Tuberculosi i infecció pel VIH

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TRACTAMENT

El problema de les interaccions:

-Quins antituberculosos

-Quins ARV

IRIS

Quan iniciar el Tractament

DIAGNÒSTIC

CASUÍSTICA

El tractament de la tuberculosi en pacients VIH

Treatment of drug-susceptible active TB disease

(*refer to Table 3 for dosing recommendations*)

Initial phase (2 months) **(AI)**

Isoniazid (INH)† + [rifampin (RIF) or rifabutin (RFB)] + pyrazinamide (PZA) + ethambutol (EMB); if drug susceptibility report shows sensitivity to INH & RIF and PZA, then EMB may be discontinued before 2 months of treatment is completed **(AI)**

Continuation phase

- INH + (RIF or RFB) daily or tiw **(AIII)** or biw (if CD4+ count >100/μL) **(CIII)**

Duration of therapy:

Pulmonary TB – 6 months **(AI)**

Pulmonary TB w/ cavitary lung lesions & (+) culture after 2 months of TB treatment **(AII)** – 9 months

Extrapulmonary TB w/ CNS, bone, or joint infections – 9 to 12 months **(AII)**;

Extrapulmonary TB in other sites – 6 to 9 months **(AII)**

nic maintenance therapy of AIDS-associated opportunistic infections

Alternative therapy	Other options/issues
	Directly observed therapy (DOT) is recommended for all HIV patients undergoing treatment for active TB **(AII)**
	Initial phase of TB treatment may also be administered 5 days weekly (40 doses) **(AII)**, or tiw (24 doses) **(BII)** by DOT
Tre	
Res • D u	
• (R (I	
• (R e n	
• A re d	
Res	
• INH + PZA + EMB + a fluoroquinolone for 2 months, followed by 10–16 additional months with INH + EMB + fluoroquinolone **(BIII)**	(EI)
	Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART
• Amikacin or capreomycin may be included in the first 2–3 months for patients with rifamycin resistance & severe disease **(CIII)**	Paradoxical reaction that is not severe may be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) without a change in anti-TB or anti-HIV therapy **(BIII)**
Multidrug resistant (MDR, i.e., INH & RIF resistant) or extensively drug resistant (XDR, i.e., resistance to INH & RIF, fluoroquinolone & at least 1 injectable agent) TB	For severe paradoxical reaction, may consider prednisone or methylprednisolone 1 mg/kg of body weight, gradually reduced after 1–2 weeks **(BIII)**
• Therapy should be individualized based on resistance pattern and with close consultation with experienced specialist **(AIII)**	

El tractament de la Tbc sensible és tant efectiu en pacients VIH com en la població no VIH (*)

www.cdc.gov/mmwr

(*)Blumberg HM Am J Respir Crit Care Med 2003; 167:603.

El problema de les interaccions

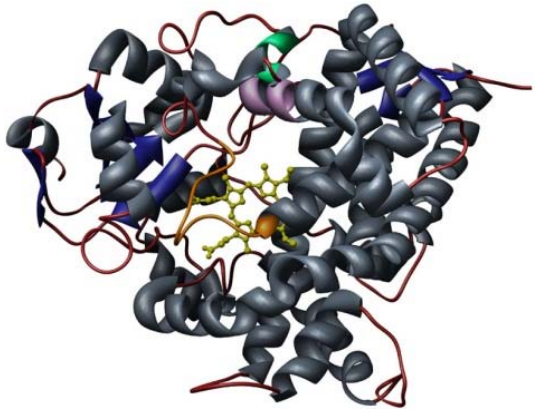
Rifampicina

Paper fonamental en la curació de la Tbc

Principal responsable de les interaccions

Quins antituberculosos elegir?
Quins antiretrovirals elegir?

El problema de les interaccions



Citocrom P450
CYP3A4

Rifampicina +++
Rifabutina -

⇊ IP

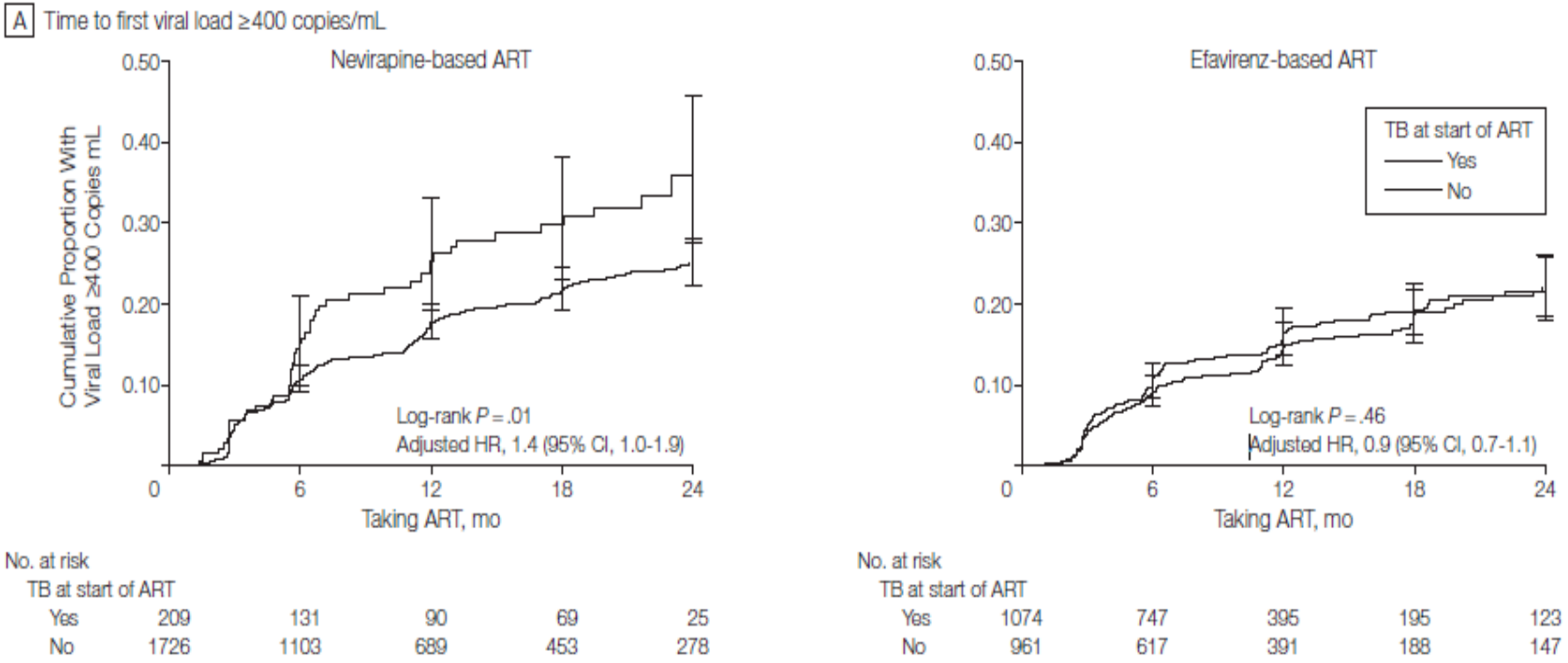
ATS/CDC/IDSA. Am J Respir Care 2003;167
Dworkin J Acquir Immune Defic Syndr. 2005;39(4):464.
Burger .Antimicrob Agents Chemother. 2006;50(10):3336
Mallolas J HIV Med 2007 Mar;8(2):131-4.

El problema de les interaccions

Règims basats en Rifampicina

Efavirenz o Nevirapina ?

Figure 3. Cumulative Estimates of Time to Elevated Viral Load and Virological Failure



No. at risk					
TB at start of ART					
Yes	209	131	90	69	25
No	1726	1103	689	453	278

No. at risk					
TB at start of ART					
Yes	1074	747	395	195	123
No	961	617	391	188	147

Boulle, A. et al. JAMA 2008;300:530-539

El problema de les interaccions

Règims basats en Rifampicina

Efavirenz o Nevirapina ?

A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: the N2R Study.

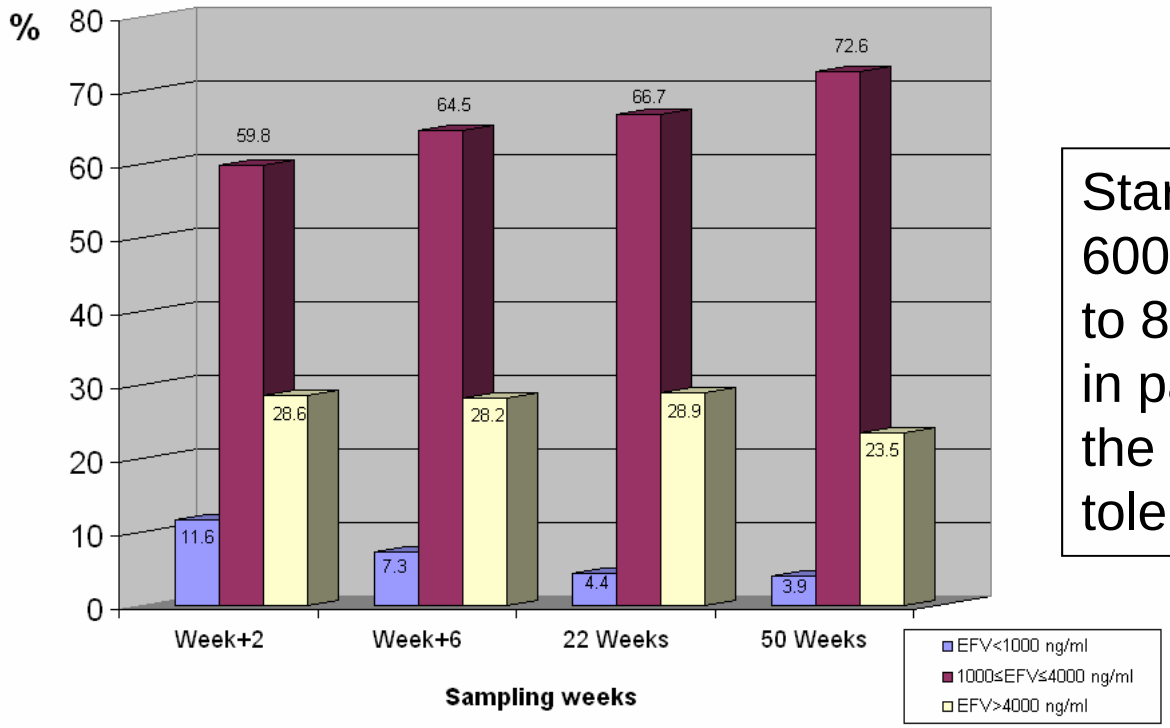
Manosuthi W ***Clin Infect Dis.*** *2009 Jun 15;48(12):1752-9*

CONCLUSIONS:
Antiretroviral therapy regimens containing efavirenz (600 mg per day) were less compromised by concomitant use of rifampicin than were those that contained nevirapine (400 mg per day) in patients with concurrent HIV-1 infection and TB. Low drug exposure and body weight are important predictive factors for treatment failure.

El problema de les interaccions

Règims basats en Rifampicina

Quina dosi d'Efavirenz ?



Start with the standard dose of 600 mg/day. Increase the dose to 800 mg/day after two weeks in patients weighing >60 kg, if the initial dose was well tolerated

Percentage of EFV plasma concentrations according to EFV therapeutic range

L. Borand IAS 2011 (Camelia CT)

El problema de les interaccions

Règims basats en Rifampicina

AN no interactuen amb la RP
Raltegravir no s'hauria d'utilitzar amb RP (red. 50%)
RP redueix els nivells plasmàtics de Maraviroc un 78%

1 Wenning LA, Antimicrob Agents Chemother. 2009;53(7):2852.

El problema de les interaccions

Règims basats en Rifabutina

Estudis més limitats
Sembla tant efectiva com la rifamplcina

Poca interacció amb drogues metabolitzades a través del CYP3A4

Rifabutina:
-dosi estandar 300mg/d
-reduïr si es dona amb IP-r

Table 3. Recommendations for Coadministering Antiretroviral Drugs with RIFABUTIN - 2007

	Antiretroviral dose change	Rifabutin dose change
Non-nucleoside reverse-transcriptase inhibitor		
Efavirenz	No change	to 450-600 mg (daily or intermittent)
Nevirapine	No change	No change (300 mg daily or thrice-weekly)
Delavirdine	Rifabutin and delavirdine should not be used together	
Etravirine	No change	No change (300 mg daily or thrice-weekly)
Single protease inhibitors		
	Antiretroviral dose change	**Rifabutin dose change**
fos-Amprenavir	No change	to 150 mg/day or 300 mg 3x/week
Atazanavir	No change	to 150 mg every other day or 3x/week
Indinavir	1000 mg every 8 hours	to 150 mg/day or 300 mg 3x/week
Nelfinavir	No change	to 150 mg/day or 300 mg 3x/week
Dual protease inhibitor combinations		
	Antiretroviral dose change	**Rifabutin dose change**
Lopinavir / ritonavir (Kaletra)	No change	to 150 mg every other day or 3x/week
Ritonavir (any dose) with saquinavir, indinavir, amprenavir, fos-amprenavir, atazanavir, tipranavir or darunavir	No change	to 150 mg every other day or 3x/week
CCR-5 receptor antagonists		
Maraviroc	No change	No change
Integrase inhibitors		
	No change	No change

http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm

El problema de les interaccions

Règims basats en Rifabutina

Beneficis

Es pot administrar amb IP/r
Es pot donar 150mg 3xset:
- **Amb DRV/r**
- **Amb ATZ/r**
- **Amb LPV/r**
  (NP baixos de RFB?) (*)

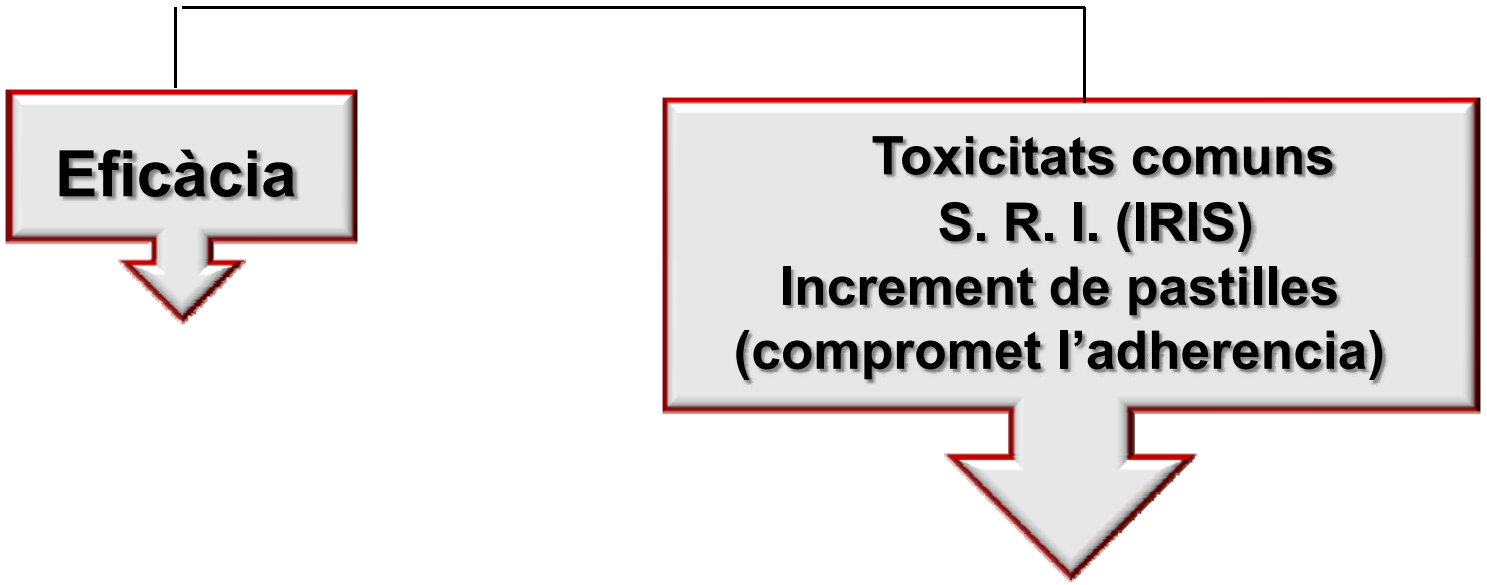
Inconvenients

Cost
No coformulada
Menys experiència
Tox: Afect medular, artràlgies, uveitis
No dades d'us concomitant amb : DRV, RAL ni MRV

(*) Boulanger C: Clin Infect Dis. 2009;49(9):1305.

Moment d' inici dels antiretrovirals

El moment d'iniciar els ARV, quan les dues infeccions es diagnostiquen , no està del tot establert



Immune reconstitution inflammatory syndrome (IRIS)

Paradoxical worsening of a preexisting infectious process following ART-associated immune recovery and functional restoration of CD4+ T cells

Inflammatory reaction :

- **Self-limited**
- **Significant morbidity and mortality**
- **Wide spectrum of clinical manifestations**

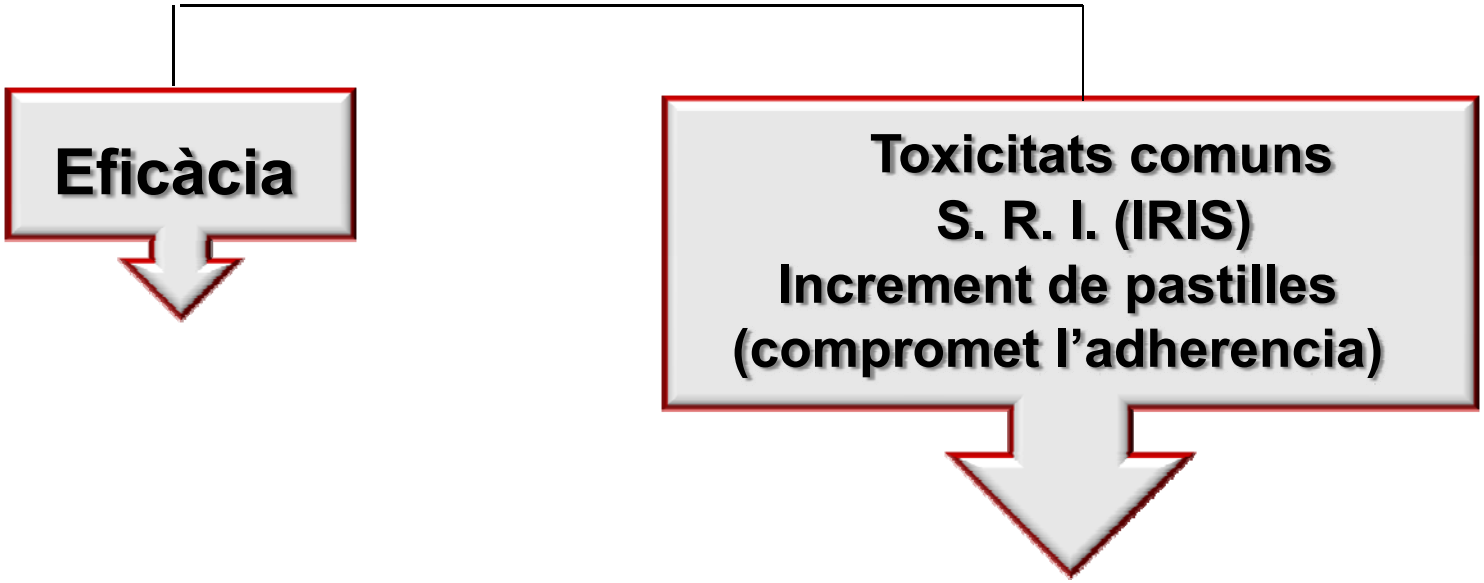
The risk of IRIS appears to depend on the baseline CD4 cell and it's highest among those with CD4 counts <50 cells/mm3 or CD4+ cell counts < 100 cells/mm^3

IRIS can usually be treated with nonsteroidal antiinflammatory agents, and more significant manifestations can be treated with prednisone or methylprednisolone 1 mg/kg/day for 1-2 months, followed by dose tapering.

French MA Clin Infect Dis. 2009;48(1):101 ; DeSimone JA, Ann Intern Med. 2000;133(6):447.
Kaplan 2009; Blumberg 2003; DHHS 2011

Moment d' inici dels antiretrovirals

El moment d'iniciar els ARV, quan les dues infeccions es diagnostiquen , no està del tot establert

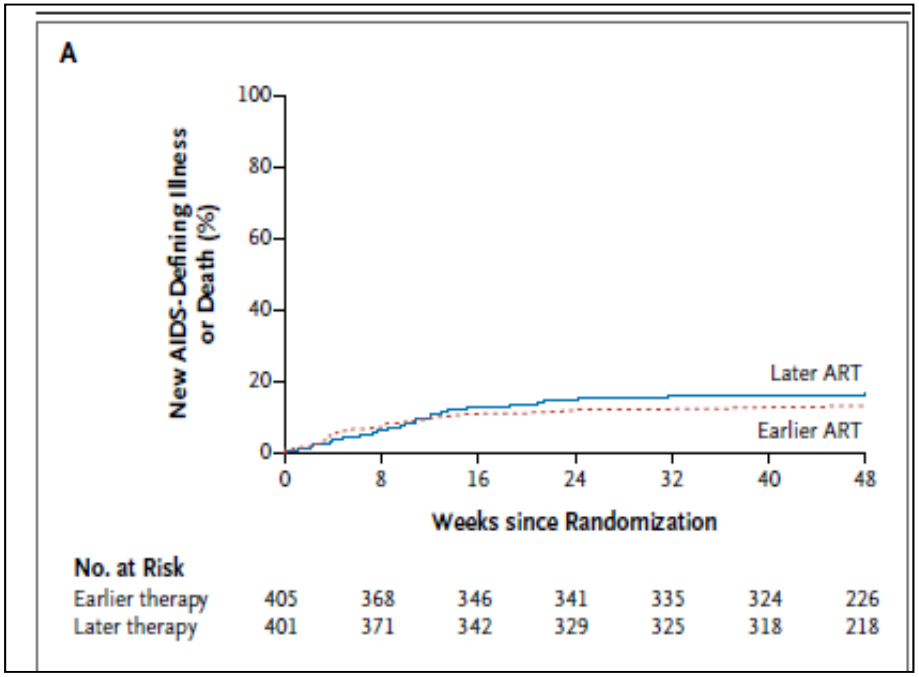


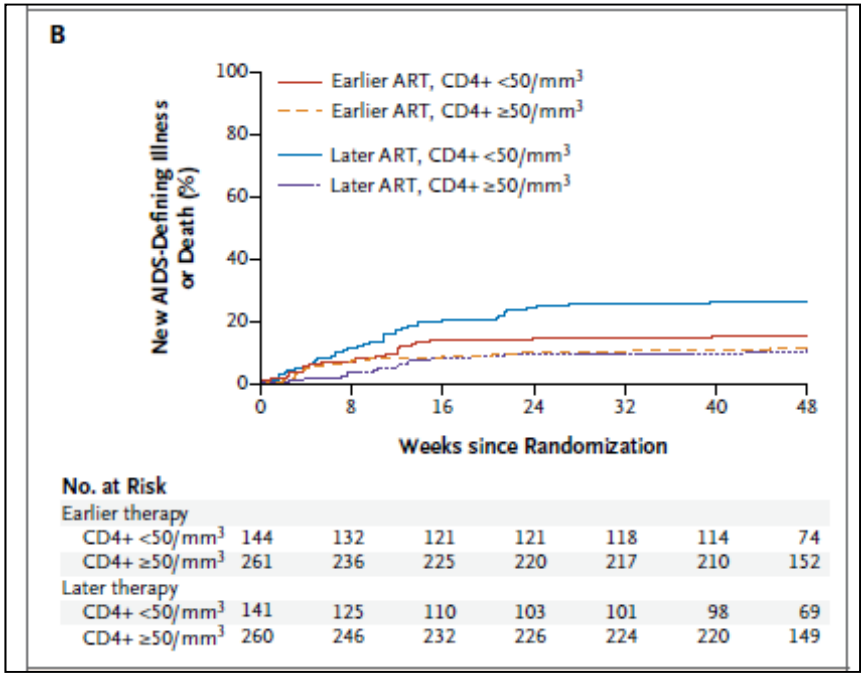
Tractament simultani o diferit ?

- **SAPiT**
- **STRIDE Study (ACTG 5221)**
- **CAMELIA**
- **World Health Organization 2010 guidelines**

SAPiT: Early vs Late ART Initiation During Integrated TB/ART Therapy

- **Early Integrated:** ART started within 4 wks of starting TB Rx
- **Late Integrated:** ART started 8-12 weeks after initiating TB treatment
- 68% lower AIDS/death rate with early integrated Rx in patients with CD4+ counts < 50 cells/mm^3





Abdool Karim S, et al. CROI 2011. Abstract 39LB. Graphics used with permission.

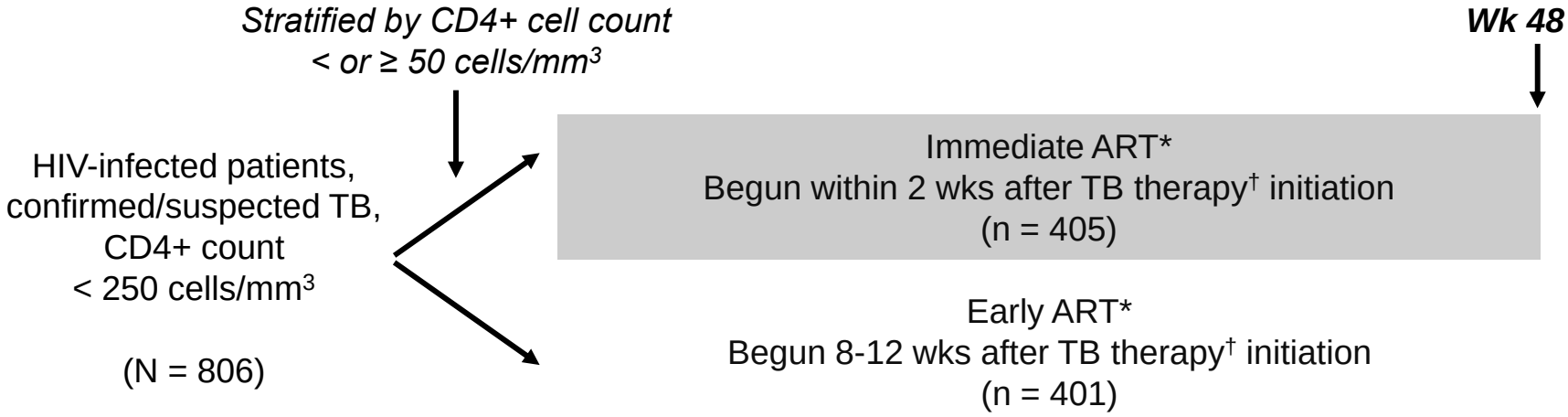
Abdool Karim NEJM 2010

STRIDE Study (ACTG 5221): Immediate vs Early ART Initiation in TB Patients

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

Diane V. Havlir aCTG 5221

, N Engl J Med 2011;365:1482-91.



*ART comprised EFV, FTC, and TDF. †TB therapy comprised standard rifampicin-based regimen.

Outcome, %	Immediate (n = 405)	Early (n = 401)	95% CI for Difference	*P* Value
Deaths or new AIDS-defining events by Wk 48				
▪ Overall population	12.9	16.1	-1.8 to 8.1	.45
▪ CD4+ cell count < 50 cells/mm^3	15.5	26.6	1.5 to 20.5	.02
▪ CD4+ cell count ≥ 50 cells/mm^3	11.5	10.3	-6.7 to 4.3	.67
TB IRIS	11	5		.002

Havlir D, et al. CROI 2011. Abstract 38.

STRIDE Study (ACTG 5221)

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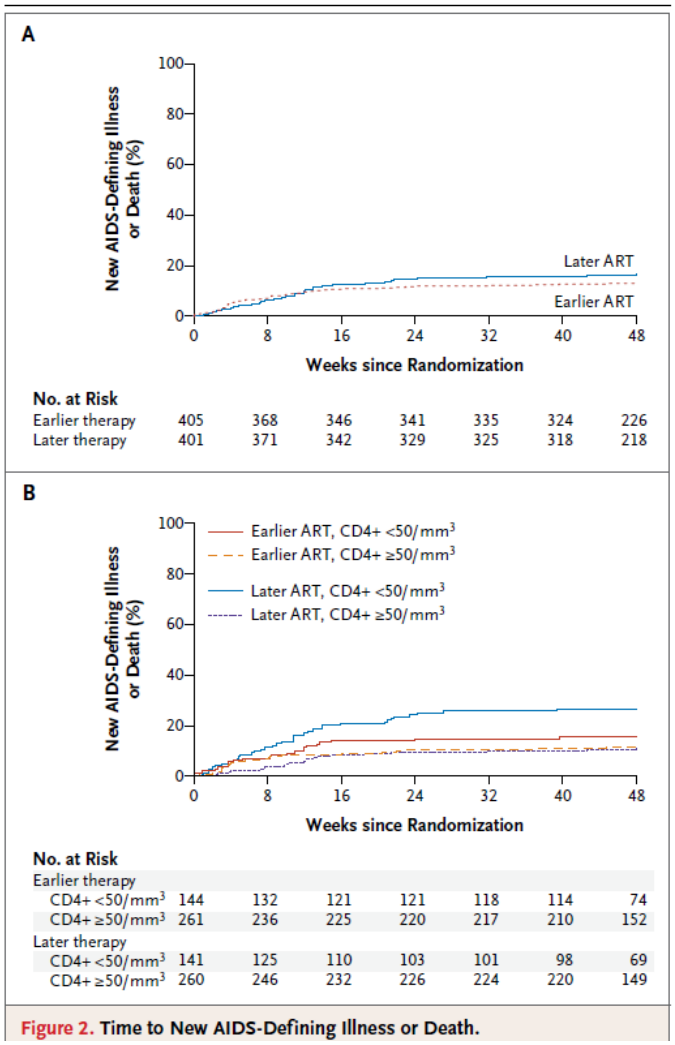


Figure 2. Time to New AIDS-Defining Illness or Death.

Overall, earlier ART did not reduce the rate of new AIDS-defining illness and death, as compared with later ART.

In persons with CD4+ T-cell counts of less than 50 per cubic millimeter, earlier ART was associated with a lower rate of new AIDS-defining illnesses and death.

Tuberculosis-associated immune reconstitution inflammatory syndrome was more common with earlier ART than with later ART (11% vs. 5%, P = 0.002).

Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis
CAMELIA (ANRS 1295–CIPRA KH001) Study Team

François-Xavier Blanc ,N Engl J Med 2011;365:1471-81.

The **CAMELIA** study enrolled patients with <200 CD4 cells/uL to start ARVs within 2 weeks or 8 weeks of initiating TB treatment. This study population had a median CD4 cell count of 25 cells/uL and showed that there was a significantly greater risk of death amongst those who waited until 8 weeks to start ARVs

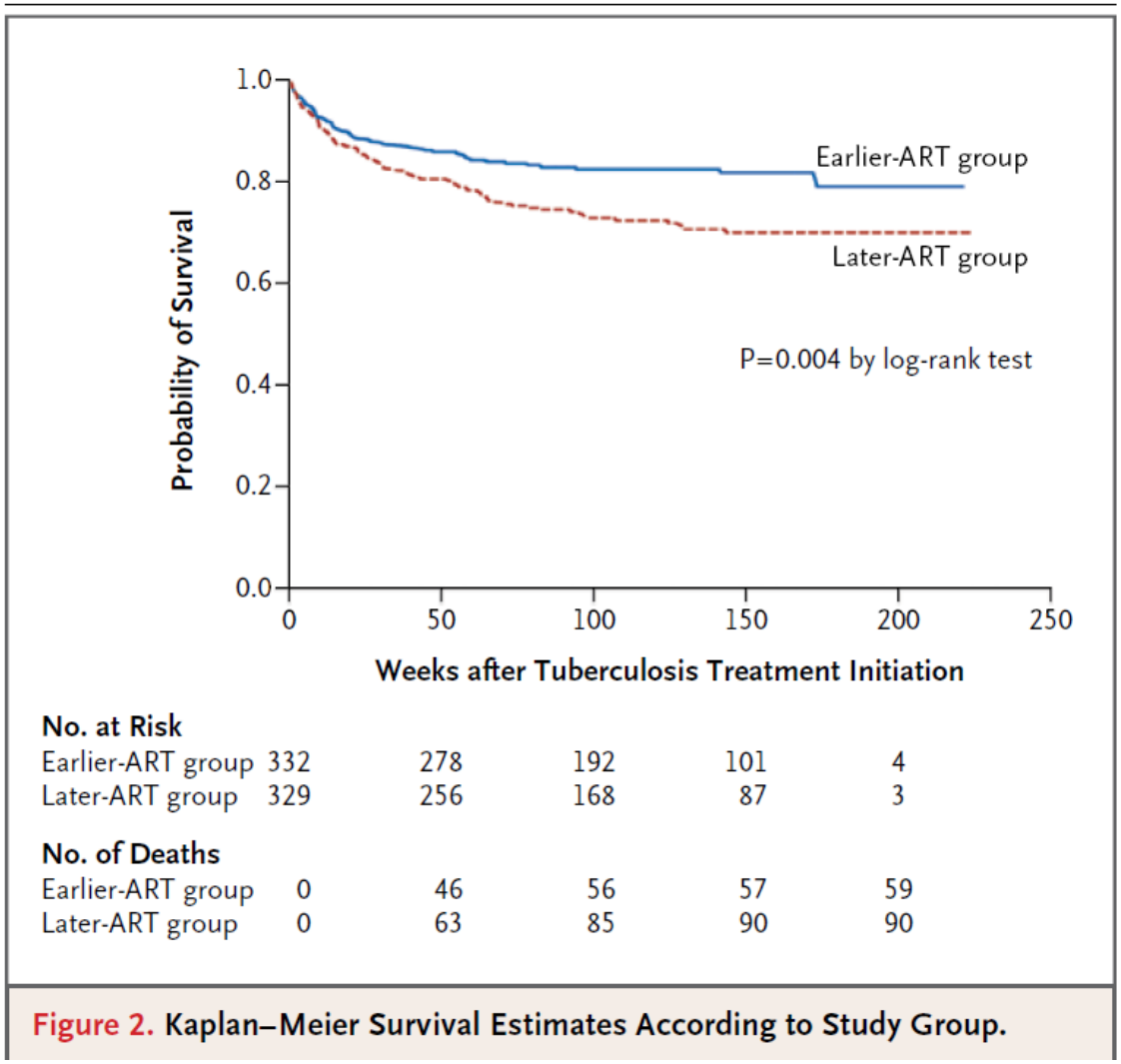


Figure 2. Kaplan–Meier Survival Estimates According to Study Group.

Background: Timing of ART Initiation in Patients Initiating TB Treatment

- **SAPiT: higher incidence of death in patients deferring ART therapy to end of TB treatment (sequential) vs initiation during TB therapy (integrated).[1]**
- **STRIDE Study (ACTG 5221) reduce the risk of AIDS or death in patients with a CD4 count <50 cells/mm3. IRIS increases**
- **CAMELIA: significant reduction in mortality with ART initiation at Wk 2 vs Wk 8 of TB therapy in pts with CD4+ counts ≤ 200 cells/mm$^{3.}$ IRIS increases [2]**
- **World Health Organization 2010 guidelines recommend[3]**
  - **Initiate ART in all HIV-infected patients with TB, regardless of CD4+ count**
  - **Initiate TB therapy before ART, with ART added as soon as possible, within 8 wks**

1. Abdool Karim SS, et al. N Engl J Med. 2010;362:697-706. 2. Blanc FX, et al. IAC 2010. Abstract THLBB106. 3. WHO antiretroviral guidelines 2010.

Diagnòstic de la tuberculosi pulmonar en pacients VIH

A wide range of acid-fast smear positivity has been reported (31 to 81 percent)

The yield on sputum culture is substantially higher (85 to 100 percent),

Steingart KR, Lancet Infect Dis. 2006;6(10):664
Hassim Clin Infect Dis. 2010;50(7):1053.
Reid MJ, Shah NS
Lancet Infect Dis. 2009;9(3):173

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

1730 patients with suspected drug-sensitive or multidrug-resistant pulmonary tuberculosis.
From Peru, Azerbaijan, South Africa, and India

Among culture-positive patients, a single, direct MTB/RIF test identified:

- **551 of 561patients with smear-positive tuberculosis (98.2%)**
- **124 of 171 with smear-negative tuberculosis (72.5%).**

The test was specific in 604 of 609 patients without tuberculosis (99.2%).

As compared with phenotypic drug-susceptibility testing, MTB/RIF testing correctly identified 200 of 205 patients (97.6%) with rifampin-resistant bacteria and 504 of 514 (98.1%) with rifampin-sensitive bacteria.

NEJM 363;11 september 9, 2010

IF gamma

IAS 2011

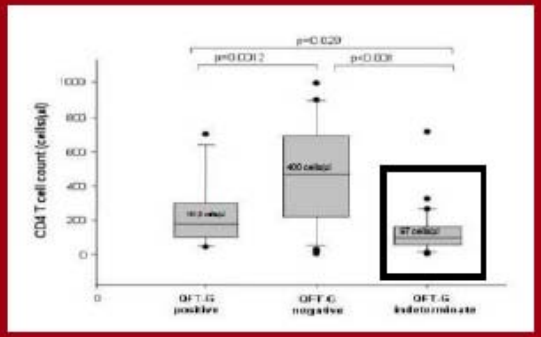
1 Cross-sectional study

QFT-GIT assay and TST results

	HIV-infected patients (n = 207)† QFT-GIT		
	Positive (n = 35) n (%)	Negative (n = 122) n (%)	Indeterminate (n = 40) n (%)
TST-positive	25 (71)	40 (33)	16 (40)
TST-negative	10 (29)	82 (67)	24 (60)

The agreement between two test was 68% (κ = 0.30)

2 Impact of CD4 on QFT-GIT results



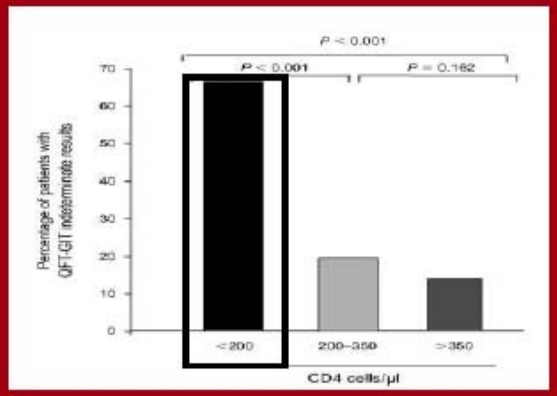
The median CD4 T cell count was significantly lower in patients with indeterminate QFT-GIT

3 Indeterminate results

Indeterminate QFT-GIT results

	OR (95% CI)	*P*-value
CD4< 200cells/µl	5.80 (2.13-16.618)	0.001

The univariate analysis confirmed that a CD4 count < 200 was associated with indeterminate result



The 67% of the patients with CD4 <200 cells/µl had an indeterminate result, compared with 20% and 12% of individuals with 200–350 and >350 cells/µl respectively

www.ias2011.org

TUPE107

Pacients amb infecció VIH i tuberculosi

Període revisat: 2001-2011

Sexe

	Frequency	Percent
Dona	19	20,7
Home	73	79,3
Total	92	100,0

Rosa Palma, Laia Utrillo, Teresa Puig

Pacients amb infecció VIH i tuberculosi

Immigració

	Frequency	Percent
No	60	65,2
Si	32	34,8
Total	92	100,0

País orígen

	Frequency	Percent
Espanya	57	62,0
Sudamèrica	3	3,3
Àfrica nord	1	1,1
Àfrica -sub	28	30,4
Europa Est	1	1,1
Europa	2	2,2
Total	92	100,0

hospital universitari arnau de vilanova

Pacients amb infecció VIH i tuberculosi

Via transmissió del VIH

	Frequency
Heterosexual	52
Homosexual	4
ADVP	36
Total	92

Pacients amb infecció VIH i tuberculosi

CV i CD4

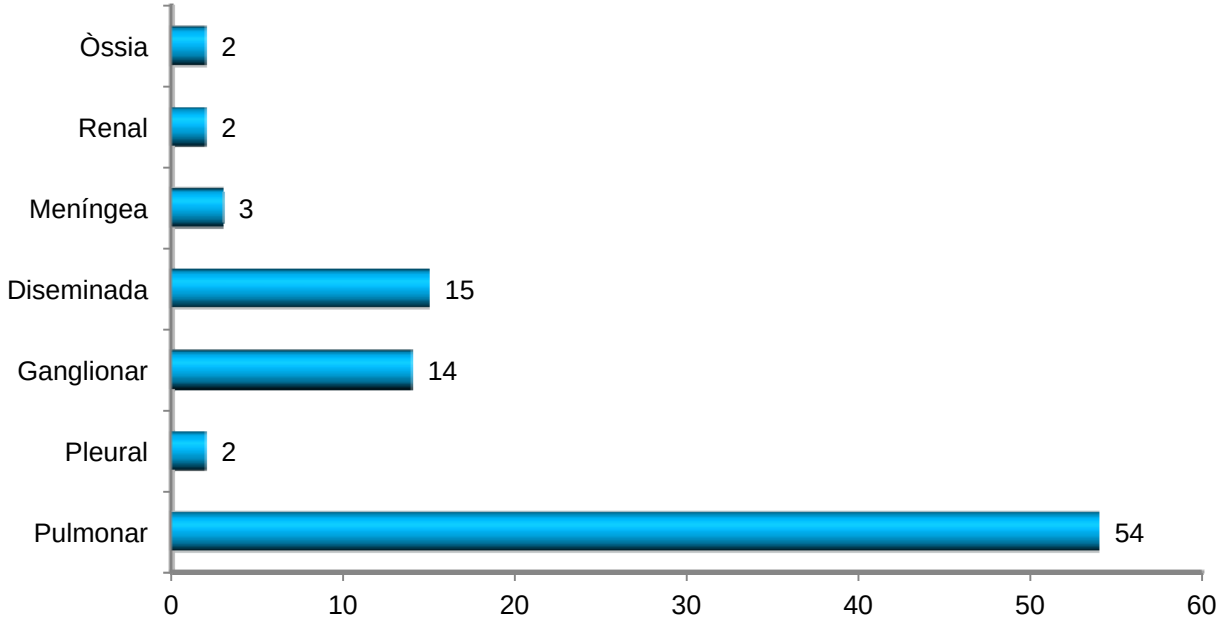
		CD4	CV
N	Valid	84	84
	Missing	8	8
Median		188,0000	77503,50
Percentiles	25	68,5000	632,50
	50	188,0000	77503,50
	75	401,2500	274031,00

TARV previ

	Frequency	Percent
No	51	55,4
Si	41	44,6
Total	92	100,0

Pacients amb infecció VIH i tuberculosi

Localització de la tuberculosi



Localització

	Frequency	Percent	Valid Percent	Cumulative Percent
Pulmonar	54	58,7	58,7	58,7
Pleural	2	2,2	2,2	60,9
Ganglionar	14	15,2	15,2	76,1
Diseminada	15	16,3	16,3	92,4
Meningea	3	3,3	3,3	95,7
Renal	2	2,2	2,2	97,8
Osea	2	2,2	2,2	100,0
Total	92	100,0	100,0	

Pacients amb infecció VIH i tuberculosi

ZN esput

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Negatiu	33	35,9	54,1	54,1
	Positiu	28	30,4	45,9	100,0
	Total	61	66,3	100,0	
Missing	No realizado	16	17,4		
	System	15	16,3		
	Total	31	33,7		
Total		92	100,0		

ZN esput negatiu: 54,1% (41,72 – 65,99)
ZN esput positiu: 45,9% (34,01 – 58,28)

Cultiu esput

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Negatiu	22	23,9	37,3	37,3
	Positiu	37	40,2	62,7	100,0
	Total	59	64,1	100,0	
Missing	No realitzat	18	19,6		
	System	15	16,3		
	Total	33	35,9		
Total		92	100,0		

Cultiu esput negatiu: 37,3% (26,08 – 50,05)
Cultiu esput positiu: 62,7% (49,95 – 73,92)

Pacients amb infecció VIH i tuberculosi

ETODA

		Frequency	Percent
Valid	no	48	52,2
	si	44	47,8
	Total	92	100,0

Toxicitat

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	no	77	83,7	93,9	93,9
	si	5	5,4	6,1	100,0
	Total	82	89,1	100,0	
Missing	System	10	10,9		
Total		92	100,0		

Pacients amb infecció VIH i tuberculosi

Curació

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	no	1	1,1	1,2	1,2
	si	81	88,0	98,8	100,0
	Total	82	89,1	100,0	
Missing	System	10	10,9		
Total		92	100,0		

CONCLUSIONS

1- En pautes amb Rifampicina, donar Efavirenz a les dosis habituals
2- Quan s'hagin de administrar IP-r, elegir la Rifabutina
3- Evitar donar els ARV més nous amb Rifampicina
4- Començar el TARV dels pacients *naïves* que presenten tuberculosi dins de les 2 primeres setmanes si estan molt immunodeprimits
5- El SRI el tractarem amb antinflamatoris o esteroidals, sense parar els ARV
6- La determinació d'IF-gamma, no funciona be pel diagnòstic de Tbc en pacients molt immunodeprimits
7- Expectatives de noves tècniques moleculars que permetran un diagnòstic precoç i detecció de R a Rifampicina amb rapidesa i altes S i E