# HIV-TB CO-INFECTION

## Update on current & planned clinical trials: Where's the momentum?

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**4th IAS Conference on HIV pathogenesis, treatment and prevention.**

**Sydney, 22 July 2007. Satellite panel discussion.**

# HAART AND TB TREATMENT MANAG$^{T}$

High pill burden, overlapping drug toxicities, IRIS / PR, adherence challenge…

Strategy trials needed+++.

**Three strategy questions in adult patients:**

Which HAART regimen?

When to start HAART?

How to (better) diagnose/manage IRIS? **N/A for this sympo.**

# METHODOLOGY

- Registered trials
- International database
- Informations gathered at http://www.clinicaltrials.gov and http://www.controlled-trials.com (accessed 19 July 2007)
- Direct contact with some of the chairs / PIs

- Query on http://www.clinicaltrials.gov: TB and HIV [condition].
- 30 studies found, 14 remaining after exclusion of trials focusing on prevention/LTBI (5), TB vaccine (2), basic science (4), nutrition (1), adjunctive therapy (1) or observational studies (2) + discard 1 duplicate.

# WHICH HAART REGIMEN?

# WHICH HAART REGIMEN?

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

No large prospective randomized clinical trial published.

Efficacy of a once-daily HAART regimen?

Nevirapin or efavirenz?

Nevirapin 400 or 600 mg?

Data on pharmakokinetics?

# 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 HAART 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. Actual enrollment: 42.**

**Date of completion: end of 2008.**

# Secondary endpoints

- Course of plasma HIV-1 RNA
- TB cured rate
- Safety of study drugs
- Frequency of changing / stopping study drugs
- Clinical progression of HIV disease
- Course of CD4+ and CD8+ lymphocytes
- Proviral DNA evolution
- Resistance profile when virological failure
- PK of antiTB drugs

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

# NVP 400/600 STUDY

A 48 week, randomized, open-label, 2 arm study to compare the efficacy, safety and tolerability of HAART containing **nevirapine 400mg/day *vs.* nevirapine 600 mg/day** in HIV-1 infected patients started at 2-6 weeks after initiating rifampin containing antiTB therapy: NCT 00476853, Thailand.

CD4 < 200. Proven TB.

Primary outcome: HIV-1 RNA quantification in plasma at W 48.

**Started in October 2005.**

**Target *n*=100.**

**Date of completion: October 2008.**

More info: Anchalee Avihingsanon, anchalee.a@hivnat.org

# NVP/EFZ THAI STUDY

Efavirenz-based vs. nevirapine-based antiretroviral therapy among HIV-infected patients receiving rifampin (N2R): NCT 00483054, Thailand. CD4 < 250, AFB-positive not mandatory.

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 HAART.

**Started in January 2007.**

**Target ?**

**Date of completion: ?**

More info: Supeda Thongyen, supeda_t@yahoo.com

# 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.

HAART 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 HAART.

**Started in June 2006.**

**Target *n*=180.**

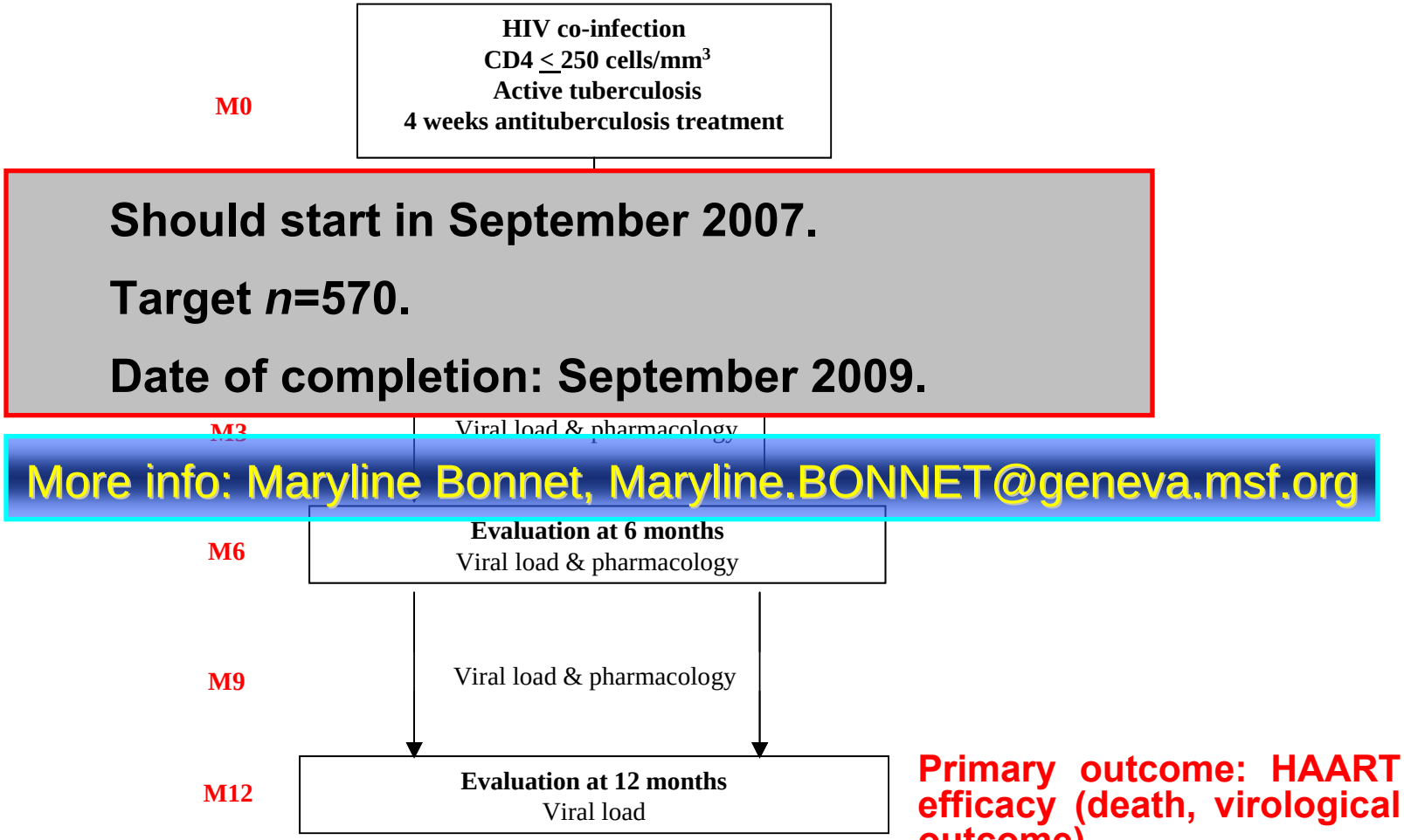
**Date of completion: December 2009.**

More info: Soumya Swaminathan, doctorsoumya@yahoo.com

# NVP/EFZ ANRS STUDY

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

NCT 00495326, Mozambique.




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

# WHICH HAART REGIMEN?

**Pharmakokinetics**

- PK of emtricitabine / tenofovir + efavirenz in HIV-infected patients with TB (PETE): NCT 00474435, Tanzania.
50 < CD4 < 350, smear-positive pulmonary TB.

**Target *n*=30. Should start in September 2007.**

**Date of completion: end of 2008.**

More info: Gibson Kibiki, gkibiki@gmail.com

- Intensive PK of the nelfinavir-rifabutin interaction in patients with HIV-related TB treated with a rifabutin-based regimen: NCT 00018083. Obj.: to compare the PK of rifabutin (600 mg twice a week) in combination with EFZ (600 mg daily) *vs.* rifabutin (300 mg twice a week) without EFZ.

# WHICH HAART REGIMEN?

**Pharmakokinetics**

- The pharmacokinetics and safety of ritonavir-boosted indinavir 600/100mg Bid combined with NRTIs in ARV naïve HIV/TB co-infected patients receiving rifampicin containing anti-TB therapy: NCT 00411996, Thailand.

**Target *n*=20. Started in December 2006.**

**Date of completion: December 2007.**

# WHEN TO START HAART?

# PART STUDY

Delaying HIV disease progression with punctuated antiretroviral therapy in HIV-associated TB: NCT 00078247, Uganda. Designed to determine whether 6 months of anti-HIV drugs given along with TB treatment will delay the onset of AIDS in HIV-infected African patients with CD4 > 350.

Primary outcomes: CD4+ decline (slope), time to AIDS.

**Initial HAART vs. delay HAART until CD4 drop below 250.**

**Started in October 2004.**

**Target *n*=350. Actual enrollment: 150.**

**Date of completion: ?**

**AZT + 3TC + abacavir**

More info: Christopher C. Whalen, ccw@case.edu

# TB-HAART STUDY

An evaluation of the impact of early initiation of HAART 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 HAART with anti-TB vs. delay HAART at 6 months.**

**Started in March 2007.**

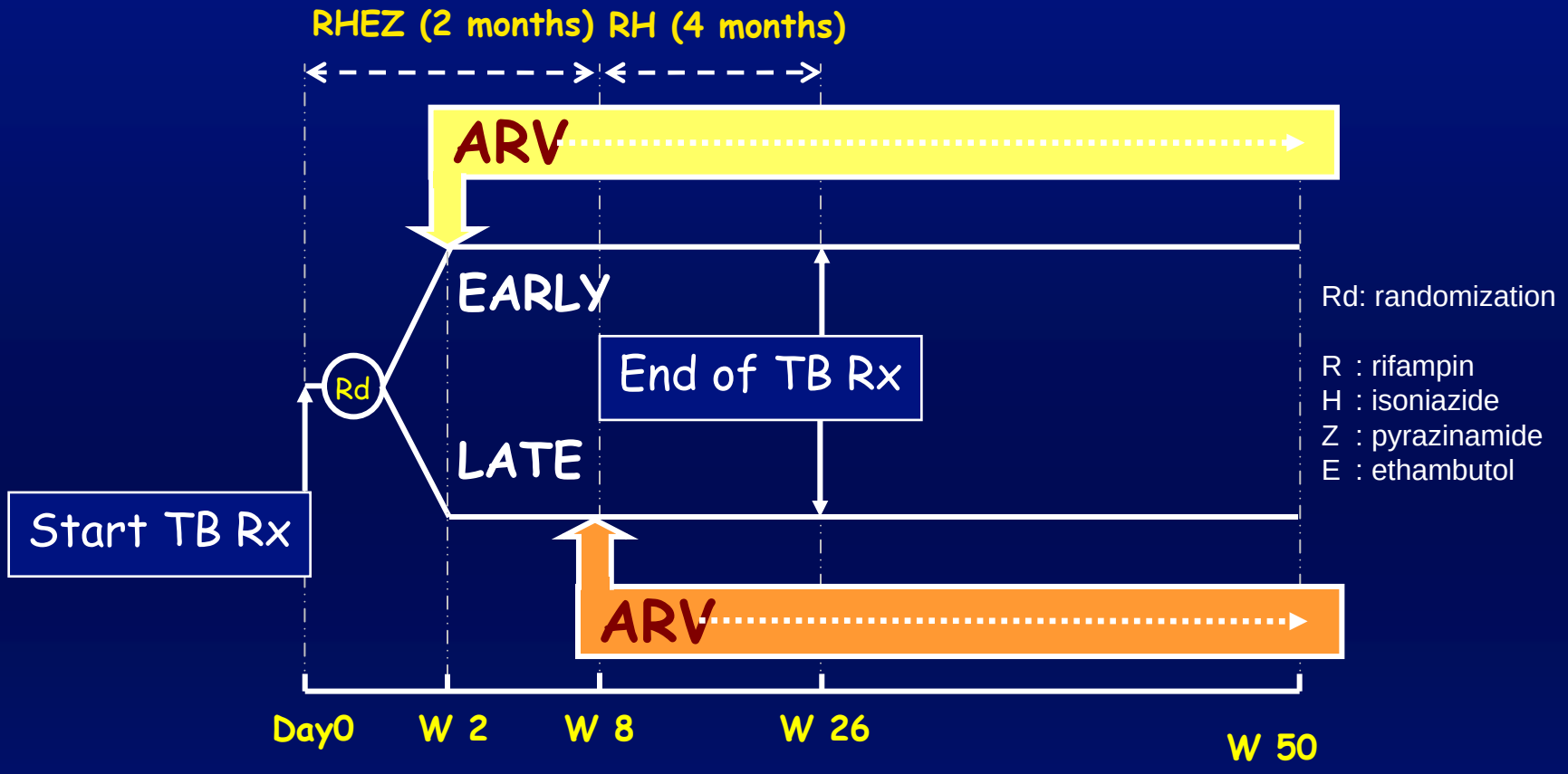
**Target *n*=1900. Actual enrollment: 33.**

**Date of completion: 2011.**

**AZT + 3TC + efavirenz**

More info: Philip Onyebujoh, onyebujohp@who.int

# CAMELIA (ANRS1295/CIPRA KH001)




**All patients receive the same TB treatment and the same initial HAART regimen (D4T + 3TC + efavirenz).**

**Two arms: EARLY (2 wks after onset of TB treatment) vs. LATE (8 wks) introduction of HAART.**

**Primary endpoint = survival.**

**Five study sites in Cambodia.**

# CAMELIA (ANRS 1295 / CIPRA KH001)

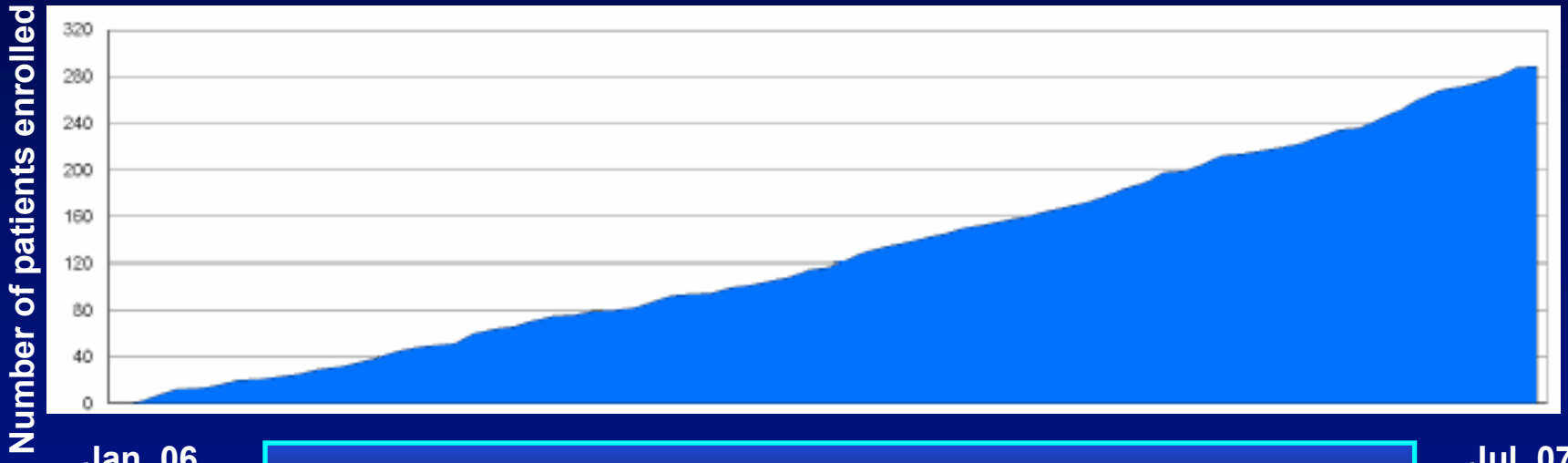
**Patients can be enrolled when:**
- CD4 ≤ 200 / mm$^3$
- AFB+ on any smear
- Naïve to both TB Rx and HAART
- LFT < 5 N, no icterus
- At least 18 years old
- Not pregnant

**Started in January 2006.**

**Target *n*=660.**

**Actual enrollment: 289 patients on 16 July 2007 (343 screened).**

**Date of completion: end of 2009.**




More info: F.Xavier Blanc, xavier.blanc@bct.aphp.fr

# AACTG 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.**

**Target *n*=800. Actual enrollment: 5.**

**Date of completion: ?**

**Emtricitabine/Tenofovir disoproxil fumarate + efavirenz**

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

# TB MENINGITIS STUDY

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

Clinical diagnosis of TB meningitis. No CD4 restriction criteria.

ART 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.

**Started in September 2005.**

**Target *n*=247.**

**Date of completion: ?**

**AZT + 3TC + efavirenz**

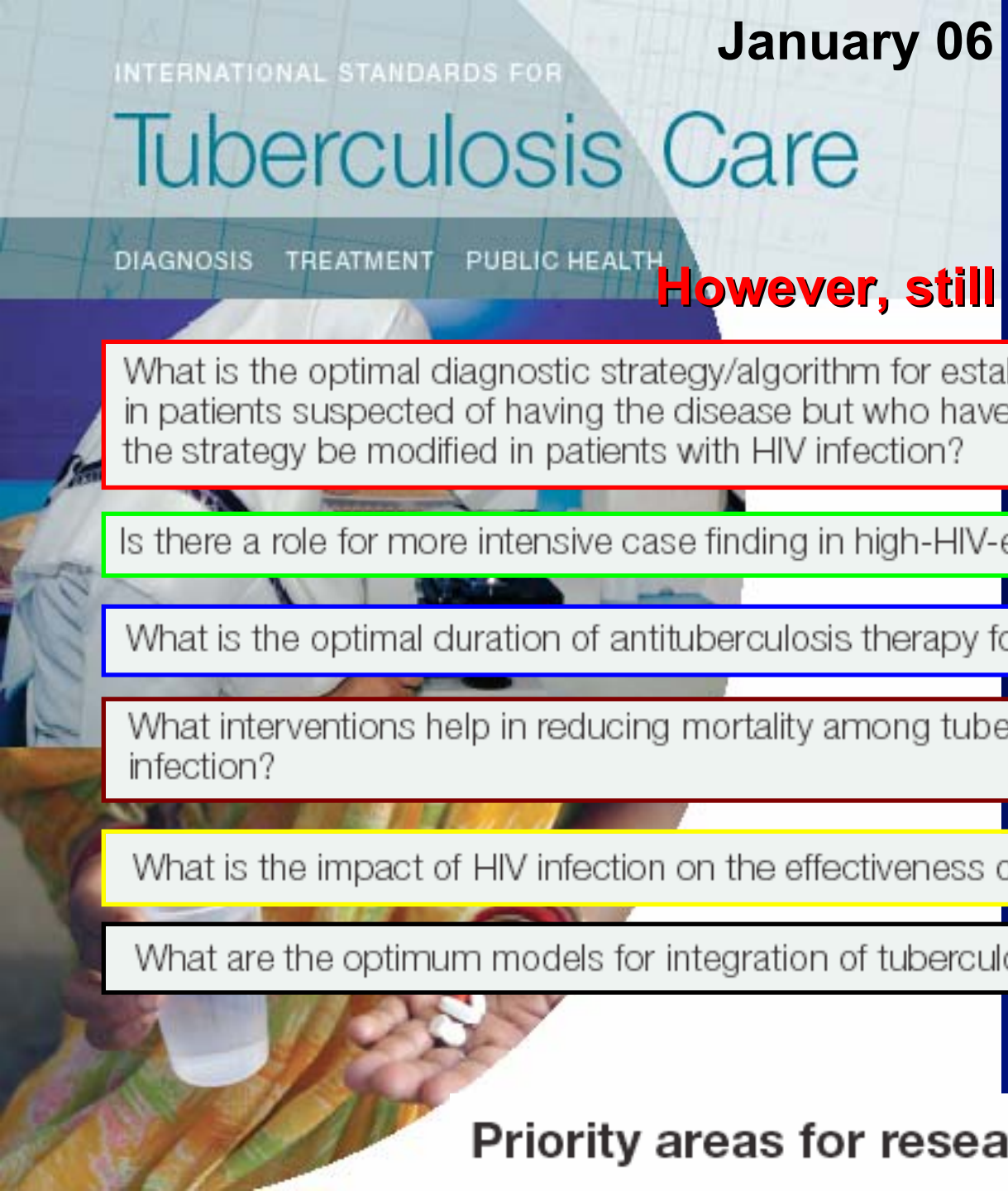
More info: Estee Torok, etorok@oucru.org

# CONCLUSION

Despite some general difficulties in funding and sometimes slower than anticipated enrollment, the following studies are likely to answer these 2 questions in the next 2 or 3 years:

Which HAART regimen? BKVIR, NVP 400/600 study, NVP/EFZ Thai study, NVP/EFZ Indian study, NVP/EFZ ANRS study + PK studies.

When to start HAART in patients treated for TB? PART, TB-HAART, CAMELIA, AACTG A5221, TB meningitis study.




January 06

# CONCLUSION

**However, still some gaps remaining:**

What is the optimal diagnostic strategy/algorithm for establishing a diagnosis of tuberculosis in patients suspected of having the disease but who have negative sputum smears? Should the strategy be modified in patients with HIV infection?

Is there a role for more intensive case finding in high-HIV-endemic settings?

What is the optimal duration of antituberculosis therapy for patients who are HIV-positive?

What interventions help in reducing mortality among tuberculosis patients who have HIV infection?

What is the impact of HIV infection on the effectiveness of DOTS programs?

What are the optimum models for integration of tuberculosis and HIV care?

**Priority areas for research and evaluation**

# FOR FURTHER INFORMATION…

SUPPLEMENT ARTICLE

## Treatment Strategies for HIV-Infected Patients with Tuberculosis: Ongoing and Planned Clinical Trials

François-Xavier Blanc,[1,2] Diane V. Havlir,[3] Philip C. Onyebujoh,[5] Sok Thim,[6] Anne E. Goldfeld,[4,6] and Jean-François Delfraissy[1,2]

The Journal of Infectious Diseases 2007; 196:S46–51

**A regularly updated table can also be found at:**
http://www.hivforum.org
http://www.tbhiv-create.org

# THANKS FOR YOUR ATTENTION !


# FRENCH NATIONAL AGENCY FOR RESEARCH ON AIDS AND VIRAL HEPATITIS

# 2006 BUDGET (Personnel not incl.)

RECEIPTS: 44 million euros

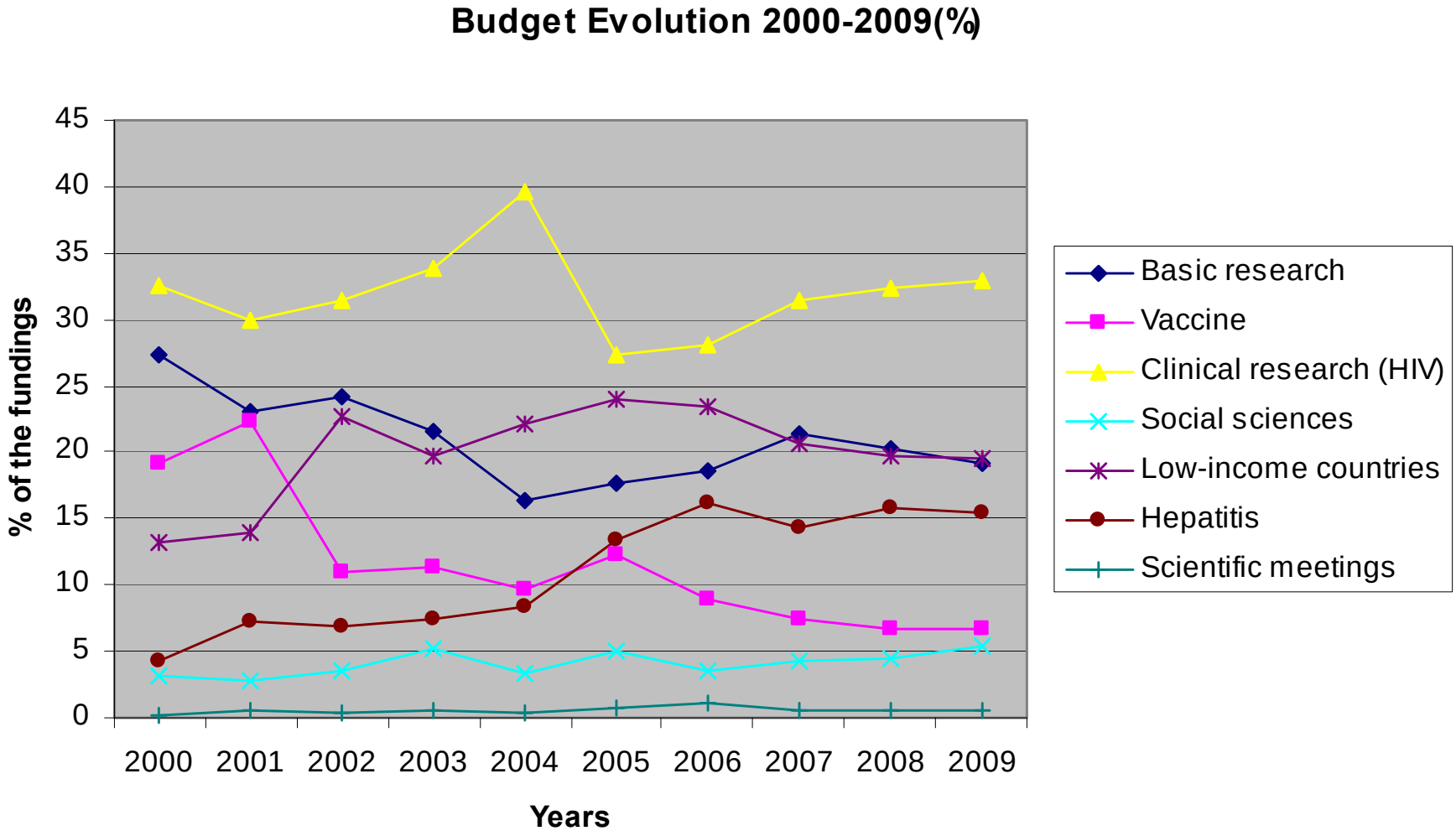
- 97% coming from the French Gov$^{t}$:
  - Research: 40M
  - Foreign Affairs: 1.5M
- 3% private ressources, incl. industry support (2.5 M).

EXPENSES:

- 97% of the funds directly support research projects
- 3% of the budget allocated to pay salaries of the 42 persons who work at the Agency to coordinate the scientific projects

Agence nationale de recherches sur le sida et les hépatites virales

# BUDGET DISTRIBUTION



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Agence nationale de recherches sur le sida et les hépatites virales

# Publications 2002 - 2005 *

| | IF > 5 | IF < 5 | Total |
|---|---|---|---|
| Basic science | 247 | 206 | 453 |
| Clinical trials | 192 | 73 | 265 |
| Low-income countries | 60 | 120 | 180 |
| Social science | 13 | 86 | 99 |
| Vaccines | 6 | 12 | 18 |
| Hepatitis | 67 | 40 | 107 |
| Total | 585 | 537 | 1122 |

* Accurate on 30.3.2006

IF: impact factor

# INTERNATIONAL PARTNERSHIP

- **EUROPE**
  - **Therapeut. trial : NEAT**
  - **Cohorts : COHERE**
  - **Network Vaccine**
  - **Microbicides**
  - **EDCTP**

- **« PAYS DU SUD » (low-income countries) sites**
  - **Africa → ESTHER**
  - **Eastern Europe**
  - **Egypt**

- **NIH - CIPRA (CAMELIA)**
- **ACTG**
- **Global Vaccine Entreprise**

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# Early HAART initiation and/or 6-month isoniazid chemoprophylaxis in HIV-infected adults at early stages of immunosuppression in Abidjan, Côte d'Ivoire

## ANRS 12136 "TEMPRANO" Trial

**Rationale** :

In HIV-infected sub-Saharan African adults, high rates of severe morbidity persist within the first year following HAART initiation.

**Design** : Multicentric 2 x 2 factorial randomized trial (4 arms)

**Sponsor** : ANRS

**Principal Investigators** :

- **Pr S. Eholié**, CHU de Treichville, Abidjan, Côte d'Ivoire
- **Dr X. Anglaret**, Unité INSERM 593, Bordeaux, France

# Early HAART initiation and/or 6-month isoniazid chemoprophylaxis in HIV-infected adults at early stages of immunosuppression in Abidjan, Côte d'Ivoire

## ANRS 12136 "TEMPRANO" Trial

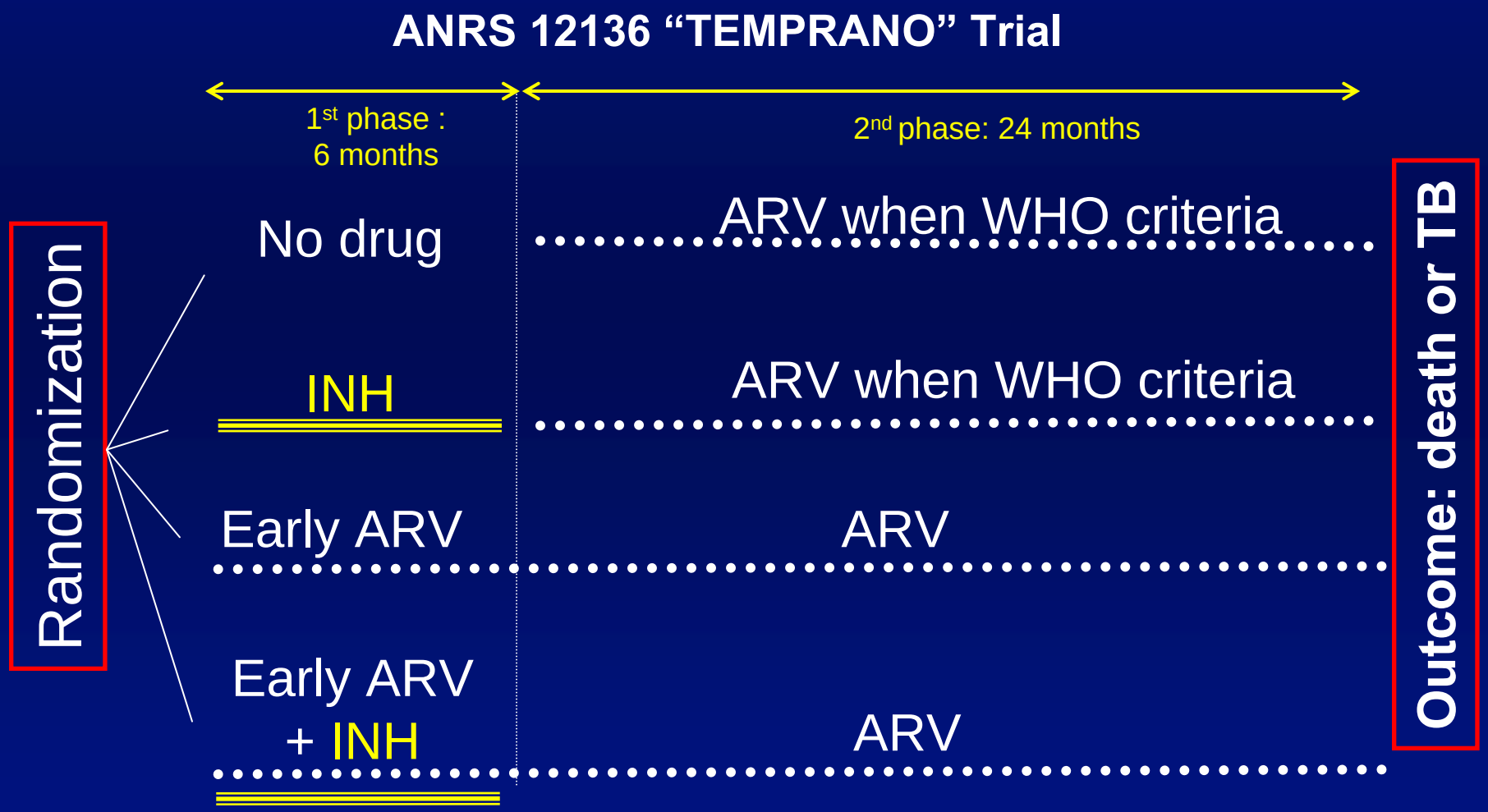
**Inclusion criteria**

- Age ≥ 18 years
- HIV-1 positive
- Informed consent
- No past history of ARV treatment (except for pMTCT)
- Immune and clinical stage:
  - CD4 nadir 250-350/$mm^3$ and WHO stage 1
  - Or CD4 nadir 350-500/$mm^3$ and WHO stage 1, 2 or 3
- No ongoing active tuberculosis
- Serum transaminases < 5 x ULN

**Outcomes at month-30**

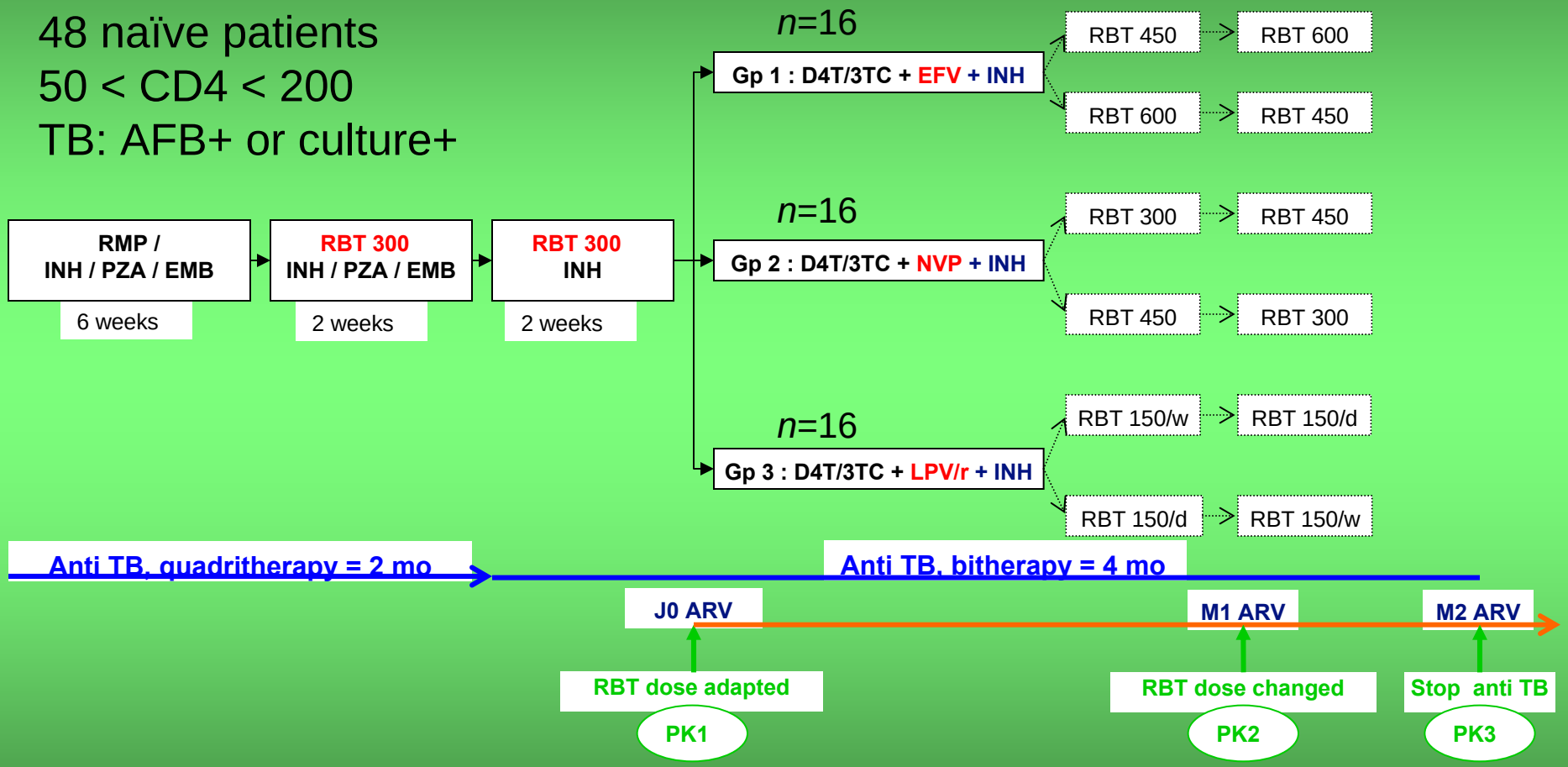
- Primary : Death or TB
- Secondary : Other severe morbidity events, severe side effects, immunological evolution, virological evolution, adherence

# Early HAART initiation and/or 6-month isoniazid chemoprophylaxis in HIV-infected adults at early stages of immunosuppression in Abidjan, Côte d'Ivoire



# ANRS 12150 phase II study

48 naïve patients
50 < CD4 < 200
TB: AFB+ or culture+




**RMP: rifampicine**
**RBT: rifabutine**

# CALL FOR PROPOSALS

- Twice a year: deadline = March, 15 and September, 15
- Application in French or in English (but incl. French team)
- Answers by the end of June / December
- Next 'Top to bottom' TB-HIV meeting planned by end 2007

- Examples of budget:
  - ANRS 1295 (CAMELIA): 1 700 000 euros
  - ANRS 12146 (NVP/EFZ Mozamb.): 485 000 euros
  - ANRS 12136 (TEMPRANO): 3 400 000 euros
  - ANRS 12150 (rifabutine PK) : 400 000 euros

x 2.5 for the total cost of the studies (incl. salaries…)


CONTACT: Dr Brigitte BAZIN, brigitte.bazin@anrs.fr
or Dr Séverine BLESSON, severine.blesson@anrs.fr

# TB IN HIV-INFECTED ADULT PATIENTS

Increased frequency of:

- smear negative (Corbett, CID 2002)
- extra-pulmonary TB (Ackah, Lancet 1995)
- non specific radiological abnormalities (Tshibwabwa-Tumba, J Radiol 1997)