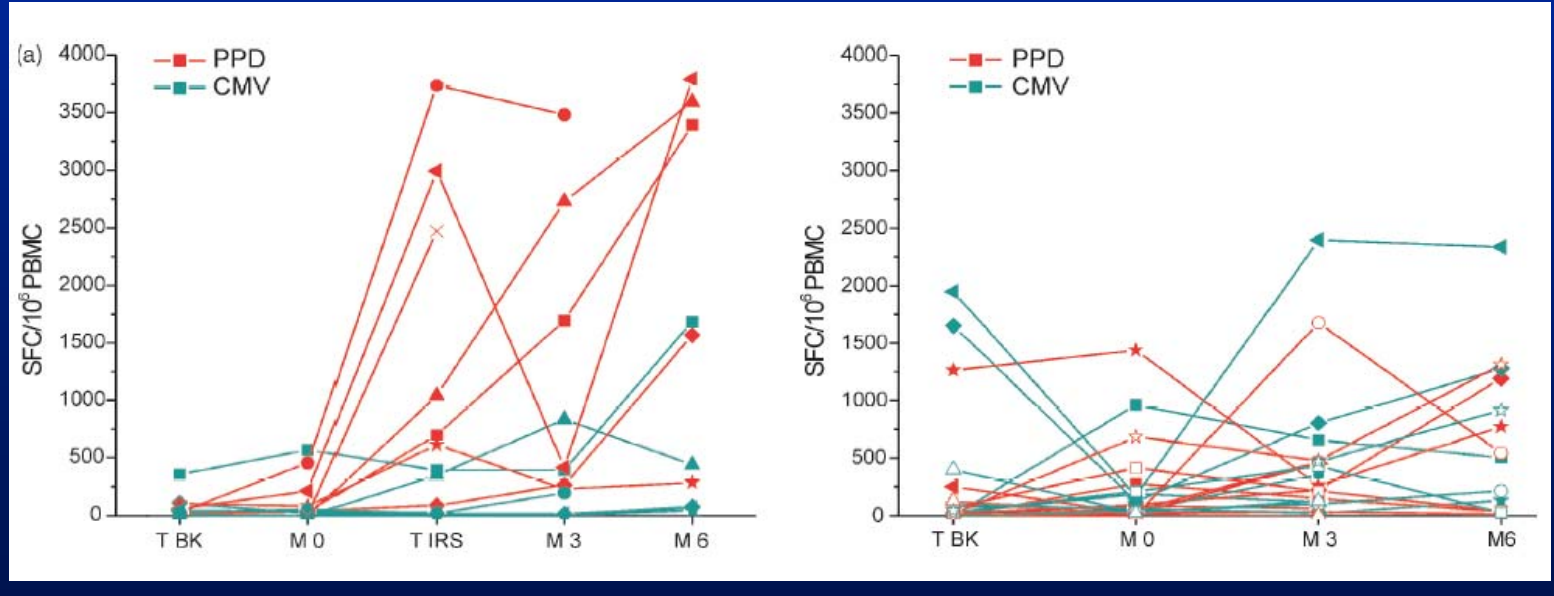
Bacterial infections
Fungal infections
NTM infections
Malignancies

DRUG REACTION

Drug fever vs TB-IRIS fever
Hepatic involvement

Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients

Anne Bourgarit[a,b], Guislaine Carcelain[a], Valerie Martinez[a], Caroline Lascoux[b], Veronique Delcey[c], Brigitte Gicquel[d], Eric Vicaut[e], Philippe H. Lagrange[f], Daniel Sereni[b] and Brigitte Autran[a]



IRIS + **IRIS -**

AIDS 2006, **20**:F1–F7

Case Definition

- Diagnosis of HIV and TB **– WHO criteria**
- Response to TB treatment **– improved/stabilised**
- On ART
  - **Response documented by >1 log decrease in HIV RNA, though seldom available**
- Onset **within 3 mo (up to 6) of starting/changing ART**
- Exclusion of alternative explanation
  - **TB treatment failure due to drug resistance**
  - **Another opportunistic infection or neoplasm**
  - **Drug toxicity or reaction**
  - **Complete non-adherence to ART**

Case Definition
Clinical Criteria

Major

1) New/enlarging lymph nodes, cold abscesses or other focal tissue involvement
2) New/worsening radiological features of TB
3) Breakthrough TB meningitis or new/enlarging focal CNS lesion
4) New or worsening serositis

Minor

1) Constitutional symptoms- e.g., fever, night sweats
2) Respiratory symptoms - e.g., cough, dyspnea, stridor
3) Abdominal pain and/or hepatomegaly
4) Resolution of clinical and/or radiological findings without change in TB treatment

1 major or 2 minor

Treatment
Corticosteroids

- Case reports documenting response
- Potential complications
  - KS, herpes reactivations and other side effects
- Many cases self-limiting
- Dose and duration?

Delaying ART Initiation in Patients Diagnosed with TB?

PRO

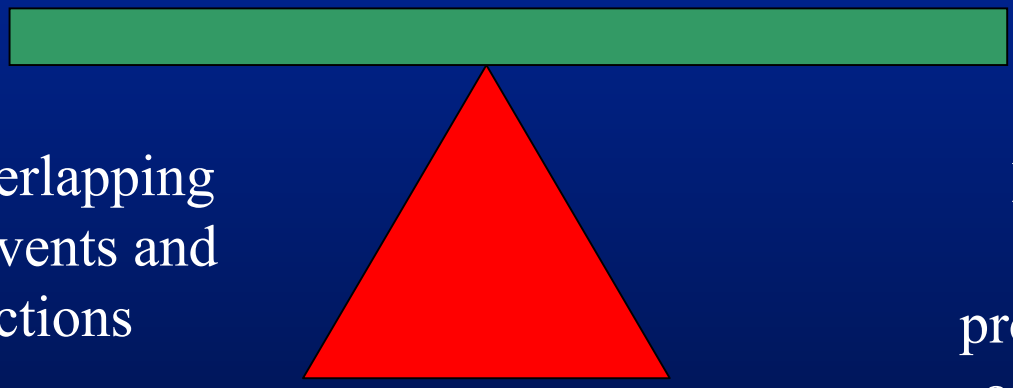
- It may be prudent to delay the initiation of antiretroviral therapy for two months in order to avoid a paradoxical worsening of TB due to immune reconstitution.
- Delaying HAART can also decrease the risk of overlapping drug adverse effects and interactions.

CON

- Delaying HAART in patients with advanced immunosuppression may increase the risk of opportunistic infections and death.

Optimal Timing of ART Initiation in Those on TB Treatment?

EARLY **DELAYED**



IRIS ; overlapping adverse events and interactions

Risk of disease progression and death

Outcome of HIV-Associated Tuberculosis in the Era of Highly Active Antiretroviral Therapy

Retrospective study comparing outcomes between 36 patients starting TB treatment during the pre-HAART and 60 patients starting in the post-HAART era.

Main Results

- At a median follow-up of 3.6 years, one-half of all deaths or new AIDS-defining illnesses occurred within the first two months of TB treatment in the approximately one-third of patients with a CD4+ counts below 100/microL at baseline.
- In contrast, only 15 percent of such events occurred in the first two months in patients with higher CD4+ counts.
- HAART use was associated with a marked and significant decrease in the risk of death (adjusted HR 0.18) or a new AIDS-defining illnesses (adjusted HR 0.38).
- Most deaths were due to HIV-related causes not to TB complications

Dheda K, et al. J Infect Dis 2004; 190: 1670

“UNMASKING” TB-IRIS

"Unmasking" TB-IRIS in Developing Country Settings

- High rates of incident TB in the period after ART initiation
  - 17.6/100 person years (Bonnet 2006)
  - 23/100 person years in first 90 days (Lawn 2006)
- Cases of accelerated TB (John 2006)
- Background of high TB incidence in those not on ART
- Unclear extent of role IRIS plays in the presentation of incident TB early after ART initiation

Important Issues in TB/HIV
Prevention

- Antiretroviral therapy
- Treatment of *M. tuberculosis* infection
  - Isoniazid
- Both antiretroviral therapy + isoniazid
  - Golub J. AIDS 2007;21:1441-8.
- Post-TB treatment isoniazid
- BCG vaccination

LTBI

- HIV infection carries a high risk for progression to active disease so LTBI therapy is recommended for all PPD-positive, HIV-infected patients, regardless of age.
- In addition, the risk is considered so great that the threshold for interpreting a PPD as positive is the presence of 5 mm or more of induration 48 to 72 hours after intradermal administration of 5 tuberculin units of PPD.

Tuberculin Skin Test

- Although interpretation of the tuberculin skin test in HIV patients is somewhat problematic, knowledge of the CD4 count helps to guide the approach to these patients.
- In one report of HIV-infected patients with TB, for example, a positive skin test (ie, greater than 5 mm of induration) was seen in 10 of 11 patients with a CD4 count above 300 cells/mm3 versus none of 13 with fewer than 100 CD4 cells/mm3
- A negative test, particularly in patients with CD4 counts less than 300 cells/mm3, does not rule out active or latent infection.

Jones BA, et al. Am Rev Respir Dis 1993; 148:1292

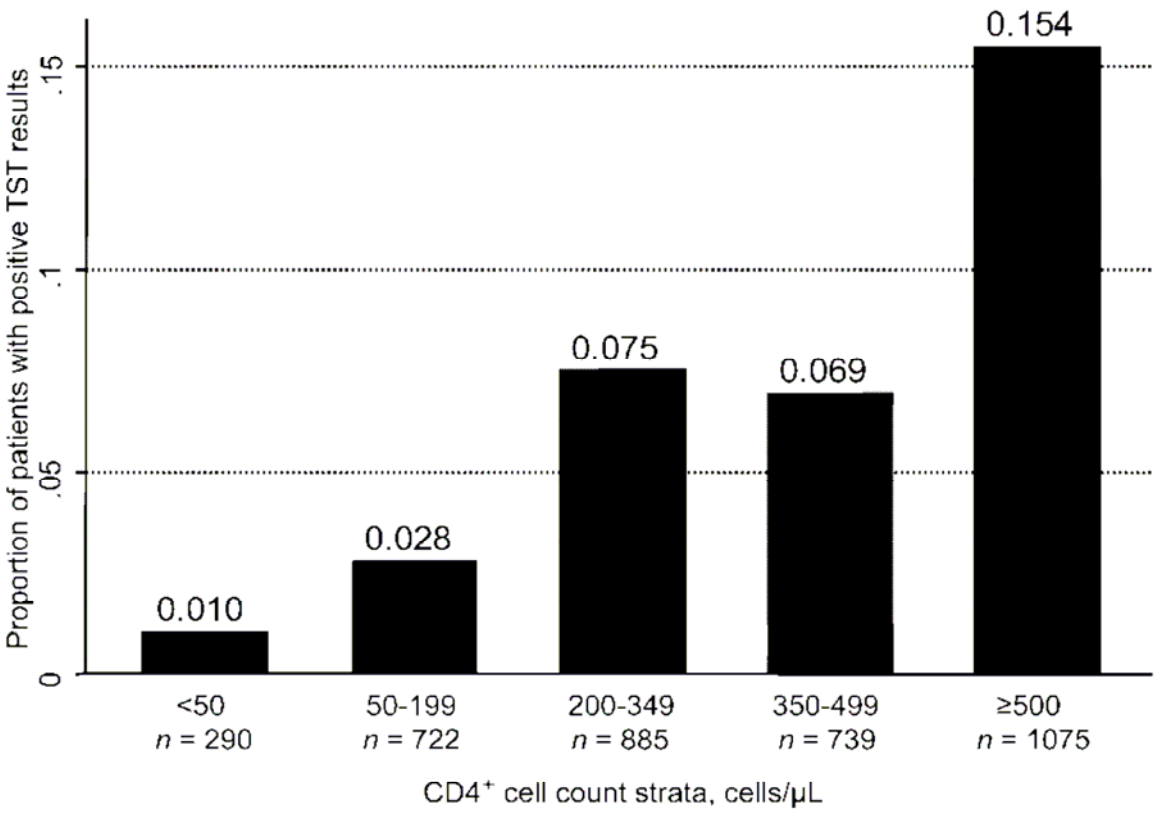


Figure 1. Proportion of patients with positive tuberculin skin test (TST) results according to $CD4^+$ cell count stratum at the time of TST ($P <$ .001 for trend statistics).

Elzi L. Clinical Infectious Diseases 2007; 44:94–102

Reducing Tuberculosis Incidence By Tuberculin Skin Testing, Preventive Treatment, And Antiretroviral Therapy In An Area Of Low Tuberculosis Transmission

Retrospective study on 6160 participants the Swiss HIV Cohort Study after 1995

Parameter	Adjusted HR (95% CI)	*P*
TST result missing (as compared with negative TST result)	9.9 (4.8-20.3)	<.001
TST result positive (as compared with negative TST result)	25 (10.8-57.4)	<.001
Sub-Saharan Africa (as compared with low-risk region)	5.8 (2.7-12.5)	<.001
Medium-risk region (as compared with low-risk region)	3.6 (1.5-8.6)	.003
Baseline $CD4^+$ cell count (per 100 cells/μL increase)	0.76 (0.65-0.89)	.001
Baseline plasma HIV RNA level (per $\log_{10}$ increase)	1.33 (1.08-1.7)	.007
Female sex	0.96 (0.54-1.7)	.9
Heterosexual HIV transmission (as compared with MSM)	2.32 (0.80-6.7)	.1
IDU HIV transmission (as compared with MSM)	1.91 (0.61-6.0)	.3
Other/unknown HIV transmission (as compared with MSM)	1.05 (0.19-5.7)	1.0
Age per 10-year increase	0.81 (0.58-1.13)	.2
Start of triple ART	0.44 (0.24-0.81)	.008

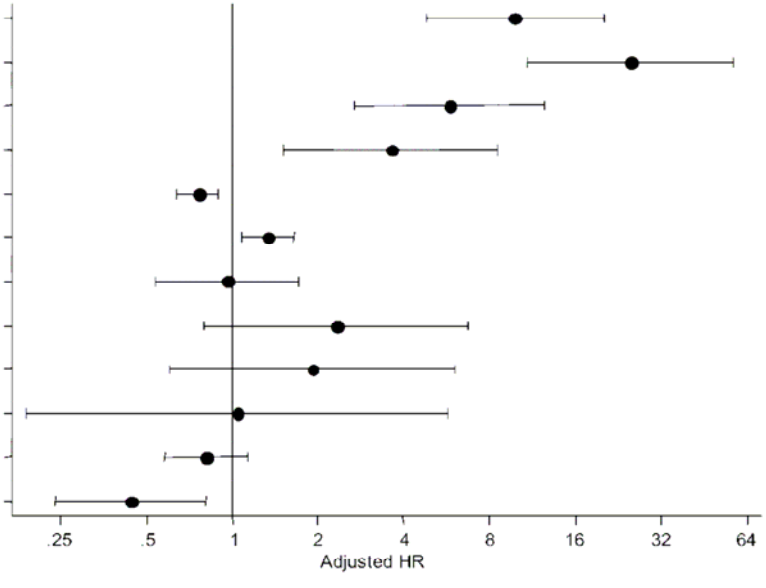


Figure 3. Results of a Cox proportional hazards model of developing tuberculosis during follow-up. The model included all of the variables shown. *Bars*, 95% CI. ART, antiretroviral therapy; HR, hazard ratio; IDU, injection drug use; TST, tuberculin skin test.

Elzi et al. Clin Infect Dis 2007; 44:94

Comparison of an Interferon- G Release Assay to Tuberculin Skin Testing in HIV-Infected Individuals

- **4 studies with Elispot**
  - Elispot >TST
  - Lower positive results than in immunocompetents
- **1 study with QFT-G**
  - Low prevalence
  - > Indetrerminate results if CD4+ < 100/mm3

Menzies et al, Ann Intern Med. 2007; 146:340-354

Comparison Of An Interferon- g Release Assay To Tuberculin SkinTesting In HIV-Infected Individuals

- Concordance between QFT and TST was 89.3% (kappa=0.37, p=0.007).
- TST-positive/QFT-negative discordant results were found in 5.1% of subjects
- TST-negative/QFT-positive discordance in 5.6%
- Indeterminate QFT results occurred in 5.1%, all due to a failure to respond to the PHA -positive control
- Subjects with a CD4< 100 cells/mm had RR of indeterminate result of 4.24 (95% confidence interval, 1.55-11.61; p=0.003) compared with those with a CD4(+) count of 100 or more

Luetkemeyer et al. Am J Respir Crit Care Med. 2007

LTBI Therapy is Recommended in the Following Circumstances

- Recent contact with a patient with infectious TB, regardless of PPD status or a history of previous preventive TB treatment
- A history of prior untreated or inadequately treated prior TB, regardless of PPD status
- HIV-positive and PPD-negative persons with an unavoidable high risk of TB exposure (eg, residents of prisons of homeless shelters)

LTBI Treatment

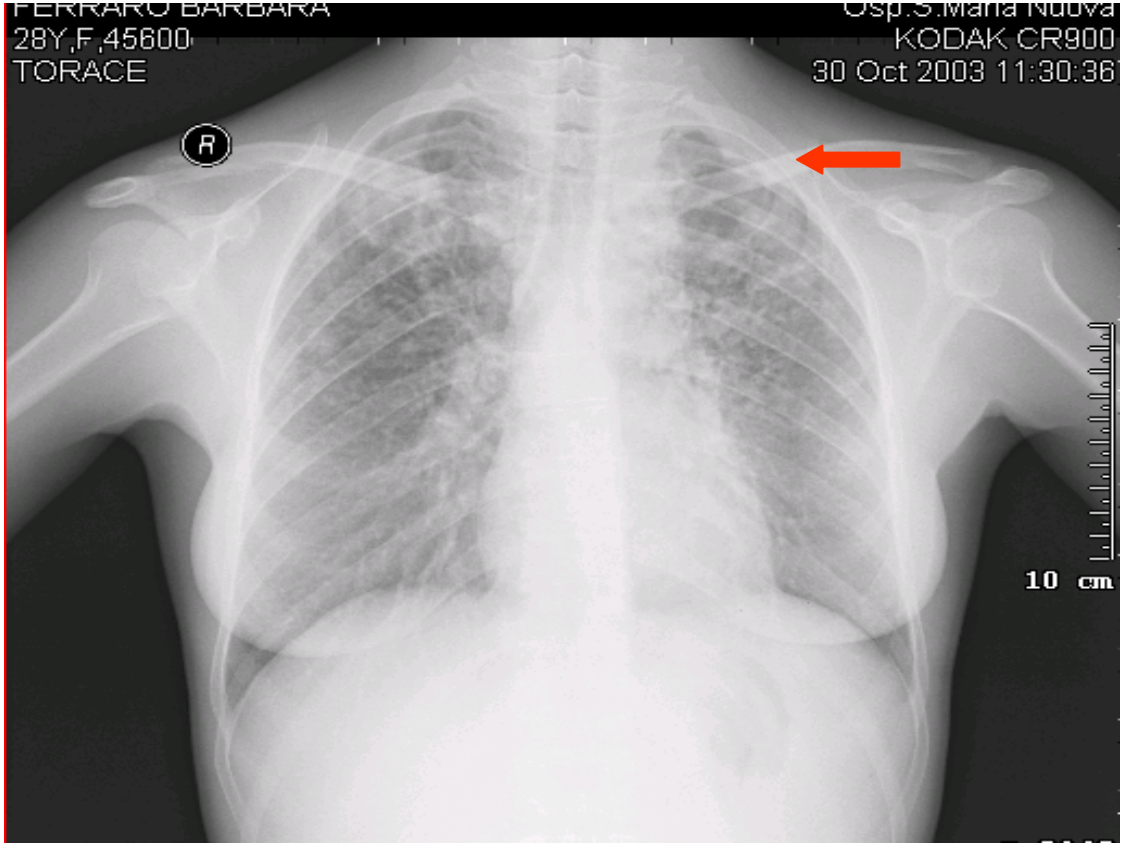
- INH (300 mg daily or 900 mg twice weekly) for a period of nine months or
- Rifampin (600 mg daily or twice weekly) for four months in patients exposed to INH-resistant, rifampin-sensitive M. tuberculosis.
- No longer recommend the combination of Rifampin plus Pyrazinamide (RZ) for any patients by ATS and CDC.

BCG Vaccination Recommendations
World Health Organization

- **Contraindications to BCG vaccination:**
  - Persons known to be HIV-infected
    - Replaces previous recommendation that asymptomatic HIV + infants should receive BCG in settings with high TB burden
  - Persons with impaired immunity
  - Persons receiving immunosuppressive treatment
    - Corticosteroids, etc
  - Pregnancy

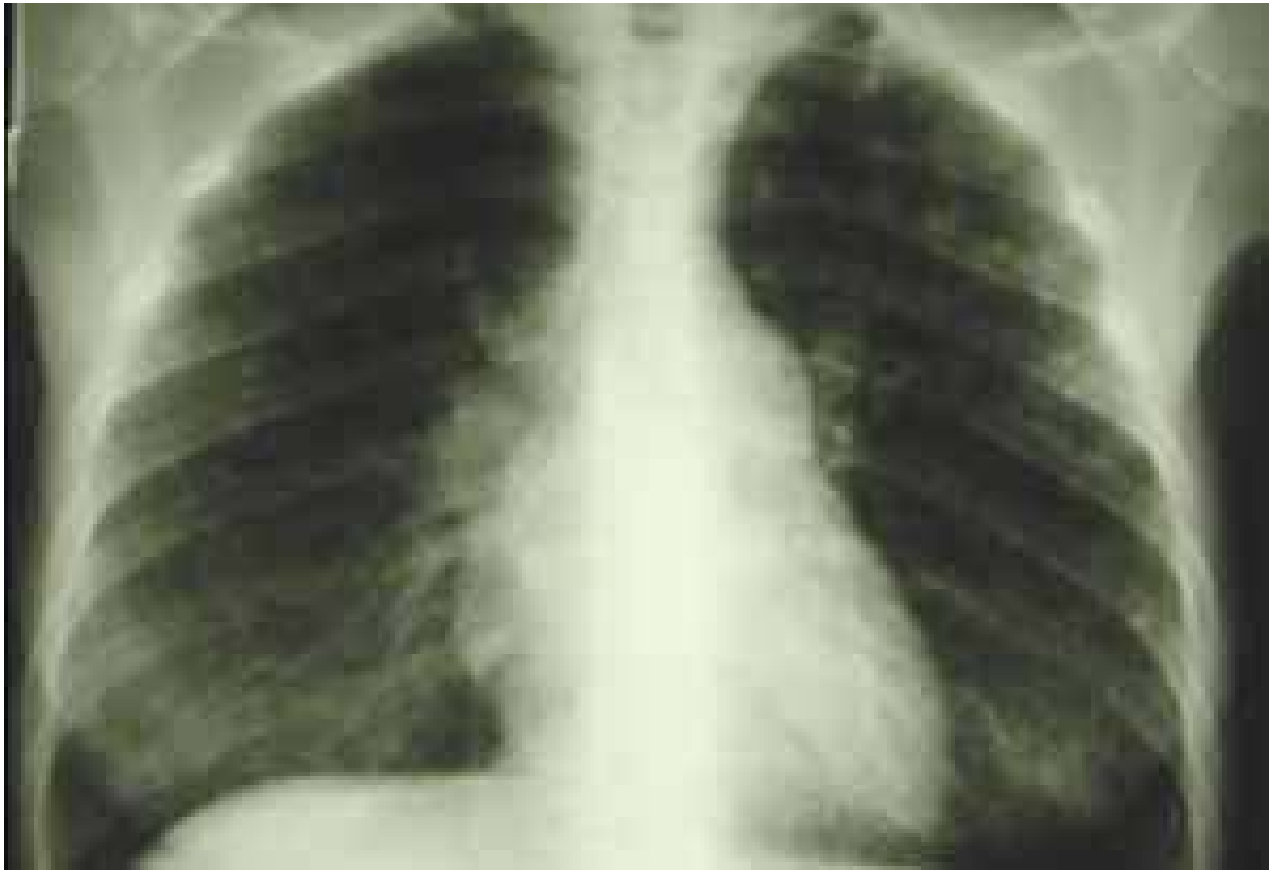
Wkly Epidemiol Rec 2007;82:21 (25 May 2007)

Paziente HIV POS, CD4+ 230 /ml
Escreato Positivo per *M. tuberculosis*

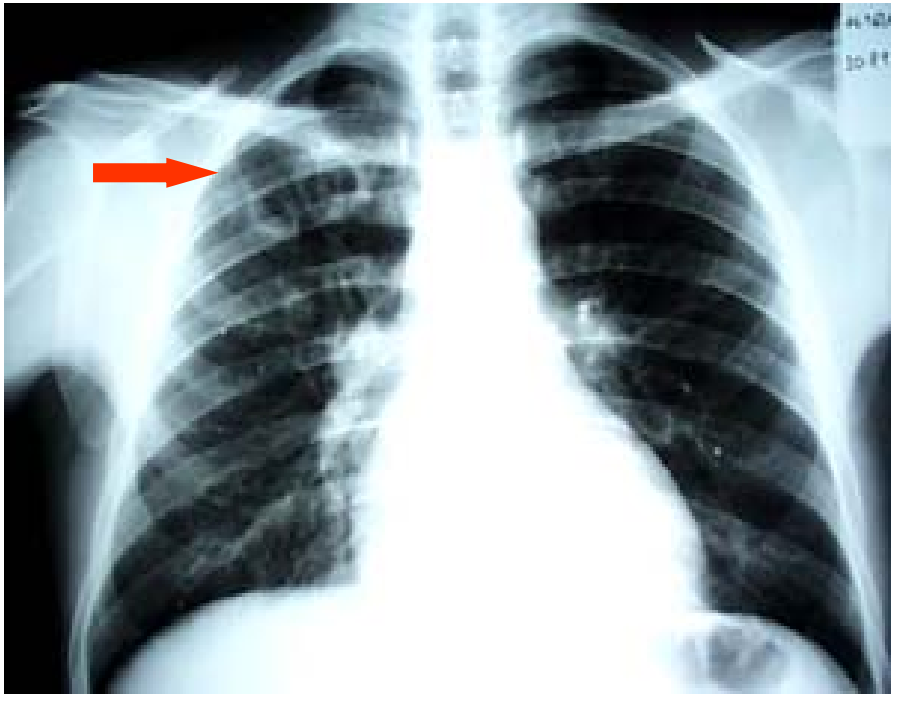


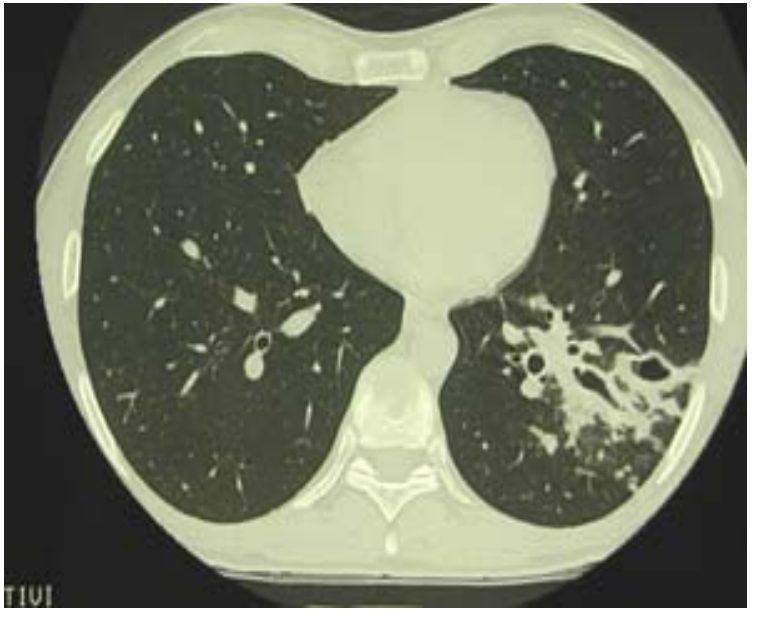
Rx torace: aspetti miliarici bi-polmonari ai campi medio superiori ed area scavata in apice sx e addensamento retroclaveare dx.

Paziente HIV POS, CD4+ 2 /ml
Escreato, BAL e Sangue Positivi per *M. tuberculosis*

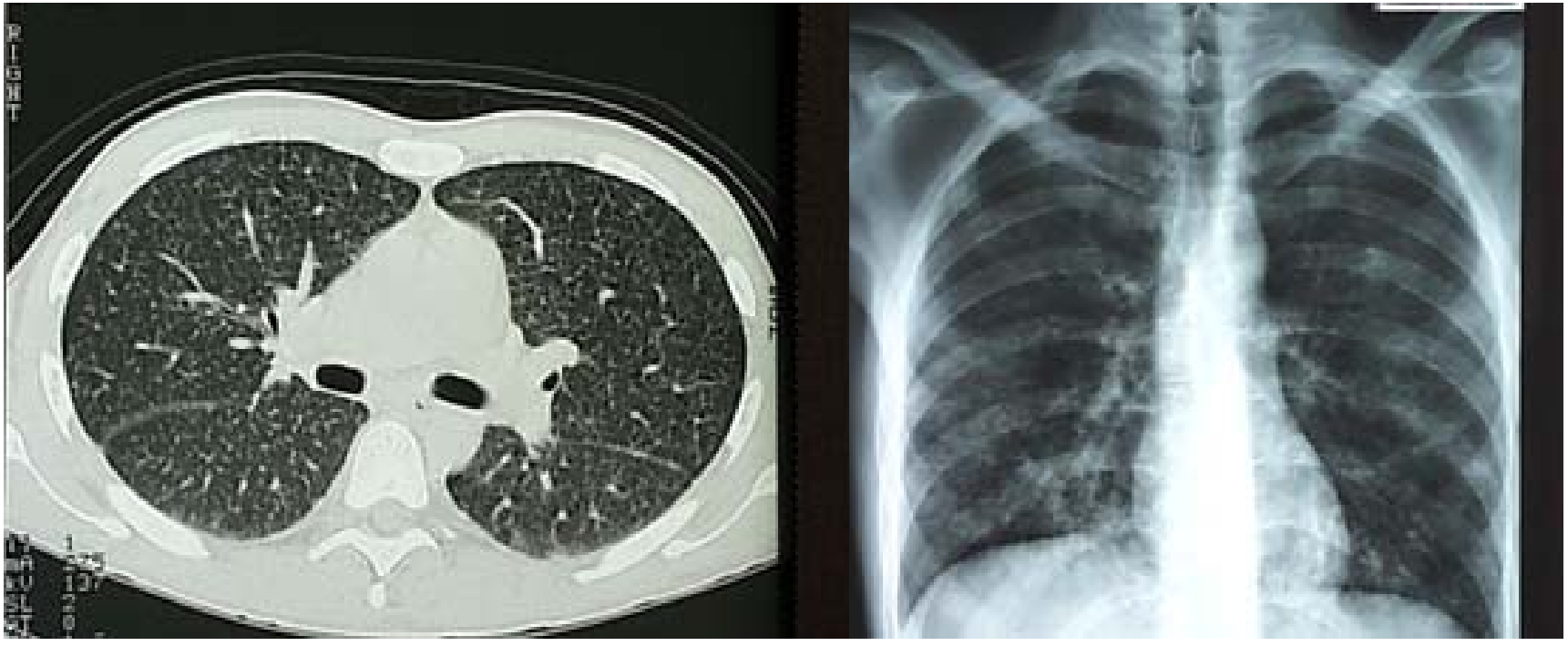


Senegalese, 20 anni, HIV POS, CD4+ 380/ml
In Italia da 18 mesi
Ricoverato per febbre persistente e tosse

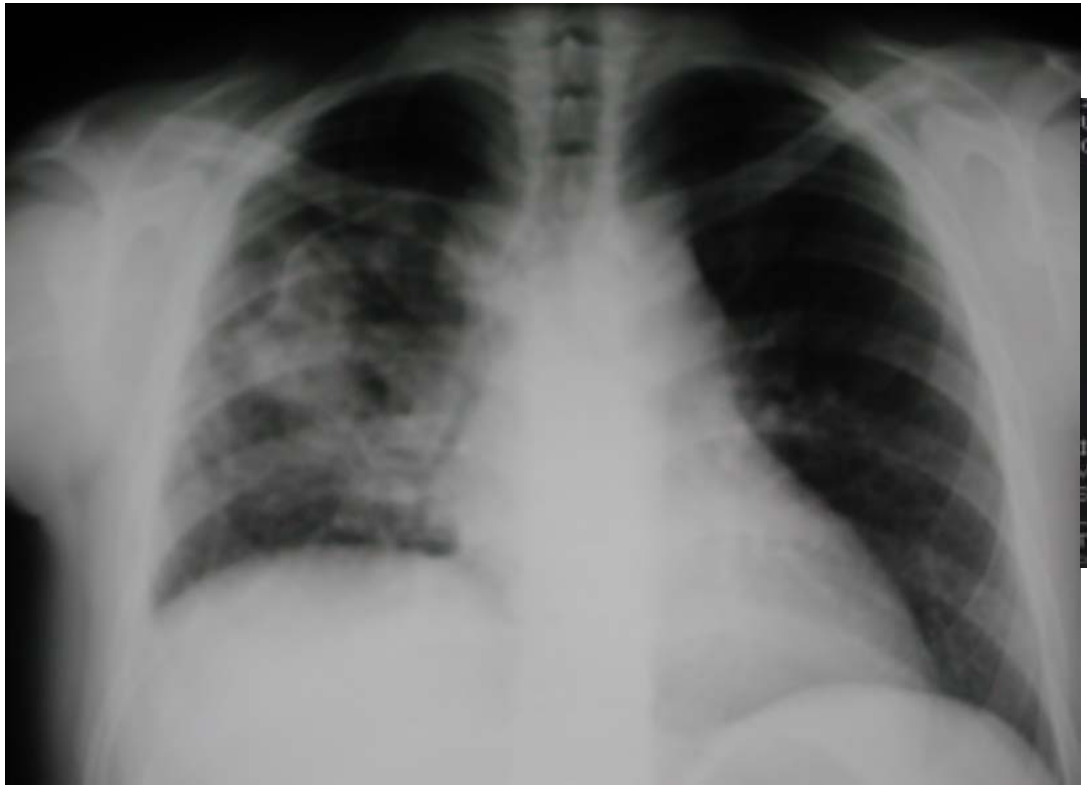


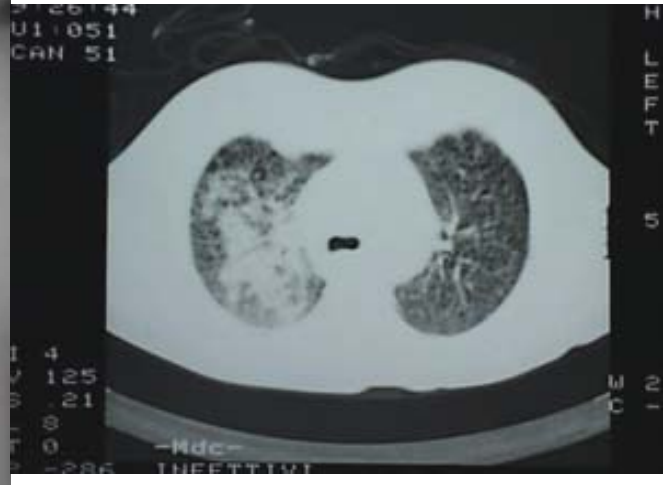


Tossicodipendente, HIV POS, 24 anni, CD4+ 35/ml
Due anni prima trattato per TB
Isolamento di *M. tuberculosis* da Escreato e BAL

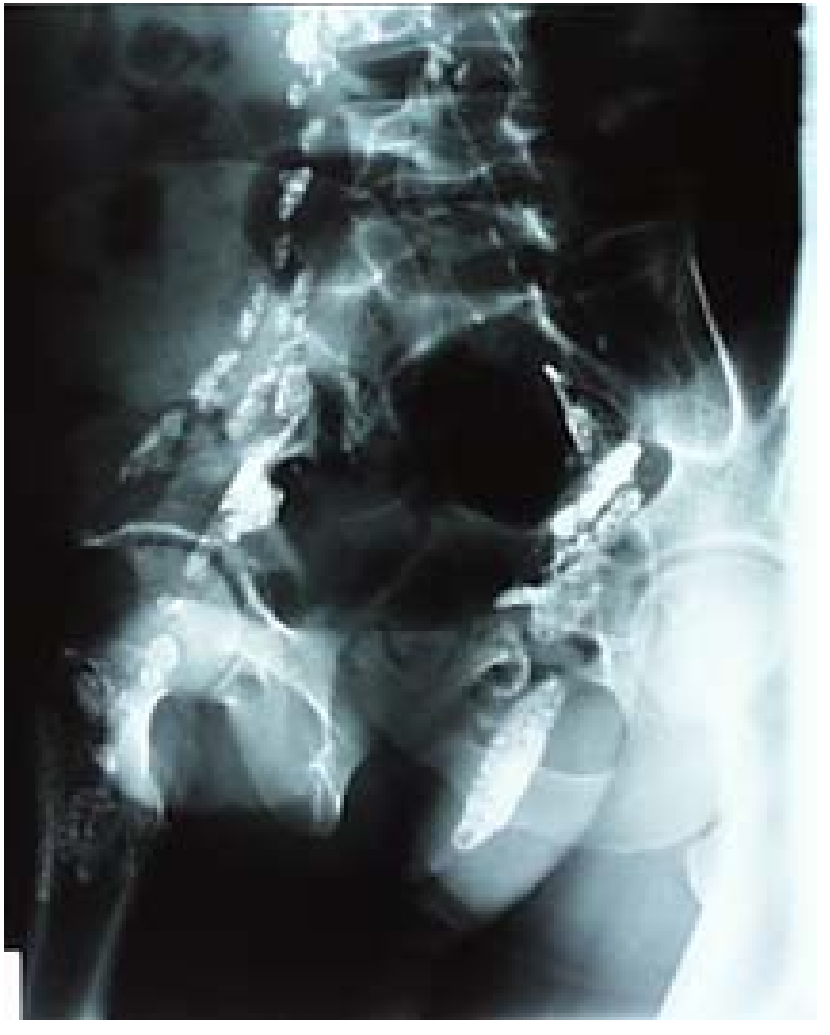


Tossicodipendente, HIV POS, CD4+ 2/ml
Isolamento di *M. tuberculosis* da Escreato e Sangue

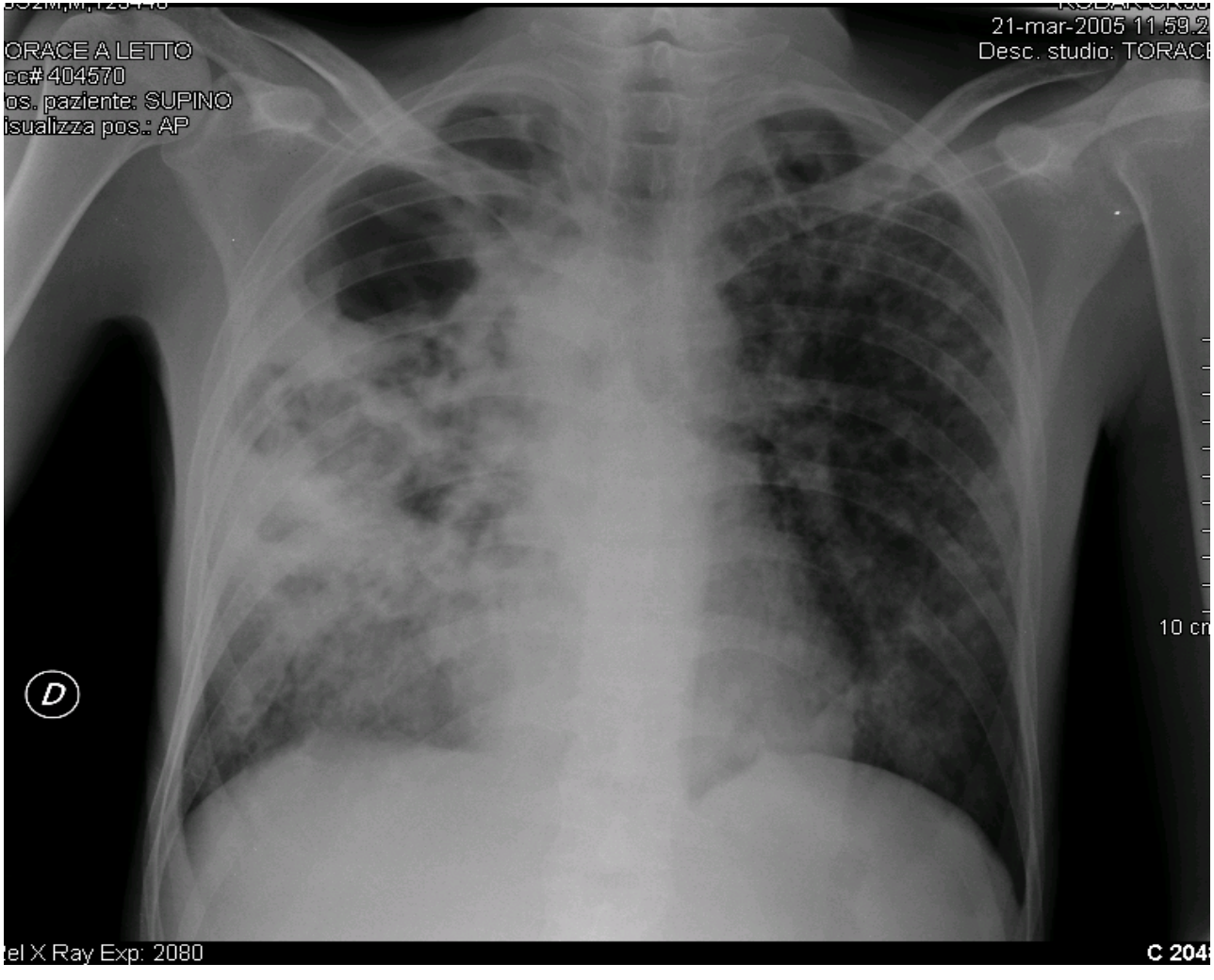




Senegalese di 35 anni, HIV POS, CD4+ 20/ml



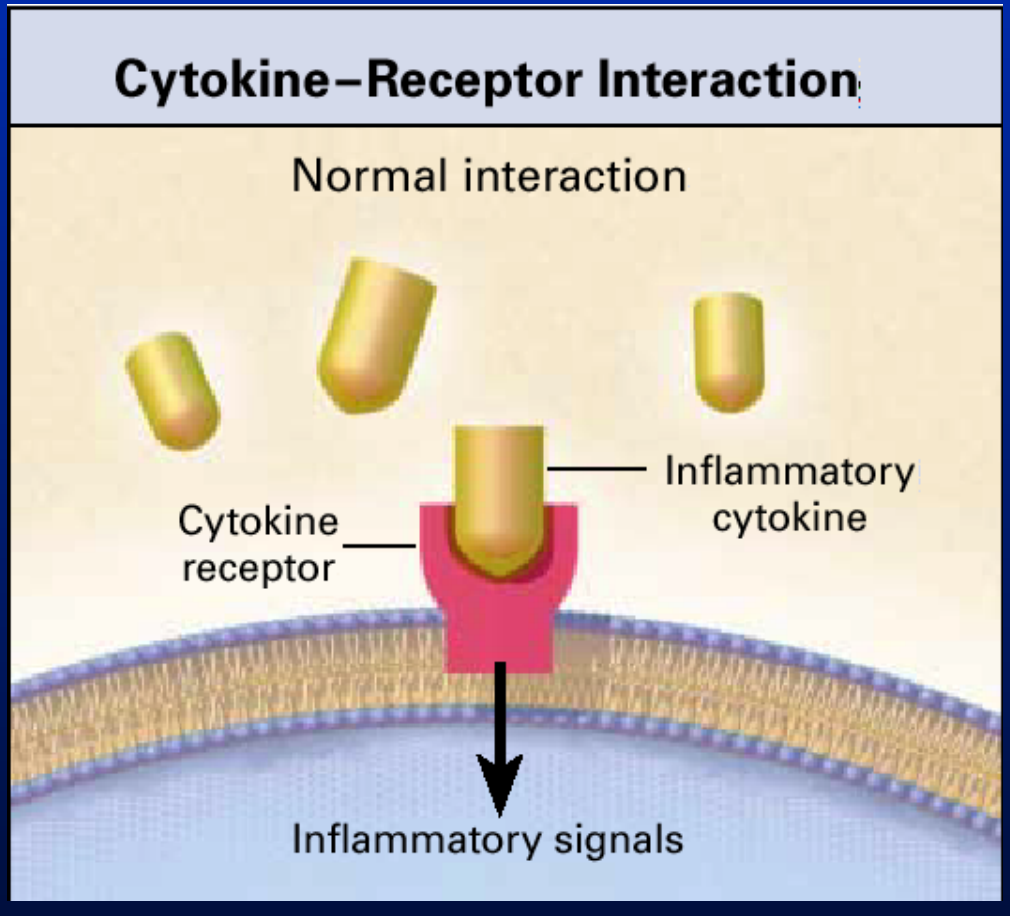
PazientePakistano, HIV POS, CD4+ 2/ml



Decesso dopo 1 settimana

ANTI-TNF ALFA E TB

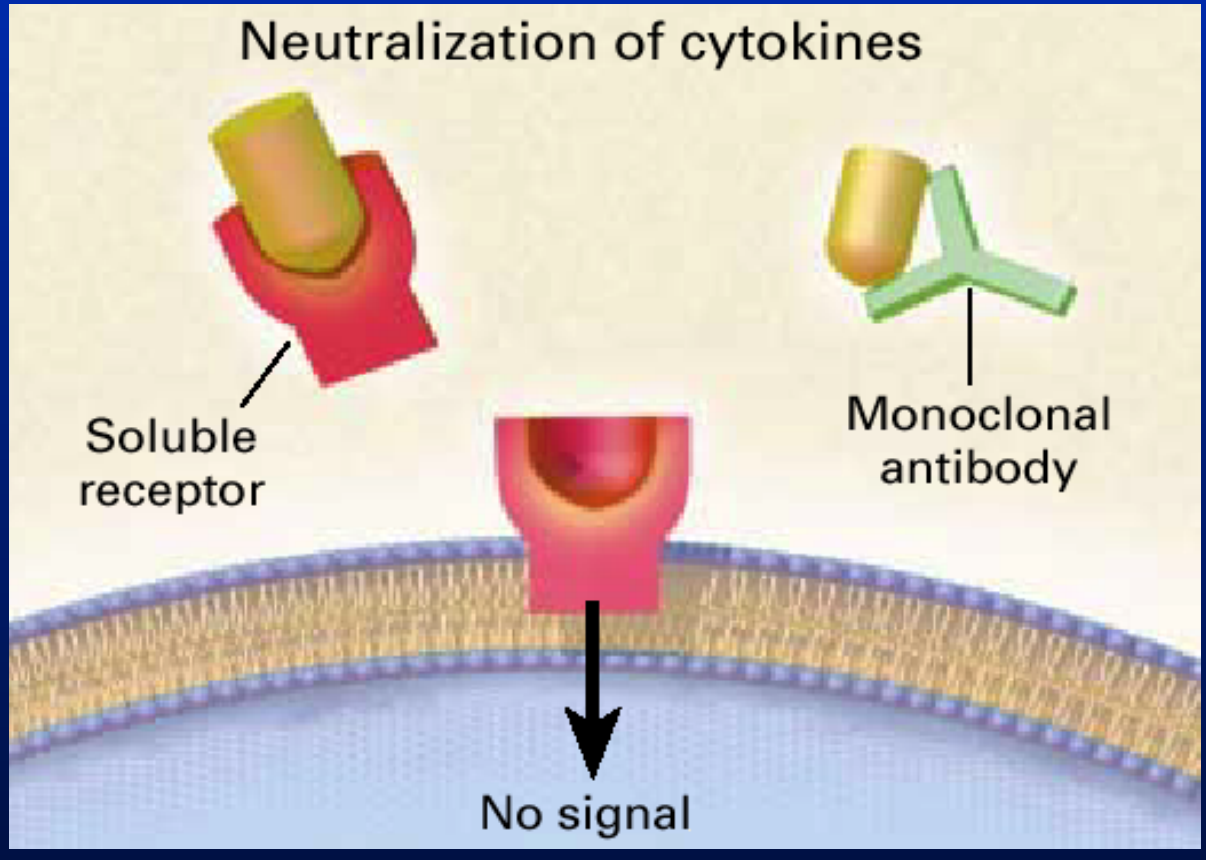
Interazione Citochine-Recettore



Farmaci biologici anti- α TNF

- **Etanercept:** proteina ricombinante di fusione tra il recettore solubile del TNF e la porzione Fc di una Ig
- **Infliximab:** anticorpo monoclonale anti TNF chimerico (topo-uomo)
- **Adalimumab:** anticorpo monoclonale anti TNF totalmente umano

Meccanismo d'azione anti-TNF



α-TNF Antagonists
Characteristics

	Infliximab	Etanercept	Adalimumab
Structure	chimeric mAb	TNF IgG1 fusion protein	Human mAb
Binding target	TNF	TNF,lymphotoxin	TNF
Bindinf affinity	$1,8 \times 10^{9}$	10^{10}	$2,3 \times 10^{10}$
Half-life days	8-9,5	4-5	12-14
In vitro complement Mediated cell lysis	+	-	+
Dose	q 60 days	q 3-4 days	q 7-14 days
Efficacy in Crohn's disease	+	-	+

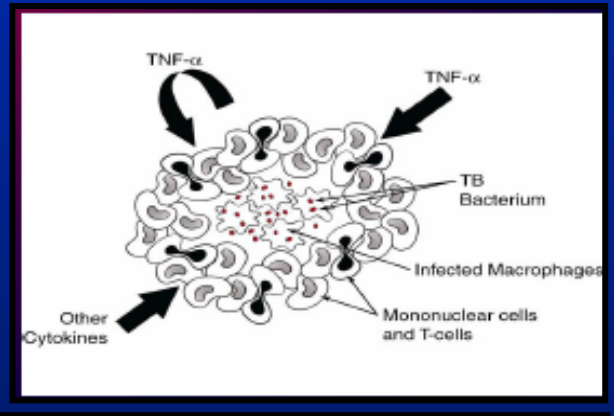
Rischi Correlati agli Anti α -TNF

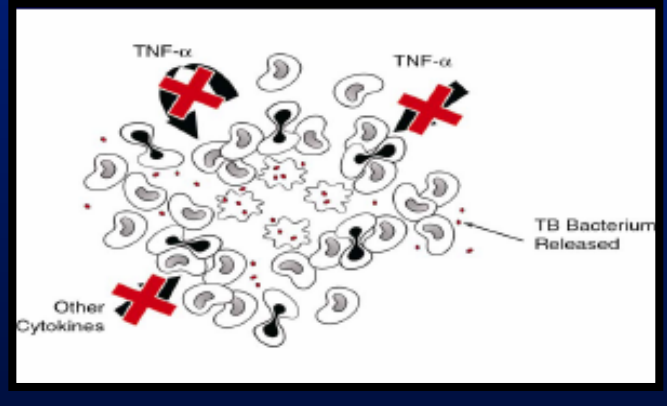
- Tubercolosi
- Tumori (linfomi)
- Scompenso cardiaco (CHF)
- Sindromi lupus-like
- Malattie demielinizzanti

Tubercolosi ed Anti α-TNF

- α-TNF **ha un ruolo chiave nella clearance della infezione da *Mycobacterium tubercolosis:* → α-TNF mantiene l'omeostasi del granuloma**

- **la riattivazione della TB con** anti-TNF **è dovuta alla incapacità del granuloma di compartimentalizzare il *Mycobacterium tubercolosis***





Tubercolosi ed Anti α-TNF

- 1999 : infliximab (approvazione FDA)
- 2000 : infliximab (approvazione EMEA)
- Ottobre 2001 : 70 casi di tubercolosi sotto infliximab

Keane et al. N Engl J Med, vol 345, N°. 15. Oct. 11, 2001

TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR α–NEUTRALIZING AGENT

JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

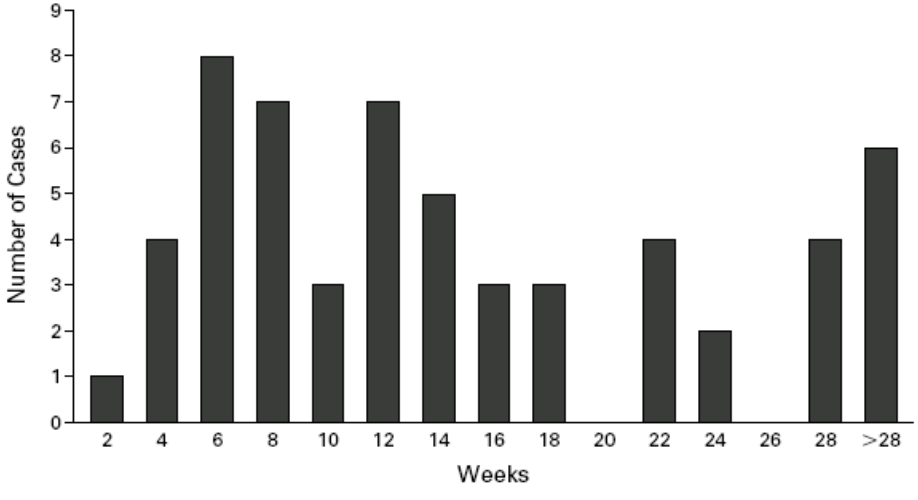
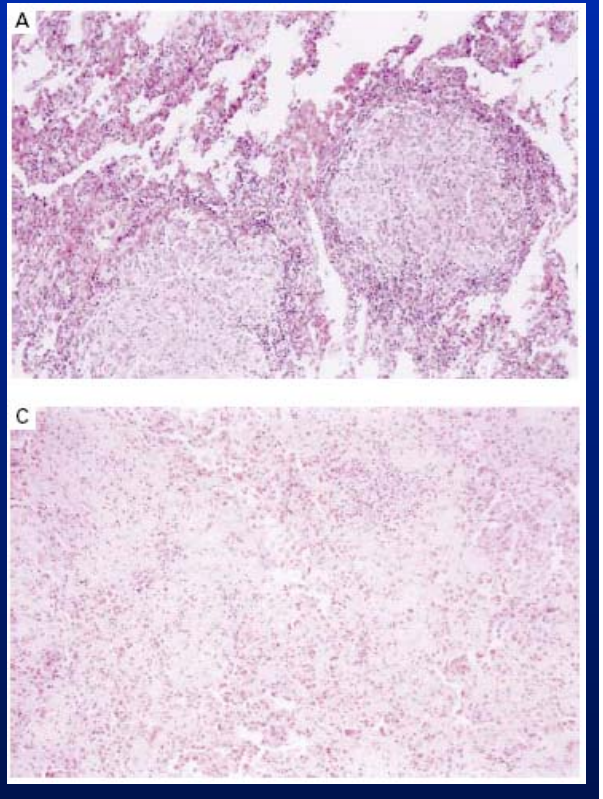


Figure 1. Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis.
Data were available for 57 patients, most of whom had received monthly infusions of infliximab.

No

Anti TNF



N Engl J Med, Vol. 345, No. 15 · October 11, 2001

Incidence of Tuberculosis under Etanercept and Infliximab

Table 1. Pathogens that caused granulomatous infections in US patients who received infliximab or etanercept.

Pathogen, type of infection	Infliximab group (n = 233,000)	Etanercept group (n = 113,000)	Rate ratio	P
Mycobacterium tuberculosis	335 (143.8)	39 (34.5)	4.17	<.001[a]
Histoplasma capsulatum	39 (16.7)	3 (2.7)	6.30	<.001[b]
Candida species				
Any	38 (16.3)	8 (7.1)	2.30	.006[b]
NS	26 (11.2)	7 (6.2)	1.80	.065[b]
Systemic	10 (4.3)	1 (0.9)	4.85	.046[b]
Listeria species	36 (15.5)	2 (1.8)	8.73	<.001[b]
Mycobacterium species (NS)	30 (12.9)	7 (6.2)	2.08	.023[b]
Aspergillus species	29 (12.4)	10 (8.8)	1.41	.17[b]
Cryptococcus species	11 (4.7)	8 (7.1)	0.67	.91[b]
Nocardia species	10 (4.3)	1 (0.9)	4.85	.046[b]
Salmonella species	7 (3.0)	4 (3.5)	0.85	.75[b]
Toxoplasma species	5 (2.1)	0 (0)	...	.088[b]
Brucella species	2 (0.9)	0 (0)	...	.38[b]
Bartonella species	1 (0.4)	0 (0)	...	.62[b]
Leishmania species	1 (0.4)	0 (0)	...	.62[b]
Mycobacterium leprae[c]	1 (0.4)	0 (0)	...	.62[b]
Overall	556 (238.6)	83 (73.5)	3.25	<.001[a]

NOTE. Data are no. of patients (no. per 100,000 patients who received the drug). NS, species was not specified.

[a] By χ^2 analysis.
[b] By Poisson analysis.
[c] Resulted in leprosy.

Incidence of Tuberculosis under Etanercept and Infliximab

	Etanercept	Infliximab
N.of treated patients with RA	113,000	197,000
N. of tuberculosis	32	106
N/100,000 treated patients	28.3	53.8

Wallis, CID 2004;39:1254-55

Tuberculosis Reactivation and TNF antagonists

M.T.B.in patient with RA treated with TNF antagonists after approval of drug

	Etanercept *	**Infliximab** ***
No.of patient treated	230,000	277,000
Exposure	423,000	466,000
Use		
USA	90%	64%
EU/Norway	10%	36%
MTB reports	38	242
Geography		
USA	26	90
Outside USA	12	152
Time onset, mo	Median 11.20 mo	By 3 infusion : 60% By 7 months: 97%
Characteristics		
Extrapulmonary	34%	30-45%
Miliary	16%	-

*As of Dec 2003.** As of Oct 2003, EU: european Union

Tuberculosis Reactivation and TNF Antagonists

	Etanercept (Enbrel®)	Infliximab *(Remicade®)*	*Adalimumab (Humira®)*	
	Postmarketing		Clinical studies	Post marketing
Patients/years	*230,000*	*230,000*	*4,900*	*5,566*
Tuberculosis	*38*	*173*	13	1
Onset months	*1-22*	*1-8*	3-8	2
Extra- pulmonary	*50%*	*45%*	40%	NA

ACR Hotline 2003

Données post-marketing période Janv-Juillet 2003, patients hors études cliniques

The RATIO study

February 2004 – 2007 : Prospective registry on severe bacterial infections, opportunistic infections and lymphoma

23 tuberculosis during 20 months

Underlying disease :

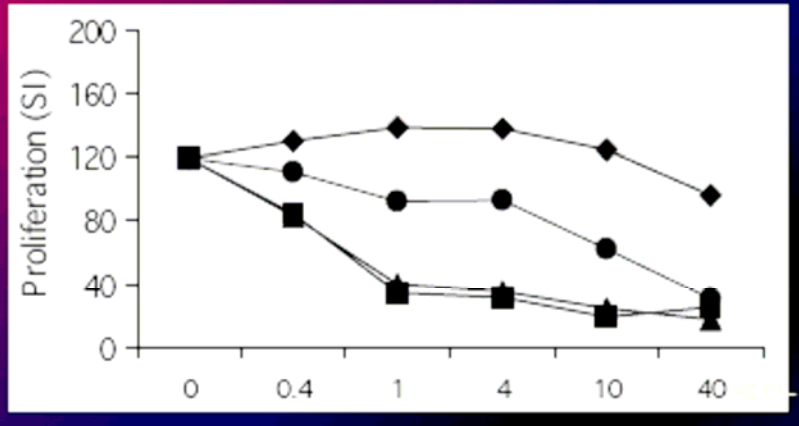
- PR : 16
- SPA : 5
- Crohn : 1
- Others : 1 (Takayashu)

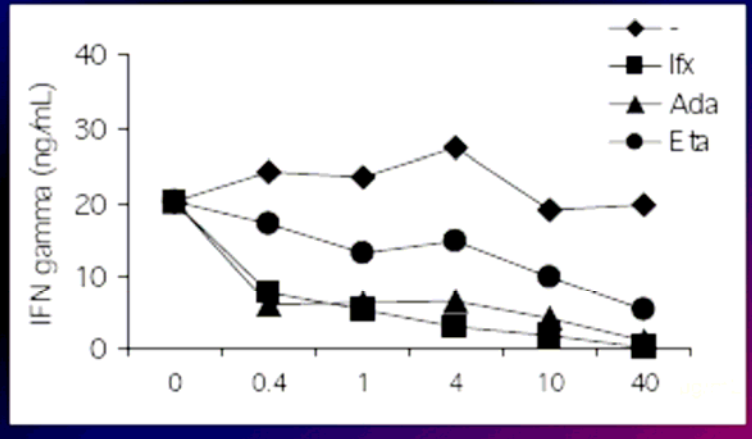
Mediane time between anti-TNF onset and TB: 26 weeks

Drugs involved :

- Infliximab : 10
- Adalimumab : 10
- Etanercept : 3

Effect of TNF antagonists on the activation of anti-TB T lymphocytes





Hamdi H, Arthritis ResTher 2006

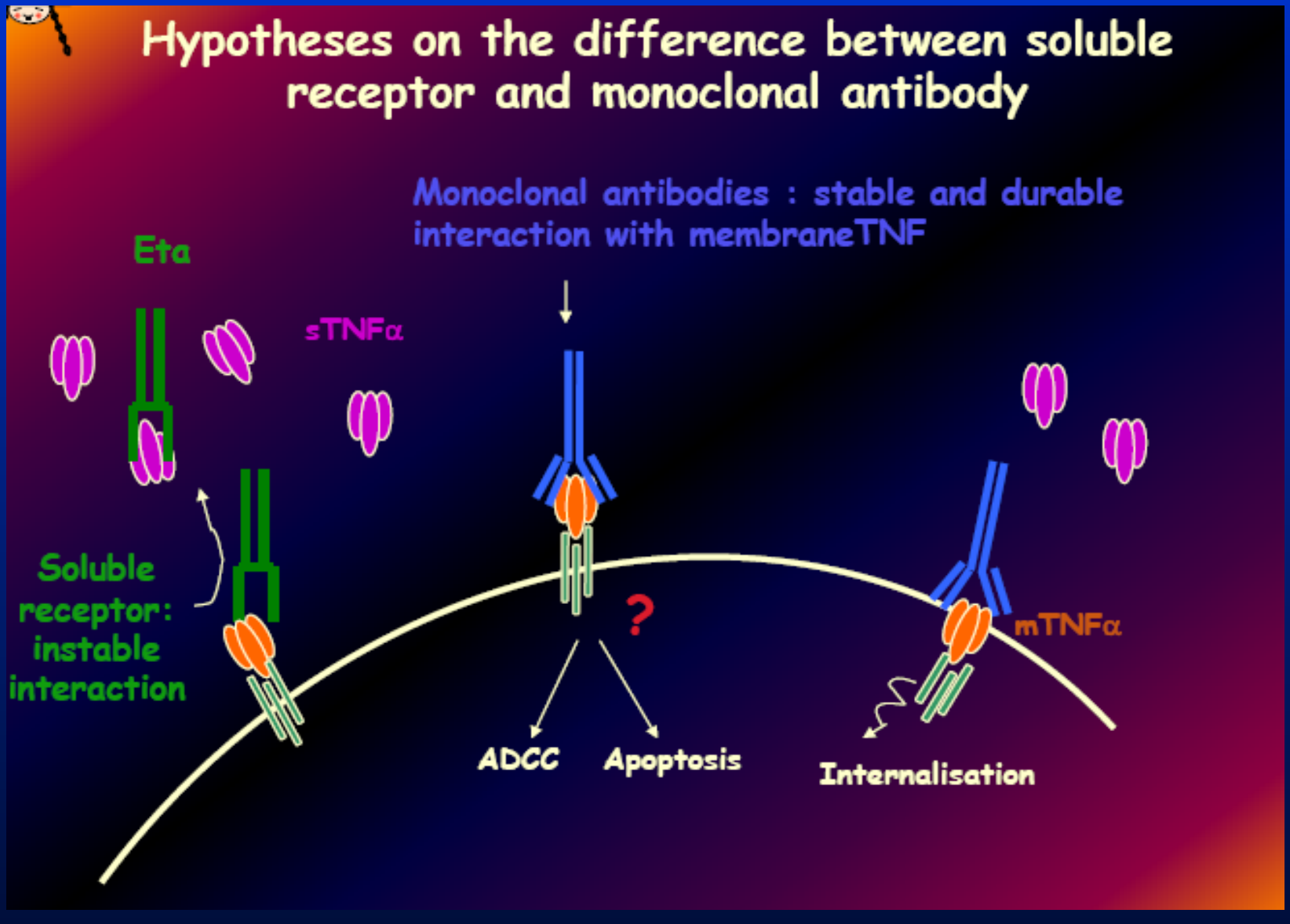
Monoclonal Ab are 10 to 100 times more effective than soluble receptor for inhibiting proliferation and IFNg secretion by activated T cells stimulated with PPD

In vitro effect of TNF antagonists on anti-TB response

- **Impairment of activated T cells**
- **Decrease of membrane TNF by internalization or shedding**

Monoclonal antibodies >> soluble receptor

Hypotheses on the difference between soluble receptor and monoclonal antibody



Differenze tra Infliximab ed Etanercept

- Differenze nel *meccanismo d'azione* e nella capacità di neutralizzazione del TNF
- E*mivita* più lunga di Infliximab (8.9 giorni vs etanercept (3.4 giorni)
- Maggior uso di Infliximab in *Europa* dove vi è una incidenza di fondo di TB più alta
- Aumentata frequenza di *terapie combinate* di Infliximab con altri immunosoppressori

Cosa Fare Prima di Utilizzare gli α-TNF Antagonisti

- Storia familiare
- Storia personale
- Rx Torace
- TST (QFT-TB)
- Se TST o QFT-TB positivi: trattamento anti TB prima di α-TNF Antagonisti
  - Isoniazide 5 mg/Kg per 6 mesi;
  - Rifampicina x 4 mesi nei resistenti

Clinical Evaluation of QuantiFERON TB-2G Test for Immunocompromised Patients

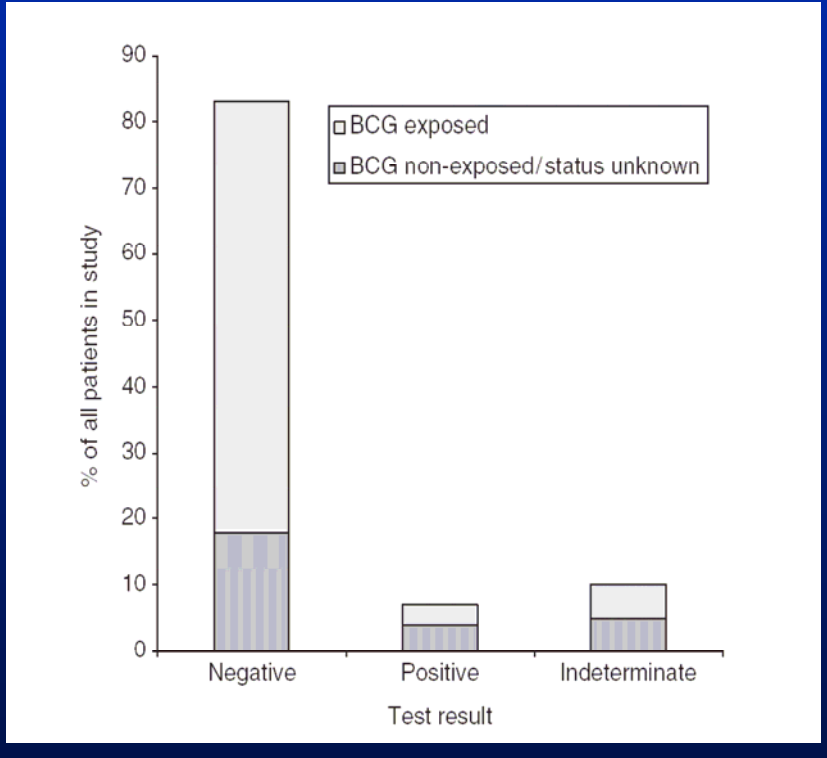
252 immunocompromised pts suspected of TB infection
- 74 cancers,
- 72 on immunosopressive treatment
- 52 diabetes mellitus
- 50 CRF
- 4 HIV

- QFT + = 78,1%
- TST + = 50,0%
- QFT : 13% indeterminate results
  - 28% in pts receiving immunosuppressive treatment
    - +++ if lymphocytopaenia due to severe underlying diseases

Kobashi Y, et al. Eur Respir J. 2007; 30:945-50

Use of the Quantiferon TB Gold Test as Part of a Screening Programme in Patients with RA under Consideration for Treatment With Anti-TNF- α Agents:the Newcastle (UK) Experience

- 101 consecutive RA patients, over 2 year
- BCG status was known in 92% of the patients
- Patients were exposed to methotrexate and 40% of them to corticosteroid



Pratt et al. Rheumatology 2007;46:1036–1037

CASI CLINICI

Anti α -TNF e TB

Caso Clinico

Maschio, 69 anni

Aprile 2007

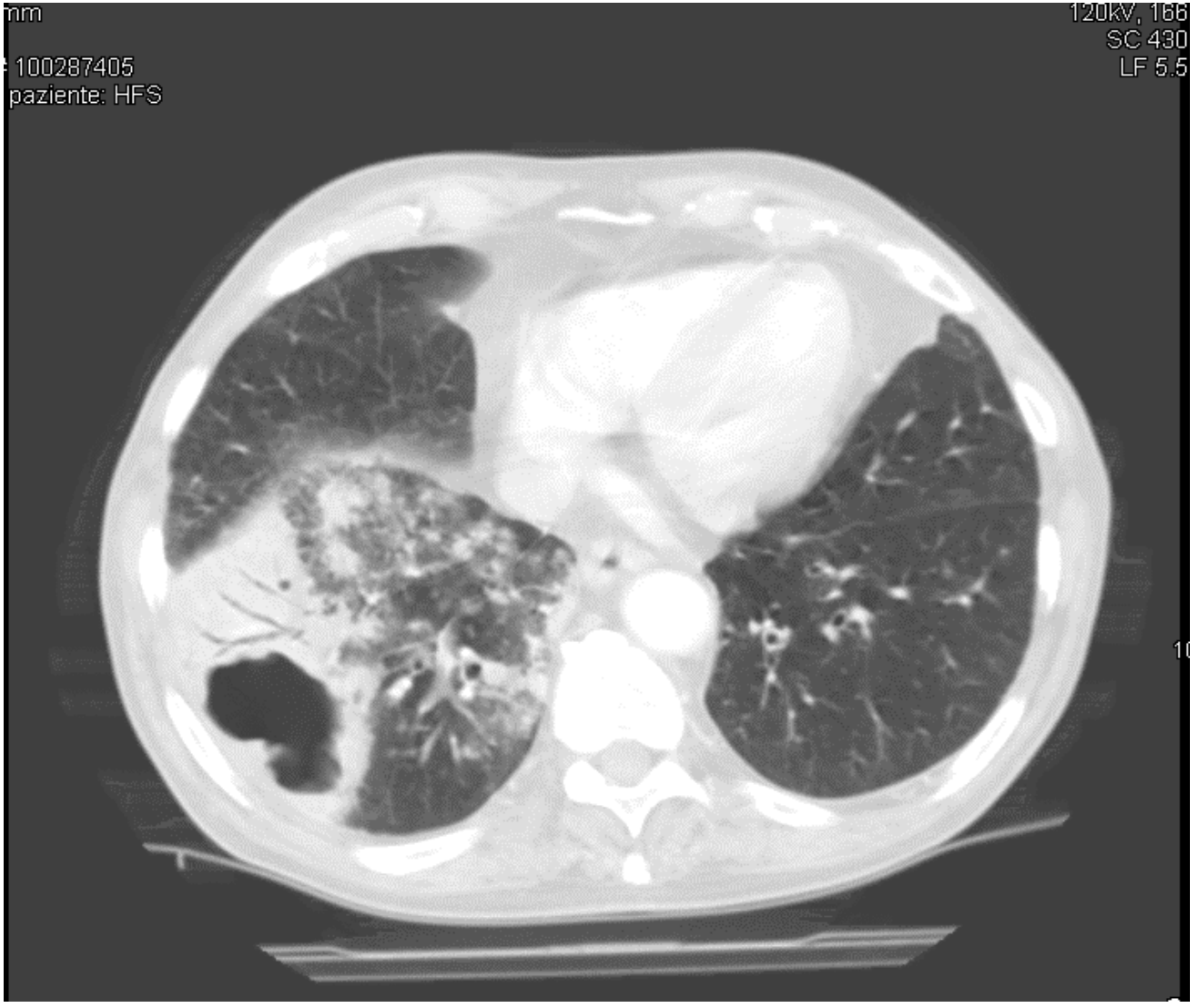
- **Diagnosi di AR sieropositiva ad alto titolo con S. Syogren nell'aprile 2006.**
- **Terapia iniziale**: idroclorochina 1 cp x 2 , prednisone 50 mg/die a scalare (sino a 4 mg), leflunomide 20 mg 1 cp al di**, adalimumab 20 mg la settimana.**

Maggio 2007

- Febbricola e tosse produttiva.
- **Rx torace**: ispessimento interstiziale diffuso in particolare al campo polmonare destro con addensamento parenchimale al lobo inferiore omolaterale e versamento pleurico sinistro.
- **TST** negativa**.**
- Ripetuti cicli di terapia antibiotica con ceftriaxone + claritromicina.

Giugno 2007

TAC polmonare: noduli multipli (da pochi mm a 2 cm) con aspetto escavato, grossolana lesione escavata di circa 7 cm in sede lobare inferiore destra con livello idroaereo, circondato da addensamento parenchimale con broncogramma. Modesto ingrandimento dei linfonodi ilari e paratracheali destra.



1a

Caso Clinico

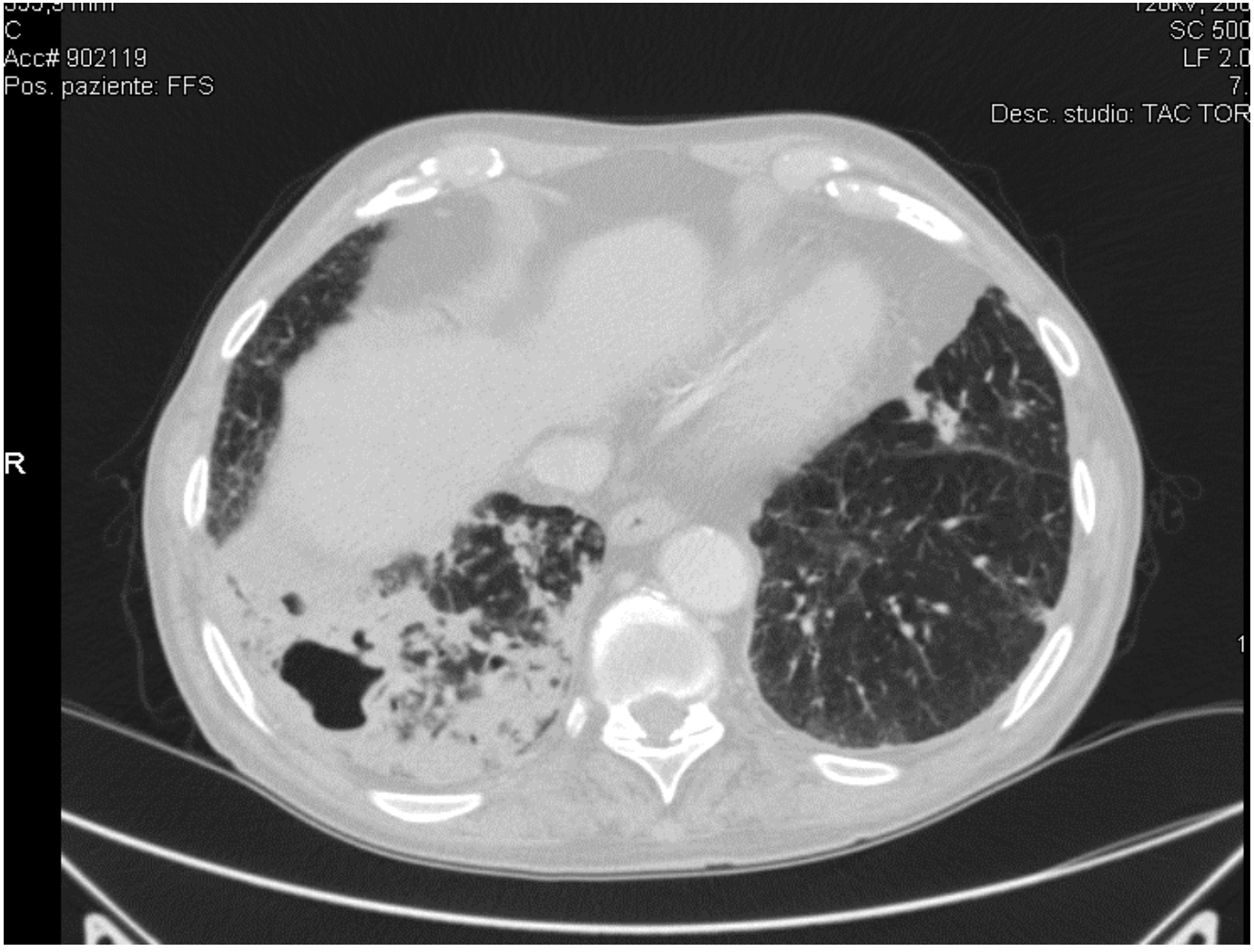
Agosto 2007

Ricovero in Reumatologia nel sospetto di una nodulosi reumatoide al polmone

- **RX torace**: lesioni nodulari con escavazione a destra.
- **BAL**: esame microscopico positivo per BAAR + LCX positiva
  esame colturale positivo per **Micobacterium Tuberculosis**

Agosto 2007

- Trasferimento presso l'UO di Malattie infettive
- **Quantiferon TB** (ESAT-6, CFP-10, TB 7.7) immunoenzimatico: negativo.
- **Terapia**: rifampicina (sospesa a 15 gg per esantema), isoniazide, pirazinamide (sospeso al 2 mese), etambutolo (sospeso al 6 mese per disturbi visivi), moxifloxacina e + piridossina.
- Seguito ambulatorialmente (dopo 30 gg di ricovero) sino al termine della terapia (9 mesi).


C
Acc# 902119
Pos. paziente: FFS
SC 500
LF 2.0
Desc. studio: TAC TOR
R

1b

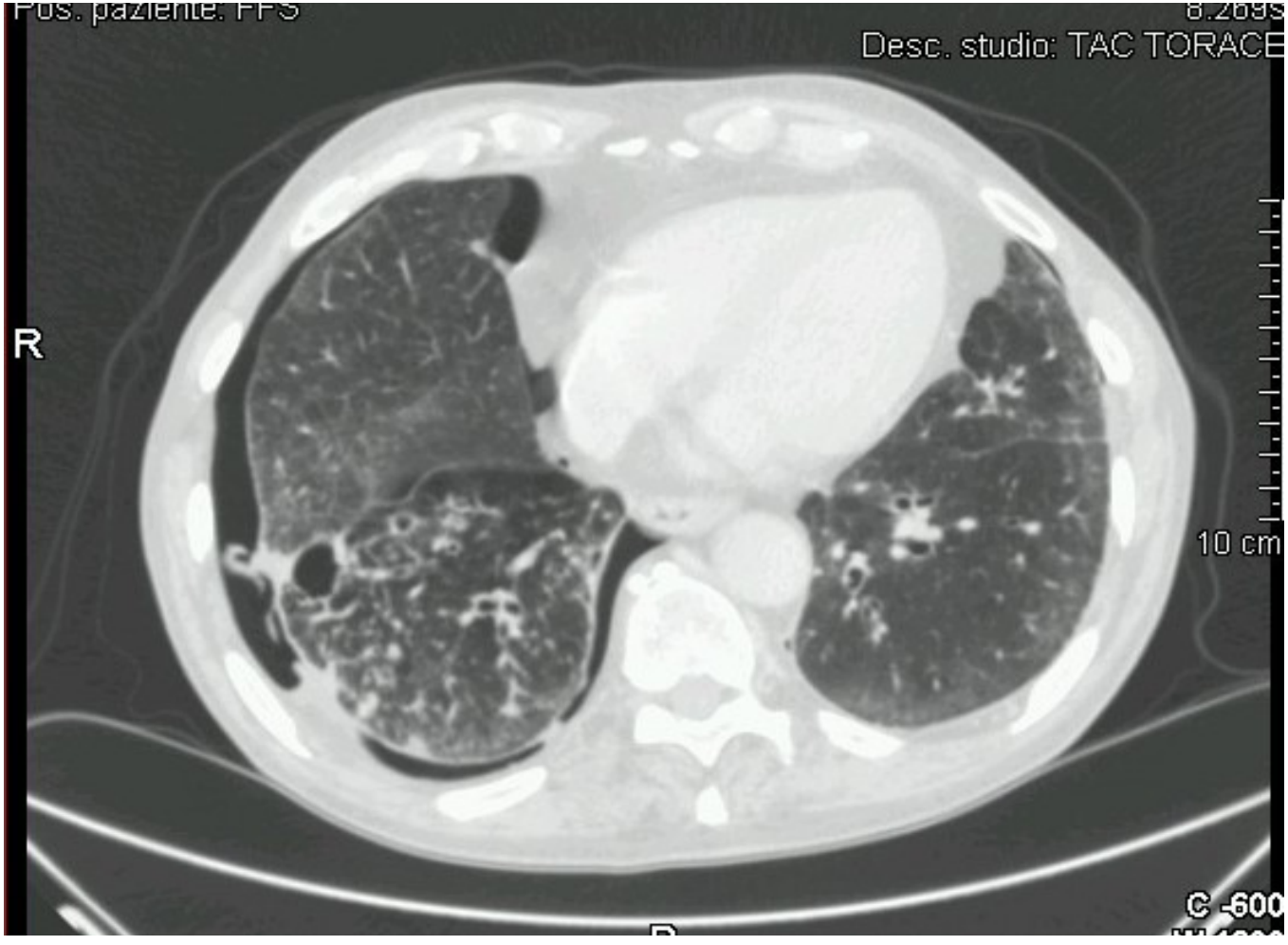
Caso Clinico

Febbraio 2008

- Comparsa pneumotorace da trazione.
- **TAC polmonare**: netta riduzione delle aree di consolidamento parenchimale, alcuni linfonodi mediastinici di circa 1 cm, falda di pnx a dx .

Maggio 2008

- Termina terapia antitubercolare.
- Escreato negativo per MTB.
- Continua follow-up clinico e microbiologico con cadenza semestrale.



1c

Caso clinico

Donna, 63 anni

- **AR da 36 anni.**
- **Terapia**: **Adalimumab** 40 mg sc ogni 2 settimane, methotrexate 10 mg la sett, deflazacort 6 mg/die.

Luglio 2007

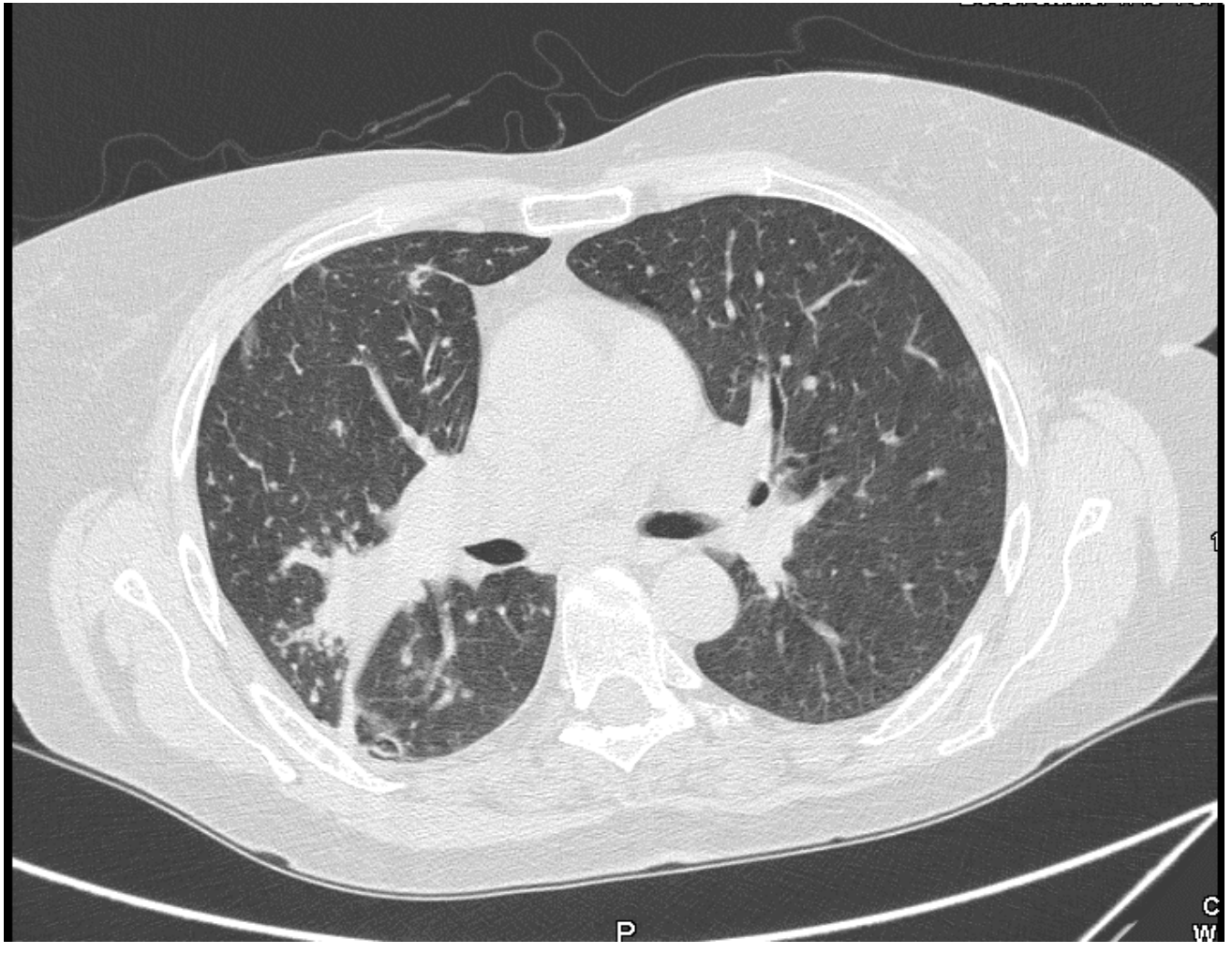
- Ricovero presso l'Ospedale di Castel Nuovo Monti.
- Febbre persistente da 10 gg, tosse, malessere generale,
- **Rx torace**: focolaio broncopneumonico inferiore destro.
- Trattamento: ceftriaxone e levofloxacina per 14 gg.

Agosto 2007

- Persistenza della sintomatologia.
- **TAC torace**: Consolidamento parenchimale destro con aspetti di trazione all'ilo; linfodonodi di 2 cm alla loggia di Bartley ed all'arco aortico, ispessimento pleurico basale all'ascellare media ed anteriore destra con estensione alla grande scissura.
- **Broncoscopia**: esame microscopico diretto negativo per BAAR.

Settembre 2007

- Esame colturale del BAL di agosto2007 positivo per **Micobacterium Tuberculosis**.



2a

Caso clinico

Settembre 2007

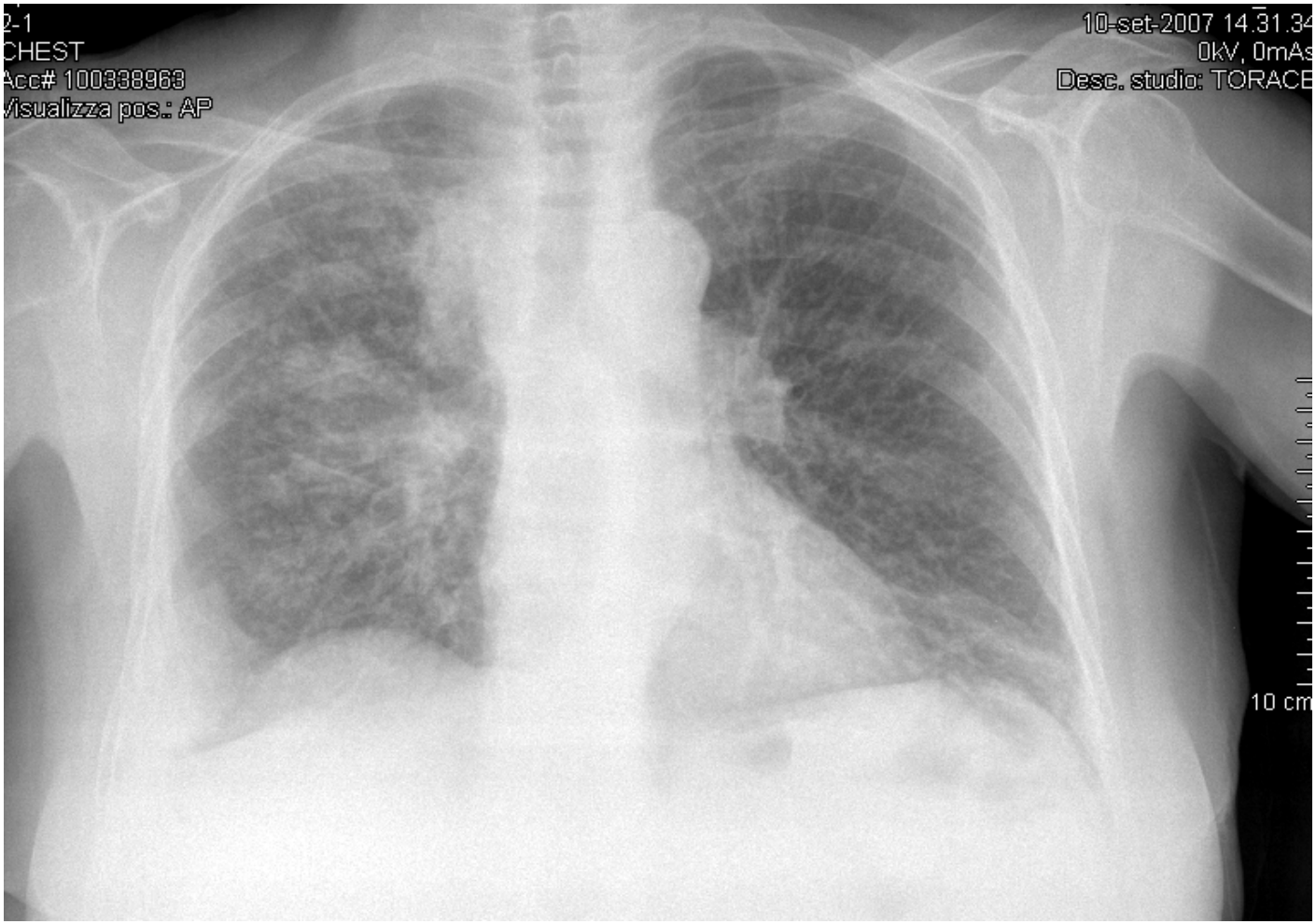
- Ricovero presso U.O. Malattie Infettive.
- Febbre (38°C), rantoli alla base polmonare destra.
- **TST**: negativo
- **Quantiferon TB** (ESAT-6, CFP-10, TB 7.7): positivo.
- **Rx torace**: addensamento pneumonico destro.
- **Terapia antitubercolare**:

  isoniazide, etambutolo, rifampicina e pirazinamide, sospesa dopo 10 gg per epatite tossica (BT= 2,2 mg/dl, GOT =169, GPT=144, g-GT= 337 UI/ml).

  Nuova terapia con etambutolo, isoniazide, streptomicina (per 2 mesi) e moxifloxacina (per 2 mesi).
- Prosecuzione terapia per AR con metotrxate + deflazacort

Dicembre 2007

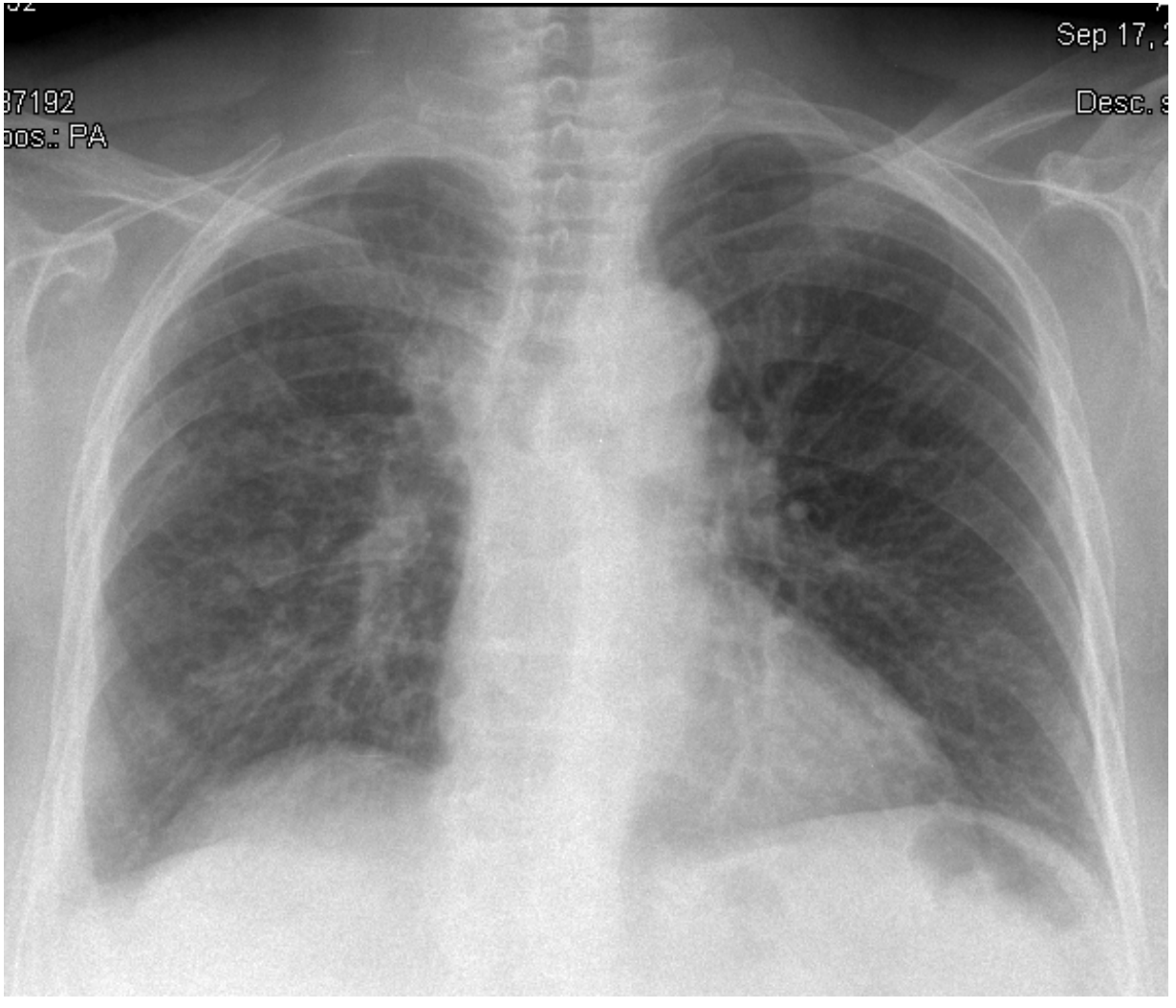
- Ricovero presso l'U.O. Malattie Infettive per assunzione incongrua dei farmaci antitubercolari.
- BAAR negativi su escreato e succo-gastrico.
- Redifinizione della durata della terapia (termine previsto 30.9.2008).


2-1
CHEST
Acc# 100338963
Visualizza pos.: AP
10-set-2007 14.31.34
0kV, 0mAs
Desc. studio: TORACE
10 cm

Caso clinico

Settembre 2008

- Termina trattamento antitubercolare.
- **Rx torace**: non addensamenti parenchimali a focolaio.
- **Escreato negativo per BAAR**.
- Prosecuzione terapia per AR con metotrexate + deflazacort.
- Prosegue follow-up clinico e microbiologico semestrale.



2b