# MODALITÉS DE TRAITEMENT DE LA TUBERCULOSE-MALADIE CHEZ LE PATIENT INFECTÉ PAR LE VIH

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# ANTITUBERCULEUX ET ANTIRÉTROVIRAUX

TRAITEMENT DE LA TUBERCULOSE-MALADIE :

- QUELLES MOLÉCULES ?
- QUELLE DURÉE DE TRAITEMENT ?

ANTIRÉTROVIRAUX ASSOCIÉS AUX ANTITUBERCULEUX :

- QUELLES MOLÉCULES ?
- QUAND DÉBUTER ?

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# QUELLES MOLÉCULES ?

Activité *in vivo* des antibiotiques antituberculeux de première ligne, en cas de tuberculose cavitaire.

| Antibiotiques | Activité sur les bacilles | | | Proportion de mutants résistants au sein d'une population sensible | Apport dans le traitement |
|---|---|---|---|---|---|
| | À multiplication active (caverne) ~$10^8$ bacilles | À multiplication lente | | | |
| | | À pH acide (macrophage) ~$10^5$ bacilles | À pH neutre (foyers caséeux) ~$10^5$ bacilles | | |
| Isoniazide (INH) | ++ | + | 0 | $10^{-6}$ | Antibiotique le plus rapidement bactéricide |
| Rifampicine (RMP) | ++ | + | + | $10^{-7}$ | 18 mois -> 9 mois |
| Pyrazinamide (PZA) | 0 | ++ | 0 | > $10^{-5}$ | 9 mois -> 6 mois |
| Éthambutol (EMB) | ± | ± | 0 | $10^{-6}$ | Empêche sélection de RMP-R si résistance primaire à INH |

+, ++ : activité bactéricide ; ± : activité bactériostatique ; 0 : pas d'activité.

*Rev Mal Respir* 2003; 20: 7S13-7S19

# American Thoracic Society Documents

## American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis

THIS OFFICIAL JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY, CENTERS FOR DISEASE CONTROL AND PREVENTION, AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA WAS APPROVED BY THE ATS BOARD OF DIRECTORS OCTOBER 2002, THE CENTERS FOR DISEASE CONTROL AND PREVENTION OCTOBER 2002, AND THE COUNCIL OF THE IDSA OCTOBER 2002.

Am J Respir Crit Care Med Vol 167. pp 603–662, 2003

# 8. TREATMENT IN SPECIAL SITUATIONS

## 8.1. HIV Infection

Am J Respir Crit Care Med Vol 167. pp 603–662, 2003

### TUBERCULOSIS AND HIV INFECTION

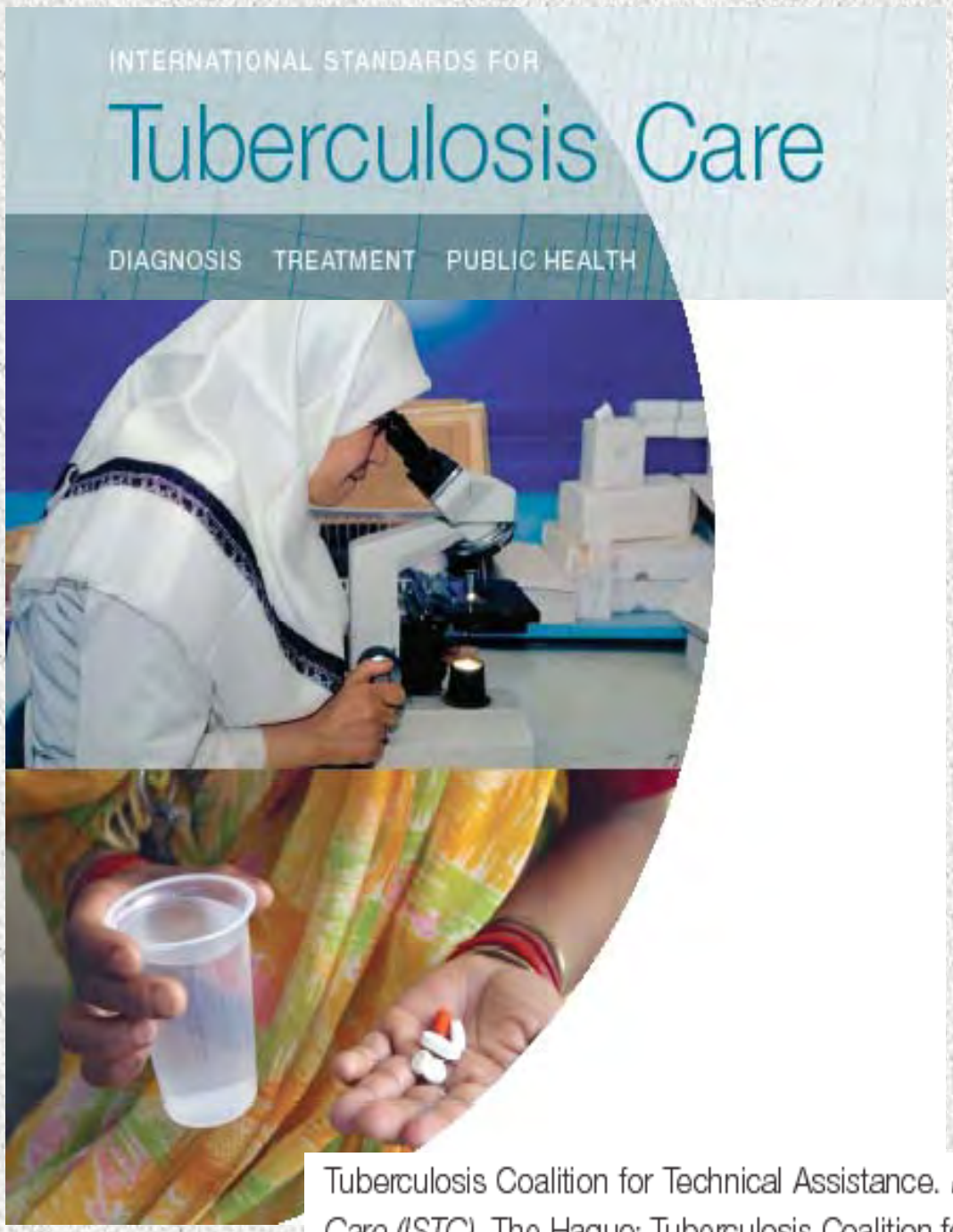
The treatment of tuberculosis in persons with HIV infection is essentially the same as for patients without HIV infection. There are two important exceptions to this generalization: (*1*) Once weekly INH–rifapentine in the continuation phase should not be used in any HIV-infected patient; and (*2*) twice weekly INH–RIF or rifabutin should not be used for patients with $CD4^+$ lymphocyte counts less than 100/μl. Providers must be alert to the potential for interactions among many of the antiretroviral drugs and the rifamycins. Paradoxical reactions that mimic worsening of tuberculosis are more common in patients with HIV infection and may complicate therapy.

*8.1.2. Treatment recommendations.* Recommendations for the treatment of tuberculosis in HIV-infected adults are, with two exceptions, identical to those for HIV-uninfected adults: a 6-month regimen consisting of an initial phase of INH, RIF, PZA, and EMB given for 2 months followed by INH and RIF for 4 months when the disease is caused by organisms that are known or presumed to be susceptible to the first-line agents.

Am J Respir Crit Care Med Vol 167. pp 603–662, 2003

Six months should be considered the minimum duration of treatment for adults, even for patients with culture-negative tuberculosis. If there is evidence of a slow or suboptimal response (e.g., cultures are still positive after 2 months of therapy), prolongation of the continuation phase to 7 months (a total of 9 months treatment) should be strongly considered. DOT and other adherence-promoting strategies should be used in all patients with HIV-related tuberculosis. Although there are no data on which to base recommendations, the American Academy of Pediatrics recommends that for HIV-infected children the minimum duration of therapy be 9 months (17).

Am J Respir Crit Care Med Vol 167. pp 603–662, 2003




Tuberculosis Coalition for Technical Assistance. *International Standards for Tuberculosis Care (ISTC)*. The Hague: Tuberculosis Coalition for Technical Assistance, 2006.

## Recommended treatment for persons not treated previously[24]

| RANKING | INITIAL PHASE | CONTINUATION PHASE |
|---|---|---|
| Preferred | INH, RIF, PZA, EMB[1,2] daily, 2 months<br>INH, RIF, PZA, EMB[1,2] 3x/week, 2 months | INH, RIF daily, 4 months<br>INH, RIF 3x/week, 4 months |
| Optional | INH, RIF, PZA, EMB[2] daily, 2 months | INH, EMB daily, 6 months[3] |

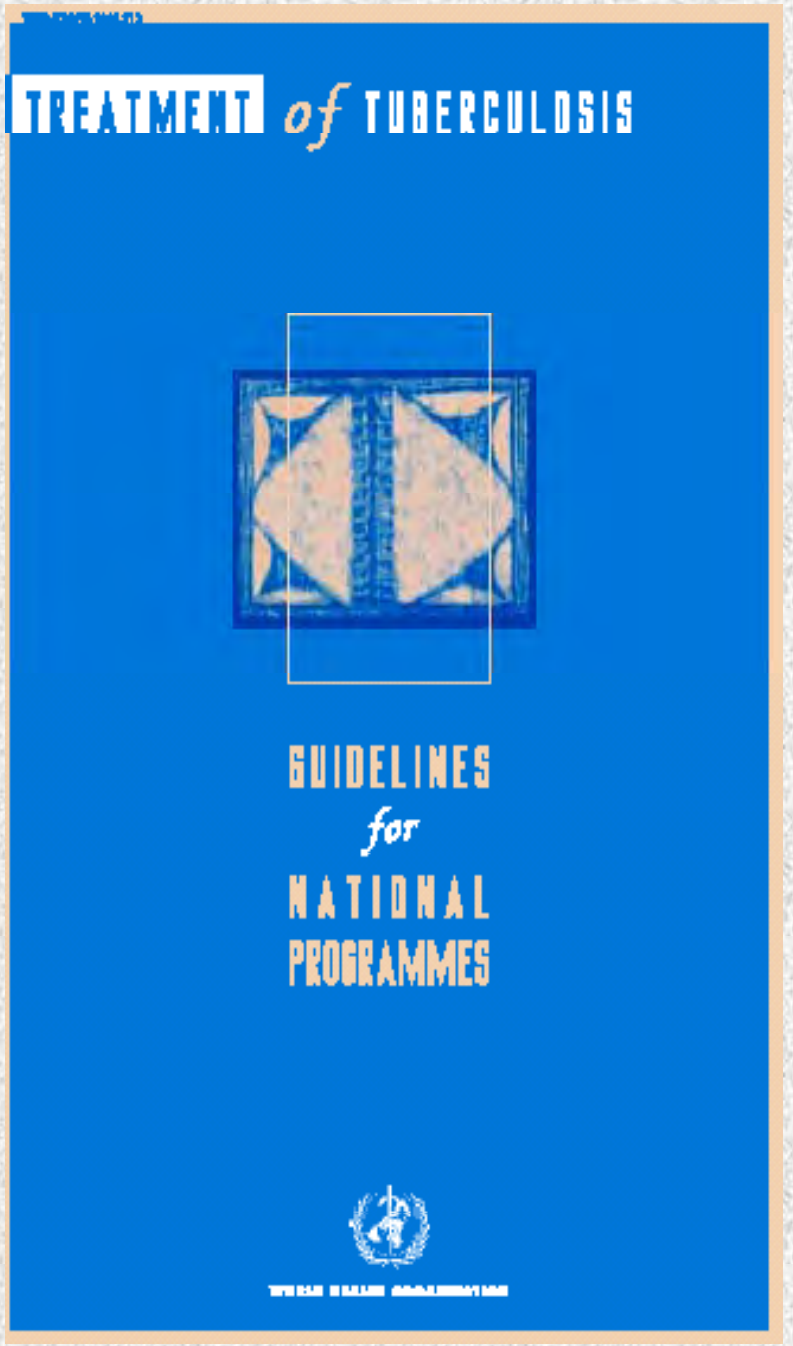
**INH** = isoniazid; **RIF** = rifampicin; **PZA** = pyrazinamide; **EMB** = ethambutol

1 Streptomycin may be substituted for ethambutol.
2 Ethambutol may be omitted in the initial phase of treatment for adults and children who have negative sputum smears, do not have extensive pulmonary tuberculosis or severe forms of extra-pulmonary disease, and who are known to be HIV negative.
3 Associated with higher rate of treatment failure and relapse; should generally not be used in patients with HIV infection.

# QUELLES COMBINAISONS ?

| Treatment category | Patients | Tuberculosis treatment* | |
|---|---|---|---|
| | | Initial phase (daily or three times per week) | Continuation phase (daily or three times per week) |
| I | New cases of smear-positive pulmonary tuberculosis or severe extrapulmonary tuberculosis or severe smear-negative pulmonary tuberculosis or severe concomitant HIV disease | 2 months $H_3R_3Z_3E_3$ or 2 months $H_3R_3Z_3S_3$<br>2 months HRZE or 2 months HRZS | 4 months $H_3R_3$<br>4 months HR<br>6 months HE† |
| II‡ | Previously treated smear-positive pulmonary tuberculosis; relapse; treatment failure; treatment after default | 2 months $H_3R_3Z_3E_3S_3$/1 month $H_3R_3Z_3E_3$<br>2 months HRZES/1 month HRZE | 5 months $H_3R_3E_3$<br>5 months HRE |
| III§ | New cases of smear-negative pulmonary tuberculosis or with less severe forms of extrapulmonary tuberculosis | 2 months $H_3R_3Z_3E_3$<br>2 months HRZE | 4 months $H_3R_3$<br>4 months HR<br>6 months HE† |

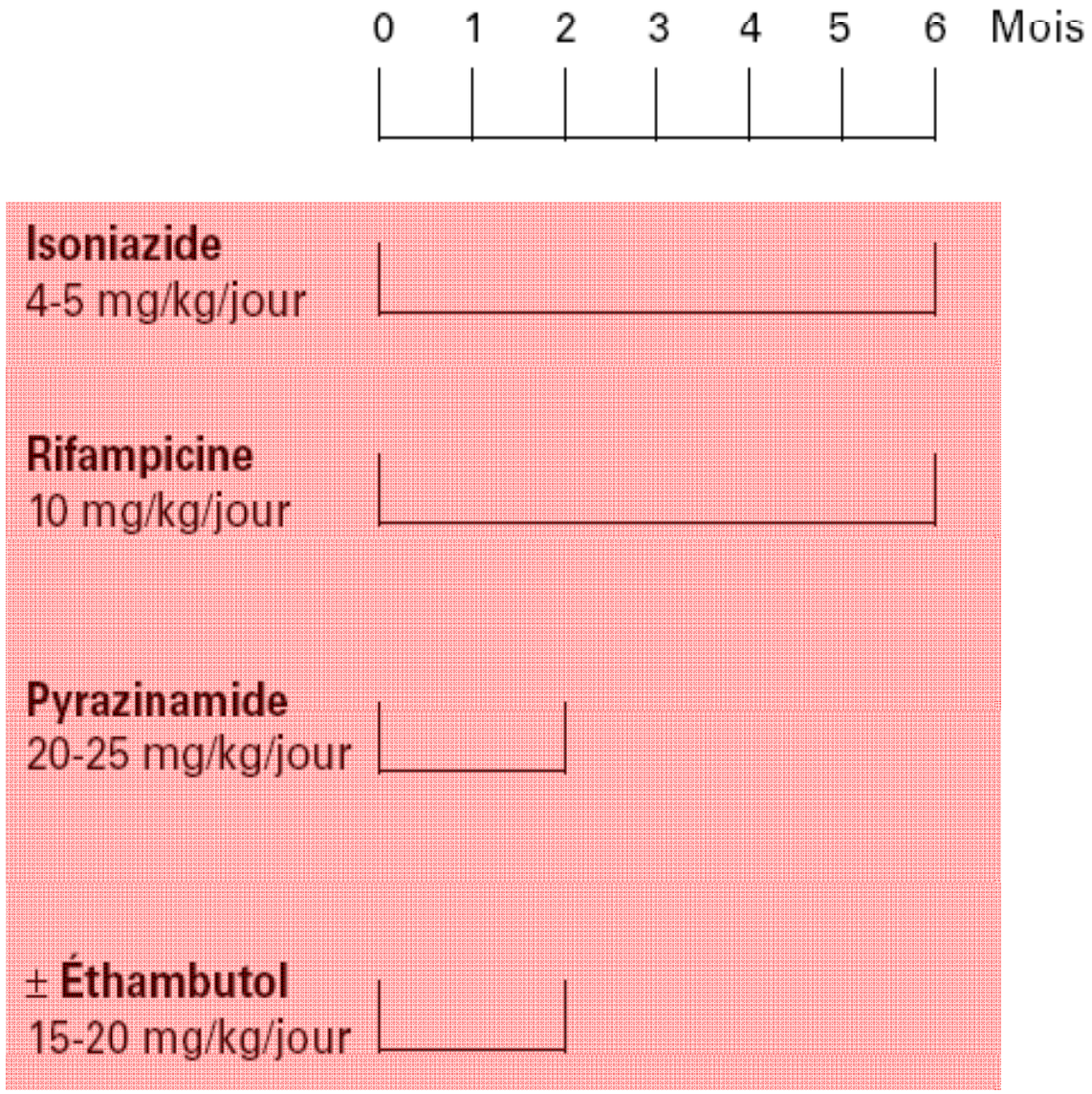
*Lancet* 2003; 362: 887-99


TREATMENT of TUBERCULOSIS
GUIDELINES
for
NATIONAL
PROGRAMMES

## *TB treatment in HIV-infected TB patients*

The same criteria determine diagnostic categories for TB patients irrespective of HIV status. Thus, HIV-infected new TB patients receive Category I treatment if they have smear-positive pulmonary TB, smear-negative pulmonary TB with extensive parenchymal involvement, or severe forms of extrapulmonary TB.

Generally, TB treatment is the same for HIV-infected as for non-HIV-infected TB patients, with the exception of the use of thioacetazone. Streptomycin remains a useful drug in countries that can ensure the use of disposable or sterile needles and syringes.




*Rev Mal Respir* 2003; 20: 7S13-7S19

**Ne pas oublier les interactions médicamenteuses !!!**

- corticoïdes
- AVK
- contraceptifs oraux
- antidiabétiques oraux
- ciclosporine
- cotrimoxazole
- méthadone

**Concentrations ↘ (effet inducteur enz. de la rifampicine)**

- phénytoïne
- carbamazépine

**Concentrations ↗ (isoniazide)**

- paracétamol: à éviter si INH (↗ métabolites toxiques)

# Interactions rifampicine - antirétroviraux

| Drug | Rifampicin | |
|---|---|---|
| | Interaction with rifampicin | Recommended antiretroviral therapy dose |
| **Non-nucleoside reverse transcriptase inhibitor** | | |
| Efavirenz | Efavirenz[#] ↓ 20–30% | Can consider increasing the dose to 800 mg once daily if weight >60 kg |
| Nevirapine | Nevirapine[¶] ↓ 20–55% | Not recommended[+] |
| Etravirine | No data | Do not use |
| Rilpivirine | Rilpivirine [¶] ↓ 90% | Do not use |
| **Protease inhibitors** | | |
| Ritonavir-boosted atazanavir | Atazanavir[¶] ↓ | Do not use |
| Ritonavir-boosted darunavir | No data[¶] | Do not use |
| Indinavir | Indinavir[¶] ↓ 89% | Do not use |
| Ritonavir-boosted lopinavir | Lopinavir[¶] ↓ 75% | Add high dose ritonavir (300 mg every 12 h) or double lopinavir/ritonavir dose but do not use in case of hepatotoxicity |
| Nelfinavir | Nelfinavir[¶] ↓ 75% | Do not use |
| Ritonavir | Ritonavir[#] ↓ 35% | Poorly tolerated and only used as booster for other PIs |
| Ritonavir-boosted saquinavir | Saquinavir[¶] ↓ 80% | Can add high dose ritonavir but do not use in case of hepatotoxicity |
| **Integrase inhibitors** | | |
| Raltegravir | Raltegravir[¶] ↓ 60% | Use with caution, even with 800 mg *b.i.d.* |
| Elvitegravir | Elvitegravir[¶] ↓ level | Do not use |
| **CCR5 antagonist** | | |
| Maraviroc | Maraviroc[#] ↓ level | Double the dose |
| **Enfuvirtide** | No interaction | Same dose |

Data for interaction with rifampicin are presented as % of changes in area under the plasma concentration time curve. [#]: potential interaction; [¶]: definite interaction, do not combine; [+]: if nevirapine needs to be used, start at 200 mg twice daily (no lead-in dose).

***Eur Respir J* 2010; 36: 1460-1481**

# *Interactions avec les INNTI*

- L'association des INNTI avec la rifampicine est à l'origine d'une baisse de leur concentration plasmatique d'environ 1/3;
- L'utilisation concomitante de la rifampicine et de l'EFV ou de la NVP est néanmoins possible ;

| Névirapine | Efavirenz | Rifampicine |
|---|---|---|
| En cours d'éval. | Pas de modif dose | Pas de modif dose |

- L'utilisation de la rifabutine est possible avec l'efavirenz (en augmentant à 450 mg/j).
- L'association rifabutine + névirapine est possible sans modification de dose.
- site internet : www.hiv-druginteractions.org

# *Interactions avec les IP (1)*

- La *rifampicine*, puissant inducteur enzymatique, est contre-indiquée avec tous les IP non associés au ritonavir. En effet, elle diminue leurs concentrations plasmatiques qui deviennent inférieures aux concentrations virales inhibitrices.

- S'il n'y a pas d'alternative thérapeutique, l'utilisation concomitante de rifampicine et d'un IP boosté par ritonavir toutefois possible, sous réserve d'augmenter la posologie de l'IP.

# *Interactions avec les IP (2)*

- La *rifabutine* est un inducteur moins puissant et des adaptations de posologie sont proposées en tenant compte des interactions réciproques :
  - diminution des concentrations de l'IP par l'effet inducteur de la rifabutine
  - effet inhibiteur de l'IP entrainant une augmentation de la rifabutine : augmentation des risques d'uvéite, d'arthralgies et de leucopénie.
- La rifabutine doit être réduite de moitié (150 mg/j) lorsqu'elle est associée au nelfinavir. La rifabutine doit être réduite au quart de dose (150 mg/j 3 jours par semaine) avec tout IP associé à une faible dose de ritonavir.

# Si ART avec IP ou INN : rifampicine → rifabutine

| Inhibiteurs de protéase | Posologie de rifabutine |
|---|---|
| Indinavir 1 000 ou 1 200 mg x 3/j | 150 mg/j ou 300 mg x 2/semaine |
| Nelfinavir 1 250 mg x 2 /j | 150 mg/j ou 300 mg x 2/semaine |
| Amprenavir 1 200 mg x 2 /j | 150 mg/j ou 300 mg x 2/semaine |
| Saquinavir/Ritonavir 400 mg/400 mg x 2/j | 150 mg x 3/semaine |
| Lopinavir/Ritonavir 400/100 mg x 2/j | 150 mg x 3/semaine |
| Tout inhibiteur de protéase associé à Ritonavir (100 mg x 2/j) | 150 mg x 3/semaine |
| **Inhibiteur non nucléosidique de la reverse transcriptase (INN)** | |
| Efavirenz 600 mg/j | 450 à 600 mg/j |
| Nevirapine 200 mg x 2 /j | 300 mg /j |

*Rev Mal Respir* 2003; 20: 7S13-7S19

# TUBERCULOSE

## Effets indésirables liés aux médicaments

| | Any Serious* | | Rash/Fever† | | Hepatitis‡ | | GI Upset§ | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Female sex (versus male) | 2.5 | 1.3 to 4.7 | 1.9 | 0.7 to 4.8 | 2.2 | 0.7 to 6.9 | 3.6 | 0.6 to 11.8 |
| Age, yr | | | | | | | | |
| 35–59 (versus < 35) | 1.7 | 0.8 to 3.8 | 1.0 | 0.3 to 3.1 | 4.8 | 0.9 to 25 | 2.1 | 0.3 to 14.9 |
| 60+ (versus < 35) | 2.9 | 1.3 to 6.3 | 1.3 | 0.4 to 4.1 | 7.7 | 1.5 to 40 | 6.4 | 1.2 to 36 |
| From Asia (versus all others) | 2.5 | 1.3 to 5.0 | 2.8 | 1.1 to 7.5 | 2.2 | 0.7 to 6.9 | 3.6 | 0.8 to 15.2 |
| Method of detection passive (versus active) | 2.5 | 0.9 to 6.6 | 2.3 | 0.6 to 8.3 | —‖ | — | 2.6 | 0.6 to 11.7 |
| Smear positive (versus smear negative) | 1.3 | 0.7 to 2.6 | 1.0 | 0.4 to 2.7 | 1.8 | 0.6 to 5.7 | 0.5 | 0.1 to 2.4 |
| Drug resistant (versus pansensitive) | 1.8 | 0.8 to 4.3 | 1.0 | 0.2 to 4.5 | 2.7 | 0.7 to 10.5 | 0.9 | 0.1 to 7.3 |
| Abnormal baseline LFTs (versus normal)¶ | 1.6 | 0.6 to 4.2 | 2.3 | 0.6 to 8.0 | — | — | 3.9 | 0.8 to 19.5 |
| HIV-positive (versus negative or NA) | 3.8 | 1.05 to 13.4 | 5.1 | 1.02 to 27 | 4.3 | 0.5 to 38 | — | — |

*Am J Respir Crit Care Med* 2003; 167: 1472-7

# TUBERCULOSE

## Effets indésirables liés aux médicaments

| | INH | | RIF | | PZA | |
|---|---|---|---|---|---|---|
| Characteristics (Comparison) | HR* | 95% CI | HR* | 95% CI | HR* | 95% CI |
| Female sex (versus male) | 2.5 | 0.96 to 6.6 | 2.2 | 0.8 to 6.1 | 2.2 | 0.96 to 4.8 |
| Age, yr | | | | | | |
| 35–59 (versus < 35) | 3.4 | 1.1 to 10.3 | 2.3 | 0.6 to 8.7 | 1.1 | 0.4 to 3.0 |
| 60+ (versus < 35) | 1.9 | 0.5 to 8.1 | 3.9 | 1.02 to 14.9 | 2.6 | 1.01 to 6.6 |
| From Asia (versus all others) | 2.1 | 0.8 to 5.6 | 2.8 | 0.9 to 8.4 | 3.4 | 1.4 to 8.3 |
| Method of detection passive (versus active) | —† | — | — | — | 1.5 | 0.5 to 4.1 |
| Smear positive (versus smear negative) | 1.2 | 0.5 to 3.3 | 0.8 | 0.2 to 2.5 | 1.5 | 0.7 to 3.5 |
| Drug resistant (versus pansensitive) | 3.4 | 1.1 to 10.9 | 1.4 | 0.3 to 6.6 | 1.9 | 0.7 to 5.3 |
| Abnormal baseline LFTs (versus normal)‡ | 0.5 | 0.1 to 4.1 | 1.7 | 0.4 to 8.1 | 2.2 | 0.7 to 6.6 |
| HIV-positive (versus -negative or NA) | 2.4 | 0.3 to 19.5 | 8.0 | 1.5 to 43 | 2.1 | 0.3 to 17.1 |

*Am J Respir Crit Care Med* 2003; 167: 1472-7

# Effets secondaires du traitement anti TB chez les patients VIH+

**Rifampicine 10-12 %, Isoniazide 3-6 % > Ethambutol, Pyrazinamide**

**Experience au CHU St Pierre, Bruxelles**

| | HIV ⊕ (n=34) | HIV ⊖ (n=34) | p |
|---|---|---|---|
| All side effects | 17 (50 %) | 8 (23.5 %) | < 0.05 |
| Fever / rash | 12 (35 %) | 3 (9 %) | < 0.05 |
| Liver toxicity | 9 (26 %) | 6 (18 %) | |
| Arthritis | 4 | 0 | |
| Uveitis | 1 | 0 | |
| Polyneuropathy | 2 | | |

**D'après une communication de S. De Wit**

# TUBERCULOSE

## Hépatotoxicité

American Thoracic Society Documents

### An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy

Jussi J. Saukkonen, David L. Cohn, Robert M. Jasmer, Steven Schenker, John A. Jereb, Charles M. Nolan, Charles A. Peloquin, Fred M. Gordin, David Nunes, Dorothy B. Strader, John Bernardo, Raman Venkataramanan, and Timothy R. Sterling, on behalf of the ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee

THIS OFFICIAL STATEMENT WAS APPROVED BY THE ATS BOARD OF DIRECTORS, MARCH 2006

*Am J Respir Crit Care Med* 2006; 174: 935-52

2. If serum transaminase concentrations are more than five times the ULN (with or without symptoms) or more than three times the ULN with jaundice and/or hepatitis symptoms, then potentially hepatotoxic medications should be stopped immediately and the patient evaluated promptly.
3. Serologic tests for hepatitis A, B, and C viruses should be obtained, and the patient should be evaluated for biliary disease, use of alcohol, and other hepatotoxic drugs.
4. Some experts recommend interrupting treatment for lesser increases in patients with cirrhosis or encephalopathy.
5. If indicated, until the specific cause of abnormalities can be determined, clinicians should treat with at least three anti-TB agents that are less likely to cause hepatotoxicity.

*Am J Respir Crit Care Med* 2006; 174: 935-52

1. After ALT returns to less than two times the ULN, rifampin may be restarted with or without ethambutol.
2. After 3 to 7 days, isoniazid may be reintroduced, subsequently rechecking ALT.
3. If symptoms recur or ALT increases, the last drug added should be stopped.
4. For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with rifampin and isoniazid, rechallenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months.

Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity (144), the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide rechallenge.

*Am J Respir Crit Care Med* 2006; 174: 935-52

## QUELLE ATTITUDE EN CAS D'EFFETS INDÉSIRABLES ?

**Elévation des transaminases**

- si < 3 N : surveillance rapprochée (⚠ doses)
- entre 3 et 6 N : pas de consensus
  - arrêt pyrazinamide
  - surveillance
- si > 6 N : arrêt immédiat des antituberculeux (pyrazinamide > isoniazide > rifampicine).

Pour certains, poursuivre rifampicine + ethambutol.

**Ne jamais reprendre le pyrazinamide si > 6-10 N**

# Principales toxicités médicamenteuses

| Toxicity | Antiretroviral | Anti-TB |
|---|---|---|
| **Peripheral neuropathy** | Stavudine, didanosine | INH, ethionamide, cycloserine |
| **Gastrointestinal intolerance** | All | All |
| **Hepatotoxicity** | Nevirapine, efavirenz and PI (especially if ritonavir boosting) | INH, rifampicin, rifabutin, pyrazinamide, moxifloxacin |
| **Central nervous system toxicity** | Efavirenz | INH, cycloserine, quinolones, ethionamide |
| **Bone marrow suppression** | Zidovudine | Rifabutin, rifampicin, INH |
| **Skin rash** | Abacavir, amprenavir, nevirapine, efavirenz, darunavir, fosamprenavir | INH, rifampicin, pyrazinamide, ethambutol, streptomycine |
| **Renal toxicity** | Tenofovir | Aminoglycosides, capreomycin, rifampicin |
| **Ocular effects** | Didanosine | Ethambutol, rifabutin |

***Eur Respir J* 2010; 36: 1460-1481**

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- QUAND DÉBUTER ?

# Recommandations de la Société de Pneumologie de Langue Française sur la prise en charge de la tuberculose en France

## Conférence d'experts – texte court

Société de Pneumologie de Langue Française

Rev Mal Respir 2004 ; 21 : 414-20

Le niveau de preuve de chacune des recommandations a été coté selon une gradation adaptée de celle de l'ANAES :

**A :** preuve scientifique établie (essais comparatifs randomisés de forte puissance, méta-analyse d'essais comparatifs randomisés, analyse de décision basée sur des études bien menées)

**B :** présomption scientifique (essais comparatifs randomisés de faible puissance, études comparatives non randomisées bien menées, études de cohorte)

**C :** faible niveau de preuve (études cas-témoins)

**D :** avis d'experts.

Rev Mal Respir 2004 ; 21 : 414-20

## Question 5 : Quel traitement proposer, en dehors du traitement antituberculeux standard ?

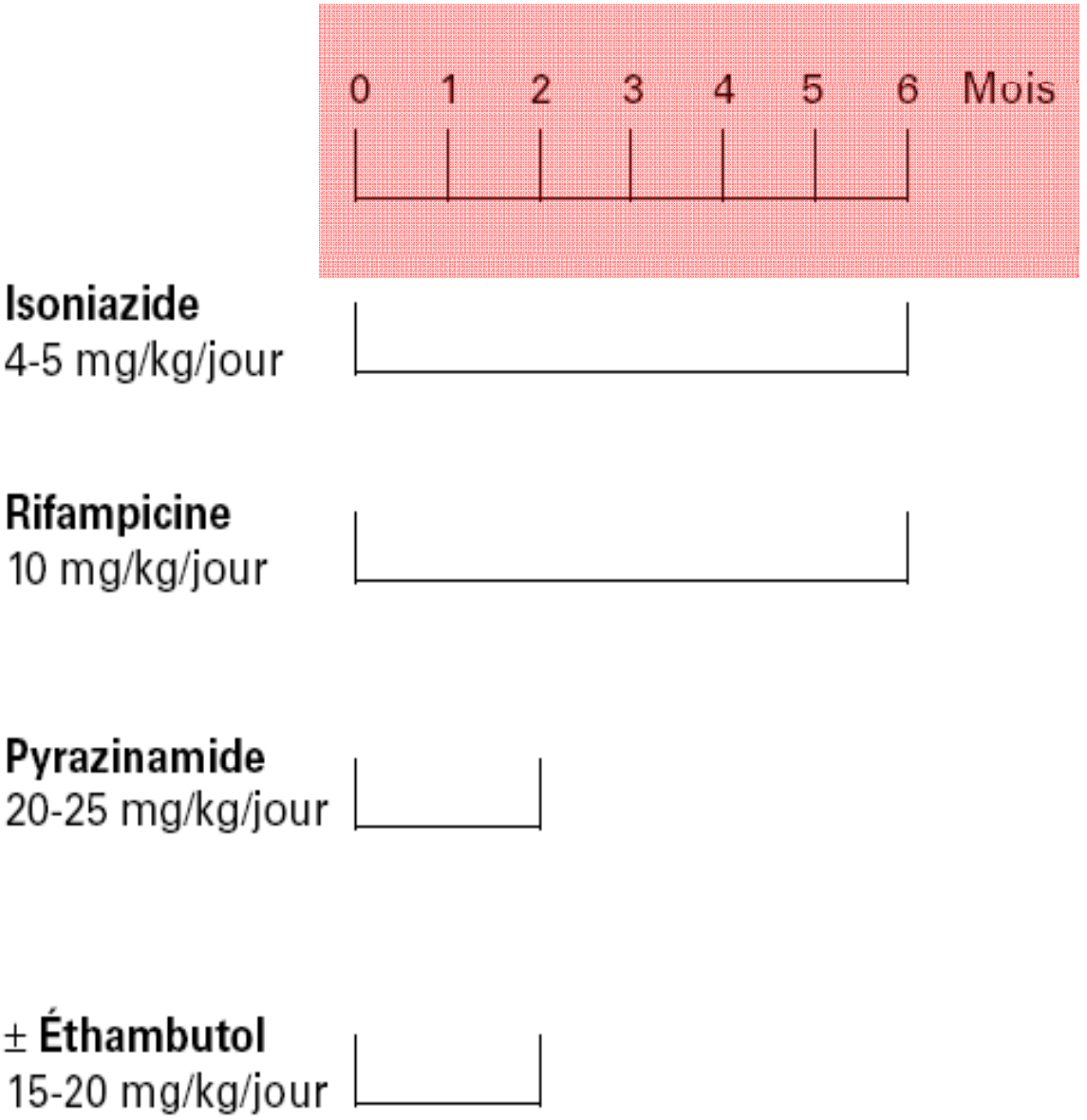
### • quel est le traitement standard de la tuberculose ?

• Le *traitement standard de la tuberculose maladie* recommandé en France chez l'adulte, est le traitement quotidien en deux phases comprenant durant la première phase de 2 mois l'association de 4 antibiotiques : isoniazide, rifampicine, pyrazinamide et éthambutol, puis durant la deuxième phase de 4 mois l'association isoniazide et rifampicine (A).

• Malgré l'absence d'études démonstratives, les formes galéniques *combinées* sont recommandées afin de favoriser l'observance (avis d'experts).

• Chez les patients séropositifs pour le *VIH*, il est recommandé d'utiliser le traitement standard, avec la même durée de traitement (A).

Rev Mal Respir 2004 ; 21 : 414-20




*Rev Mal Respir* 2003; 20: 7S13-7S19

**Rapport 2010**

sous la direction
du Pr. **Patrick Yeni**

# Prise en **charge médicale** des **personnes infectées** par le **VIH**

Recommandations
du groupe d'**experts**

## Traitement curatif

### *Bacilles tuberculeux sensibles*

En cas de tuberculose-maladie, le traitement comporte deux mois de quadrithérapie ou de trithérapie incluant l'isoniazide (3 à 5 mg/kg/j), la rifampicine (10 mg/kg/j) (ou rifabutine en cas de coprescription d'IP), le pyrazinamide (25 mg/kg/j) et l'éthambutol (15 mg/kg/j).

Après le résultat de l'antibiogramme et en l'absence de résistance, le traitement sera poursuivi au-delà du 2e mois par une bithérapie associant rifampicine (ou rifabutine en cas de prescription d'un IP) et isoniazide. Il est recommandé d'associer la prise de vitamine B6 (50 mg/j) pour limiter le risque de neuropathie iatrogène sous isoniazide, surtout en cas de dénutrition.

La durée prévisionnelle totale du traitement est de 6 mois mais la durée sera au minimum de 9 mois en présence de caverne (pouvant de plus faire appel à la chirurgie), chez les patients encore bacillifères à 2 mois de traitement, ou si les modalités d'administration n'ont pu être respectées du fait d'intolérance cutanée ou hépatique (20 à 30 % des cas). Une durée de traitement d'au moins 12 mois est recommandée dans les formes disséminées, ostéoarticulaires ou neuro-méningées [11].

En cas de positivité initiale des prélèvements, il est recommandé de vérifier la guérison microbiologique par un contrôle bactériologique avant l'arrêt du traitement et trois mois après.

Rapport Yéni 2010

ELSEVIER

European Journal of Internal Medicine 17 (2006) 427–429

EUROPEAN JOURNAL OF
INTERNAL
MEDICINE

www.elsevier.com/locate/ejim

Original article

# Tuberculosis treatment duration in France: From guidelines to daily practice

P. Tattevin [a,*], J.-M. Chapplain [a], P. Lesprit [b], C. Billy [c], F. Roblot [d], S. Alfandari [e], L. Bernard [f], E. Rouveix [g], E. Bouvet [h]

- Mai 2004
- 375 membres de la SPILF contactés
- questionnaire sur les habitudes de pratique dans leur institution
- 66 réponses (17,6%), anonymes

List of questions sent to the 375 physician members of the French infectious diseases society (Société de Pathologie Infectieuse de Langue Française, SPILF)

In general,

1. How long do you treat pulmonary tuberculosis?
2. How long do you treat tuberculous lymphadenitis?
3. How long do you treat tuberculous meningitis?
4. How long do you treat osteo-articular tuberculosis?
5. How long do you treat miliary tuberculosis?
6. How long do you treat pulmonary tuberculosis in HIV-infected patients?
7. When do you systematically prescribe corticosteroids at the initiation of tuberculosis treatment?

Usual tuberculosis treatment duration in France according to clinical presentation and HIV status

| Treatment duration (months) | Tuberculosis localization | | | | | |
|---|---|---|---|---|---|---|
| | Pulmonary (non-HIV) | Miliary | Lympha-denitis | Neuro-meningeal | Osteo-articular | Pulmonary (HIV) |
| 6 | 90.9 | 45.3 | 23.1 | 9.2 | 7.7 | 35.9 |
| 9 | 9 | 28.1 | 56.9 | 12.3 | 10.8 | 42.2 |
| 12 | 0 | 26.6 | 18.5 | 78.5 | 64.6 | 20.3 |
| 18 | 0 | 0 | 1.5 | 0 | 16.9 | 1.6 |
| Total | 100 | 100 | 100 | 100 | 100 | 100 |

In each column, the numbers represent the percentage of physicians indicating a given treatment duration (6, 9, 12 or 18 months). The darkened boxes indicate the recommended treatment duration in the USA (Centers for Disease Control and Prevention, American Thoracic Society, Infectious Diseases Society of America) [1] and in France (Conseil Supérieur d'Hygiène Publique) [2].

# A Review of Efficacy Studies of 6-Month Short-Course Therapy for Tuberculosis among Patients Infected with Human Immunodeficiency Virus: Differences in Study Outcomes

**Wafaa M. El-Sadr,[1] David C. Perlman,[2] Eileen Denning,[3] John P. Matts,[3] and David L. Cohn[4]**

[1]Harlem Hospital Center and Columbia University, College of Physicians and Surgeons, and [2]Beth Israel Medical Center, New York; [3]Division of Biostatistics, University of Minnesota, Minneapolis; and [4]Denver Public Health, Denver

**Clinical Infectious Diseases 2001;32:623–32**

| Patient characteristic | Reference | | | | | |
|---|---|---|---|---|---|---|
| | Perriens et al. [12] | Kassim et al. [13] | Kennedy et al. [14] | Chaisson et al. [15] | Vernon et al. [16] | El-Sadr et al. [17] |
| Eligible, no. | 168[a] | 553 | 34 | 159 | 35 | 51 |
| Tuberculosis confirmed by culture, no. (%) | 168 (100) | 0 | 34 (100) | 67 (38) | 35 (100) | 51 (100) |
| AIDS diagnosis, % | NR | 62 | NR | NR | NR | 25.5 |
| CD4 cell count, median cells/mm$^3$ (% CD4 cell count) | 317 | ND | NR | 475 (16) | 137 | 86 |
| No. with pulmonary site only/other site only | 168/0 | 553/0 | 34/0 | 130/29[c] | 35/0 | 51/0 |
| Age, mean y ± SD | 30 ± 7.3 | 34.8 | 35.7 ± 12.7 | 30[b] | 42.1 ± 8.7 | 39.2 ± 8.6 |
| % male | 40 | 84.6 | 64 | 56 | 88.6 | 86.3 |

NOTE. ND, not done; NR, not reported.

[a] Estimated from text, on basis of total enrollment of 335 patients.

[b] Median.

[c] Intrathoracic lymphadenopathy

| Phase of study, patient variable | Perriens et al. [12] | Kassim et al. [13] | Kennedy et al. [14] | Chaisson et al. [15] | Vernon et al. [16] | El-Sadr et al. [17] |
|---|---|---|---|---|---|---|
| Treatment | | | | | | |
| Eligible, no. | 168 | 553 | 34 | 159 | 35 | 51 |
| Lost to follow-up or with incomplete or inadequate treatment phase, no. (% of patients eligible) | 15[a] (8.9) | 94 (16.9) | 4 (11.7) | 13 (8.1) | 1 (2.8) | 0 |
| Failure during treatment phase, no. [no. confirmed] (% of patients eligible) | 3 [3] (0.8) | 8 [0] (1.4) | 0 | 3 (1.8) | 0 [0] | 1 [1] (1.9) |
| Died during treatment phase, no. (% of patients eligible) | 22[a] (13) | 57 (10.3) | NR | 14 (8.8) | 0 | 0 |
| Cured at end of treatment phase, no. (% of patients eligible) | 124 (73.8) | 329 (59.4) | 30 (88.2) | 129 (81.1) | 34 (97.1) | 44 (86.2) |
| Follow-up | | | | | | |
| Entering follow-up phase, no. (% of patients eligible) | 119 (73.8) | 329 (59.4) | 30 (88.2) | 129 (81.1) | 31 (88.6) | 44 (86.2) |
| Lost during follow-up phase, no. (% of patients entering follow-up phase) | 36 (30.2) | NR | NR | NR | 1 (3.2) | 7 (15.9) |
| Died, no. (% of patients entering follow-up phase) | 19 (15.9) | 64 (19.4) | NR | 39 (30.2) | 7 (22.6) | 21 (47.7) |
| Relapsed, no. (% of patients entering follow-up phase) | 9 (7.5) | 15 (4.5) | 0 | 7 (5.4) | 3 (10) | 1 (2.2) |
| Duration of follow-up from end of treatment phase, mo | 12 | 18 | 6 | 22 | 20 | 17.6 |
| Died, overall %[b] | 37.5 | 21.8 | NR | 33.3 | 20 | 41.1 |

NOTE. NR, not reported.

[a] Estimated on basis of text.

[b] No. died/total eligible for study.

| Outcome | HIV+ patients, %, by reference | | | | | | HIV− patients, %, by reference | | |
|---|---|---|---|---|---|---|---|---|---|
| | Perriens et al. [12] | Kassim et al. [13] | Kennedy et al. [14] | Chaisson et al. [15] | Vernon et al. [16] | El-Sadr et al. [17] | Combs et al. [18] | Cohn et al. [19] | Snider et al. [20] |
| Cured[a] | 73.8 | 59.4 | 94.1 | 81.1 | 97.1 | 86.2 | 62.3 | 88.0 | 71.4 |
| Relapsed | 7.5 | 4.5 | 0 | 5.4 | 10.0 | 2.2 | 3.4 | 1.6 | 0 |
| Treatment successful | 44.3 | 75.9[b] | 100[b] | 64.3[b] | 58.8 | 34.0 | 91.9[b] | 95.2 | 98.8 |
| Treatment effective | 32.7 | 45.3 | 88.2[b] | 52.2[b] | 57.2 | 29.4 | 77.3[b] | 83.8 | 70.6 |

[a] At 6 months.
[b] Maximum estimate, because patients who were lost to follow-up, withdrew from the study, or died were not reported.

- Le traitement recommandé des cas de tuberculose *pleurale, péricardique, ganglionnaire ou osseuse* est le traitement standard de 6 mois (avis d'experts).
- En cas de *méningite* tuberculeuse, il est recommandé de prolonger le traitement standard, pour une durée totale de 9 mois (avis d'experts).

Rev Mal Respir 2004 ; 21 : 414-20

# ACTG Study: 6 vs 9 mo Rx for HIV/TB

| | 6 months | 9 months |
|---|---|---|
| • Enrolled | 50 | 51 |
| • Completed therapy | 41 | 37 |
| • Treatment Failure | 1 | 0 |
| • Relapse | 1 | 1 |

Clin Infect Dis 1998;26:1148-58

## DURÉE DE TRAITEMENT : TB ganglionnaires

- Amrane R. et coll., *Rev Mal Respir* 1989; 6: 53-57
- Alger, 1982
- preuve bactériologique ou histologique
- phase initiale: HRZ + Streptomycine pendant 2 mois
- puis RH pendant 4 ou 7 mois
- 117 patients (58% de femmes)
- après un suivi de 2 ans post-traitement, 9 échecs : 5 dans le bras 6 mois *vs.* 4 dans le bras 9 mois (NS)

## DURÉE DE TRAITEMENT : TB ganglionnaires

- Campbell IA et coll., *Respir Med* 1993; 87: 621-3
- 199 patients
- 157 ont terminé leur traitement comme prévu
- 50 = E2H9R9, 56= Z2 H9R9 et 51 = Z2H6R6
- pas de différence sur la taille des ADP, la survenue d'autres ADP, le recours chirurgical ou le % d'ADP mesurables à 30 mois
- 9 « rechutes » (4 E2H9R9; 2 Z2H9R9; 3 Z2H6R6) mais sans confirmation bactério pour les 5 où un prélèv$^{t}$ a été envoyé (NS)
- **donc régime de 6 mois = OK**

## DURÉE DE TRAITEMENT : TB ganglionnaires

- Etude de P. Clevenbergh et coll. (*Presse Med.* 2010; 39: e223-e230) : 92 TB ganglionnaires prises en charge à Lariboisière entre mars 1996 et avril 2005.

  - 62 hommes, 30 femmes
  - âge moyen 38 ± 15 ans
  - 12 patients nés en France
  - 24 patients VIH +
  - durée médiane de traitement : 7,5 mois
  - le traitement TB a dépassé 9 mois chez 79% des patients infectés par le VIH (vs. chez 39% des VIH -) !

  - Étude de N. Valin et coll. (*BMC Public Health* 2010; 10:495)

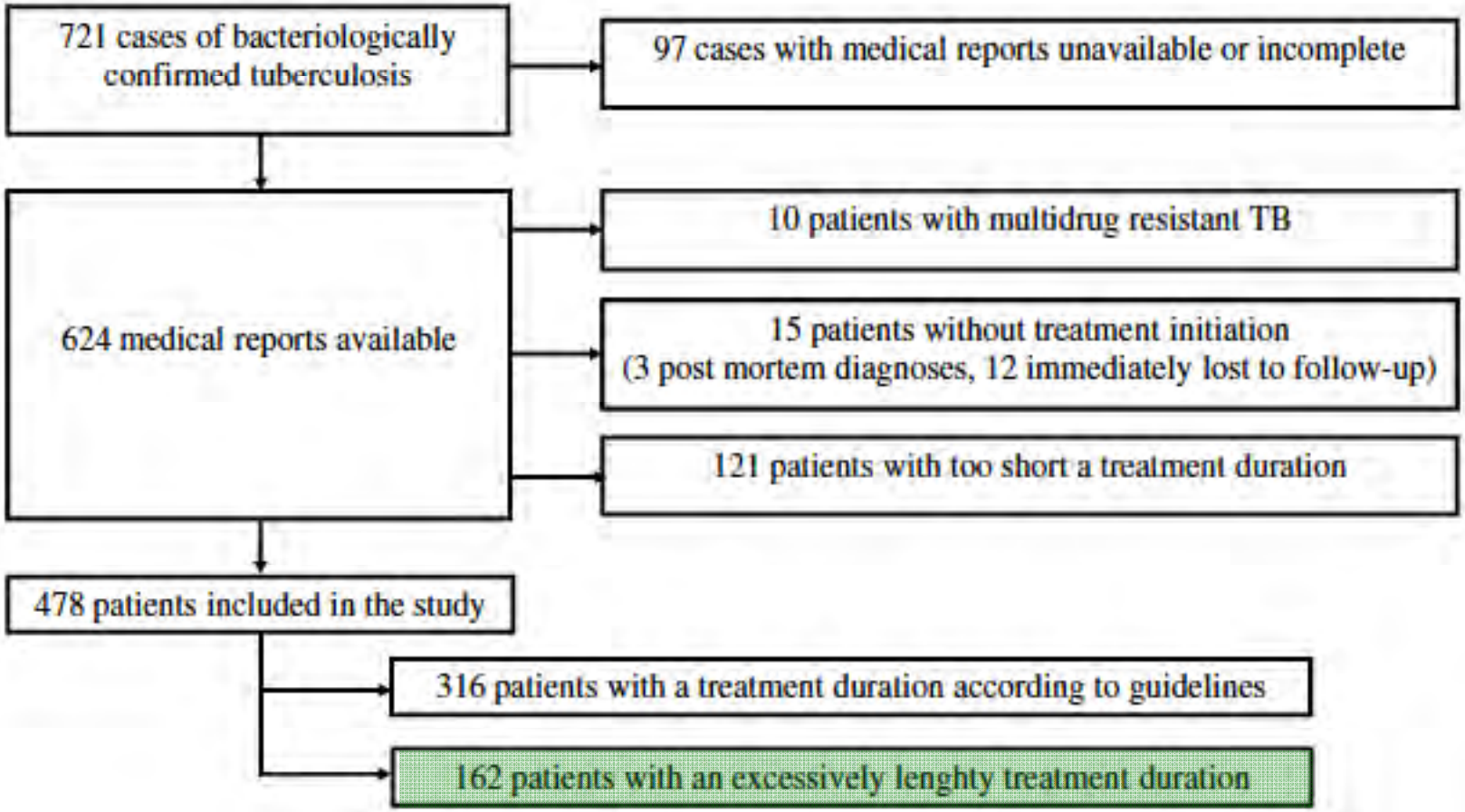
# DURÉE DE TRAITEMENT : TB ganglionnaires

Valin *et al. BMC Public Health* 2010, **10**:495
http://www.biomedcentral.com/1471-2458/10/495


RESEARCH ARTICLE Open Access

## Factors associated with excessively lengthy treatment of tuberculosis in the eastern Paris region of France in 2004

Nadia Valin[1*], Gilles Hejblum[2,3,5], Isabelle Borget[3], Henri-Pierre Mallet[4], Fadi Antoun[5], Didier Che[6], Christos Chouaid[3,5,7]


721 cases of bacteriologically confirmed tuberculosis
97 cases with medical reports unavailable or incomplete
624 medical reports available
10 patients with multidrug resistant TB
15 patients without treatment initiation
(3 post mortem diagnoses, 12 immediately lost to follow-up)
121 patients with too short a treatment duration
478 patients included in the study
316 patients with a treatment duration according to guidelines
162 patients with an excessively lenghty treatment duration

| Feature | Treatment duration | | | | Statistical analyses | | | |
|---|---|---|---|---|---|---|---|---|
| | All patients N = 478 | According to guidelines N = 316 | Excessive duration N = 162 | | Univariate analysis | | Multivariate analysis | |
| | | | Number of patients | Median duration [IQR] | Odds Ratio [95%CI] | P value | Odds Ratio [95%CI] | P value |
| ***Clinical characteristics*** | | | | | | | | |
| *Previous TB* | 53 (11.1%) | 22 (7.0%) | 31 (19.1%) | 315 [252-387] | 3.0 [1.8-5.8] | <0.0001 | 2.9 [1.6-5.4] | 0.001 |
| *Isolated thoracic TB* | 279 (58.4%) | 172 (54.4%) | 107 (66.0%) | 275 [250-311] | 1.6 [1.1-2.4] | 0.02 | 2.2 [1.4-3.5] | <0.0001 |
| *HIV seropositivity* | 74 (16.9%) | 36 (11.4%) | 38 (23.5%) | 361 [289-418] | 2.3 [1.4-3.8] | 0.001 | 2.5 [1.4-4.4] | 0.002 |
| *Alcoholism* | 83 (19.4%) | 42 (13.3%) | 41 (25.3%) | 287 [266-367] | 2.0 [1.2-3.3] | 0.004*** | - | - |
| *Injecting drug use* | 10 (2.1%) | 02 (0.6%) | 08 (4.9%) | 352 [305-419] | 7.5 [1.6-35.8] | 0.01*** | - | - |
| *Psychiatric disorders* | 38 (7.9%) | 23 (7.3%) | 15 (9.3%) | 321 [274-367] | 1.2 [0.6-2.3] | 0.62 | | |
| *Precarious situation** | 210 (43.9%) | 137 (43.4%) | 73 (45.1%) | 292 [274-407] | 1.0 [0.7-1.5] | 0.98 | | |
| *Isoniazid resistance* | 27 (5.6%) | 17 (5.4%) | 10 (6.2%) | 273 [241-396] | 1.1[0.5-2.6] | 0.72 | | |
| ***Management modalities*** | | | | | | | | |
| *Prescriber* | | | | | 0.002 | | | 0.01 |
| Chest specialist | 211 (44.1) | 157 (49.7%) | 54 (33.3%) | 274 [265-315] | 1 (reference) | | 1 (reference) | |
| Infectious disease specialist | 171 (35.8%) | 98 (31.0%) | 73 (45.1%) | 354 [274-427] | 2.2 [1.4-3.3] | | 2.1 [1.3-3.4] | |
| Other | 96 (20.1%) | 61 (19.3%) | 35 (21.6%) | 379 [287-498] | 1.7 [1.0-2.8] | | 1.9 [1.1-3.3] | |
| *Number of institutions per patient* | | | | | | 0.01 | | 0.001 |
| 1 | 295 (61.7%) | 210 (66.7%) | 85 (52.8%) | 282 [257-375] | 1 (reference) | | 1 (reference) | |
| 2 | 152 (31.8%) | 93 (29.5%) | 59 (36.6%) | 366 [274-448] | 1.6 [1.0-2.4] | | 1.7 [1.1-2.7] | |
| ≥3 | 29 (6.5%) | 12 (3.8%) | 17 (10.6%) | 356 [292-471] | 3.5 [1.6-7.6] | | 4.3 [1.9-10.1] | |

| Type of patients | Treatment duration (months) | | | | |
|---|---|---|---|---|---|
| | 6 | 6-9 | 9-12 | 12-18 | > 18 |
| *Isolated thoracic TB, N = 279* | *163 (58.4%)** | *46 (16.5%)* | *58 (20.8%)* | *10 (3.6%)* | *2 (0.7%)* |
| Four-drug regimen, N = 241 | 146 (60.6%) | **30 (12.5%)** | **53 (22.0%)** | **10 (4.1%)** | **2 (0.8%)** |
| Three-drug regimen without ethambutol, N = 23 | 14 (60.9%) | **7 (30.4%)** | **2 (8.7%)** | - | - |
| Three-drug regimen without pyrazinamide, N = 8 | 3 (37.5%) | 2 (25.0%) | **3 (37.5%)** | - | - |
| Four drug regimen and isoniazid resistance, N = 7 | | 7 (100%) | | | |
| *Extrathoracic TB N = 199* | *53 (26.6%)* | *34 (17.1%)* | *57 (28.7%)* | *44 (22.1%)* | *11 (5.5%)* |
| Meningeal, N = 7 | 2 (28.6%) | 0 | 2 (28.6%) | **3 (42.8%)** | - |
| Isolated nodal, N = 98 | 34 (34.7%) | 18 (18.4%) | 29 (29.5%) | **13 (13.3%)** | **4 (4.1%)** |
| Isolated osteoarticular, N = 22 | 2 (9.1%) | 2 (9.1%) | 6 (27.3%) | **9 (40.9%)** | **3 (13.6%)** |
| Disseminated or military, N = 41 | 6 (14.6%) | 4 (9.8%) | 11 (26.8%) | **16 (39.0%)** | **4 (9.8%)** |
| Other, N = 31 | 9 (29.0%) | 10 (32.3%) | 9 (29.0%) | **3 (9.7%)** | - |

**Abnormally lengthy treatments are in bold.**

# ANTITUBERCULEUX ET ANTIRÉTROVIRAUX

TRAITEMENT DE LA TUBERCULOSE-MALADIE :

- QUELLES MOLÉCULES ?
- QUELLE DURÉE DE TRAITEMENT ?

ANTIRÉTROVIRAUX ASSOCIÉS AUX ANTITUBERCULEUX :

- QUELLES MOLÉCULES ?
- QUAND DÉBUTER ?

# ANTITUBERCULEUX ET ANTIRÉTROVIRAUX

TRAITEMENT DE LA TUBERCULOSE-MALADIE :

- QUELLES MOLÉCULES ?
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ANTIRÉTROVIRAUX ASSOCIÉS AUX ANTITUBERCULEUX :

- QUELLES MOLÉCULES ?
- QUAND DÉBUTER ?

# TB AND HIV: LOTS OF TRIALS

**Clinicaltrials.gov website:** keywords «tuberculosis and HIV»

- accessed Aug. 13, 2009: 132 studies
- accessed Mar. 28, 2011: 168 studies

Not all related to both TB and HIV.

**Relevant topics in HIV-infected persons:**

- new TB vaccines: pre-exposure, post-exposure or therapeutic
- intensive case finding/isoniazid preventive therapy
- IRIS: ART-associated *vs.* unmasking TB-IRIS

# WHICH ART REGIMEN?

2 NRTIs + 1 PI si rifabutine
2 NRTIs + 1 NNRTI (incl. generics in low-income settings)
3 NRTIs

No large prospective randomized clinical trial published.

Efficacy of a once-daily ART regimen?

Nevirapin or efavirenz?

Pharmacokinetics? New ARVs …

L'association des INNTI avec la rifampicine est à l'origine d'une baisse de leurs concentrations plasmatiques d'environ un tiers; l'utilisation concomitante de l'efavirenz (800 mg/j si le poids est supérieur à 60 kg, au risque d'une tolérance neurologique difficile, ou 600 mg/j pour les poids inférieurs) et de la rifampicine est possible sous réserve d'un dosage du taux plasmatique de l'efavirenz pouvant amener à moduler la posologie initiale. En France, l'étude ANRS-189 BKVIR vient de montrer une bonne efficacité (> 80 % de succès virologique et bactériologique) et une bonne tolérance de l'association ténofovir-emtricitabine-efavirenz en monoprise quotidienne, instaurée dans les trois mois suivant la mise en place d'un traitement antituberculeux classique.

*La rifabutine* est un inducteur moins puissant et les adaptations de posologie proposées (tableau 2) tiennent compte de l'interaction réciproque, à savoir une diminution des concentrations de l'IP par l'effet inducteur de la rifabutine et un effet inhibiteur de l'IP (d'autant plus important que l'IP est associé à une faible dose de ritonavir) qui provoque une augmentation des concentrations de la rifabutine et de son métabolite, augmentant les risques d'uvéite, d'arthralgies et de leucopénie.

| **Antirétroviral*** | **Posologie de rifabutine** |
|---|---|
| Tout **IP/r** | 150 mg/j ou 150 mg x 3/sem ou 150 mg 1 j sur 2 |
| **INNTI** | |
| EFV, 600 mg/j | 450 mg/j |
| NVP, 200 mg x 2/j | 300 mg/j |

*Le dosage de l'IP/r ou de l'EFV est recommandé.

# BKVIR (ANRS 129) STUDY

Non comparative phase III pilot trial in naïve co-infected patients: NCT 00115609, France.

Efficacy and safety of a once daily ART regimen: **tenofovir disoproxil fumarate - emtricitabine (300/200 mg) + efavirenz (600 mg, increased to 800 mg when used with Rif)**.

***Therapeutic success***: VL < 50 copies/ml **AND** TB cured.

| |
|---|
| **1st inclusion: January 2006.** |
| **Target *n*=100. Enrollment stopped at 70.** |
| **Date of completion: 2010.** |

More info: Caroline.Roussillon@isped.u-bordeaux2.fr

anRS
Agence nationale de recherches sur le sida et les hépatites virales

# NEVIRAPINE 400 mg / EFAVIRENZ 600 mg

DOI: 10.1111/j.1468-1293.2008.00563.x
*HIV Medicine* (2008), 9, 294–299


ORIGINAL RESEARCH

## Standard-dose efavirenz *vs.* standard-dose nevirapine in antiretroviral regimens among HIV-1 and tuberculosis co-infected patients who received rifampicin

W Manosuthi,[1,2] W Mankatitham,[1] A Lueangniyomkul,[1] S Chimsuntorn[1] and S Sungkanuparph[2]

[1]*Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand and* [2]*Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

**Retrospective cohort study, Thailand. All with rifampicin.**
**CD4 = 36/mm$^3$.**
**77 patients initiated on EFV-based ART (BW 52.8 ± 8.4 kg).**
**111 patients initiated on NVP-based ART (BW 53.7 ± 8.7 kg).**

# NEVIRAPINE 400 mg / EFAVIRENZ 600 mg

| Plasma HIV-1 RNA | EFV group ($n = 77$) | NVP group ($n = 111$) | *P*-value | OR, 95% CI |
|---|---|---|---|---|
| Week 24 | | | | |
| < 400 copies/mL | 67 (87.0%) | 84 (75.7%) | 0.601 | 0.674, 0.306–1.487 |
| < 50 copies/mL | 66 (85.7%) | 89 (80.2%) | 0.816 | 0.816, 0.405–1.645 |
| Week 48 | | | | |
| < 400 copies/mL | 60 (77.9%) | 75 (67.6%) | 0.140 | 0.590, 0.302–1.153 |
| < 50 copies/mL | 60 (77.9%) | 75 (67.6%) | 0.140 | 0.590, 0.302–1.153 |

CI, confidence interval; EFV, efavirenz; NVP, nevirapine; OR, odds ratio.

| Outcomes | EFV group ($n = 77$) | NVP group ($n = 111$) | *P*-value |
|---|---|---|---|
| Drug allergy | 0 (0%) | 8 (7.2%) | 0.084 |
| Lost to follow-up | 10 (12.9%) | 6 (5.4%) | 0.108 |
| Died | 1 (1.3%) | 7 (6.3%) | 0.144 |
| Treatment failure | 2 (2.6%) | 9 (8.1%) | 0.204 |
| Transferred care | 0 (0%) | 2 (1.8%) | 1.000 |

*HIV Med* 2008; 9: 294-99.

# NVP/EFZ THAI $N_2R$ STUDY

Efavirenz-based vs. nevirapine-based antiretroviral therapy among HIV-infected patients receiving rifampin (N2R): NCT 00483054, Thailand. CD4 < 350, AFB and/or culture positive.

D4T-3TC **+ nevirapine** (400 mg/day twice daily)

*vs.* D4T-3TC **+ efavirenz** (600 mg/day).

Primary outcome: to compare proportion of patients who achieved undetectable plasma HIV-1 RNA< 50 copies/mL at 48 *(96 and 144)* weeks after initiation of ART.

**Started in December 2006.**

***n*=142 (71 per group).**

**Published in 2009 (*CID*).**

More info: Weerawat Manosuthi, idweerawat@yahoo.com

# NVP/EFZ THAI $N_2R$ STUDY

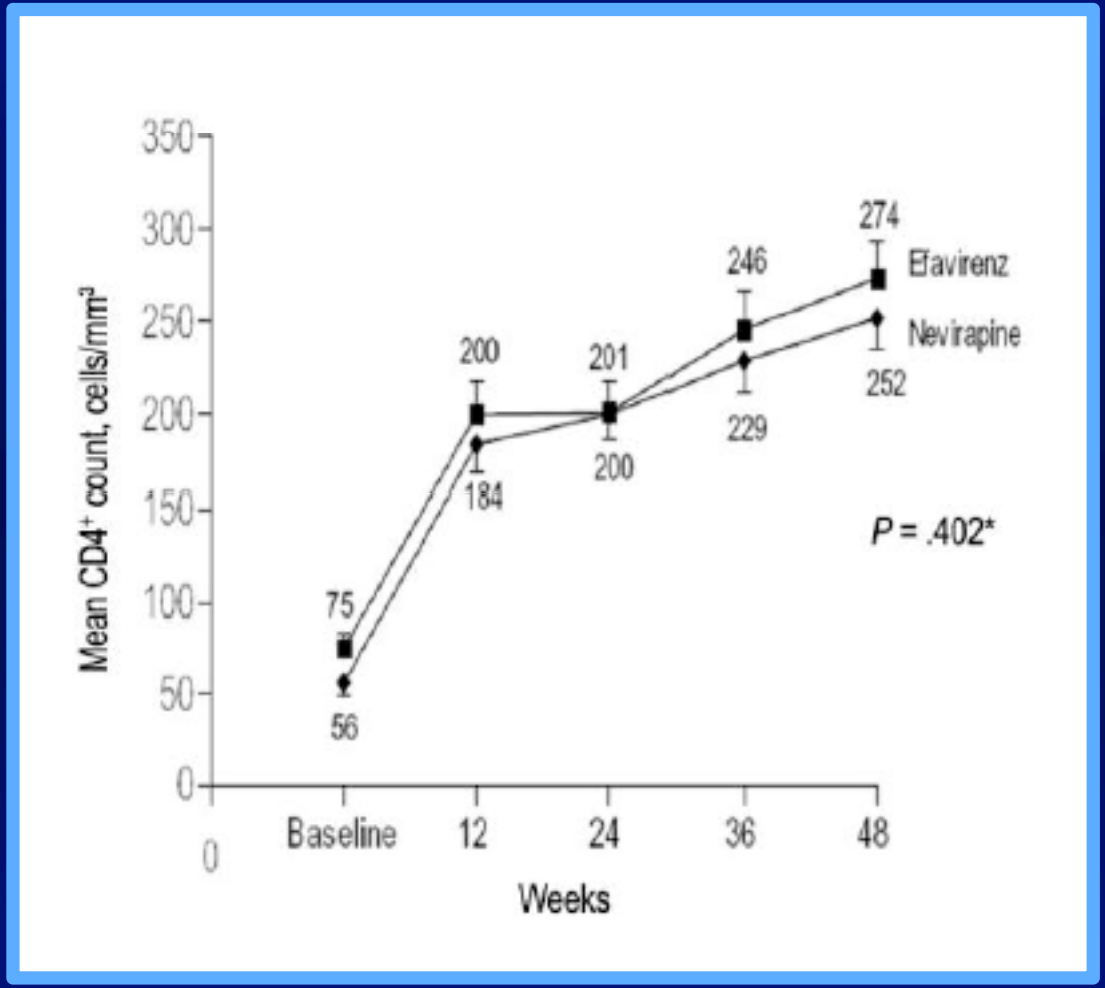
## A Randomized Trial Comparing Plasma Drug Concentrations and Efficacies between 2 Nonnucleoside Reverse-Transcriptase Inhibitor–Based Regimens in HIV-Infected Patients Receiving Rifampicin: The $N_2R$ Study

**Weerawat Manosuthi,[1,2] Somnuek Sungkanuparph,[2] Preecha Tantanathip,[1] Aroon Lueangniyomkul,[1] Wiroj Mankatitham,[1] Wisit Prasithsirskul,[1] Sunantha Burapatarawong,[1] Supeda Thongyen,[1] Sirirat Likanonsakul,[1] Unchana Thawornwa,[1] Vilaiwan Prommool,[1] and Kiat Ruxrungtham,[3,4] for the $N_2R$ Study Team**

[1]Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, and [2]Faculty of Medicine, Ramathibodi Hospital, Mahidol University, [3]The HIV Netherlands-Australia-Thailand Research Collaboration, Thai Red Cross AIDS Research Centre, and [4]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Manosuthi, *CID* 2009

# NVP/EFZ THAI $N_2R$ STUDY




Manosuthi, *CID* 2009

# NVP/EFZ THAI $N_2R$ STUDY

| Analysis | Proportion of patients (%) who achieved and HIV-1 RNA level <50 copies/mL: Efavirenz group | Nevirapine group | OR (95% CI) | *P* |
|---|---|---|---|---|
| ITT analysis | 52/71 (73.2) | 51/71 (71.8) | 0.932 (0.446–1.947) | >.99 |
| OT analysis[a] | 52/62 (83.9) | 51/55 (92.7) | 2.452 (0.722–8.323) | .164 |

**NOTE.** CI, confidence interval; HIV-1, human immunodeficiency virus type 1; ITT, intention-to-treat; OR, odds ratio; OT, on-treatment.

[a] Analysis excluded patients who were lost to follow-up, died, discontinued nonnucleoside reverse-transcriptase treatment because of adverse reactions, or transferred to another hospital.

Manosuthi, *CID* 2009

# NVP/EFZ THAI $N_2R$ STUDY

| Possible risk factor | Treatment outcome at week 48, proportion of patients (%) | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | Success | Failure | OR (95% CI) | *P* | OR (95% CI) | *P* |
| $C_{12}$ for NNRTIs less than the recommended level | 9/103 (8.7) | 7/32 (21.9) | 2.924 (0.991–8.626) | .060 | 3.610 (1.046–12.453) | .042 |
| Baseline body weight, <55 kg | 31/103 (30.1) | 21/39 (53.8) | 2.710 (1.271–5.780) | .011 | 2.370 (1.017–5.525) | .046 |
| Positive hepatitis C antibody test result | 22/103 (21.4) | 14/39 (35.9) | 2.062 (0.920–4.609) | .097 | 2.000 (0.792–5.102) | .149 |
| Receipt of efavirenz vs. nevirapine | 52/103 (50.5) | 19/39 (48.7) | 0.932 (0.446–1.947) | >.99 | 1.655 (0.670–4.089) | .275 |
| Baseline HIV-1 RNA level, <5.5 $\log_{10}$ copies/mL | 76/103 (73.8) | 34/39 (87.2) | 2.415 (0.857–6.803) | .166 | 1.785 (0.594–5.367) | .302 |
| Baseline $CD4^+$ cell count, <50 cells/$mm^3$ | 59/103 (57.3) | 25/39 (64.1) | 1.332 (0.622–2.849) | .567 | 1.012 (0.995–1.009) | .545 |
| Baseline serum albumin level, <3 mg/L | 14/103 (13.6) | 10/39 (25.6) | 2.192 (0.880–5.464) | .130 | 1.044 (0.633–1.727) | .863 |

**NOTE.** CI, confidence interval; $C_{12}$, concentration at 12 h after dosing; HIV-1, human immunodeficiency virus type 1; NNRTI, nonnucleoside reverse-transcriptase inhibitor; OR, odds ratio.

EFV 600 mg/d > NVP 400 mg/d in this trial.

Manosuthi, *CID* 2009

# NVP/EFZ INDIAN STUDY

Safety and efficacy of 2 once daily anti retroviral treatment regimens along with anti-TB treatment: NCT 00332306, India.

CD4 < 250; AFB-positive not mandatory.

ART begun at the end of intensive phase of anti-TB Rx (2EHRZ3/4RH3). **ddI + 3TC + NVP** *vs.* **ddI + 3TC + EFZ**.

Primary outcome: suppression of VL to < 400 copies/ml or a 2 log reduction in VL from the baseline value at the end of 6 months and a VL<400 copies/ml at 24 months of ART.

**Started in June 2006.**

**Target *n*=180. Inclusions finished.**

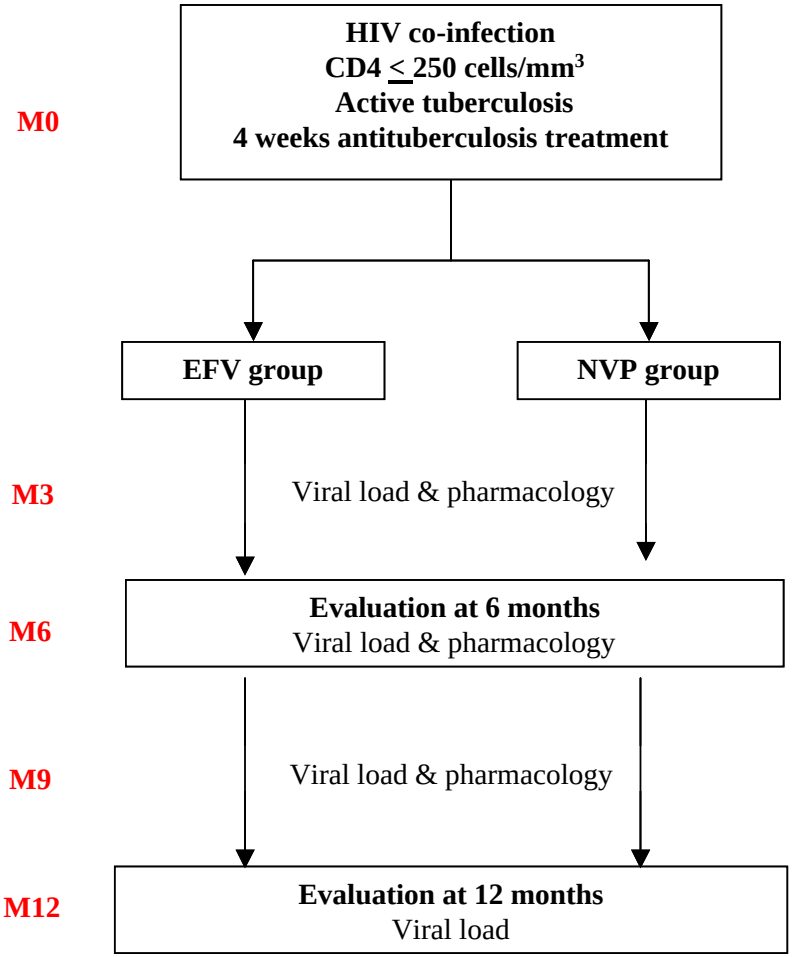
**Date of completion: December 2011.**

More info: Soumya Swaminathan, doctorsoumya@yahoo.com

# NVP/EFZ ANRS STUDY:CARINEMO

**Non-inferiority trial comparing the nevirapin-based ART versus the standard efavirenz-based ART for the treatment of HIV-TB co-infected patients on rifampicin-based therapy (ANRS 12146 trial).**

NCT 00495326, Mozambique.




anRS
Agence nationale de recherches sur le sida et les hépatites virales

**Primary outcome: ART efficacy (death, virological outcome)**

Agence nationale de recherches sur le sida et les hépatites virales

Triomune 30 (NVP 400*+3TC150+D4T30)

N=285

EFV 600 +3TC150+D4T30

N=285

* No lead-in

**Started in November 2007.**

**Target *n*=570.**

**Date of completion: March 2011.**

More info: Maryline Bonnet, Maryline.BONNET@geneva.msf.org

# REFLATE TB: ANRS 12180 study

⇒**Phase II study in Brazil**

- ⇒ **2 doses of raltegravir will be compared (because of RIF)**
- ⇒ **3 arms : comparison with a ref. arm**

⇒**Duration of the study: 48 wks.**

- ⇒ **Merck & Co : raltegravir**
- ⇒ **Gilead : tenofovir**

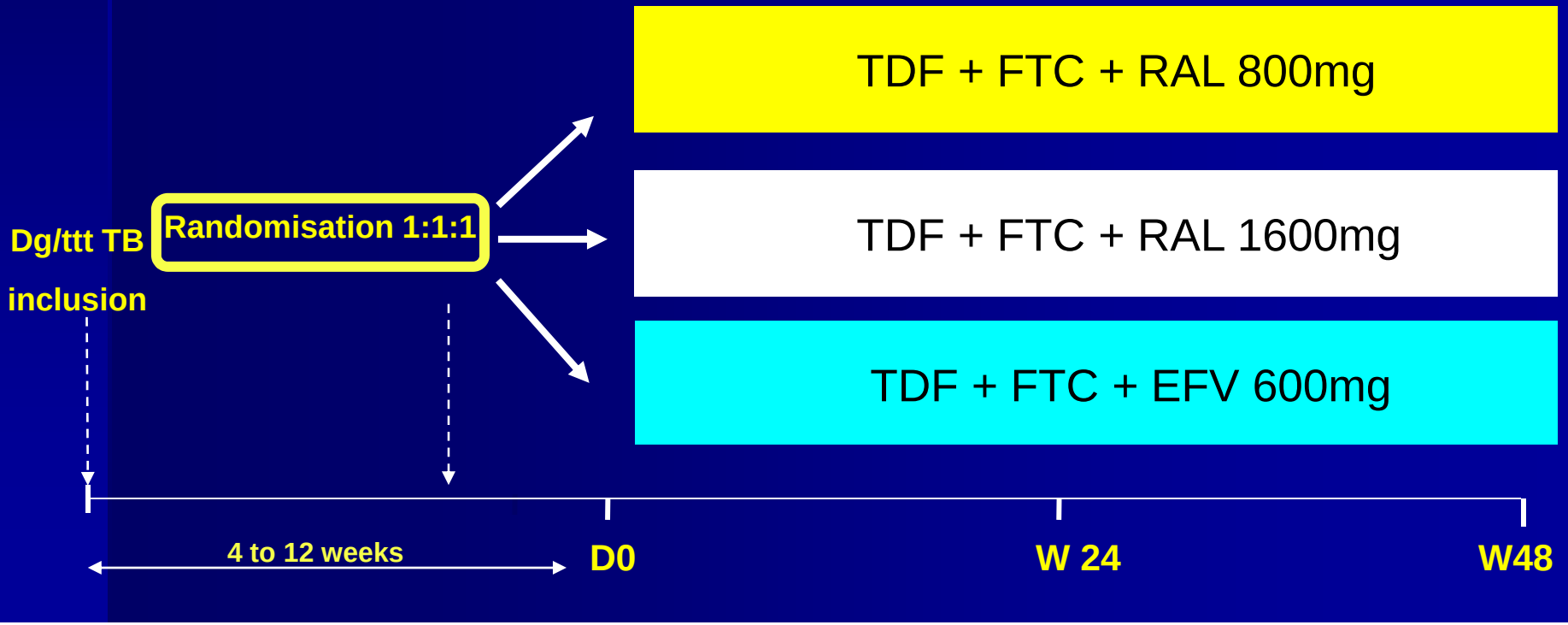
anRS
Agence nationale de recherches sur le sida et les hépatites virales

# REFLATE TB (ANRS 12180)

Agence nationale de recherches sur le sida et les hépatites virales

Randomized multicenter phase II study
Open-label
50 patients/arm: *n*=150
Primary endpoint: VL<50 copies/ml at W24

**ARV naïve patients, CD4<350/mm$^3$**
**Treated by RIF for TB (since 4 to 12 weeks)**



# ANTITUBERCULEUX ET ANTIRÉTROVIRAUX

TRAITEMENT DE LA TUBERCULOSE-MALADIE :

- QUELLES MOLÉCULES ?
- QUELLE DURÉE DE TRAITEMENT ?

ANTIRÉTROVIRAUX ASSOCIÉS AUX ANTITUBERCULEUX :

- QUELLES MOLÉCULES ?
- QUAND DÉBUTER ?

# ART in TB-HIV: Early or late?

| START TB TREATMENT AND ART SIMULTANEOUSLY | START TB TREATMENT FIRST AND DELAY ART |
|---|---|
| **PROS** | **PROS** |
| Lower risk of HIV disease progression or death in advanced patients (CD4 < 50 cells/$mm^3$) | Avoid overlapping side effects<br>Avoid PK interactions<br>Lower pill burden<br>Lower risk of IRIS |
| **CONS** | **CONS** |
| Overlapping side effects<br>PK interactions<br>Higher pill burden<br>Risk of immune reconstitution disease | Higher risk of HIV disease progression or death in advanced patients (CD4 < 50 cells/$mm^3$ ) |

Adapted from *J Acquir Immune Defic Syndr* 2007; 46: S9-S18

# Treatment of HIV-related Tuberculosis in the Era of Effective Antiretroviral Therapy

WILLIAM J. BURMAN and BRENDA E. JONES

Denver Public Health and the Department of Medicine (Division of Infectious Diseases), University of Colorado Health Sciences Center, Denver, Colorado; and Los Angeles County/University of Southern California Medical Center, Los Angeles, California

TABLE 3. SUMMARY OF MANAGEMENT RECOMMENDATIONS FOR USE OF ANTIRETROVIRAL THERAPY AMONG PATIENTS WITH HIV-RELATED TUBERCULOSIS

| Issue | Management Suggestions |
|---|---|
| Overlapping side effect profiles of antituberculosis and antiretroviral drugs | Defer antiretroviral therapy until there has been time to identify and manage side effects from antituberculosis drugs (1–2 mo) |
| Drug interactions between rifamycins and antiretroviral drugs (HIV-1 protease-inhibitors and non-nucleoside reverse-transcriptase inhibitors) | Frequent communication between tuberculosis and HIV care providers<br>Use rifabutin with dose-adjustments in Table E1<br>Use rifampin with efavirenz or ritonavir (at doses of > 600 mg twice-daily) |
| Paradoxical reactions after starting antiretroviral therapy | Defer antiretroviral therapy until after tuberculosis treatment if CD4 cell count is relatively high (> 300/μL)<br>Among patients with lower CD4 cell counts, defer antiretroviral therapy until tuberculosis is substantially improved (2 mo)<br>Assure that the HIV care provider and patient are aware of the frequency and clinical manifestations of paradoxical reactions<br>Schedule clinical follow-up soon after starting antiretroviral therapy to detect paradoxical reactions and/or drug side effects early |

**« Even among patients who have low CD4 cell counts, we recommend that antiretroviral therapy be delayed until the first 2 months of TB therapy has been completed ».**

Am J Respir Crit Care Med Vol 164. pp 7–12, 2001
Internet address: www.atsjournals.org

# WHO recommendations

**2003**: CD4 < 200/mm$^3$:

- Start TB treatment.

**- Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months)**

- Efavirenz-containing regimens

# BHIVA treatment guidelines for TB/HIV infection

## February 2005

**AL Pozniak[1], RF Miller[2], MCI Lipman[3], A R Freedman[4], LP Ormerod[5], MA Johnson[3], S Collins[6] and SB Lucas[7], on behalf of the BHIVA guidelines writing committee.**

[1] Chelsea and Westminster NHS Healthcare trust London SW10 9TH, [2] Centre for Sexual Health and HIV Research, Department of Primary Care and Population Sciences, Royal Free and University College Medical School, University College London, London WC1E 6AU [3] Royal Free Hospital, London NW3 2QG, [4] University of Wales College of Medicine, Cardiff ,[5] Blackburn Royal Infirmary, Blackburn, Lancashire, BB2 3LR, [6]HIV i-Base London SE1 1UN . Dept of Histopathology GKT School of Medicine St Thomas' Hospital London SE1.

# BHIVA
## February 2005

- TB treatment must be given urgently.
- The urgency of HIV treatment depends on predictors of HIV disease progression especially the CD4 cell count.

- **<100 cells/mm$^3$ - HAART ASAP (some delay up to 2 mo)**
- **100-200 cells/mm$^3$ - HAART after 2 months**
- **>200 cells/mm$^3$ - HAART after TB treatment finished**

# NIH / CDC / HIVMA / IDSA
## June 2008

- **<100 cells/mm$^3$ - HAART after 2 weeks**
- **100-200 cells/mm$^3$ - HAART after 2 months**
- **200-350 cells/mm$^3$ - HAART during anti-TB maintenance phase**
- **>350 cells/mm$^3$ - HAART after TB treatment finished**

# DHHS / OARAC
## November 2008

- <100 cells/$mm^3$ - HAART after 2 weeks
- 100-200 cells/$mm^3$ - HAART after 8 weeks
- 200-350 cells/$mm^3$ - HAART after 8 weeks (on case-by-case basis)
- >350 cells/$mm^3$ - HAART after 8 to 24 weeks or after end of TB treatment

# COMESEM Spanish cohort

- Madrid, Spain
- cohort constituted in 2000, with collection of data since 1984
- diagnosis of TB in the 1987-2004 period: 1 217, incl. 322 after 1996
- « simultaneous »: HAART within 2 months after onset of TB treatment
- « nonsimultaneous »: HAART after 3 months of TB diagnosis
- exclusion of patients receiving HAART for more than 2 months before TB diagnosis

Velasco M et al., *J Acquir Immune Defic Syndr* 2009

# COMESEM Spanish cohort

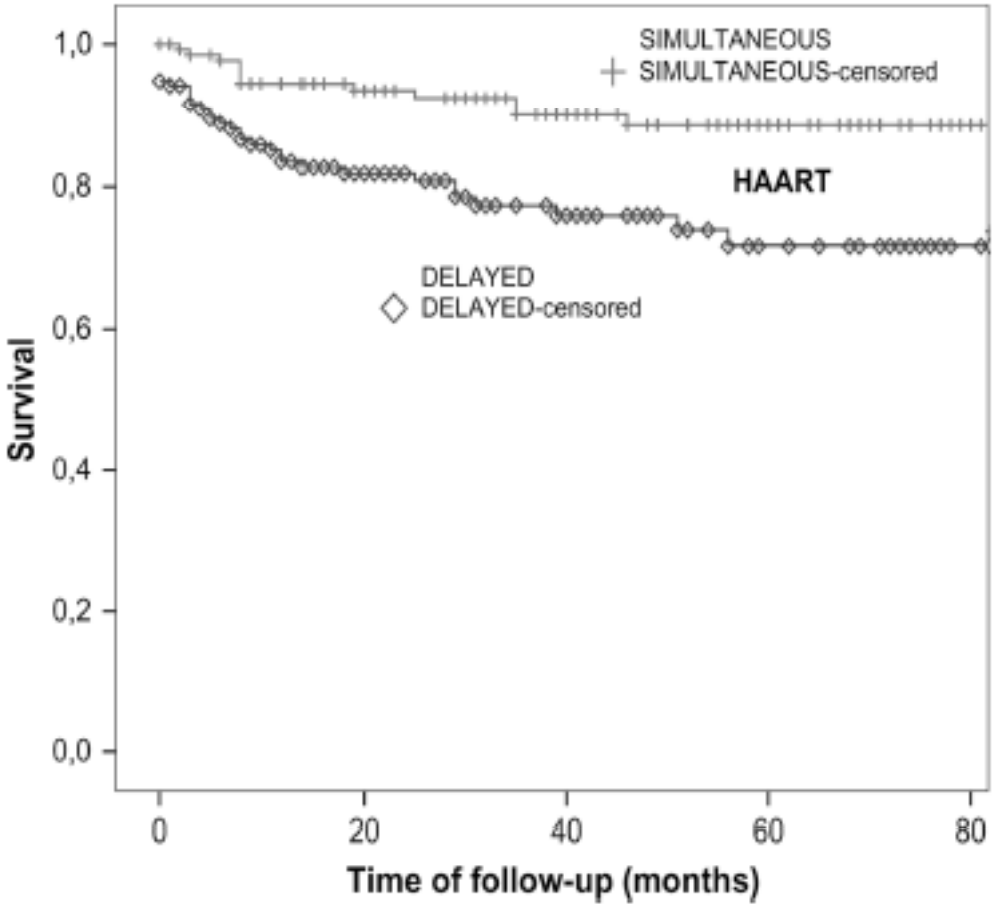



**FIGURE 1.** Survival evolution of HIV patients who started HAART and TB treatment at the same time (simultaneous) or after ≥3 months (delayed). Follow-up after the diagnosis of TB. Log-rank (Mantel–Cox) $P = 0.003$.

Velasco M et al., *J Acquir Immune Defic Syndr* 2009

# WHEN TO START HAART IN TB PATIENTS?

## Randomized controlled trials

| Trial (sponsor) | CD4 (/µl) | Time (design) | Study design | End-points |
|---|---|---|---|---|
| CAMELIA (NIH/ANRS) | <200 | 12 mo. (ROL*) | 2 wks v. 8 wks after TB initiation (*N*–660, accruing results 2009/10) | Survival |
| ACTG 5221 (NIAID) | <200 | 12 mo. (ROL*) | 2 wks v. 12 wks after TB initiation (*N*–200 of 800 accrued) | AIDS-free survival |
| SAPIT (NIAID) | >50 | 18 mo. (ROL*) | <2 mo. v. >2 mo. v. post 6 - 8 mo. TB Rx (*N*–645, DSMB stopped 3rd arm) | Survival AIDS |
| TB-HAART (WHO/TDR) | >200 <500 | 6 mo. (RPC†) | HAART at 2 wks v. placebo at 2 wks (*N*–1 900 accruing results 2011) | Survival, TB failure |
| TB meningitis (Wellcome Trust) | All | 9 mo. (RPC†) | Immediate v. 8 wks ART + steroids (*N*–247, accrued results Dec 2008) | Survival |

*Randomised open-label study.
†Randomised placebo-controlled study.
NIH – National Institute of Health; ANRS – Agence Nationale Recherche sur Le Sida; NIAID – National Institute of Allergy and Infectious Disease; WHO – World Health Organization; TDR – Tropical Disease Research.

Wood R. *Southern African Journal of HIV Medicine* 2008.

# TB-HAART STUDY

An evaluation of the impact of early initiation of ART on TB treatment outcomes for TB patients coinfected with HIV: ISRCTN77861053, Uganda, Zambia, South Africa and Tanzania. 220 < CD4 < 500.

Study hypothesis: early concomitant treatment with TB and HIV medications may improve TB outcomes and improve survival.

Primary outcome: proportion of subjects reaching the composite endpoint of treatment failure or death at 6 months after the initiation of short-course chemotherapy for TB.

**Combined ART with anti-TB vs. delay HAART at 6 months.**

**Started in March 2007.**

**Target *n*=1900.**

**Date of completion: 2011.**

**AZT + 3TC**
**+ efavirenz**

More info: Philip Onyebujoh, onyebujohp@who.int

# SAPIT STUDY

ORIGINAL ARTICLE

# Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy

Salim S. Abdool Karim, M.B., Ch.B., Ph.D., Kogieleum Naidoo, M.B., Ch.B., Anneke Grobler, M.Sc., Nesri Padayatchi, M.B., Ch.B., Cheryl Baxter, M.Sc., Andrew Gray, M.Sc. (Pharm.), Tanuja Gengiah, M.Clin.Pharm., M.S. (Epi.), Gonasagrie Nair, M.B., Ch.B., Sheila Bamber, M.B., Ch.B., Aarthi Singh, M.B., Ch.B., Munira Khan, M.B., Ch.B., Jacqueline Pienaar, M.Sc., Wafaa El-Sadr, M.D., M.P.H., Gerald Friedland, M.D., and Quarraisha Abdool Karim, Ph.D.

N Engl J Med 2010;362:697-706.

# SAPiT: Starting Antiretroviral therapy (ART) in three Points in TB

- Design: Open-Label Randomized Controlled Trial
- Randomized to one of 3 arms:
  - ***Arm 1:*** *ART initiated during intensive phase of TB treatment*
  - ***Arm 2:*** *ART initiated after intensive phase of TB treatment*
  - ***Arms 1 & 2 combined:*** *Integrated TB-HIV treatment*
  - ***Arm 3:*** *Sequential treatment - ART initiated after TB treatment completed*
- TB treatment: Standard TB regimen
- Cotrimoxazole prophylaxis: provided to all patients
- ART: Didanosine (ddI) + Lamivudine (3TC) + Efavirenz

*Once-a-day treatment* integrated with TB-DOT

# Inclusion/Exclusion Criteria

## Inclusion Criteria

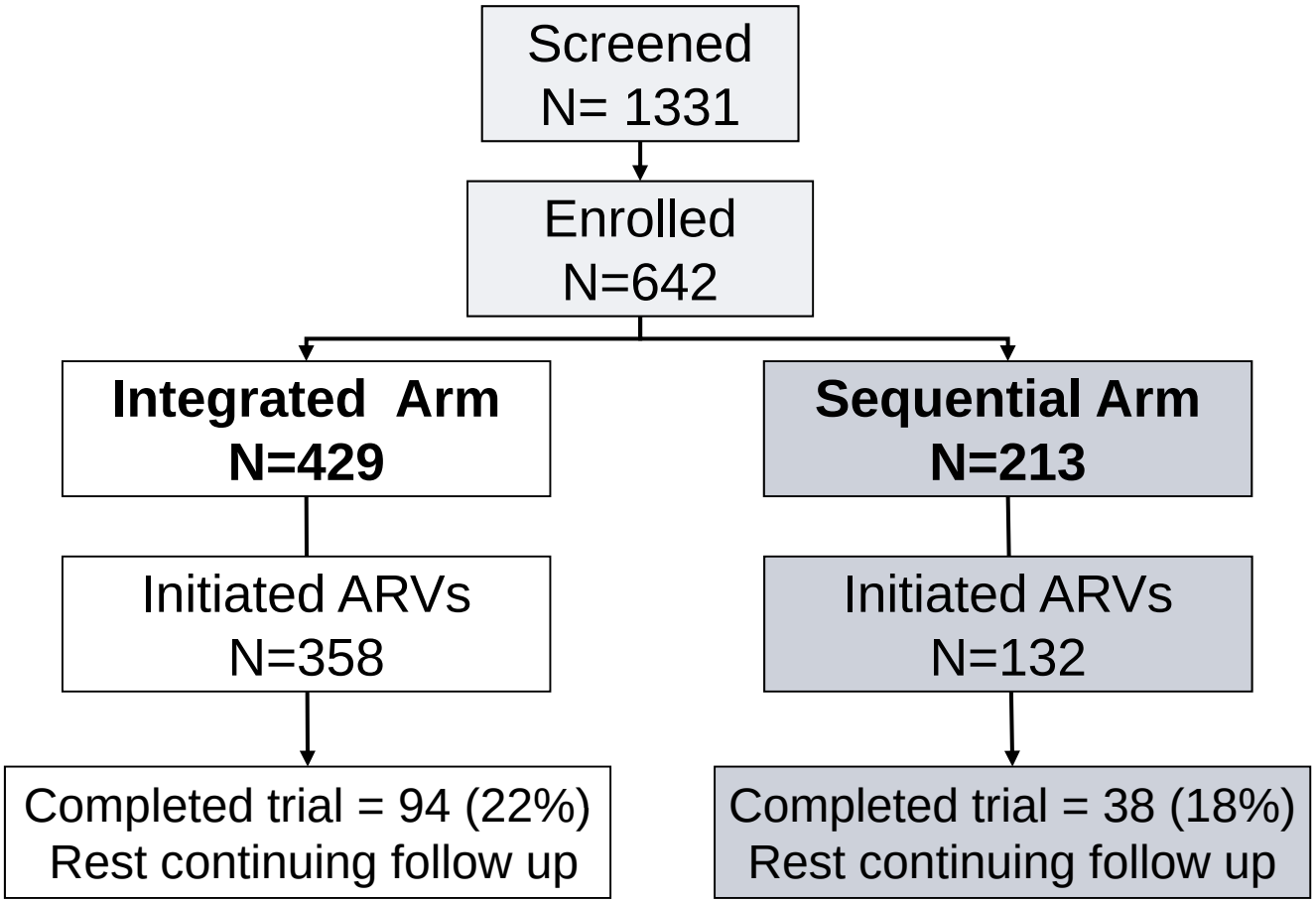
- **Sputum +ve & receiving any one of the standard anti-TB therapy regimens**
- **HIV positive**
- **CD4 count < 500**
- **Women must agree to use contraception since they will be on efavirenz**

## Exclusion Criterion

- Should patients not be clinically eligible to maintain a treatment regimen, their entry may be deferred or precluded.

**Sept. 2008: DSMB**

# Status of the trial at Safety Monitoring Committee review (September 2008)




Safety Monitoring Committee review and recommended:

- *Start ART immediately in all sequential arm patients*
  *(ie. to halt the sequential treatment arm)*
- *Continue the two integrated treatment arms in the trial*

UNIVERSITY OF KWAZULU-NATAL

CAPRISA

# Outcome at halt of sequential arm: Mortality rates

| | Integrated Treatment Arm n = 429 | Sequential Treatment Arm n = 213 |
|---|---|---|
| Number of deaths | 25 | 27 |
| Person-years of follow-up | 466 | 222 |
| Mortality rate per 100 person-years | 5.4 | 12.1 |

**Hazard Ratio: 0.44 (95% CI: 0.25 to 0.79); p = 0.003**

**56% lower mortality with integrated TB-HIV treatment**

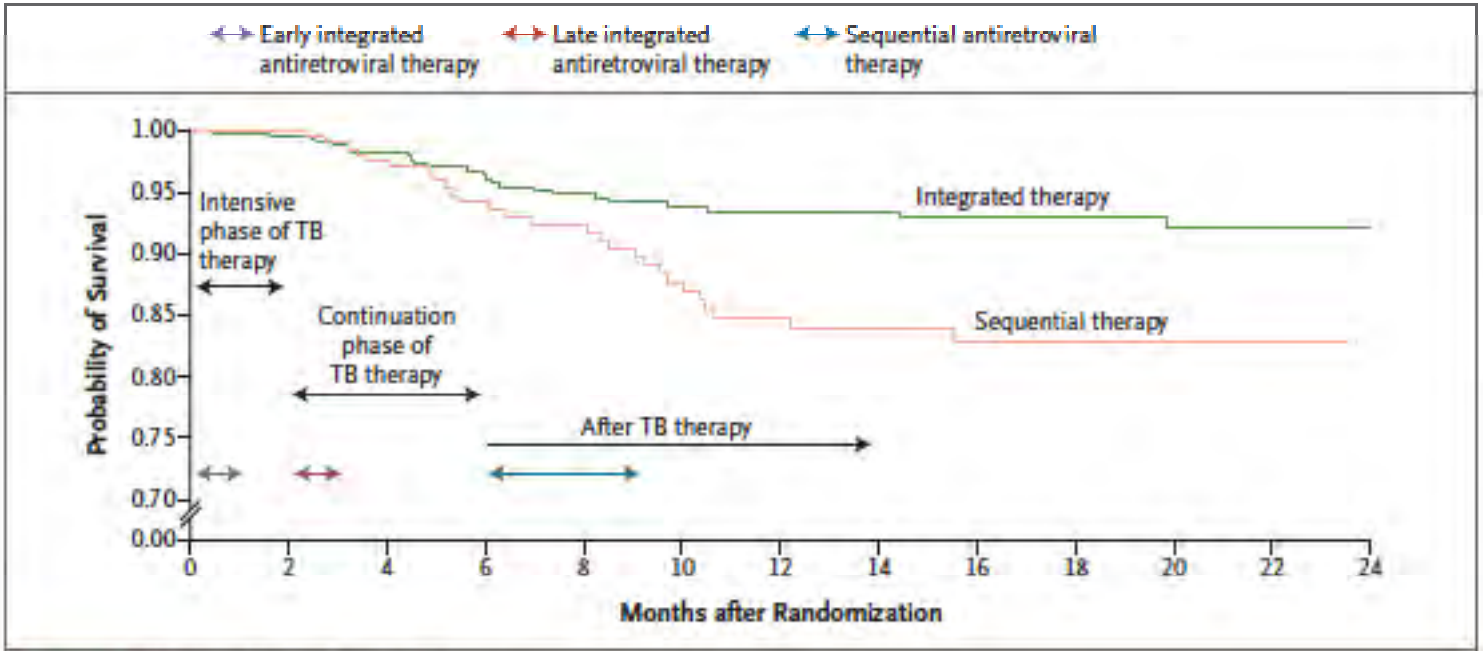



**Figure 2. Kaplan–Meier Survival Curves.**

TB denotes tuberculosis.

N Engl J Med 2010;362:697-706.

# Mortality rates in CD4 count strata

- Reduction in mortality in the Integrated arm is present in patients with CD4 <= 200 and patients with CD4 > 200 cells/mm$^3$

| | CD4 count | |
|---|---|---|
| | **≤ 200 cells/mm$^3$** | **> 200 cells/mm$^3$** |
| **Integrated arm:** | | |
| # dead/ py (n) | 23/281 (273) | 2/186 (156) |
| Mortality rate (95% CI) | **8.2** (5.2 - 12.3) | **1.1** (0.1 - 3.9) |
| **Sequential arm:** | | |
| # dead / py (n) | 21/137 (138) | 6/86 (75) |
| Mortality rate (95% CI) | **15.3** (9.57 - 23.5) | **7.0** (2.6 -15.3) |
| **Rate Ratio (95% CI)** | **0.53** (0.28-1.01) **p=0.051** | **0.15** (0.02-0.86) **p=0.022** |

*Abdool Karim S, CROI 2009, Abs. 36a*

**Table 2. Death Rates and Hazard Ratios, Stratified According to CD4+ Cell Count.**

| CD4+ Count | Integrated Therapy | | | | Sequential Therapy | | | | Hazard Ratio (95% CI)* | P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Patients | No. of Person-Yr | No. of Deaths | Death Rate/ 100 Person-Yr (95% CI) | No. of Patients | No. of Person-Yr | No. of Deaths | Death Rate/ 100 Person-Yr (95% CI) | | |
| All patients | 429 | 467 | 25 | 5.4 (3.5–7.9) | 213 | 223 | 27 | 12.1 (8.0–17.7) | 0.44 (0.25–0.79) | 0.003 |
| ≤200 cells/mm³ | 273 | 281 | 23 | 8.2 (5.2–12.3) | 138 | 137 | 21 | 15.3 (9.6–23.5) | 0.54 (0.30–0.98) | 0.04 |
| >200 cells/mm³ | 156 | 186 | 2 | 1.1 (0.1–3.9) | 75 | 86 | 6 | 7.0 (2.6–15.3) | 0.16 (0.03–0.79) | 0.02 |

* Hazard ratios are for the integrated-therapy group, as compared with the sequential-therapy group.

N Engl J Med 2010;362:697-706.

There was a reduction in the rate of death among the 429 patients in the combined integrated-therapy groups (5.4 deaths per 100 person-years, or 25 deaths), as compared with the 213 patients in the sequential-therapy group (12.1 per 100 person-years, or 27 deaths); a relative reduction of 56% (hazard ratio in the combined integrated-therapy groups, 0.44; 95% confidence interval, 0.25 to 0.79; P=0.003). Mortality was lower in the combined integrated-therapy groups in all CD4+ count strata. Rates of adverse events during follow-up were similar in the two study groups.

## CONCLUSIONS

The initiation of antiretroviral therapy during tuberculosis therapy significantly improved survival and provides further impetus for the integration of tuberculosis and HIV services. (ClinicalTrials.gov number, NCT00398996.)

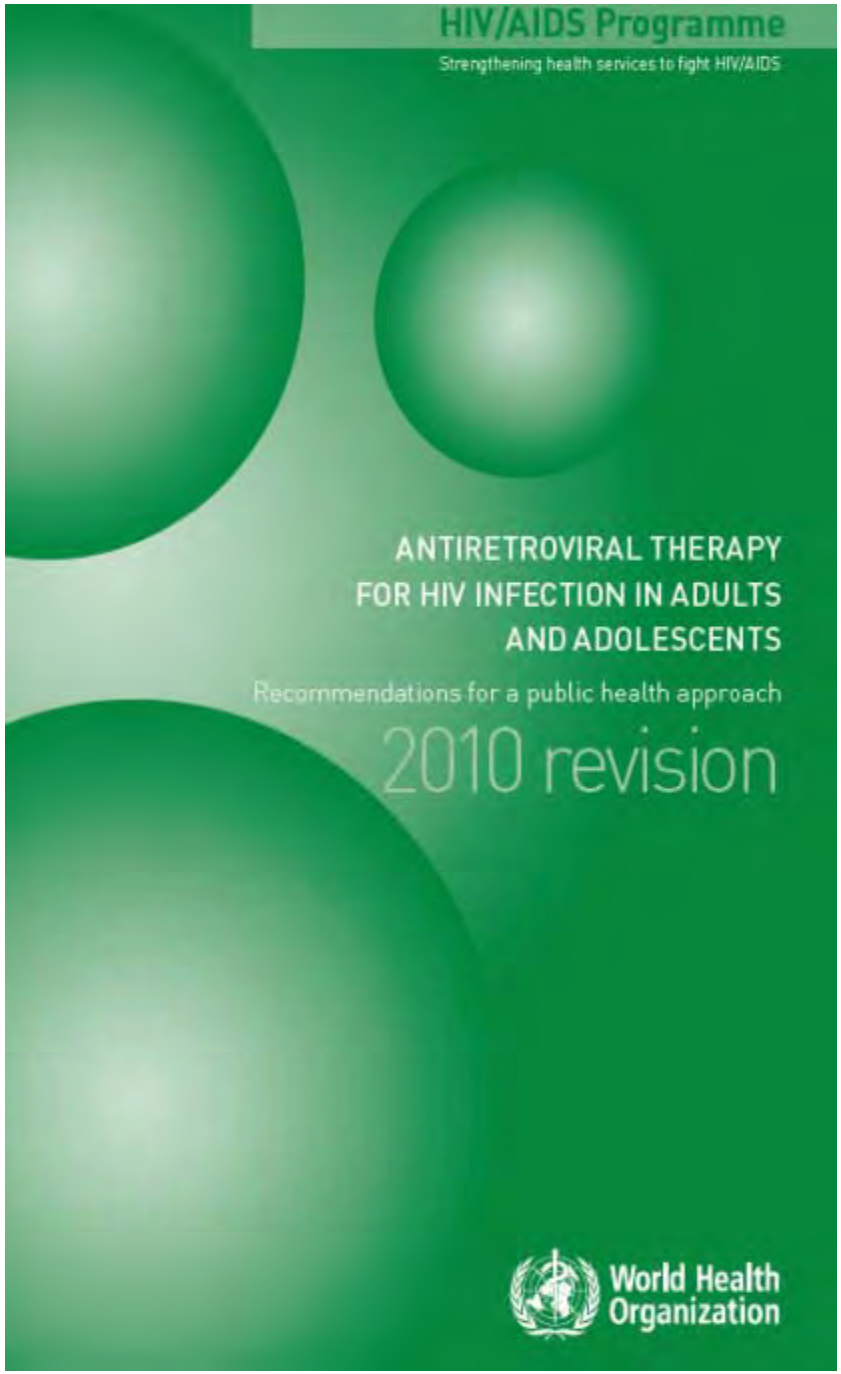
N Engl J Med 2010;362:697-706.

World Health Organization

# RAPID ADVICE

Antiretroviral therapy for HIV infection in adults and adolescents

NOVEMBER 2009



# WHO recommendations

**2003**: CD4 < 200/mm$^3$:

- Start TB treatment.

- **Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months)**

- Efavirenz-containing regimens

**2010**: - Start ART in **all** HIV-infected individuals with active TB, irrespective of the CD4 cell count.

*Strong recommendation, low quality of evidence.*

- **Start TB treatment first, followed by ART as soon as possible afterwards (and within the first eight weeks).** *Strong recommendation, moderate quality of evidence.*

- Use efavirenz as the preferred NNRTI in patients starting ART while on TB treatment.

*Strong recommendation, high quality of evidence.*

# CAMELIA

## **CAM**bodian **E**arly vs. **L**ate **I**ntroduction of **A**ntiretrovirals


ANRS 1295/CIPRA KH001-DAIDS-ES ID 10425

anRS
French National Agency for Research on AIDS and Viral Hepatitis

22nd July 2010
Late Breaker Session B-1, XVIII IAS Conference, Vienna, Austria

NATIONAL INSTITUTES OF HEALTH

# CAMELIA study design

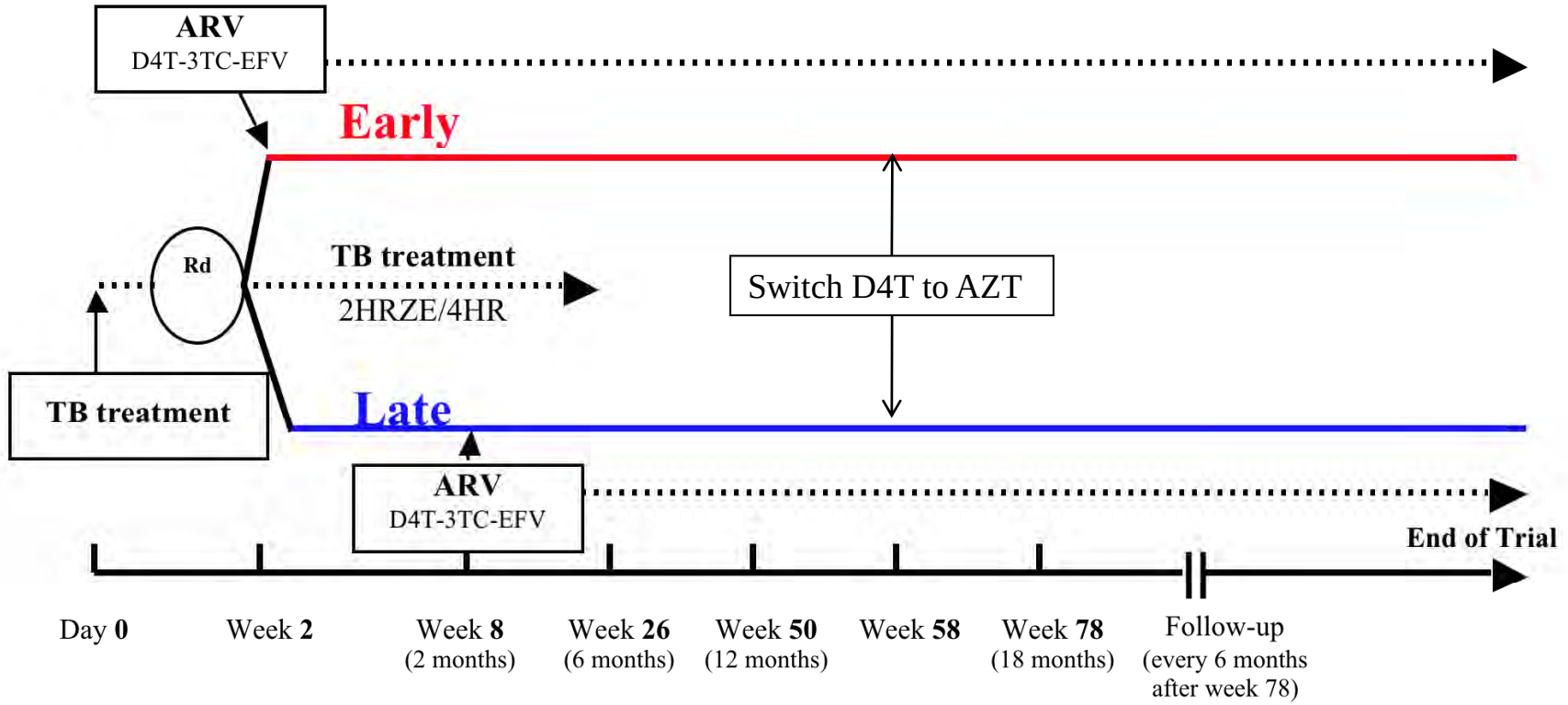
- Prospective, randomized, open-label, two-armed trial with no placebo

- Strategy trial designed as a **superiority one** to answer the question of the best timing for the introduction of HAART in severely immunosuppressed HIV-infected adult patients with newly diagnosed TB in Cambodia

- 2 arms: ***late*** introduction of ART (reference arm) *vs* ***early*** introduction of the same ART regimen

- Primary endpoint: **survival** at the end of the trial

# CAMELIA strategy




Rd : Randomization
H : isoniazid Z : pyrazinamide
R : rifampin E : ethambutol
D4T : stavudine
3TC : lamivudine
EFV : efavirenz

**XVIII IAS Conference (F.X. Blanc, présentation du 22 juillet 2010)**

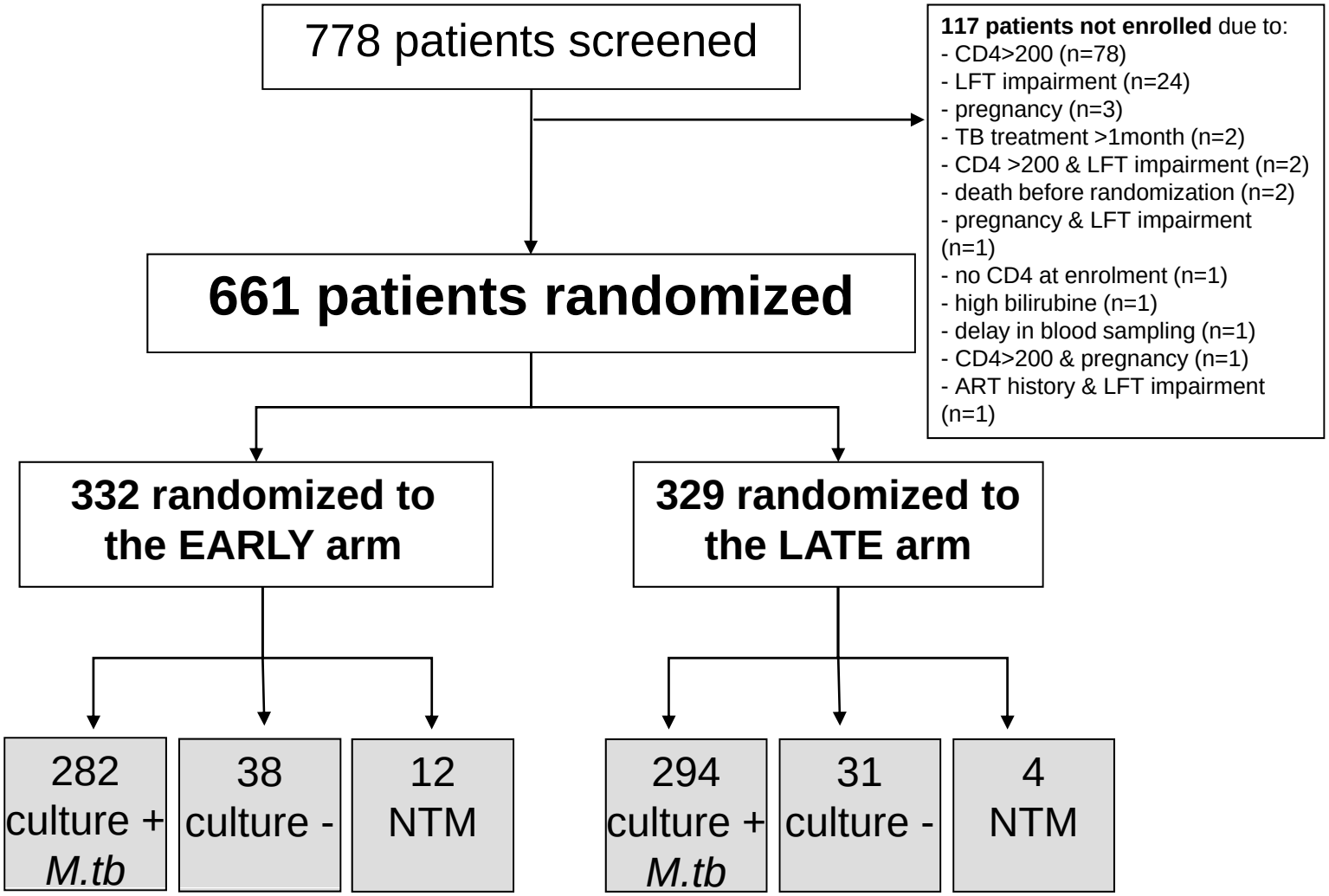
# CAMELIA study sites: urban and rural


- Phnom Penh (2 sites: KSFH & Calmette Hospital)
- Svay Rieng Provincial Hospital
- Takeo Provincial Hospital
- Siem Reap Provincial Hospital

# CAMELIA key points

- 2 sponsors: French ANRS and U.S. NIH/DAIDS (CIPRA)
- 5 study sites (rural and urban) in Cambodia
- 661 patients were AFB+ at inclusion (pulmonary or extra-pulmonary TB) with CD4 ≤ 200/$mm^3$
- 1st patient enrolled on January 31st 2006
- 6 DSMB meetings
- Last patient enrolled on May 27th 2009
- End of the study (cut-off): May 13th 2010

# CAMELIA recruitment




*M.Tb*: *Mycobacterium tuberculosis;* NTM: nontuberculous mycobacteria

# Patient characteristics at enrollment

| | Early arm (N=332) | Late arm (N=329) | *p* |
|---|---|---|---|
| **Gender** | | | 0.80 |
| Male | 215 (64.8) | 210 (63.8) | |
| Female | 117 (35.2) | 119 (36.2) | |
| **Age, years** | | | 0.38 |
| Median (IQR) | 35 (30 – 41) | 36 (30 – 42) | |
| **BMI, kg/m$^2$** | | | 0.90 |
| Median (IQR) | 16.7 (15.3 – 18.3) | 16.8 (15.2 – 18.6) | |
| **Karnofsky score** | | | 0.83 |
| ≥80 | 43 (13.0) | 44 (13.4) | |
| 50-70 | 259 (78.0) | 251 (76.3) | |
| ≤40 | 30 (9.0) | 34 (10.3) | |
| **CD4, cells/mm$^3$** | | | **0.61** |
| **Median (IQR)** | **25 (11 – 56)** | **25 (10 – 55)** | |
| **Viral load, log copies/mL** | | | 0.25 |
| Median (IQR) | 5.60 (5.20 – 6.02) | 5.66 (5.25 – 6.00) | |

# Characteristics of tuberculosis

| | Early arm (N=320) | Late arm (N=325) | *p* |
|---|---|---|---|
| **Location of TB** | | | 0.97 |
| Pulmonary | 220 (69%) | 222 (68%) | |
| Pulmonary & extra-pulmonary | 62 (19%) | 59 (18%) | |
| Extra-pulmonary | 38 (12%) | 44 (14%) | |

# Characteristics of tuberculosis

| | Early arm (N=320) | Late arm (N=325) | *p* |
|---|---|---|---|
| **Drug resistance** | | | 0.10 |
| None | 217 (67.8) | 240 (73.8) | |
| Isoniazid (INH) monoresistance | 23 (7.2) | 10 (3.1) | |
| Streptomycin monoresistance | 17 (5.3) | 10 (3.1) | |
| Rifampin monoresistance | 3 (0.9) | 4 (1.2) | |
| INH polydrug resistance | 16 (5.0) | 24 (7.4) | |
| Multidrug resistant (MDR) | 6 (1.9) | 7 (2.2) | |
| No DST | 37 (11.6) | 30 (9.2) | |
| Missing | 1 (0.3) | - | |

# Tuberculosis outcomes

| | Early arm (N=320) | Late arm (N=325) |
|---|---|---|
| **TB Rx outcome at end of TB Rx** | | |
| Cured | 154 (48.1) | 146 (44.9) |
| Completed | 114 (35.6) | 115 (35.4) |
| Failure | 5 (1.6) | 2 (0.6) |
| Death | 37 (11.6) | 54 (16.6) |
| Defaulter | 6 (1.9) | 2 (0.6) |
| Ongoing | 1 (0.3) | - |
| Withdrawal | 1 (0.3) | 1 (0.3) |
| Lost to follow-up | 2 (0.6) | 5 (1.5) |
| | Success: 268 (83.8) | 261 (80.3) |

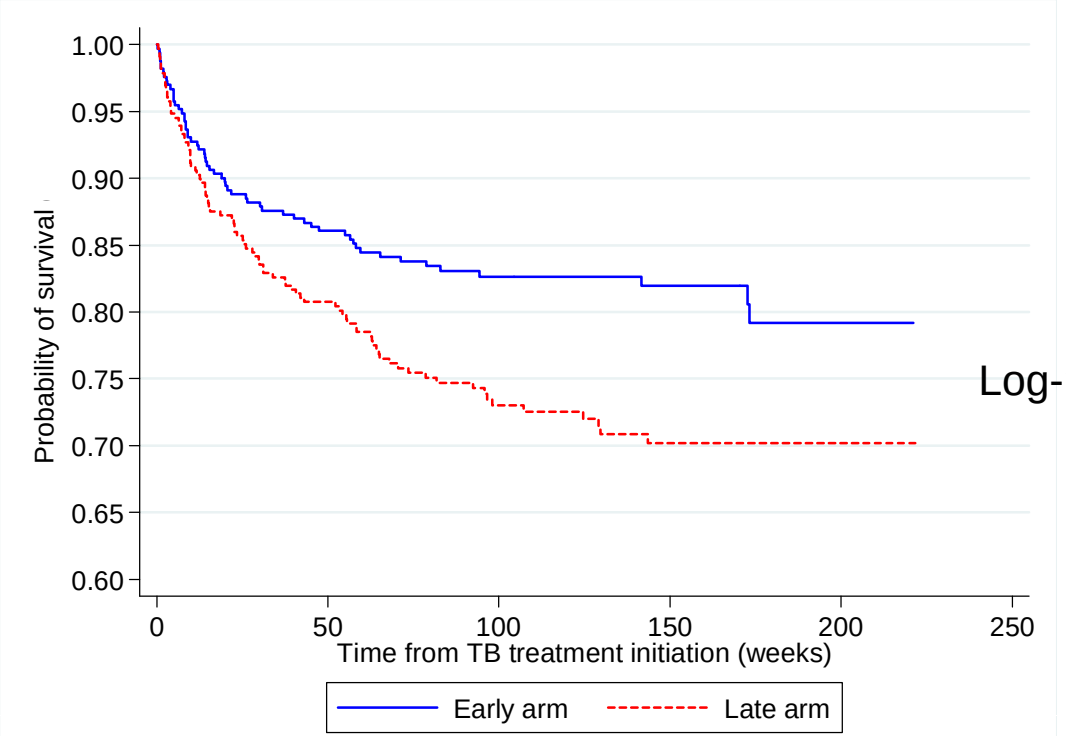
# SIGNIFICANT REDUCTION OF MORTALITY IN THE EARLY ARM

| | N | Deaths | Follow-up time* | Mortality rate** (95% CI) | *p* |
|---|---|---|---|---|---|
| **Early arm** | **332** | **59** | **712.4** | **8.28 (6.42 – 10.69)** | 0.002 |
| Late arm | 329 | 90 | 653.7 | 13.77 (11.20 – 16.93) | |

* expressed in person-years
** per 100 person-years

12 patients (1.8%) lost to follow-up.
8,955 protocol visits, <2% missed visits.

# Kaplan-Meier survival curves




Log-rank p-value: p=0.0042

| Survival probability (95% CI) | Early arm | Late arm | Log-rank *p*-value |
|---|---|---|---|
| Week 50 | 86.1 (81.8 – 89.4) | 80.7 (76.0 – 84.6) | 0.07 |
| Week 100 | 82.6 (78.0 – 86.4) | 73.0 (67.7 – 77.6) | 0.006 |
| Week150 | 82.0 (77.2 – 85.9) | 70.2 (64.5 – 75.2) | 0.002 |

**XVIII IAS Conference (F.X. Blanc, présentation du 22 juillet 2010)**

# Factors independently associated with mortality

| | | Multivariate analysis Adjusted HR (95% CI)* | *p* |
|---|---|---|---|
| **Arm** | Early | 1 | <0.00 |
| | **Late** | **1.87 (1.33 – 2.61)** | 1 |
| **BMI** | **≤16** | **1.74 (1.10 – 2.74)** | 0.03 |
| | 16-17 | 0.93 (0.52 – 1.65) | |
| | 17-18.5 | 1.23 (0.70– 2.17) | |
| | >18.5 | 1 | |
| **Karnofsky score** | ≥80 | 1 | <0.00 |
| | 50-70 | 1.53 (0.79 – 2.99) | 1 |
| | **≤40** | **4.84 (2.20 – 10.67**) | |
| **TB identification and location*** | Pulmonary | 1 | <0.00 |
| | Extra-pulmonary | 1.08 (0.55 – 2.12) | 1 |
| | **Pulm. and extra-pulm.** | **2.63 (1.83 – 3.78)** | |
| | **NTM** | **3.96 (1.66 – 9.43)** | |
| **Drug resistance** | No** | 1 | <0.00 |
| | Yes | 1.10 (0.68 – 1.76) | 1 |
| | **Yes, MDR** | **10.97 (4.93 – 24.42)** | |

Cox proportional hazard model

* Also adjusted for site and CD4 level at baseline (stratification factors)

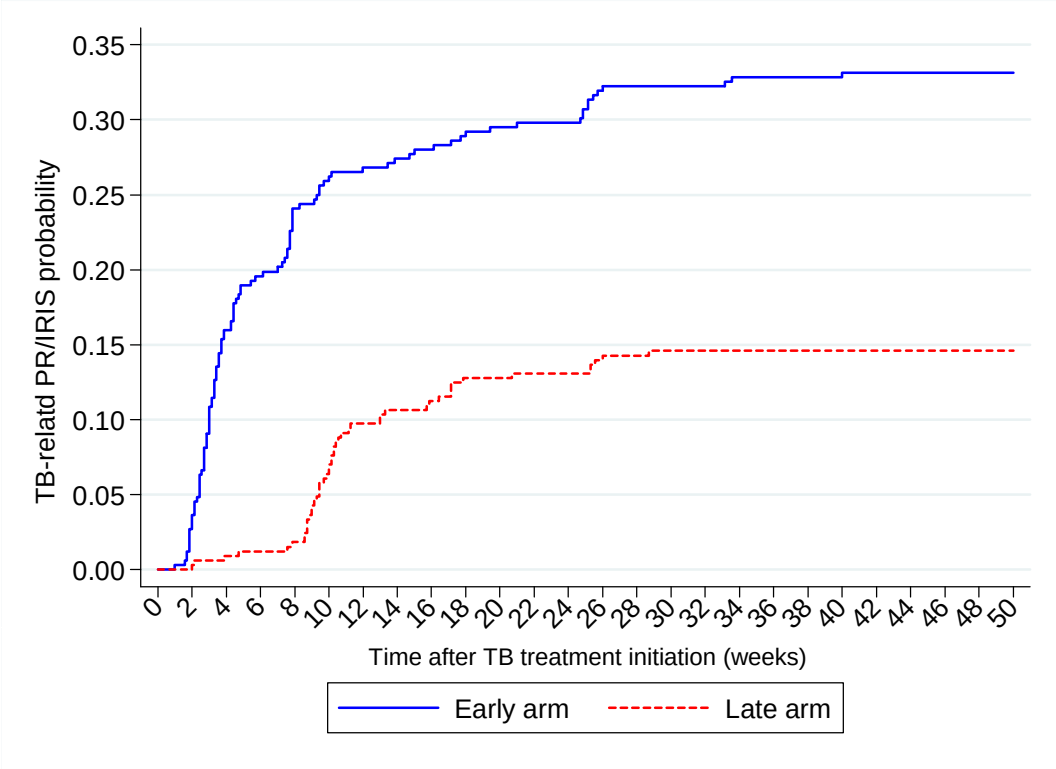
# CAUSES OF DEATH

| | Early arm (*n*=59) | Late arm (*n*=90) | Total |
|---|---|---|---|
| Tuberculosis | 13 | 29 | 42 |
| Drug toxicity | 5 | 12 | 17 |
| Gastrointestinal disorders | 6 | 10 | 16 |
| Infectious disease and PML | 6 | 7 | 13 |
| Respiratory distress | 6 | 4 | 10 |
| Cachexia | 5 | 4 | 9 |
| Neurological disorders | 2 | 6 | 8 |
| Hepatic disorder | 3 | 4 | 7 |
| Paradoxical TB-related IRIS | 7 | 0 | 7 |
| Suicide / Road traffic accident | 2 | 3 | 5 |
| Neoplasia | 0 | 3 | 3 |
| Unknown | 4 | 8 | 12 |

# IRIS significantly more frequent in the early arm

| | N | IRIS | Incidence* (95% CI) | *p* |
|---|---|---|---|---|
| **Early arm** | **332** | **109** | **3.76 (3.14 – 4.47)** | <0.001 |
| Late arm | 329 | 46 | 1.53 (1.13 – 2.03) | |

* per 100 person-months



# >95% undetectable viral load at week 50

| | W26 | W50 | W78 | W102 | W126 | W150 |
|---|---|---|---|---|---|---|
| **Early arm** | | | | | | |
| Undetectable VL | 259 (90.2) | 264 (95.6) | 184 (93.0) | 173 (93.5) | 142 (93.4) | 111 (95.7) |
| VL > 250 copies/mL | 25 (8.7) | 9 (3.3) | 6 (3.0) | 7 (3.8) | 6 (4.0) | 3 (2.6) |
| Not available | 3 (1.1) | 3 (1.1) | 8 (4.0) | 5 (2.7) | 4 (2.6) | 2 (1.7) |
| **Late arm** | | | | | | |
| Undetectable VL | 241 (88.3) | 237 (95.6) | 145 (91.8) | 143 (92.9) | 126 (96.2) | 96 (96.0) |
| VL > 250 copies/mL | 25 (9.2) | 9 (3.6) | 8 (5.1) | 5 (3.2) | 3 (2.3) | 1 (1.0) |
| Not available | 7 (2.5) | 2 (0.8) | 5 (3.1) | 9 (3.9) | 2 (1.5) | 3 (3.0) |
| *p* | 0.80 | 0.82 | 0.34 | 0.81 | 0.64 | 0.63 |

**Plasma viral load (VL) measured by real time PCR for HIV-1 RNA plasmatic quantification (ANRS kit).**

# CD4 measurement during follow-up

| | W26 | W50 | W78 | W102 | W126 | W150 |
|---|---|---|---|---|---|---|
| **Early** | | | | | | |
| N | 283 | 273 | 190 | 180 | 148 | 115 |
| Median | 152 | 201 | 251 | 292 | 293 | 331 |
| (IQR) | (104 – 236) | (145 – 286) | (177 – 347) | (204 – 396) | (227 – 404) | (233 – 422) |
| **Late** | | | | | | |
| N | 266 | 247 | 153 | 148 | 129 | 97 |
| Median | 139 | 188 | 265 | 267 | 292 | 296 |
| (IQR) | (92 – 202) | (129 – 261) | (187 – 349) | (196 – 360) | (204 – 371) | (220 – 414) |
| *p* | 0.06 | 0.17 | 0.81 | 0.18 | 0.66 | 0.72 |

# CAMELIA MAIN CONCLUSIONS

**1. Mortality was nearly halved when HAART was initiated 2 weeks *vs.* 8 weeks after onset of TB treatment.**

**2. Irrespective of study arm, HAART has been extremely successful, as evidenced by >95% of patients with undetectable viral load.**

**3. Despite extremely low CD4+ cell count at inclusion, patients enrolled in this pivotal strategic trial have been extremely adherent.**

**4. HAART initiation 2 weeks after onset of TB treatment could potentially save 150,000 of the 450,000 annual HIV-TB deaths.**

# CAMELIA-ASSOCIATED STUDIES

1. **PECAN (ANRS 12154) :** Relationship between nevirapine or efavirenz pharmacokinetics and drug metabolizing enzyme genetic polymorphism in a population of HIV-infected Cambodian patients. ***Chou Monidarin / Anne-Marie Taburet.***

1. **CAPRI-NK (ANRS 12153) :** CAMELIA-associated paradoxical reactions immune NK study. ***Eric Nerrienet / Daniel Scott-Algara.***

1. **CAPRI-T (ANRS 12164) :** CAMELIA-associated paradoxical reactions immune T-cell study. ***Pean Polidy / Anne E. Goldfeld.***

4. Women reproductive health care issues in the CAMELIA clinical trial. An anthropological approach. ***Pascale Hancart-Petitet.***

# TB MENINGITIS STUDY

Immediate *vs.* deferred antiretroviral therapy for HIV-associated tuberculous meningitis: NCT 00433719. Vietnam.

Clinical diagnosis of TB meningitis. No CD4 restriction criteria.

ART (AZT-3TC-Efavirenz) initiated immediately vs. deferred 2 months after initiation of TB treatment.

Primary outcome: mortality at 9 months.

Secondary endpoints: mortality at 12 months; fever clearance time; coma clearance time; neurological relapse; progression to new or recurrent AIDS defining illness; any grade 3 or 4 adverse event; CD4 count response; plasma HIV-1 RNA response; neurological disability.

More info: Estee Torok, etorok@oucru.org

# HIV TBM trial treatments

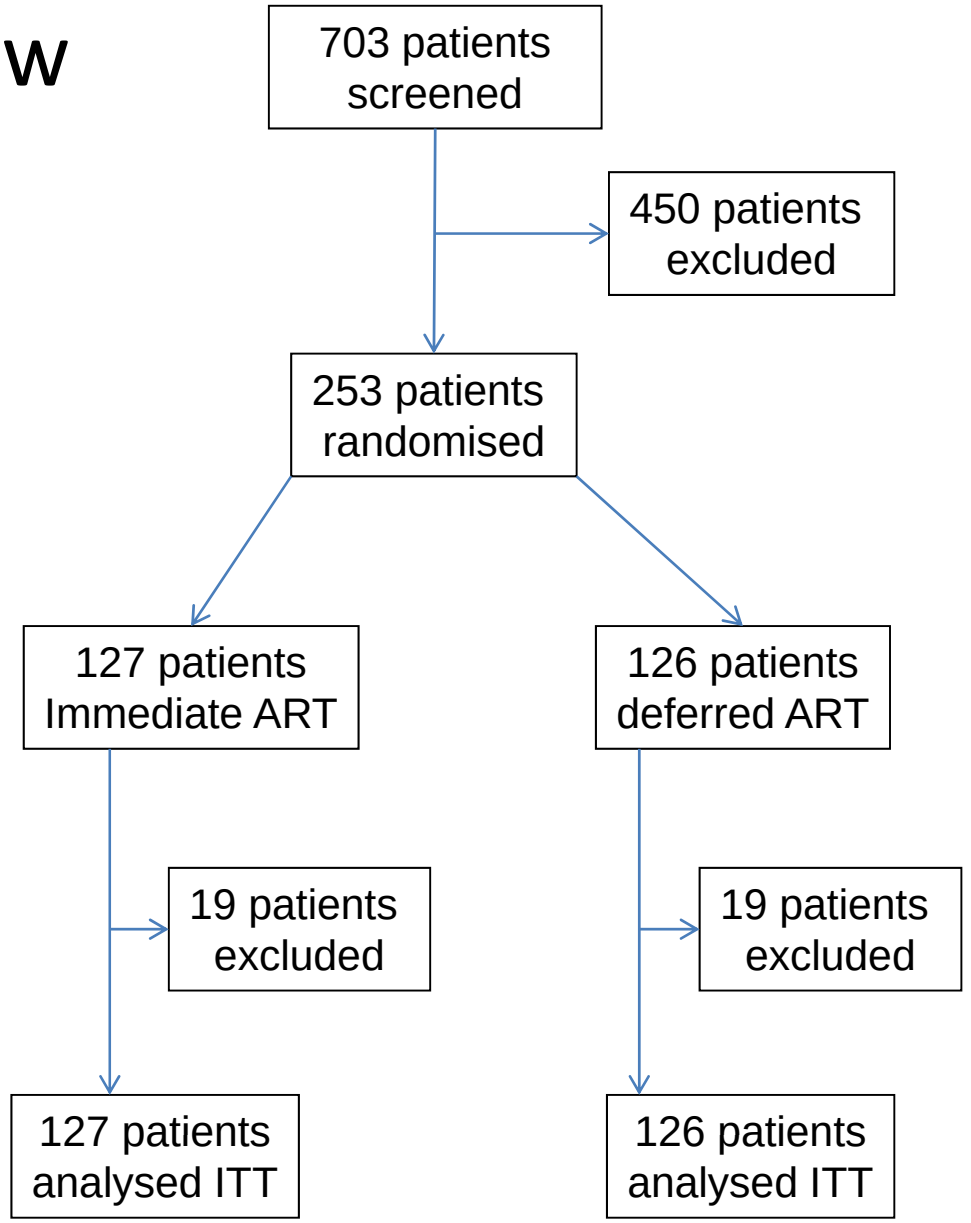
- Antiretroviral therapy
  - AZT, 3TC, EFV
  - Deferred arm: placebos for 2 months followed by ART
- Antituberculous therapy
  - RHZE for 3 months
  - RH for 6 months
- Adjunctive corticosteroids
  - Grade 1 TBM 0.3mg/kg/day tapered over 6 weeks
  - Grade 2 or 3 TBM 0.4mg/kg/day tapered over 8 weeks
- Pneumocystis prophylaxis
  - Co-trimoxazole from week 4 if baseline CD4 <200 cells



Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010

# HIV TBM trial overview

- 703 patients screened
- 450 excluded
  - 235 TB Rx
  - 166 ART
- 253 randomised
  - 127 immediate ART
  - 126 deferred ART
- 38 excluded from per protocol analysis
  - 19 per study arm
  - 23 withdrawals
  - 5 lost to follow-up
  - 10 protocol violations

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# HIV TBM trial baseline characteristics

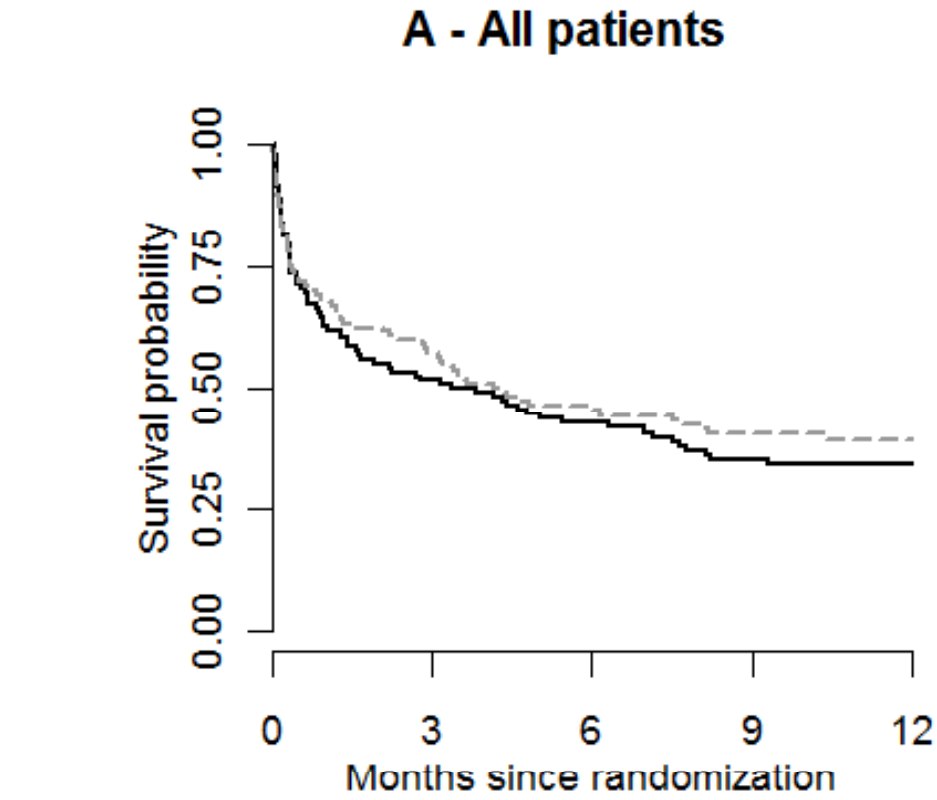
| | **Immediate ART N = 127** | **Deferred ART N = 126** |
|---|---|---|
| Age, yrs | 28 (25 – 32) | 29 (25 – 35) |
| Male | 114 (89.9%) | 114 (90.5%) |
| TBM grade 1<br>TBM grade 2<br>TBM grade 3 | 40 (31.8%)<br>52 (41.3%)<br>34 (27%) | 40 (31.8%)<br>46 (36.5%)<br>40 (31.8%) |
| CD4 count, cells/$mm^3$ | 39 (18 – 116) | 43.5 (15.7 – 84.2) |
| pHIV RNA $log_{10}$ c/mL | 5.39 (5.07 – 5.82) | 5.4 (5.15 – 5.72) |
| CSF AFB positive | 42/119 (35.3%) | 44/118 (37.3%) |
| CSF TB culture positive | 82/99 (82.8%) | 68/98 (69.4%) |
| CSF isolate MDR | 1/77 (1.3%) | 3/64 (4.7%) |



Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010

# HIV TBM trial primary outcome

- Mortality at 9 months
  - 76 in immediate arm
  - 70 in deferred arm
- Hazard ratio 1.12 (95% CI 0.81 – 1.55), p = 0.52
- KM survival estimates at 9 months
  - 35.2% in immediate arm
  - 40.3% in deferred arm
- Similar in per protocol analysis

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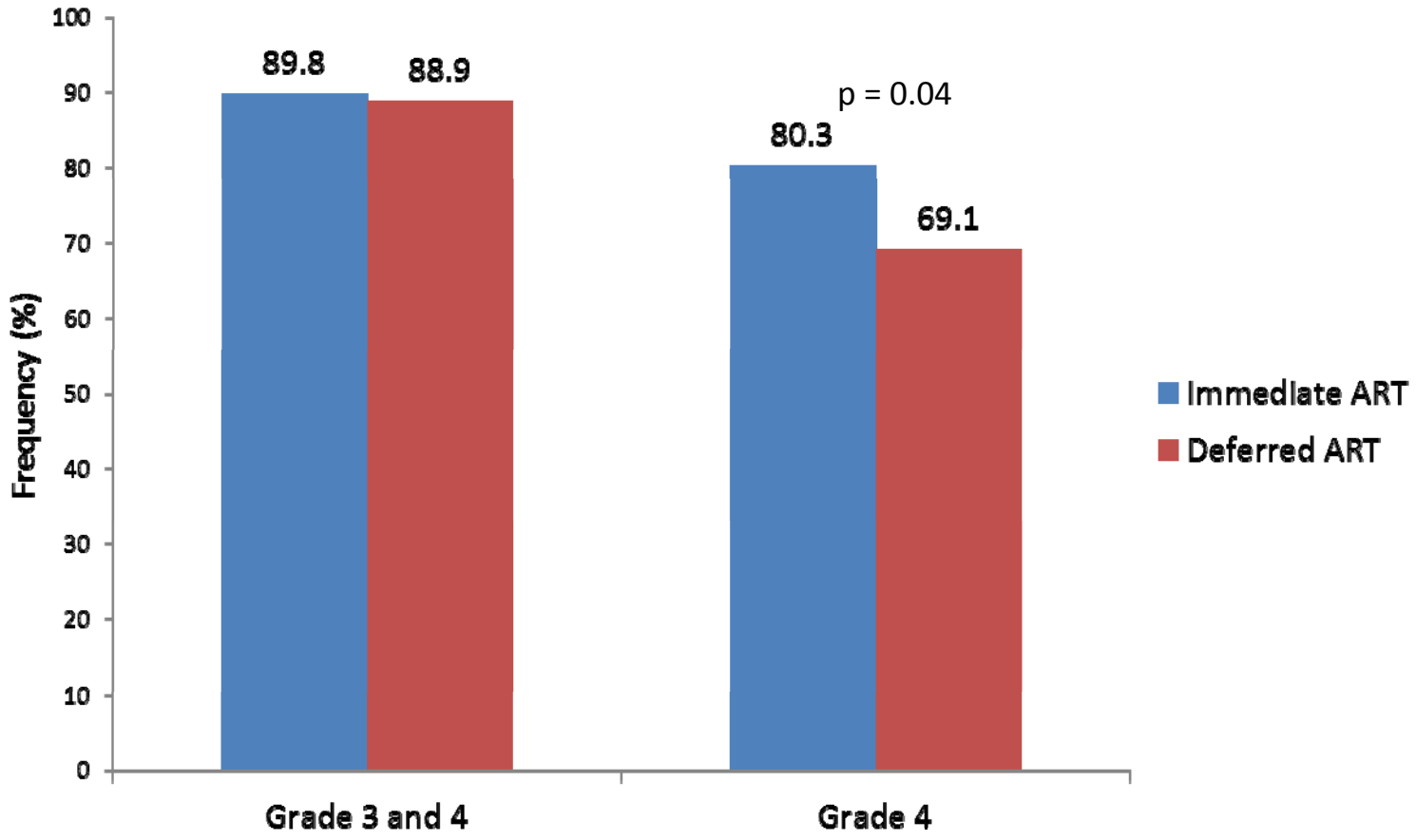
Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010

# HIV TBM trial severe adverse events

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Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010

# HIV TBM trial conclusions

- Immediate ART does not improve outcome in patients with HIV-associated TBM
- There were significantly more grade 4 adverse events in the immediate ART arm
- These data support deferred initiation of ART in HIV-associated TBM, particularly in resource-limited settings
- The optimal time to initiate ART in CNS TB may be different compared with other forms of TB



Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010

# ACTG A5221 STUDY

A strategy study of immediate versus deferred initiation of antiretroviral therapy for HIV-infected persons treated for TB with CD4 less than 200 cells/$mm^3$: NCT 00108862, 8 countries.

CD4 < 200; AFB-positive not mandatory.

ART initiated within 2 weeks after initiating TB treatment vs. ART deferred until 8 to 12 weeks after initiation of TB treatment.

Primary outcome: proportion of participants who have survived without AIDS progression by Week 48.

**Started in September 2006.**

***n*=806.**

**Completion date: end of 2010.**

**Emtricitabine/Tenofovir disoproxil fumarate + efavirenz**

More info: Diane V. Havlir, dhavlir@php.ucsf.edu

# ACTG A5221 STUDY

| | Treatment arm | | |
|---|---|---|---|
| | IMMEDIATE (N=405) | EARLY (N=401) | ALL (N=806) |
| STUDY SITE | | | |
| Africa | 275 | 279 | 554 |
| Asia | 29 | 23 | 52 |
| North America | 21 | 18 | 39 |
| South America | 80 | 81 | 161 |
| CONFIRMED TB | 48% | 45% | 46% |
| Median CD4 cells/$mm^3$ (IQR) | 70 (34, 146) | 82 (40,144) | 77 (36, 145) |
| Median $log_{10}$ HIV RNA | 5.39 | 5.50 | 5.43 |
| EFV/TDF/FTC | 98% | 96% | 97% |
| Median time to ART | 10 days | 70 days | n.a. |

CROI 2011 (D. Havlir, présentation du 28 février)

# Proportion with AIDS/death
# (116 events in 806 participants)
# (31 deaths immediate arm vs. 37 deaths early arm)

| | IMMEDIATE | EARLY | P (95% CI for difference) |
|---|---|---|---|
| All subjects | 12.9% | 16.1% | 0.45 (-1.8, 8.1) |

**Conclusion:** Overall, immediate ART did not reduce AIDS and death compared to early ART. For persons with CD4 ≤50 cells/mm$^3$ immediate ART resulted in lower rates of AIDS and death compared to early ART.

CROI 2011 (D. Havlir, présentation du 28 février)

# SAPIT final results - 1

We compared outcomes of early therapy (ART initiated within 4 weeks of TB treatment initiation, n = 214) and late therapy (ART initiated within the first 4 weeks of the continuation phase of TB treatment, n = 215) in an open-label randomized controlled trial in South Africa in sputum acid-fast bacilli smear-positive patients (n = 642) with HIV and $CD4^+$ counts <500 cells/$mm^3$.

**Results:** Median $CD4^+$ count and viral load at baseline was 150 cells/$mm^3$ and 161,000 copies/mL, and was similar in both groups. Overall, the incidence rate of AIDS or death was 6.9 (18 of 259.4) and 7.8 (19 of 244.2) per 100 person-years in the early and late therapy groups, respectively (incidence rate ratio = 0.89, 95%CI 0.44 to 1.79; $p = 0.73$). In patients with baseline $CD4^+$ counts <50 cells/$mm^3$ (n = 72), the incidence rates of AIDS or death were 8.5 in the early therapy group compared to 26.3/100 person-years in the late therapy group (IRR 0.32; 95%CI 0.07 to 1.13; $p = 0.06$).

Immune reconstitution inflammatory syndrome (IRIS) incidence rates in these patients were 46.8 in the early compared to 9.9 in the late therapy group (IRR, 4.71, $p = 0.01$). Three of the patients with $CD4^+$ counts <50 cells/$mm^3$, all in the early therapy group, required ART drug switches due to adverse events.

CROI 2011 (S. Abdool Karim, présentation du 28 février)

# SAPIT final results - 2

In patients with baseline $CD4^+$ counts ≥50 cells/$mm^3$ (n = 357), the incidence rates of AIDS or death were 6.6 and 4.4/100 person-years in the early and late therapy groups, respectively (IRR, 1.51, *p* = 0.34). In these patients, the early therapy group had a higher IRIS incidence rate (15.8 vs 7.2/100 person-years, IRR 2.18, *p* = 0.02).The early therapy group also had more antiretroviral drug switches due to adverse events; 7 in the early therapy group compared to 1 in the late therapy group (*p* = 0.04).

**Conclusions:** In patients with pulmonary TB/HIV co-infection with $CD4^+$ counts <50 cells/$mm^3$, early ART initiation within 4 weeks of TB treatment initiation was associated with better AIDS-free survival, albeit with increased risk of IRIS. However, in patients with CD4 ≥50 cells/$mm^3$, delaying initiation of ART to the first 4 weeks of continuation phase of TB reduced the risk of IRIS and drug switches without compromising AIDS-free survival.

CROI 2011 (S. Abdool Karim, présentation du 28 février)

| Study | Comparison | Median (IQR) CD4 counts (cells/μl) | Outcome |
|---|---|---|---|
| Zolopa *et al.* [29••] | Early arm: started ART within 14 days of starting treatment for OI (median = 12 days)<br>Deferred ART: started ART after OI treatment completed (median = 45 days) | Early: 31 (12–54)<br>Deferred: 28 (10–56) | No difference in primary composite end-point. But early ART associated with low risk of progression to AIDS or death (OR = 0.51, 95% CI 0.27–0.94) and no increase in adverse events or IRD |
| Abdool Karim *et al.* [31••] | Early: 2 'integrated' arms started ART with first 3 months of TB treatment<br>Late: the deferred group started ART within 1 month of the end of TB treatment | Integrated: 150 (77–254)<br>Sequential: 140 (69–247) | The hazard of death in the early 'integrated' groups was 0.44 (95% CI 0.25–0.79) overall, 0.54 (0.30–0.98) in those with CD4 counts ≤200 cells/μl and 0.16 (0.03–0.79) in those with a CD4 count >200 cells/μl |
| Blanc *et al.* [33] | Early arm: within 2 weeks<br>Late arm: after 2 months | Early: 25 (11–56)<br>Late: 25 (10–55) | 35% lower risk of mortality in the early arm |
| Torok *et al.* [30] | Immediate ART versus ART deferred for 2 months | Early: 39 (18–116)<br>Late: 43.5 (16–84) | Hazard of death in immediate arm were 1.12 (95% CI 0.81–1.55; $P = 0.52$) |
| Makadzange *et al.* [32••] | Early arm: within 72 h of diagnosis<br>Late arm: after 10 weeks of treatment with fluconazole | Early: 27 (17–69)<br>Late: 51.5 (25–69.5) | The hazard of death in the early arm was 2.85 (95% CI 1.1–7.23) |

ART, antiretroviral therapy; IQR, interquartile range; OI, opportunistic infection; TB, tuberculosis.

OI (TB exclues)

TB

TB

TB

Méningite crypto

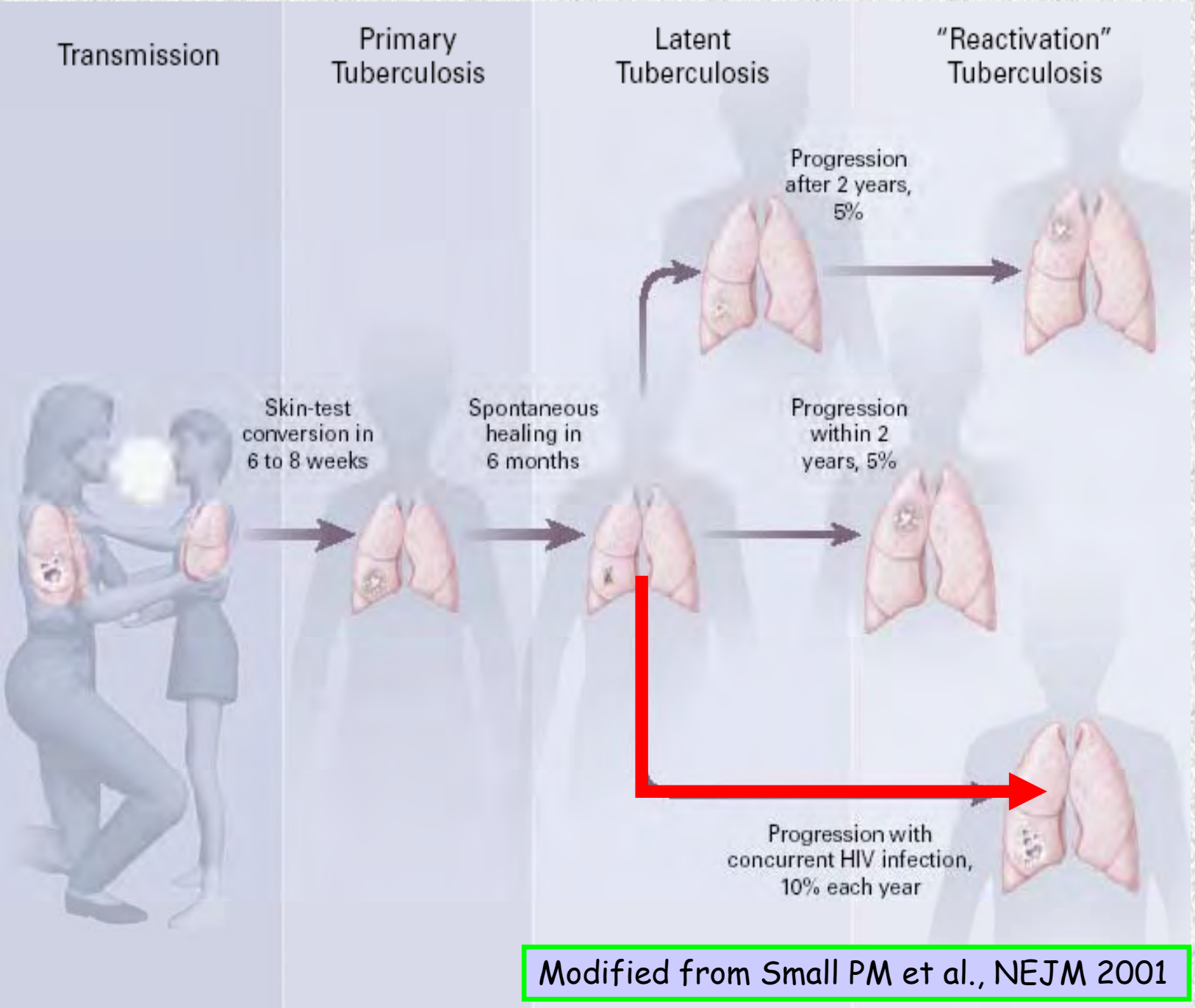
S. Lawn et al. *Curr. Opin. Infect. Dis.* 2011; 24: 34-42

# POUR L'INSTANT, EN FRANCE …

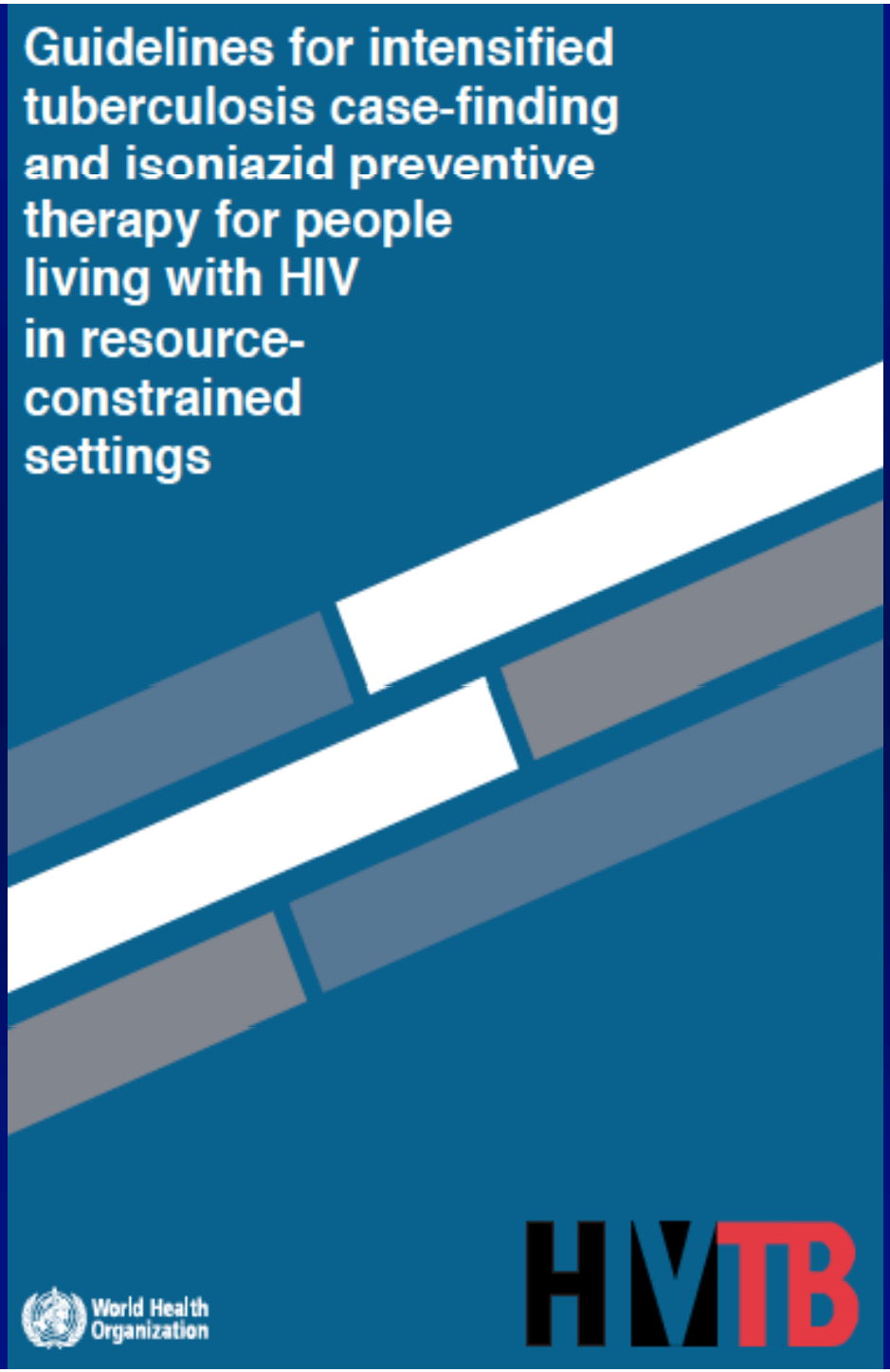
Des syndromes inflammatoires de reconstitution immune peuvent survenir chez environ un quart des patients traités pour une tuberculose, dans les trois mois suivant l'introduction d'un traitement antirétroviral (voir paragraphe «IRIS»). L'essai ANRS CAMELIA, réalisé au Cambodge chez 661 patients très immunodéprimés (CD4 médians, 25/mm$^3$), vient néanmoins de démontrer un bénéfice significatif en termes de mortalité de l'introduction précoce (2 semaines versus 8) des antirétroviraux au décours de tuberculoses principalement pulmonaires et plus rarement ganglionnaires (IAS, Vienne 2010, Late Breaker). La recommandation antérieure de reporter le début des antirétroviraux de plusieurs semaines après le début du traitement d'une tuberculose n'est donc désormais plus applicable dans les tuberculoses pulmonaires ou ganglionnaires diagnostiquées chez des patients très immunodéprimés [12]. Le délai optimal d'initiation du traitement, dans les formes pulmonaires ou ganglionnaires survenant chez des sujets moins immunodéprimés reste à déterminer; dans l'état actuel des connaissances, un report d'environ un mois semble raisonnable à respecter.

Rapport Yéni 2010

**NE PAS OUBLIER LA PRÉVENTION !**




Modified from Small PM et al., NEJM 2001




Meeting à Genève :
25-27 Jan. 2010

**12 recommandations clés**

7 pour les adultes
5 pour les enfants

World Health Organization

# Intensive case finding and IPT

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

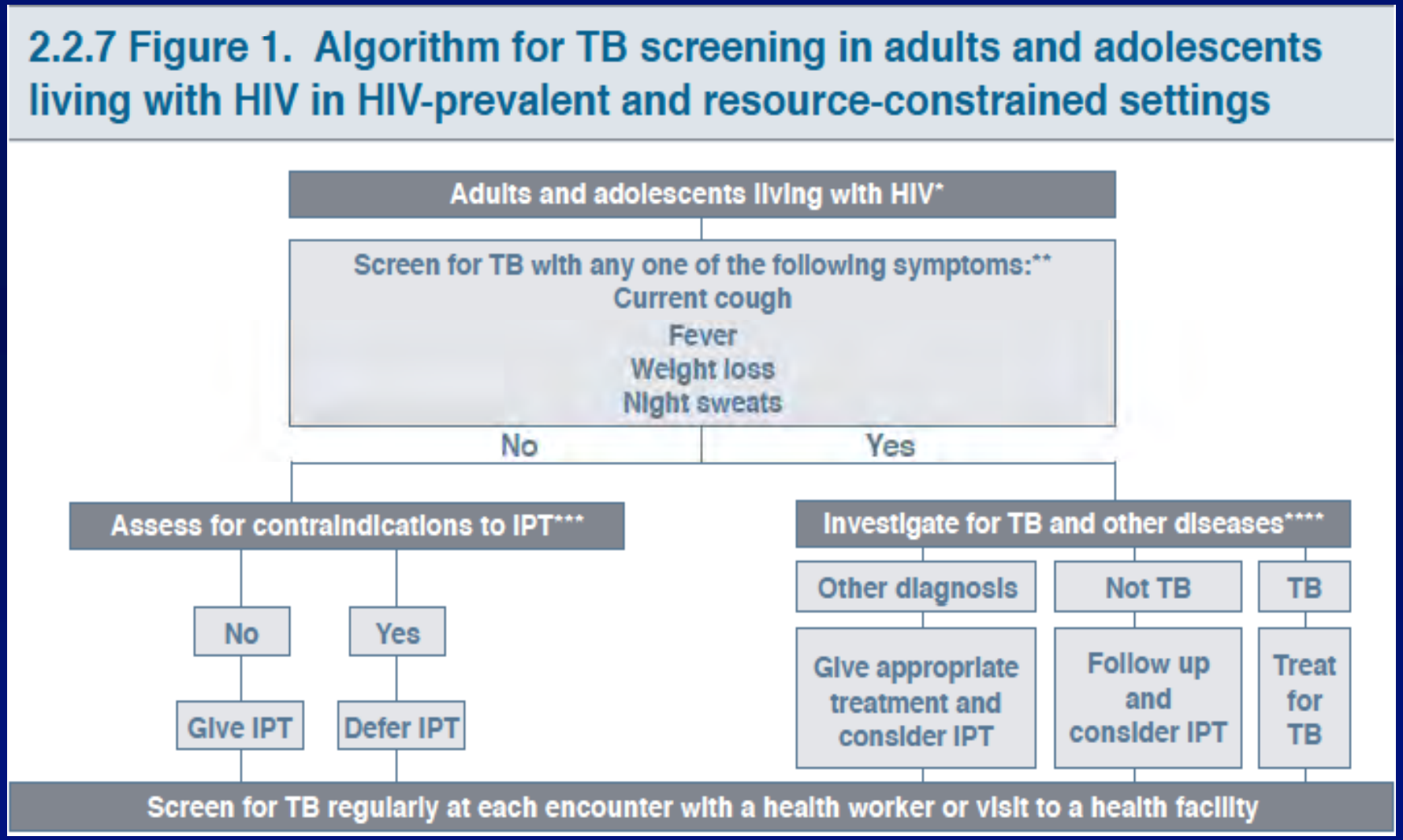
*Strong recommendation, moderate quality of evidence*[1]

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

*Strong recommendation, moderate quality of evidence*

World Health Organization

# Intensive case finding and IPT



# Intensive case finding and IPT

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

*Strong recommendation, high quality of evidence*

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

*Conditional recommendation, moderate quality of evidence*[3]

World Health Organization

# Intensive case finding and IPT

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

*Strong recommendation, moderate quality of evidence*

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

*Strong recommendation, high quality of evidence*

**7** Providing IPT to people living with HIV does not increase the risk of developing isoniazid (INH)-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

*Strong recommendation, moderate quality of evidence*

World Health Organization

# CONCLUSION

**TB regimen: same drugs and same duration than in HIV negative patients. More drug-related toxicity.**
Opportunity to perform PK studies with RIF or RBT.

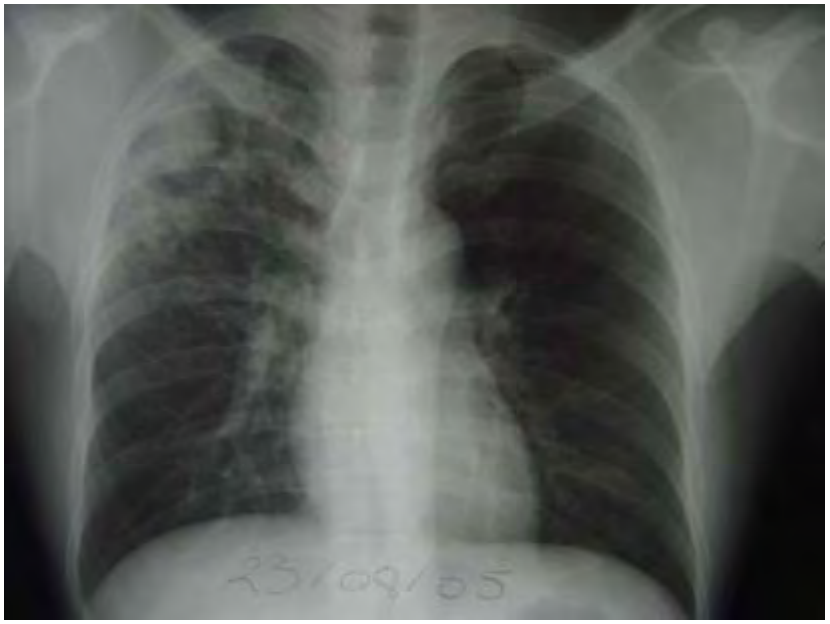
**ART regimen:**

**- 2 NRTIs + 1 NNRTI (EFV > NVP ?)**

- new potent ARV drugs are coming: studies needed+++

When to start ART in TB patients? Answer soon

thanks to the efforts of several teams/funding agencies.
**Start ART after 2 weeks of TB treatment if advanced immunodeficiency** (CD4 < 50/mm$^3$ ++; CD4 ≤ 200/mm$^3$ ?)



# Merci pour votre attention !