Intensive tuberculosis treatment to reduce the high mortality of tuberculous meningitis in HIV-infected and uninfected patients

The INTENSE-TBM project

Juan Ambrosioni

Partnering for better care in TB Meningitis

The INTENSE-TBM project is part of the EDCTP2 Programme supported by the European Union (grant RIA2017T-2019) and is sponsored by Inserm-ANRS (ANRS 12398 INTENSE-TBM)

Content

1- Background and overview of TM

2- Where INTENSE-TBM come from?

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Content

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Background and overview of TM

- Approximately 1% of all TB cases
- The clinical presentation of TB with the highest mortality (30%-40% in most series, up to 70% in HIV infected patients and MDR-Mt)
- Even with appropriate therapy, high prevalence of neurological sequels (death or permanent disability approx. 50%)
- More frequent in young children and in HIV positive individuals

Background and overview of TM

- Bad prognosis related to a series of reasons:
  -Delayed diagnosis
  -Suboptimal antimicrobial regimens

	Symptoms	Clinical signs	CSF examination
Children	Early symptoms are non-specific and include cough, fever, vomiting (without diarrhoea), malaise, and weight faltering	Initial apathy or irritability that progresses to meningism, decreased level of consciousness, signs of raised intracranial pressure (often bulging anterior fontanelle and abducens nerve palsy), and focal neurological signs (most often hemiplegia)	Usually clear and colourless; raised numbers of white cells (0·05x10⁹–1·00x10⁹/L), with mixture of neutrophils and lymphocytes; raised protein (0·5–2·5 g/L); ratio of CSF to plasma glucose <0·5 in 95% of cases
Adults	Non-specific prodrome of malaise, weight loss, low-grade fever, and gradual onset of headache over 1–2 weeks; followed by worsening headache, vomiting, and confusion, leading to coma and death if untreated	Variable degrees of neck stiffness; cranial nerve palsies (VI>III>IV>VII) develop as disease progresses and confusion and coma deepen; monoplegia, hemiplegia, or paraplegia in about 20% of cases	High opening pressure (>25 cm H_2O) in 50% of cases; raised numbers of white cells (0·05x10⁹–1·00x10⁹/L), with mixture of neutrophils and lymphocytes; raised protein (0·5–2·5 g/L); ratio of CSF to plasma glucose <0·5 in 95% of cases

Table 1: Common clinical features of tuberculous meningitis in children and adults[1]

Non-specific clinical presentation

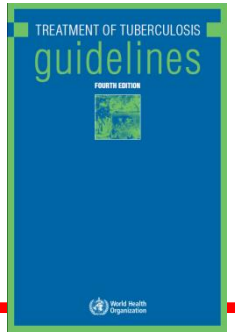
	Standard daily dose for adults	Estimated ratio of CSF to plasma concentration	Comments
Isoniazid	300 mg	80–90%	Essential drug; good CSF penetration throughout treatment
Rifampicin	450 mg (weight <50 kg) or 600 mg (weight ≥50 kg)	10–20%	Essential drug, despite relatively poor CSF penetration; higher doses might improve effectiveness
Pyrazinamide	1·5 g (weight <50 kg) or 2·0 g (weight ≥50 kg)	90–100%	Excellent CSF penetration throughout treatment
Ethambutol	15 mg/kg	20–30%	Poor CSF penetration once meningeal inflammation resolves
Streptomycin	15 mg/kg (1 g maximum)	10–20%	Poor CSF penetration once meningeal inflammation resolves
Kanamycin	15 mg/kg	10–20%	Poor CSF penetration once meningeal inflammation resolves
Amikacin	15–20 mg/kg	10–20%	Poor CSF penetration once meningeal inflammation resolves
Moxifloxacin	400 mg	70–80%	Good CSF penetration
Levofloxacin	1000 mg	70–80%	Good CSF penetration
p-Aminosalicylic acid	10–12 g	No data	Probably very poor CSF penetration unless meninges are inflamed
Ethionamide or protionamide	15–20 mg/kg (1 g maximum)	80–90%	Good CSF penetration
Cycloserine	10–15 mg/kg	80–90%	Good CSF penetration
Linezolid	1200 mg	40–70%	Variable interindividual CSF pharmacokinetics

Bedaquiline, pretomanid and delamanid: highly protein-bound, unlikely to reach high CSF concentrations…

R in CSF not higher than 20%

Thwaites GE, et al. Lancet Neurol. 2013

Current recommendations



- 4 drugs (H-R-Z-E or S) for at least 2 months + 2 drugs (H-R) for 7-10 months

  + steroids

- Almost unchanged for 40 years

  H, Z, S 1940s-1950s

  E, R 1960s

- If resistant strain, regimen and duration must be adapted

- If MDR suspected, add two drugs empirically

Treatment of tuberculosis guidelines. 4th ed. Geneva: World Health Organization, 2010
Thwaites G, et al. J Infect 2009. Thwaites G, et al. New Eng J Med 2004.

Quinolones role? The end of the debate…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

- Double blind trial in two hospitals in Vietnam
- Adult patients with suspected tuberculous meningitis
- Primary Endpoint: mortality at 9 months

Heemskerk et al. N Engl J Med 2016

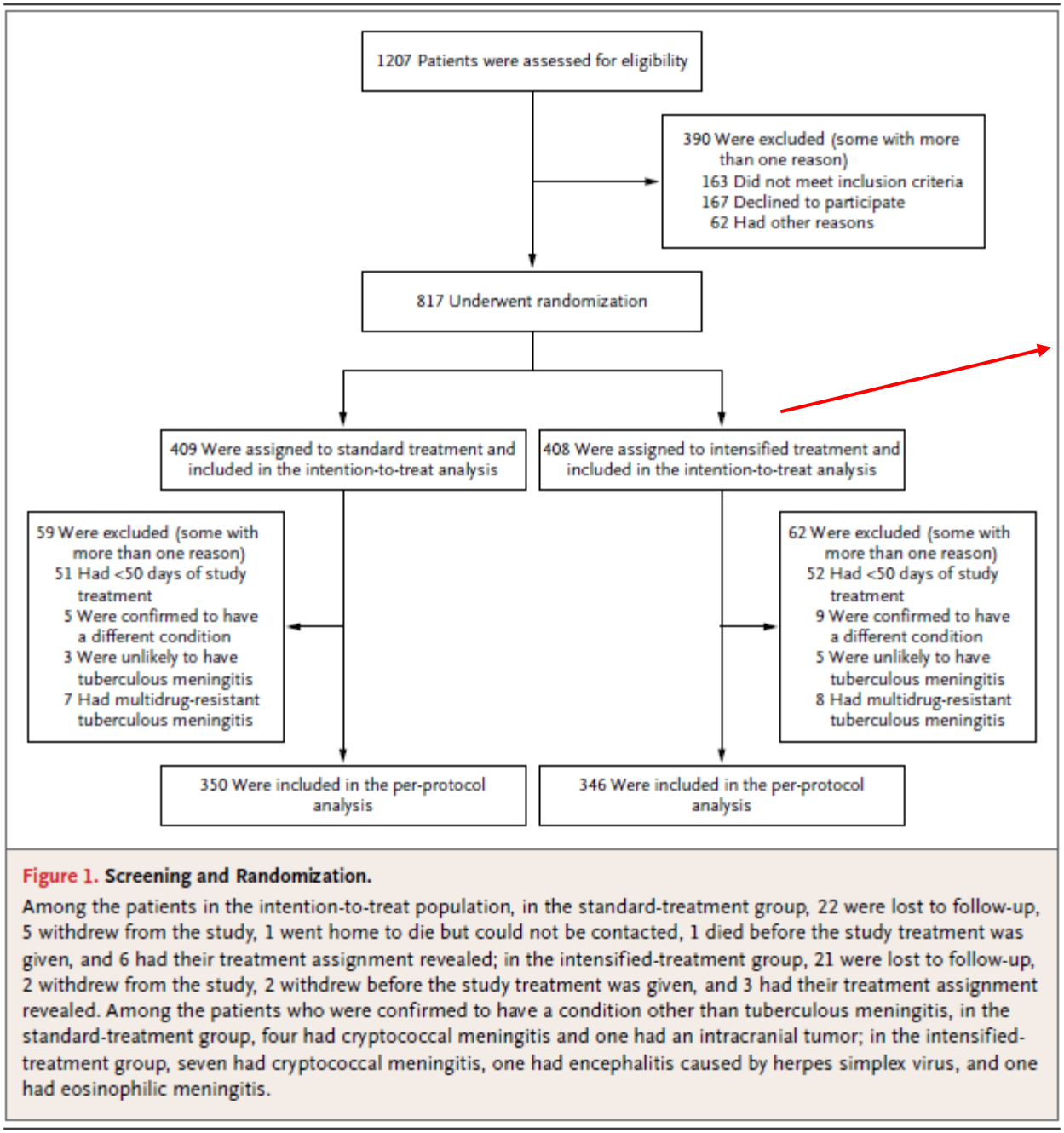


Figure 1. Screening and Randomization.

Among the patients in the intention-to-treat population, in the standard-treatment group, 22 were lost to follow-up, 5 withdrew from the study, 1 went home to die but could not be contacted, 1 died before the study treatment was given, and 6 had their treatment assignment revealed; in the intensified-treatment group, 21 were lost to follow-up, 2 withdrew from the study, 2 withdrew before the study treatment was given, and 3 had their treatment assignment revealed. Among the patients who were confirmed to have a condition other than tuberculous meningitis, in the standard-treatment group, four had cryptococcal meningitis and one had an intracranial tumor; in the intensified-treatment group, seven had cryptococcal meningitis, one had encephalitis caused by herpes simplex virus, and one had eosinophilic meningitis.

R 15mg/kg

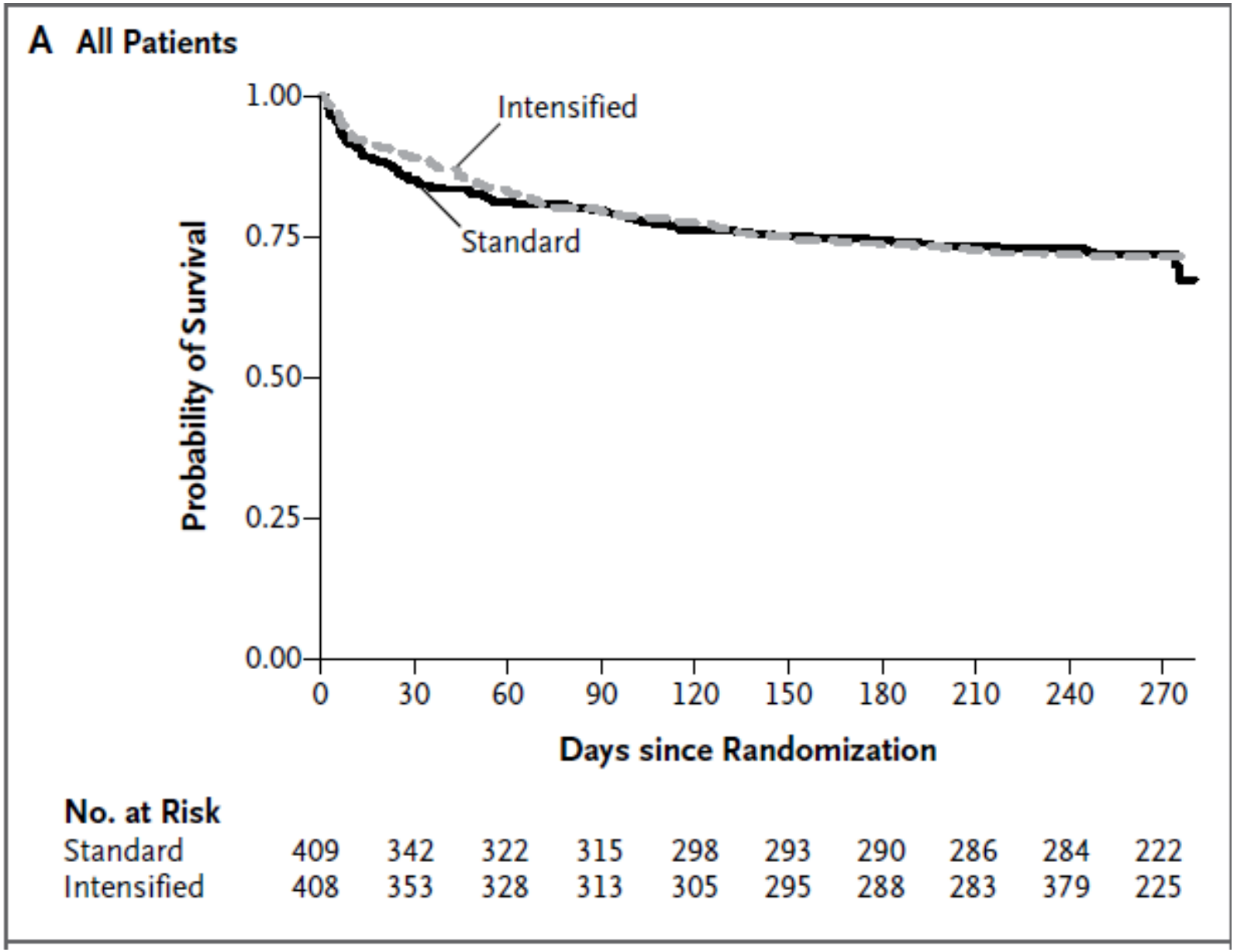
Levof 20mg/Kg

Heemskerk et al. N Engl J Med 2016

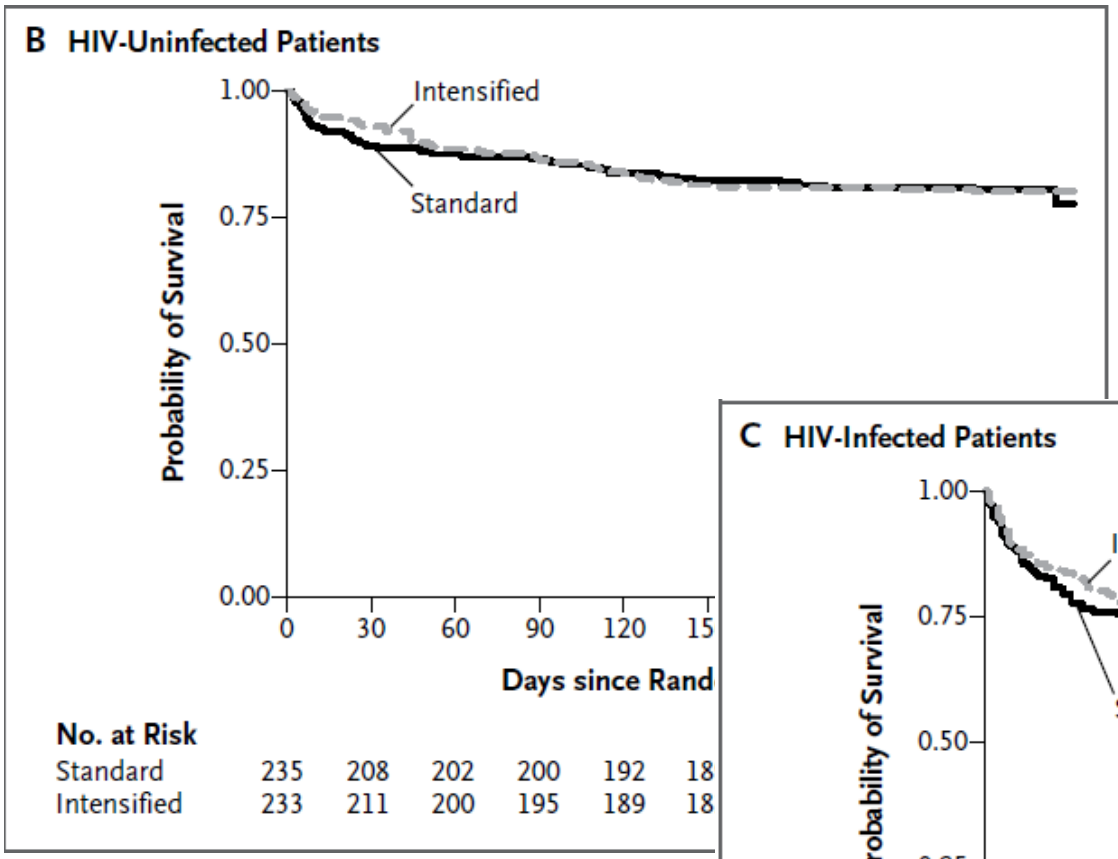
Table 1. Characteristics of the Patients at Enrollment.*

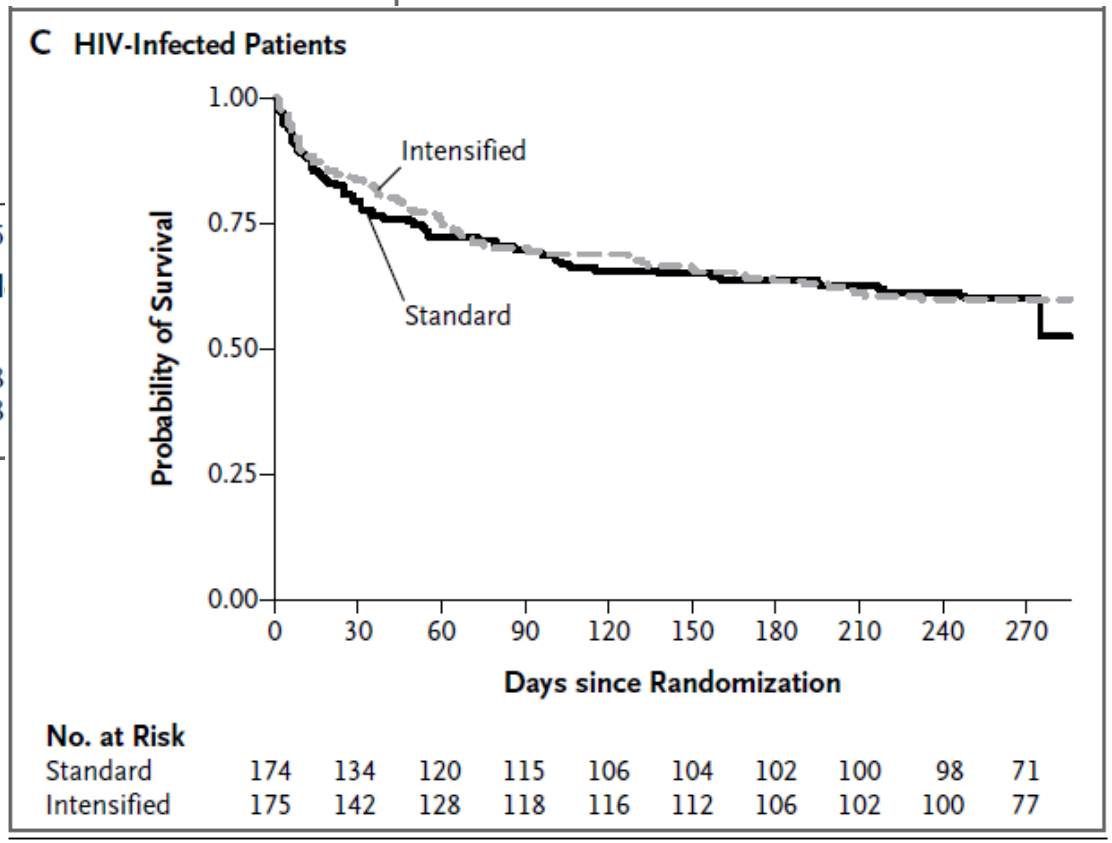
Characteristic	Standard Regimen (N=409)	Intensified Regimen (N=408)	All Patients (N=817)
Male sex — no. (%)	278 (68.0)	282 (69.1)	560 (68.5)
Median age (IQR) — yr	35 (30–47)	35 (29–45)	35 (29–46)
MRC grade — no. (%)†			
1	160 (39.1)	158 (38.7)	318 (38.9)
2	178 (43.5)	179 (43.9)	357 (43.7)
3	71 (17.4)	71 (17.4)	142 (17.4)
HIV-infected — no. (%)	174 (42.5)	175 (42.9)	349 (42.7)
Median CD4 count (IQR) — cells/mm^3‡	38 (15–82)	38 (14–113)	38 (14–101)
Diagnostic category — no. (%)§			
Definite tuberculous meningitis	201 (49.1)	206 (50.5)	407 (49.8)
Probable tuberculous meningitis	109 (26.7)	105 (25.7)	214 (26.2)
Possible tuberculous meningitis	91 (22.2)	83 (20.3)	174 (21.3)
Unlikely to be tuberculous meningitis	3 (0.7)	5 (1.2)	8 (1.0)
Confirmed other condition	5 (1.2)	9 (2.2)	14 (1.7)
Resistance category			
Drug-susceptibility test results available — no.	156	166	322
No isoniazid or rifampin resistance — no. (%)¶	107 (68.6)	113 (68.1)	220 (68.3)
Isoniazid monoresistance — no. (%)	41 (26.3)	45 (27.1)	86 (26.7)
Rifampin monoresistance — no. (%)	1 (0.6)	0	1 (0.3)
Multidrug resistance — no. (%)	7 (4.5)	8 (4.8)	15 (4.7)

Heemskerk et al. N Engl J Med 2016



Heemskerk et al. N Engl J Med 2016





Heemskerk et al. N Engl J Med 2016

Content

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The origin of the consortium

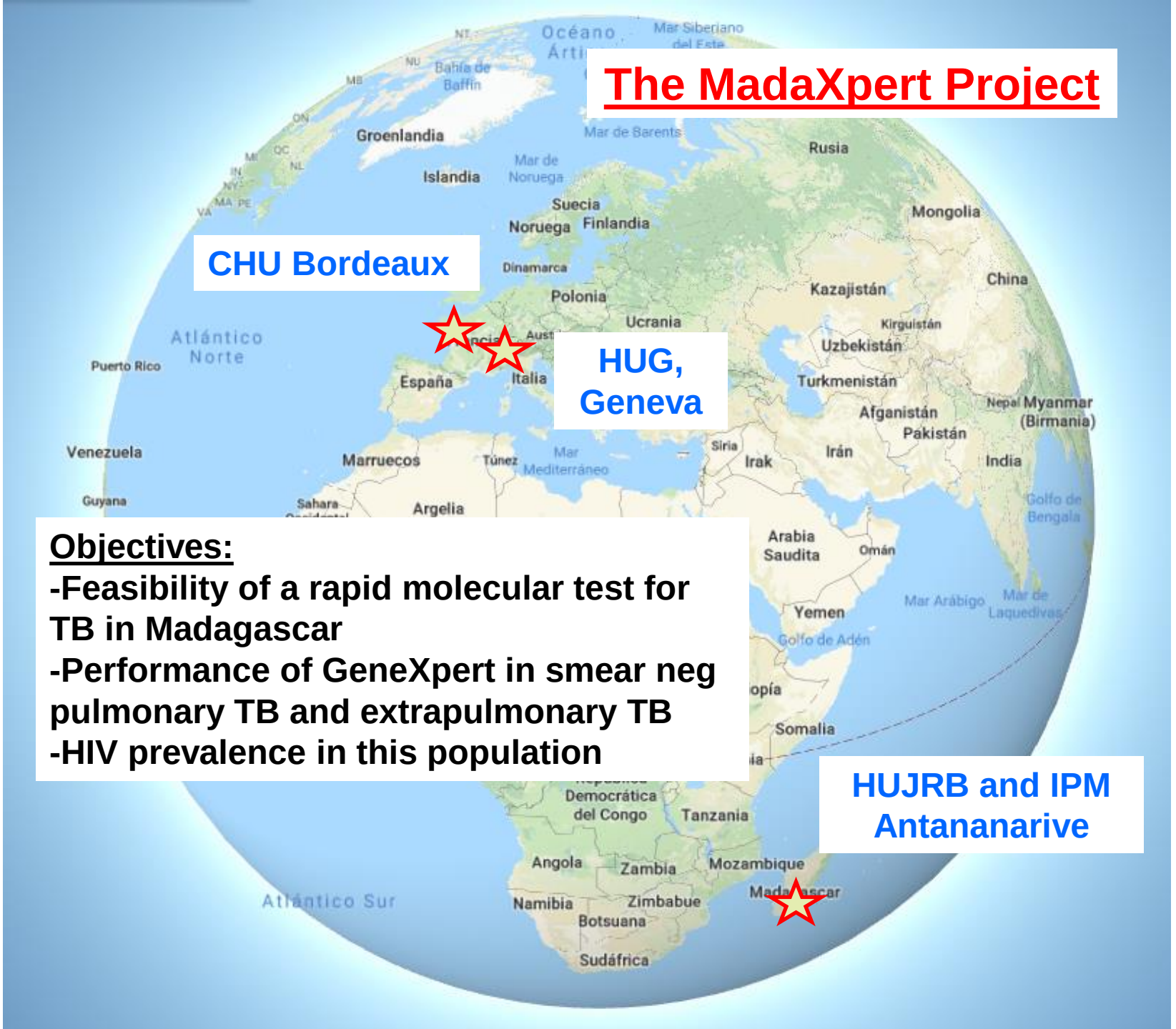
Geneva 2012

Big problem with TB in Antananarivo (capital of Madagascar)

Treatment free of charge by WHO → priorization for pulmonary forms (transmission) → very difficult to start empiric therapy for extrapulmonary forms → high mortality

Institut Pasteur de Madagascar

IPM → Available GeneXpert machine but not reactives or personnel


The MadaXpert Project
CHU Bordeaux
HUG, Geneva
HUJRB and IPM Antananarive
Objectives:
-Feasibility of a rapid molecular test for TB in Madagascar
-Performance of GeneXpert in smear neg pulmonary TB and extrapulmonary TB
-HIV prevalence in this population
Océano Ártico
Mar Siberiano del Este
Bahía de Baffin
Groenlandia
Mar de Barents
Rusia
Islandia
Mar de Noruega
Suecia
Noruega
Finlandia
Mongolia
Dinamarca
China
Polonia
Kazajistán
Ucrania
Kirguistán
Uzbekistán
Atlántico Norte
Puerto Rico
España
Italia
Turkmenistán
Afganistán
Nepal
Myanmar (Birmania)
Pakistán
Venezuela
Marruecos
Túnez
Mar Mediterráneo
Siria
Irak
Irán
India
Guyana
Sahara Occidental
Argelia
Golfo de Bengala
Arabia Saudita
Omán
Mar Arábigo
Mar de Laquedivas
Yemen
Golfo de Adén
Somalia
Democrática del Congo
Tanzania
Angola
Zambia
Mozambique
Atlántico Sur
Namibia
Zimbabue
Botsuana
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HOPITAL UNIVERSITAIRE JOSEPH
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TEL : 22 223 84 - 22 672 21 - 22 220 47


Une conférence au grand public sur le VIH Sida
« Situation actuelle à Madagascar,
prévention et traitement du VIH en 2013 »
Le 06 Décembre 2013 à partir de 08 h 30
A la salle Demi-tonneau de Médecine - Anbatsa
A l'Université d'Antananarivo
Conférence avec une participation
des experts internationaux (Genève et Bordeaux)
Dépistage de VIH gratuit
Entrée libre

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Evaluation of the Xpert MTB/RIF assay for the diagnosis of smear-negative pulmonary and extrapulmonary tuberculosis in Madagascar

R. Rakotoarivelo[a,b,1], J. Ambrosioni[c,d,1,*], V. Rasolofo[e,1], M. Raberahona[a], N. Rakotosamimanana[e], R. Andrianasolo[a], R. Ramanampamonjy[a], M. Tiaray[a], J. Razafimahefa[a], J. Rakotoson[a], M. Randria[a,2], F. Bonnet[f,2], A. Calmy[c,2], the MadaXpert Study Group[3]

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[b] Tambohobe University Hospital, Fianarantsoa, Madagascar
[c] University Hospitals of Geneva, Geneva, Switzerland
[d] Hospital Clinic-IDIBAPS, Barcelona, Spain
[e] Institut Pasteur de Madagascar, Antananarivo, Madagascar
[f] University Hospital of Bordeaux, Bordeaux, France

* Corresponding author. Infectious Diseases Service, Hospital Clinic-IDIBAPS, Villarroel 170, Barcelona 08032, Spain. Tel.: +34 640 2366 70.
E-mail address: jambrosioni@intramed.net (J. Ambrosioni).

-Implementation Xpert was feasible
-400 patients over 30 months
-Good performance of test (comparable to other studies recently published)

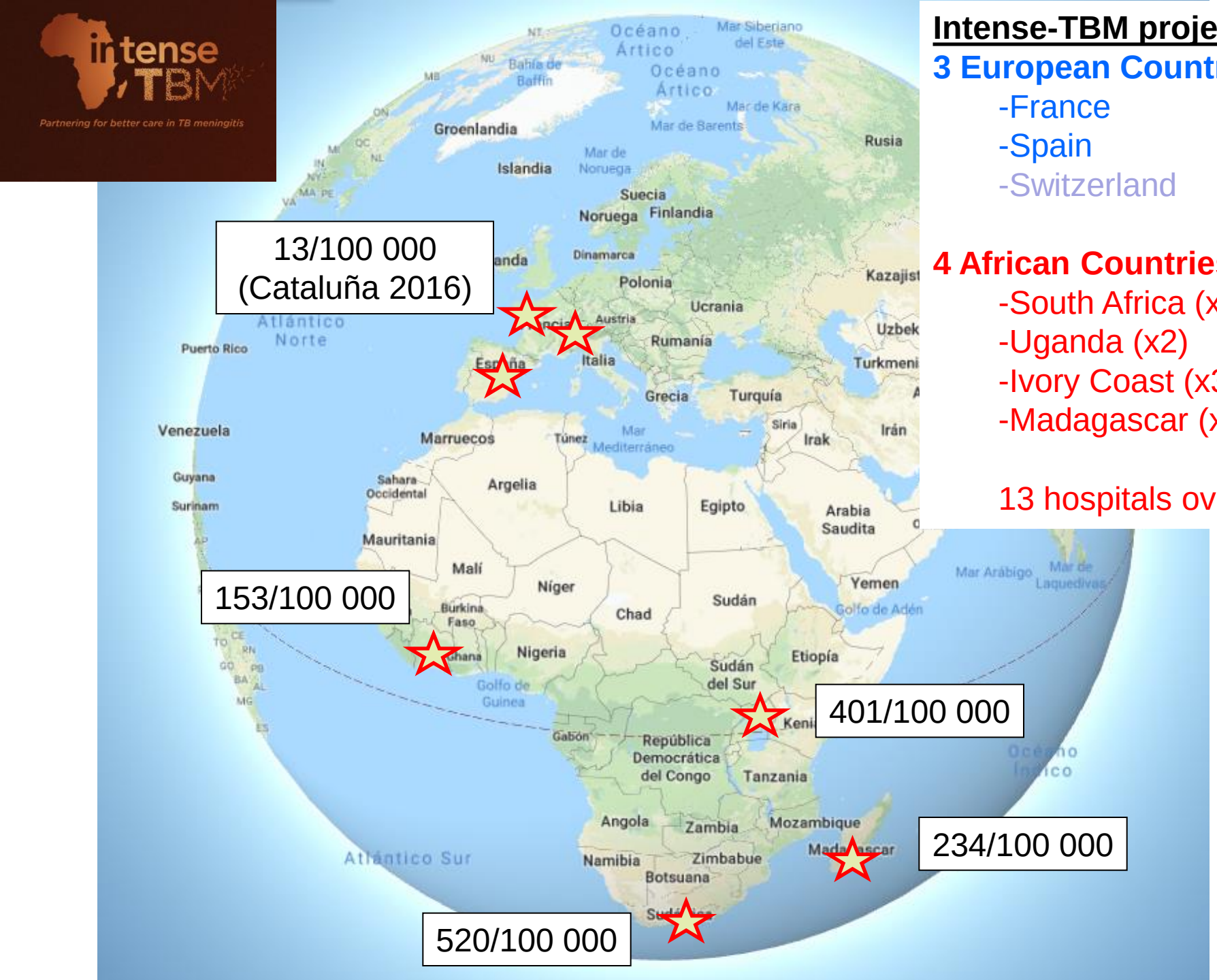
-HIV prevalence in the study: 12%

How to continue working and collaborating there?

The European & Developing Countries Clinical Trials Partnership (EDCTP) funds clinical research to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against HIV/AIDS, tuberculosis and malaria as well as other poverty-related infectious diseases in sub-Saharan Africa, with a focus on phase II and III clinical trials.

A bigger, more potent consortium was required…

E D C T P


intense TBM
Partnering for better care in TB meningitis
13/100 000
(Cataluña 2016)
153/100 000
401/100 000
234/100 000
520/100 000
Intense-TBM project:
3 European Countries:
-France
-Spain
-Switzerland
4 African Countries:
-South Africa (x5)
-Uganda (x2)
-Ivory Coast (x3)
-Madagascar (x3)
13 hospitals overall

Content

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Schematic of study design

- Factorial plan 2 x 2 Multicentre Phase III Randomized Controlled Superiority Trial
- Randomization(R) in a **1:1:1:1** ratio/192 patients per trial arm

R resistance excluded at screening by Xpert Ultra

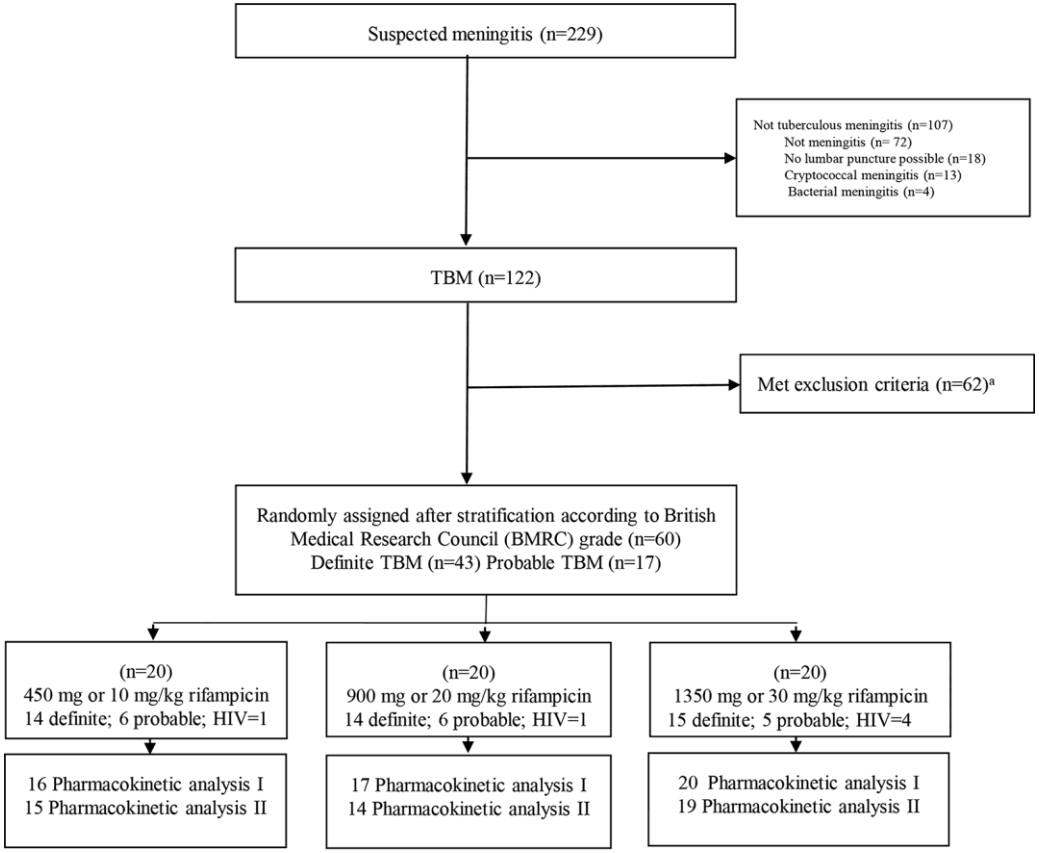
Adolescents or Adults
HIV (+) or (-), TBM suspected

WHO standard treatment		INTENSE-TBM treatment (high dose RIF + LNZ)	
Arm 1 placebo	**Arm 2** aspirin	**Arm 3** placebo	**Arm 4** aspirin

M9, Outcomes mesures

High dose rifampicin?

Several studies suggesting higher plasma and CSF levels with only mild increase in toxicity

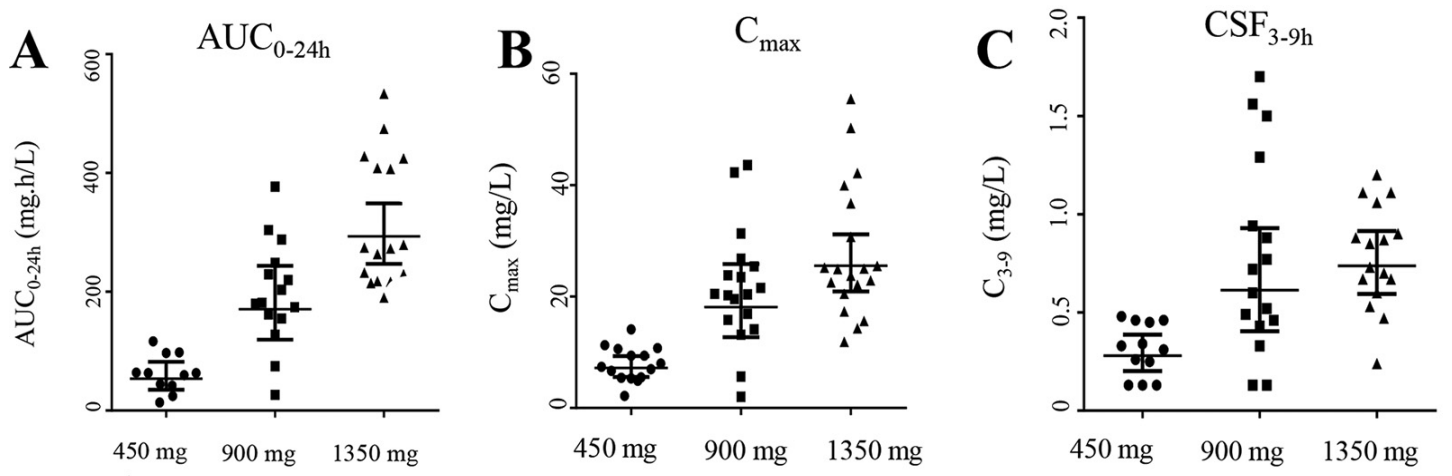


- Study performed in Indonesia
- 20 patients per arm
- All arms PO

Dian et al. Antimicrob Agents Chemother. 2019

High dose rifampicin?

Several studies suggesting higher plasma and CSF levels with only mild increase in toxicity



Mt MICs around 0.2-0.4

Non-linear increase for plasma (saturation of hepatic extraction) and linear increase for CSF

- Study also performed in Indonesia
- 20 patients per arm
- All arms PO

Dian et al. Antimicrob Agents Chemother. 2018

High dose rifampicin?

Several studies suggesting higher plasma and CSF levels with only mild increase in toxicity

TABLE 3 Safety and tolerability

Category	Treatment arm (*n* [%]) All	450 mg (10 mg/kg; *n* = 20)	900 mg (20 mg/kg; *n* = 20)	1,350 mg (30 mg/kg; *n* = 20)	*P* value
All AE[a]					
Grade I–II AE	51 (85)	17 (85)	16 (80)	18 (90)	0.676
Grade III–IV AE	15 (25)	3 (15)	8 (40)	4 (20)	0.503
Specific adverse effects					
Purpura					
Grade I–II	1 (1.7)	0	0	1 (5)	0.608
Thrombocytopenia					
Grade I–II	8 (13.3)	2 (10)	4 (20)	2 (10)	0.686
Leukopenia					
Grade I–II	3 (5)	0	1 (5)	2 (10)	0.593
Anemia					
Grade I–II	20 (33.3)	11 (55)	6 (30)	3 (15)	0.107
Grade III	1 (1.7)	0	1 (5)	0	
Hepatotoxicity					
Grade I–II	26 (43)	9 (45)	7 (35)	10 (50)	0.824
Grade III–IV	12 (20)	3 (15)	5 (25)	4 (20)	
Nausea					
Grade I–II	27 (45)	9 (45)	8 (40)	10 (50)	0.444
Vomitus					
Grade I–II	21 (35)	8 (40)	6 (30)	7 (35)	0.359
Abdominal discomfort					
Grade I–II	15 (25)	4(20)	6 (30)	5 (25)	0.189
Diarrhea					
Grade I–II	8 (13.3)	1 (5)	3(15)	4 (20)	0.602
Pruritus					
Grade I–II	27 (43.3)	9 (45)	6 (30)	12 (60)	0.442
Grade III	1 (1.7)	0	1 (5)	0	
Rash					
Grade I–II	21 (35)	5 (25)	5 (25)	11 (55)	0.410
Grade III	1(1.7)	0	1 (5)	0	

Dian et al. Antimicrob Agents Chemother. 2018

High dose rifampicin?

Several studies suggesting higher plasma and CSF levels with only mild increase in toxicity

TABLE 4 Patients' cumulative mortality per time point

Mortality assessment (day)	All TBM patients				
	Treatment arm (*n* [%])				
	All (*n* = 60)	450 mg (10 mg/kg; *n* = 20	900 mg (20 mg/kg; *n* = 20)[b]	1,350 mg (30 mg/kg; *n* = 20)	*P* value
At discharge	13 (22)	5 (25)	5 (25)	3 (15)	
30	14 (23)	5 (25)	6 (30)	3 (15)	
45	15 (25)	5 (25)	7 (35)	3 (15)	
60	15 (25)	5 (25)	7 (35)	3 (15)	
180	19 (32)	7 (35)	9 (45)	3 (15)	0.116[b]

[a]TBM was classified as definite (microbiologically proven) if either CSF microscopy for acid-fast bacilli, *Mycobacterium tuberculosis* cu
[b]One patient included with bacteriologically confirmed TBM was withdrawn from the study due to resistance to rifampin and was ir excluded from the analysis, the mortality at 180 days would be 9/19 (47%) among all TBM patients and 6/13 (46%) among bacteric and $P = 0.054$ for patients with bacteriologically confirmed TBM.

None died after discharge in the higher dose arm!!!!!

Dian et al. Antimicrob Agents Chemother. 2018

Linezolid?

- Good CSF penetration, experience for other CNS infections, very active against *Mt,* but administration limited due to toxicity (BM and neuropaty) → MDR-*Mt*
- Probably, given for shorter periods at high dose, may impact on TM outcome…

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Linezolid Dose That Maximizes Sterilizing Effect While Minimizing Toxicity and Resistance Emergence for Tuberculosis

Shashikant Srivastava,[a] Gesham Magombedze,[a] Thearith Koeuth,[a] Carleton Sherman,[a] Jotam G. Pasipanodya,[a] Prithvi Raj,[b] Edward Wakeland,[b] Devyani Deshpande,[a] Tawanda Gumbo[a,c]

Center for Infectious Diseases Research and Experimental Therapeutics, Baylor Research Institute, Baylor University Medical Center, Dallas, Texas, USA[a]; Department of Immunology, UT Southwestern Medical Center, Dallas, Texas, USA[b]; Department of Medicine, University of Cape Town, Observatory, South Africa[c]

Srivastava et al. Antimicrob Agents Chemother. 2018

Linezolid?

However, clinical experience with TM still limited…

Abstract ▾ Send to: ▾

Pediatr Infect Dis J. 2016 Feb 17. [Epub ahead of print]

Linezolid is Associated with Improved Early Outcomes of Childhood Tuberculous Meningitis.

Li H[1], Lu J, Liu J, Zhao Y, Ni X, Zhao S.

⊕ **Author information**

Abstract

BACKGROUND: Linezolid serves as an importa
linezolid use in children, especially in childhooc

METHODS: In this study, we retrospectively rev
2014. A total of 86 childhood TBM patients less

RESULTS: 32 (88.9%) of 36 linezolid-treated ca
The frequency of favorable outcome of linezolid
with fever clearance time of <1 week, the contr
than linezolid group. Furthermore, there was nc
patients with adverse events were more likely t

CONCLUSIONS: Our data demonstrate that lin
effects highlights the promising prospects for it

AAC
JournalsASM.org

Linezolid Manifests a Rapid and Dramatic Therapeutic Effect for Patients with Life-Threatening Tuberculous Meningitis

Feng Sun,[a] Qiaoling Ruan,[a] Jiali Wang,[a] Shu Chen,[a] Jialin Jin,[a] Lingyun Shao,[a] Ying Zhang,[a,b] Wenhong Zhang[a]

Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China[a]; Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA[b]

We conducted a retrospective cohort study of patients with MRC grade II/III tuberculous meningitis (TBM) who accepted a background antitubercular regimen (BR) with or without linezolid (LZD). At the 4th week, the LZD-BR group achieved a faster and higher percentage of Glasgow coma scale recovery and temperature recovery, a higher cerebrospinal fluid (CSF)/blood glucose ratio, and lower CSF white blood cell counts than did the BR group. Short-term linezolid supplementation may be a more effective treatment for life-threatening TBM.

Small retrospective studies with several limitations…

Linezolid?

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Linezolid-based Regimens for Multidrug-resistant Tuberculosis (TB): A Systematic Review to Establish or Revise the Current Recommended Dose for TB Treatment

Mathieu S. Bolhuis,[1] Onno W. Akkerman,[2,3] Marieke G. G. Sturkenboom,[1] Samiksha Ghimire,[1] Shashikant Srivastava,[4] Tawanda Gumbo,[4] and Jan-Willem C. Alffenaar[1]

[1]Clinical Pharmacy and Pharmacology and [2]Pulmonary Diseases and Tuberculosis, University Medical Center Groningen, University of Groningen, and [3]Tuberculosis Center Beatrixoord, University Medical Center Groningen, University of Groningen, Haren, The Netherlands; and [4]Center for Infectious Diseases Research and Experimental Therapeutics, Baylor Research Institute, Baylor University Medical Center, Dallas, Texas

Linezolid has been successfully used for treatment of multidrug-resistant tuberculosis (MDR-TB). However, dose- and duration-related toxicity limit its use. Here, our aim was to search relevant pharmacokinetics (PK)/pharmacodynamics (PD) literature to identify the effective PK/PD index and to define the optimal daily dose and dosing frequency of linezolid in MDR-TB regimens. The systematic search resulted in 8 studies that met inclusion criteria. A significant PK variability was observed. Efficacy of linezolid seems to be driven by area under the concentration–time curve (AUC)/minimum inhibitory concentration (MIC). Literature is inconclusive about the preferred administration of a daily dose of 600 mg. To prevent development of drug resistance, an AUC/MIC ratio of 100 in the presence of a companion drug at relevant exposure is required. A daily dose of 600 mg seems appropriate to balance between efficacy and toxicity. Being a drug with a very narrow therapeutic window, linezolid treatment may benefit from a more personalized approach, that is, measuring actual MIC values and therapeutic drug monitoring.

Bolhuis et al. Clin Infect Dis 2018.

AAS?

-Several phase II RCT support reduction in neurological sequels when AAS is added to HRZE + Steroids

-Pathogenesis: reduction in *Mt*-induced vasculitis and stroke

-Positive results in adults and children

-Doses tested between 75 and 1000 mg/d (different durations)

Misra UK et al. J neurol sci 2010

Schoeman JF et al. J Child Neurol 2011

Mai NT et al. Elife 2018

eLIFE elifesciences.org RESEARCH ARTICLE

A randomised double blind placebo controlled phase 2 trial of adjunctive aspirin for tuberculous meningitis in HIV-uninfected adults

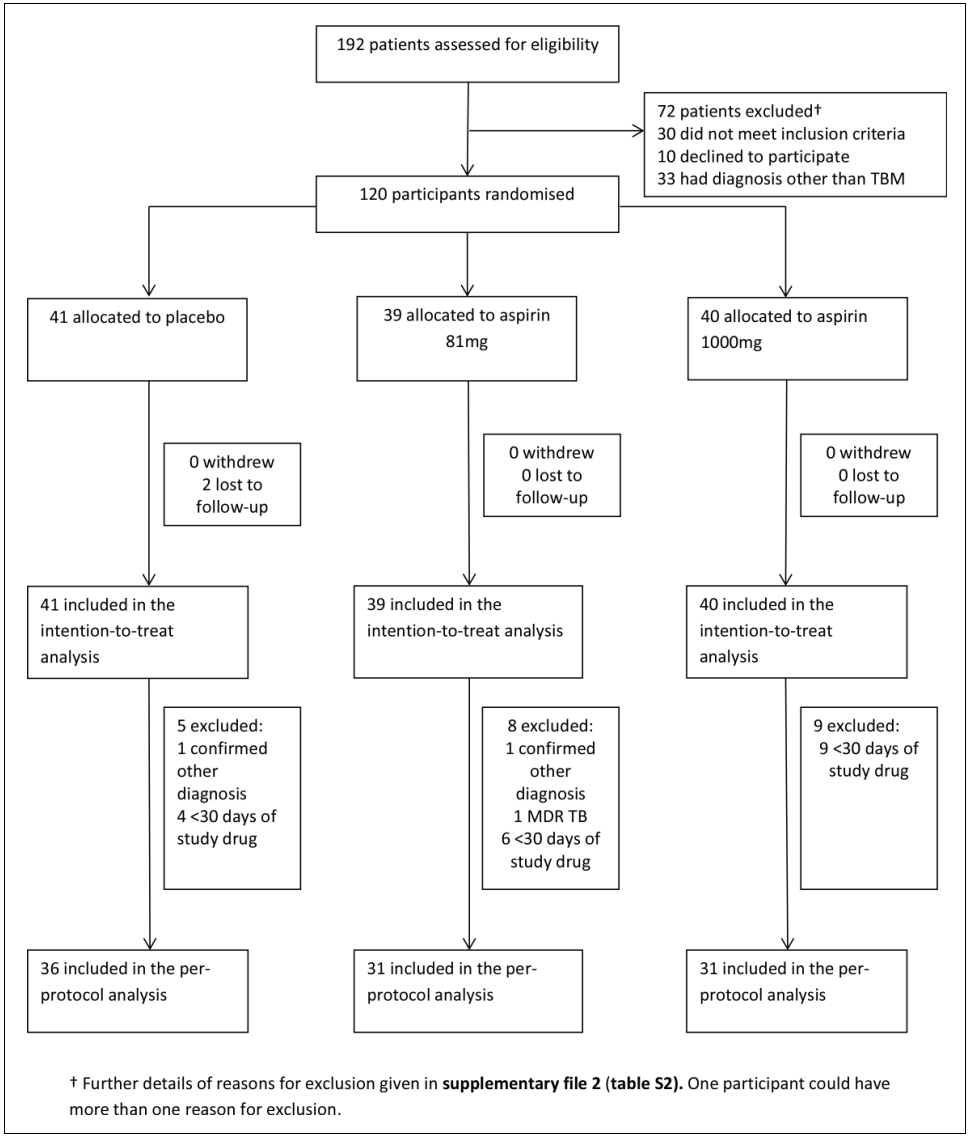
Nguyen TH Mai[1,2], Nicholas Dobbs[3], Nguyen Hoan Phu[1,2], Romain A Colas[4], Le TP Thao[1], Nguyen TT Thuong[1], Ho DT Nghia[1,2], Nguyen HH Hanh[1,2], Nguyen T Hang[1], A Dorothee Heemskerk[1,5], Jeremy N Day[1,6], Lucy Ly[4], Do DA Thu[1], Laura Merson[6], Evelyne Kestelyn[1,6], Marcel Wolbers[1], Ronald Geskus[1,6], David Summers[3], Nguyen VV Chau[1,2], Jesmond Dalli[4], Guy E Thwaites[1,6]*

[1]Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; [2]Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; [3]Western General Hospital, Edinburgh, United Kingdom; [4]Lipid Mediator Unit, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [5]Department of Medical Microbiology and Infection Control, VU medical centre, VU University Amsterdam, Amsterdam, Netherlands; [6]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

AAS?

- 1ry Safety Endpoint: GI or CNS bleeding at d60
- 1ry Efficact Endpoint: death and new brain infarction (MRI) at d60

AAS given daily for 60 days



Mai NT et al. Elife 2018

AAS?

Table 2. Primary safety and efficacy outcomes by 60 days from randomisation in the intention-to-treat population.

	Placebo (n = 41)	Aspirin 81 mg (n = 39)	Aspirin 1000 mg (n = 40)	Absolute risk difference [%] (95% confidence interval)	Overall comparison P-value
Primary safety outcomes					
Gastro-intestinal bleeding or MRI-proven intracranial bleeding event*	5/36 (13.9%)	8/35 (22.9%)	8/40 (20.0%)	Aspirin 81 mg vs placebo: 9.0% (-9.3 to 26.9%) Aspirin 1000 mg vs placebo: 6.1% (-11.5 to 22.8%)	0.59
Gastro-intestinal bleeding event	5/38 (13.2%)	7/35 (20.0 %)	8/40 (20.0 %)	Aspirin 81 mg vs placebo: 6.8% (-10.5 to 24.4%) Aspirin 1000 mg vs placebo: 6.8% (-10.2 to 23.4%)	0.71
MRI-proven intracranial bleeding event	0/35 (0%)	1/32 (3.1%)	0/38 (0%)	Aspirin 81 mg vs placebo: 3.1% (-7.1 to 15.7%) Aspirin 1000 mg vs placebo: 0.0% (-9.9 to 9.2%)	0.30
Primary efficacy outcomes					
New MRI-proven brain infarction or death	11/38 (28.9%)	8/36 (22.2%)	6/38 (15.8%)	Aspirin 81 mg vs placebo: −6.7% (-25.7 to 13.1%) Aspirin 1000 mg vs placebo: −13.2% (-31.0 to 5.7%)	0.40
New MRI-proven brain infarction†	8/35 (22.9%)	2/30 (6.7%)	5/37 (13.5%)	Aspirin 81 mg vs placebo: −16.2% (-33.1 to 2.0%) Aspirin 1000 mg vs placebo: −9.3% (-27.2 to 8.7%)	0.18
Death	4/41 (9.8%)	6/39 (15.4%)	1/40 (2.5%)	Aspirin 81 mg vs placebo: 5.6% (-9.5 to 21.1%) Aspirin 1000 mg vs placebo: −7.3% (-20.2 to 4.7%)	0.14

Mai NT et al. Elife 2018

Schematic and Rationale of study design for HIV (+) individuals

- HIV positive individuals will all initiate TDF/FTC + DTG (50mg bid) at week 4 (or later, according to VL, mycobacterial burden, CD4 level, etc)

- Rationale of ART regimen and interventions:
  - -Still on steroids (should avoid/reduce IRIS)
  - -Unexpected ‘overinduction’ of DTG metabolism induced by high R doses
  - -TDF/FTC no DDI with R
  - -Active against HBV
  - -High genetic barrier

Content

EDCTP

Horizon 2020 European Union Funding for Research & Innovation

ANRS France REcherche Nord & sud Sida-hiv Hépatites Agence autonome de l'Inserm

The INTENSE-TBM project is part of the EDCTP2 Programme supported by the European Union (grant RIA2017T-2019) and is sponsored by Inserm-ANRS (ANRS 12398 INTENSE-TBM)

INTENSE-TBM hypothesis

1. High dose rifampicin (30mg/kg) and linezolid (1200mg qd, 600mg qd later) in addition to standard dose of H-Z-E "**INTENSE-TBM regimen**" will reduce mortality by 30%, irrespective of HIV status

2. Addition of aspirin, a "host-directed therapy" to also decrease mortality by 30% and neurological complications and disability

INTENSE-TBM Endpoints

Primary: Comparison of **Mortality at 9 months** between an intensified TBM treatment during first 2 months, with or without aspirin and the standard WHO treatment among adults with suspected TBM

Secondary: large list of clinical (clinical recovery, discharge, IRIS, immunological recovery, neurological sequels, etc), microbiological (culture conversion rates, HIV VL, etc), pharmacological (PK-PD substudies for LNZ, RIF and DTG) endpoints for different populations (stratified by TM degree, HIV status, and other variables)

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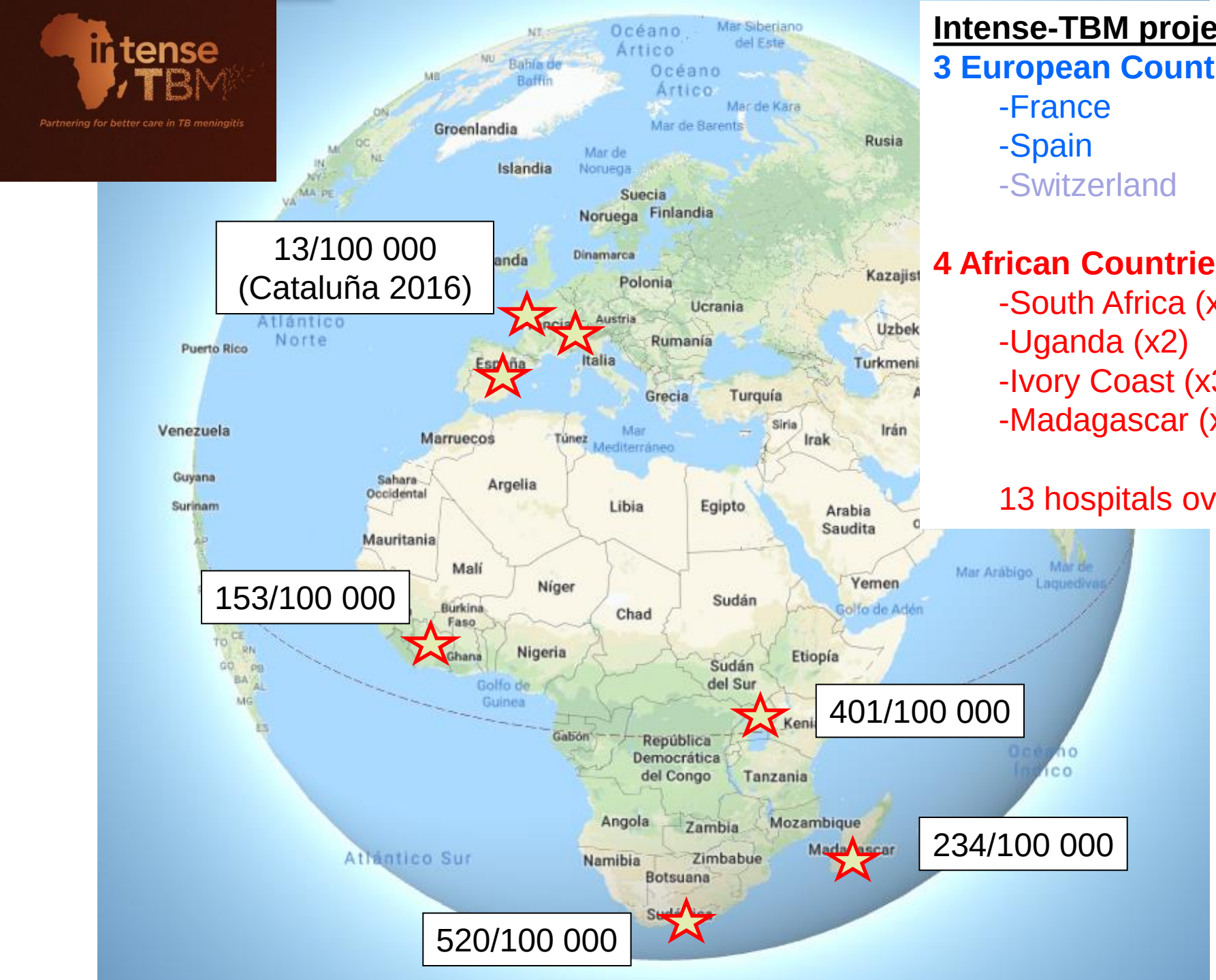
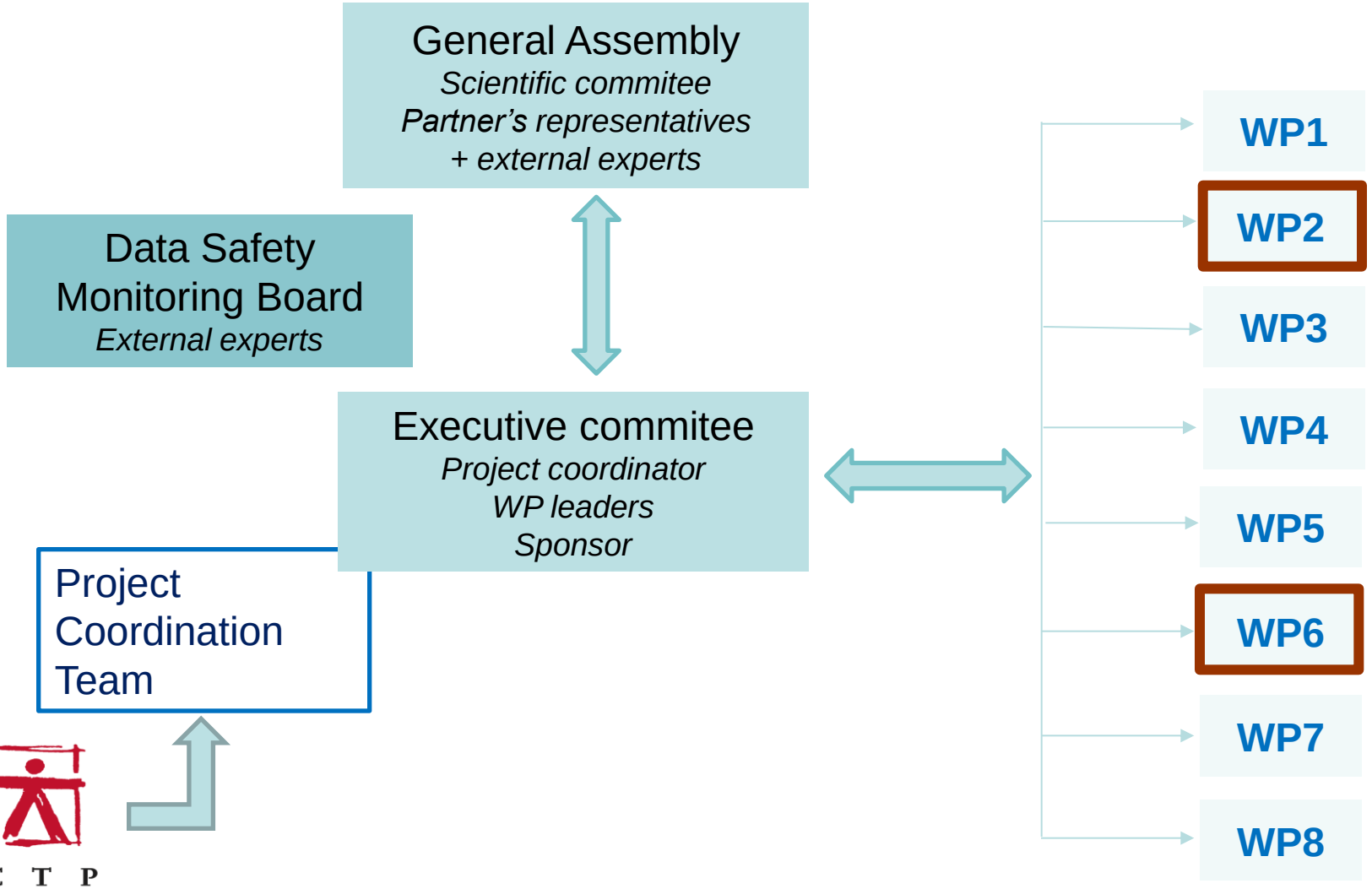
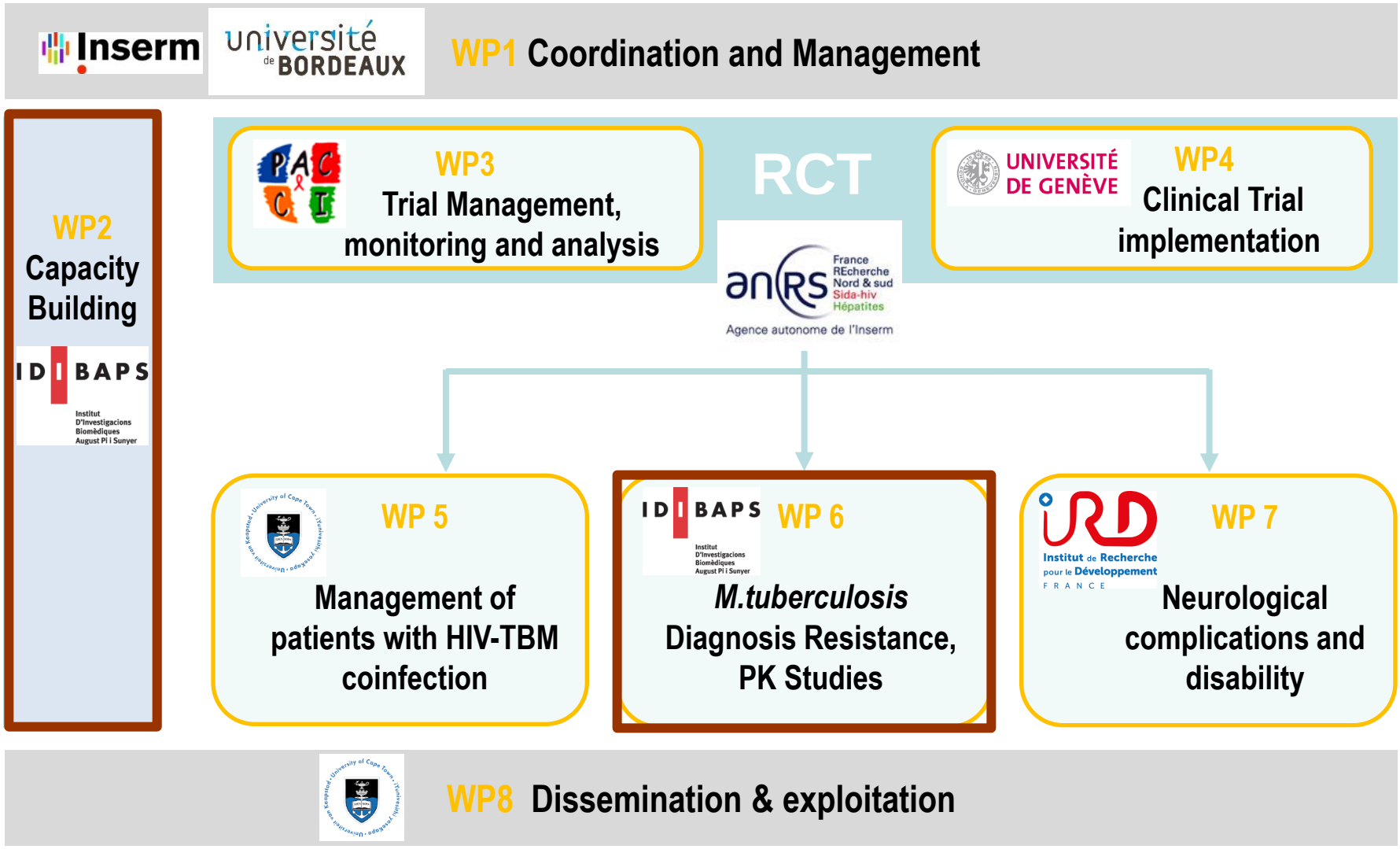

intense TBM
Partnering for better care in TB meningitis
13/100 000
(Cataluña 2016)
153/100 000
401/100 000
234/100 000
520/100 000
Intense-TBM project:
3 European Countries:
-France
-Spain
-Switzerland
4 African Countries:
-South Africa (x5)
-Uganda (x2)
-Ivory Coast (x3)
-Madagascar (x3)
13 hospitals overall

Governance



E D C T P

Work Packages



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WP2 – CAPACITY BUILDING

Coordination université de BORDEAUX

WP leader IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

Task 2.1
Set up clinical centers

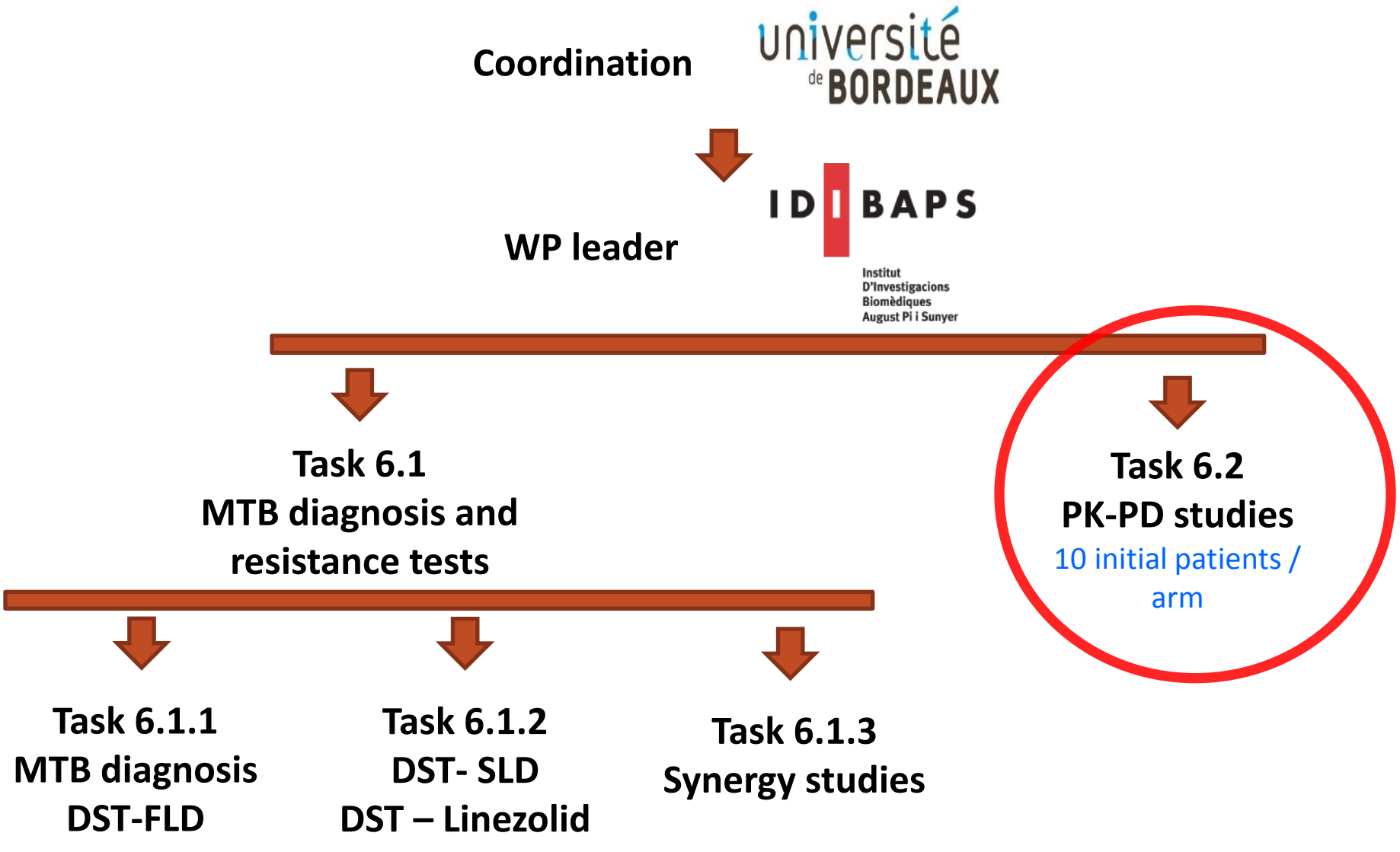
Task 2.2
Set up microbiology labs

Task 2.3
GCP and GCLP training

Task 2.4
IPC training

+ Additional trainings

WP6 - MTB diagnosis, drugs resistance, and PK studies



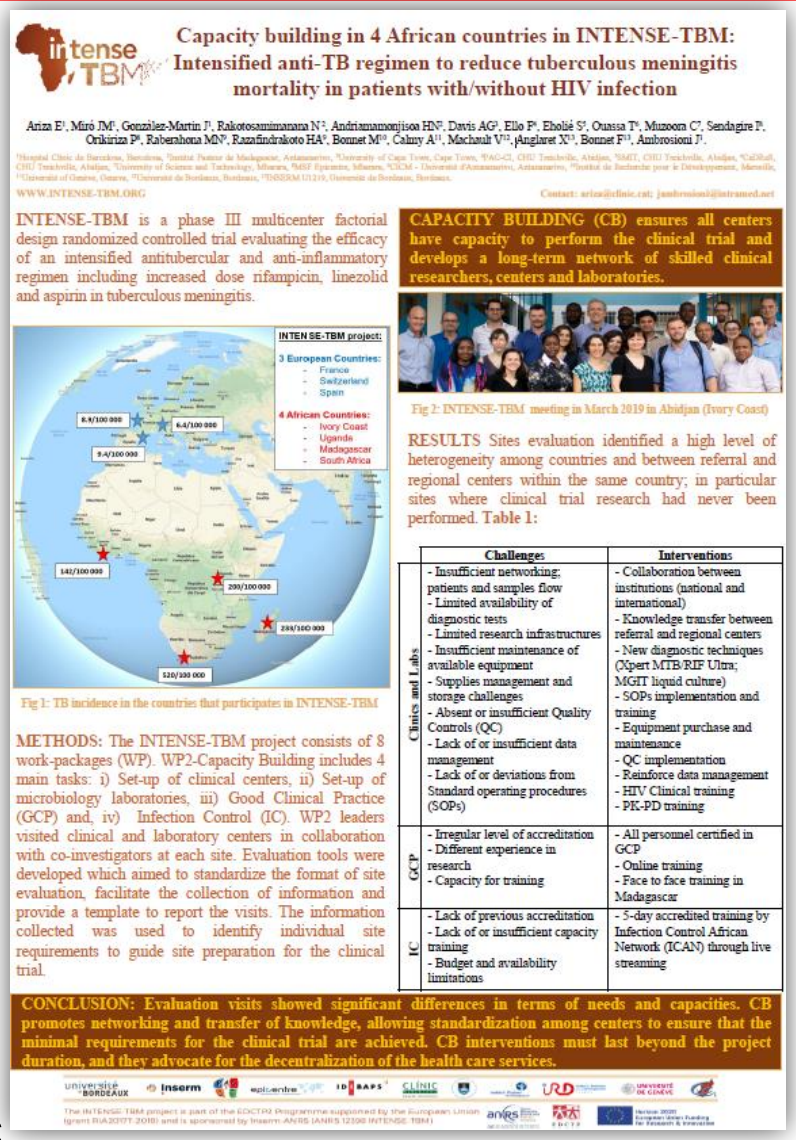
2019-2020:

WP2 – Capacity building
WP 3-4 – Protocol and CT preparation

- **Capacity Building:** huge challenge in terms of implementation (several centers have never performed a CT before, major techniques to get implemented), big differences between countries and centers

- **Hard to deal with COVID-19…**

- **Now ready to go:** RCT starting this week in Ivory Coast and starting between December and January in the other three countries



Capacity building in 4 African countries in INTENSE-TBM: Intensified anti-TB regimen to reduce tuberculous meningitis mortality in patients with/without HIV infection

Ariza E[1], Miró JM[2], Gonzalez-Martin J[3], Rakotosaunimanana N[4], Andriamamonjisoa HN[5], Davis AG[6], Ello F[6], Eholié S[7], Ouassa T[8], Muzoora C[9], Sendagire J[9], Orikiiriza J[9], Raberahona MN[10], Razafindrakoto HA[10], Bonnet M[10], Calmy A[11], Machault V[12],[Anglaret X[13], Bonnet F[13], Ambrosioni J[2].

WWW.INTENSE-TBM.ORG

INTENSE-TBM is a phase III multicenter factorial design randomized controlled trial evaluating the efficacy of an intensified antitubercular and anti-inflammatory regimen including increased dose rifampicin, linezolid and aspirin in tuberculous meningitis.

CAPACITY BUILDING (CB) ensures all centers have capacity to perform the clinical trial and develops a long-term network of skilled clinical researchers, centers and laboratories.

Fig 1: TB incidence in the countries that participates in INTENSE-TBM

Fig 2: INTENSE-TBM meeting in March 2019 in Abidjan (Ivory Coast)

METHODS: The INTENSE-TBM project consists of 8 work-packages (WP). WP2-Capacity Building includes 4 main tasks: i) Set-up of clinical centers, ii) Set-up of microbiology laboratories, iii) Good Clinical Practice (GCP) and, iv) Infection Control (IC). WP2 leaders visited clinical and laboratory centers in collaboration with co-investigators at each site. Evaluation tools were developed which aimed to standardize the format of site evaluation, facilitate the collection of information and provide a template to report the visits. The information collected was used to identify individual site requirements to guide site preparation for the clinical trial.

RESULTS Sites evaluation identified a high level of heterogeneity among countries and between referral and regional centers within the same country; in particular sites where clinical trial research had never been performed. Table 1:

	Challenges	Interventions
Clinics and Labs	- Insufficient networking; patients and samples flow - Limited availability of diagnostic tests - Limited research infrastructures - Insufficient maintenance of available equipment - Supplies management and storage challenges - Absent or insufficient Quality Controls (QC) - Lack of or insufficient data management - Lack of or deviations from Standard operating procedures (SOPs)	- Collaboration between institutions (national and international) - Knowledge transfer between referral and regional centers - New diagnostic techniques (Xpert MTB/RIF Ultra; MGIT liquid culture) - SOPs implementation and training - Equipment purchase and maintenance - QC implementation - Reinforce data management - HIV Clinical training - PK-PD training
GCP	- Irregular level of accreditation - Different experience in research - Capacity for training	- All personnel certified in GCP - Online training - Face to face training in Madagascar
IC	- Lack of previous accreditation - Lack of or insufficient capacity training - Budget and availability limitations	- 5-day accredited training by Infection Control African Network (ICAN) through live streaming

CONCLUSION: Evaluation visits showed significant differences in terms of needs and capacities. CB promotes networking and transfer of knowledge, allowing standardization among centers to ensure that the minimal requirements for the clinical trial are achieved. CB interventions must last beyond the project duration, and they advocate for the decentralization of the health care services.

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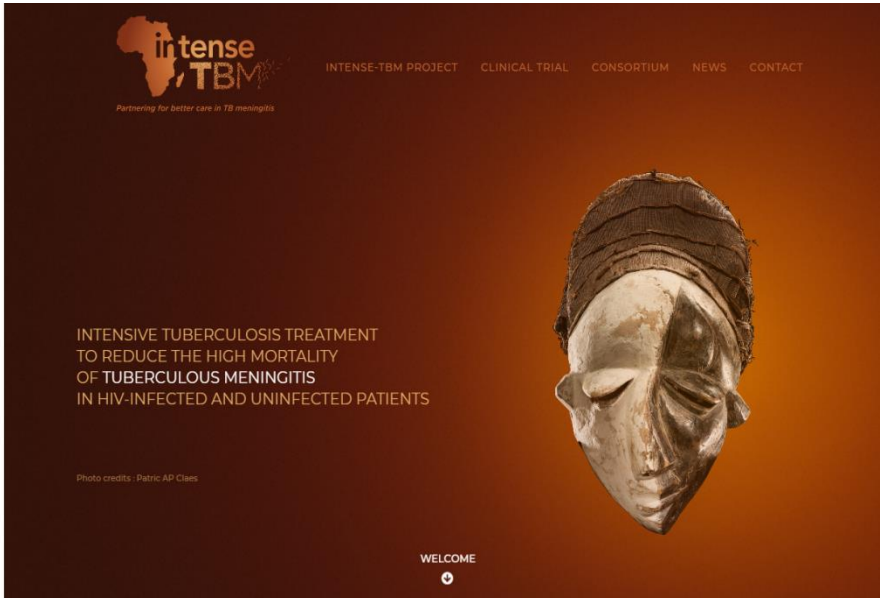
Take-home messages

- TM remains a disease with extremely high morbidity and mortality
- TM treatment has remained unchanged for decades
- Large trials have failed to prove the benefit of quinolones
- **Phase II studies suggest a role and potential improvement with much higher doses of R, of LNZ and of AAS**
- **Never tested together, to be evaluated in INTENSE-TBM as a large phase III RCT in 13 centers in 4 African centers…**
- **Looking forward to start and see…**

Thank you very much for your attention!!!!

www.intense-tbm.org



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