19es Journées Nationales d'Infectiologie
du mercredi 13 au vendredi 15 juin 2018
Cité des Congrès de Nantes
Nantes
et la région Pays de la Loire

Comment améliorer la prise en charge de la tuberculose chez les patients immunodéprimés ?

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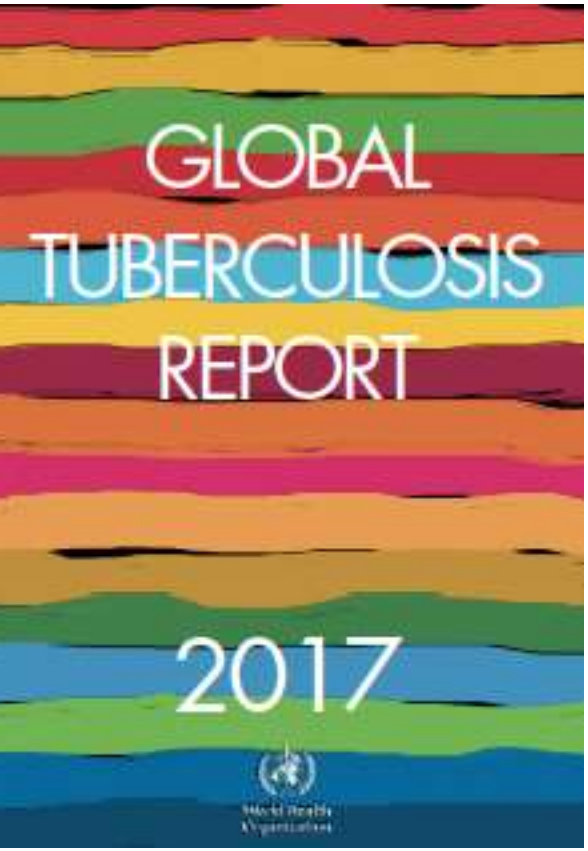
Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : BLANC F.Xavier

Titre : Comment améliorer la prise en charge de la tuberculose chez les patients immunodéprimés ?

- Consultant ou membre d'un conseil scientifique — ☐ OUI ☑ NON
- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents — ☐ OUI ☑ NON
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations — ☐ OUI ☑ NON
- Investigateur principal d'une recherche ou d'une étude clinique — ☐ OUI ☑ NON



World Health Organization

- **10,4 millions de cas incidents [8,8-12,2], incl. 0,58 million de TB multirésistantes [0,52-0,64]**

- **10% [8-12] des cas de TB surviennent chez des personnes vivant avec le VIH**

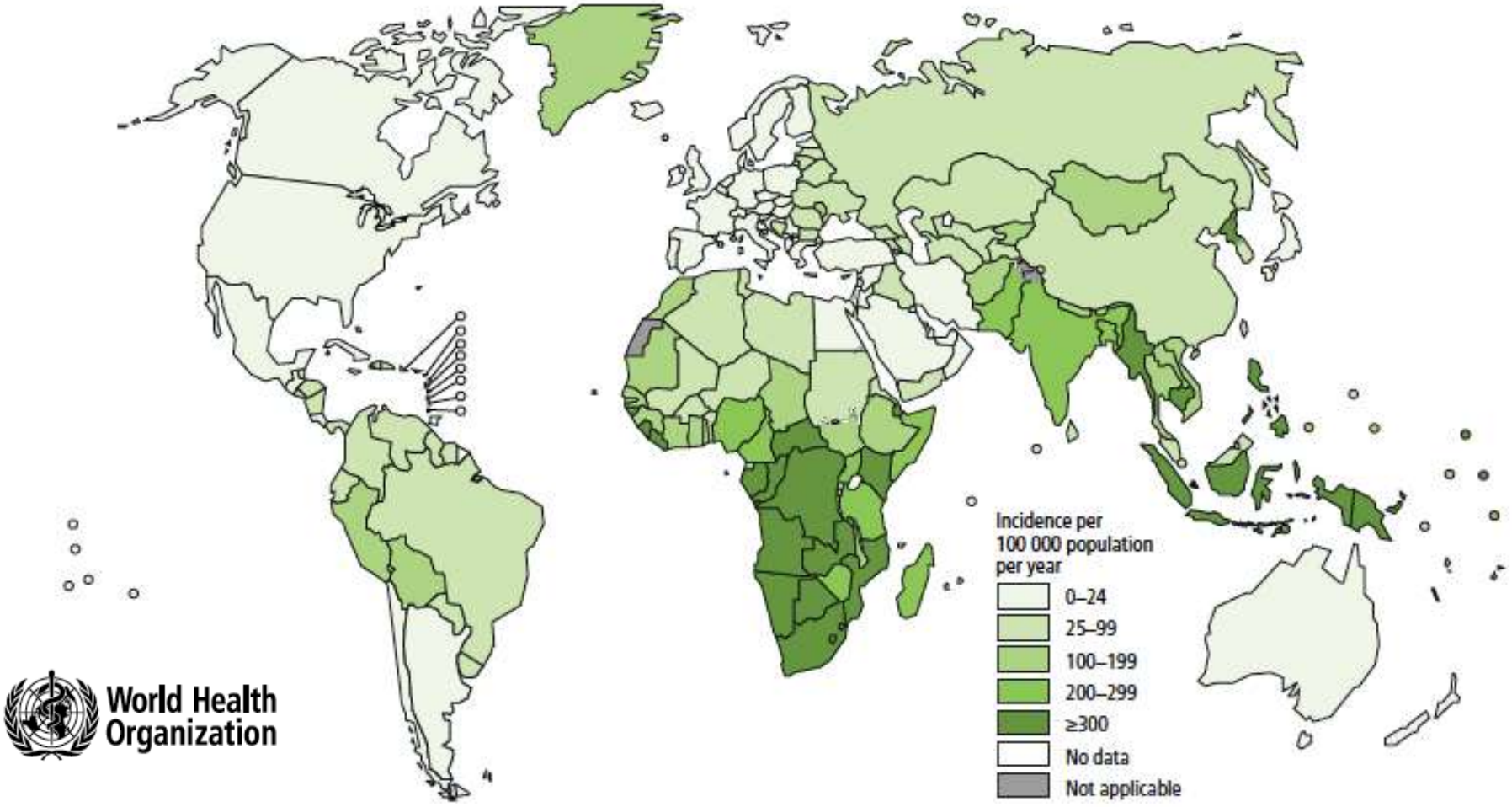
Géographie :

- **Asie du Sud-Est : 45%, Afrique : 25%**
- **45% des cas : Chine + Inde + Indonésie**

Mortalité :

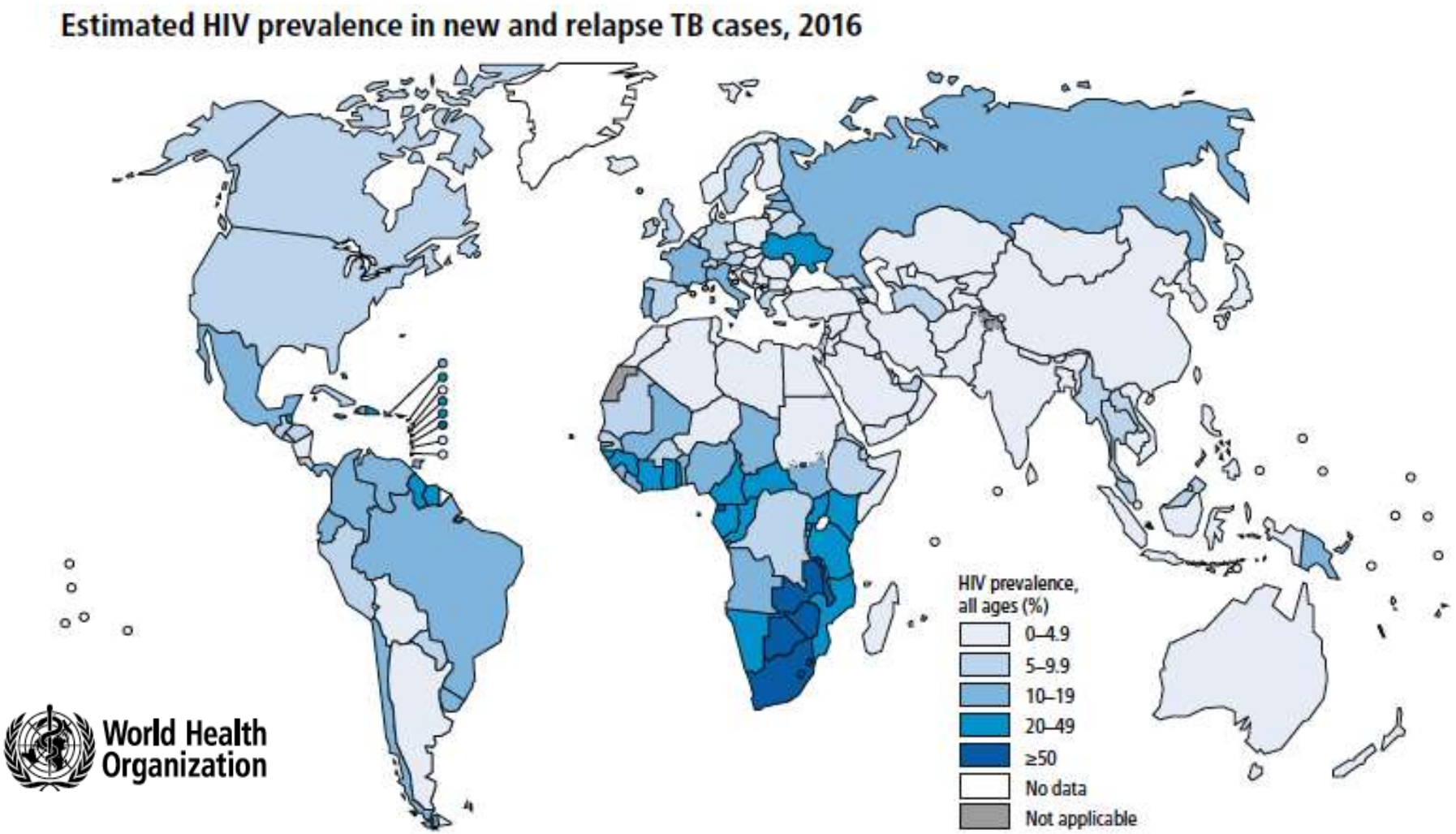
- **VIH-neg. : 1,30 million [1,16-1,44]**
- **VIH-pos. : 0,37 million [0,32-0,43]→ 22%**

Estimated TB incidence rates, 2016



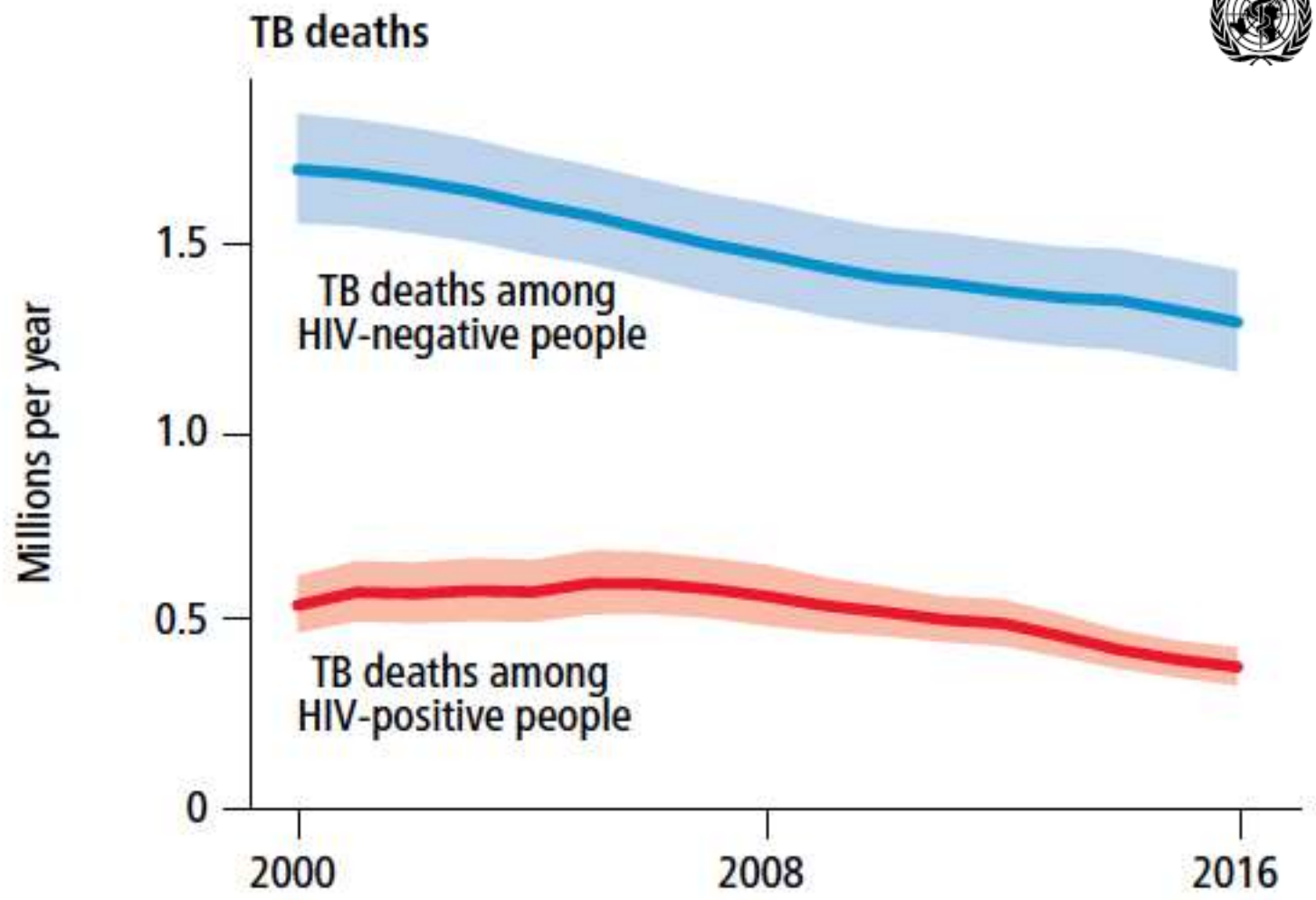
WHO Global tuberculosis report 2017

Prévalence de l'infection à VIH en cas de TB, 2016



WHO Global tuberculosis report 2017

Mortalité liée à la tuberculose, 2000-2016



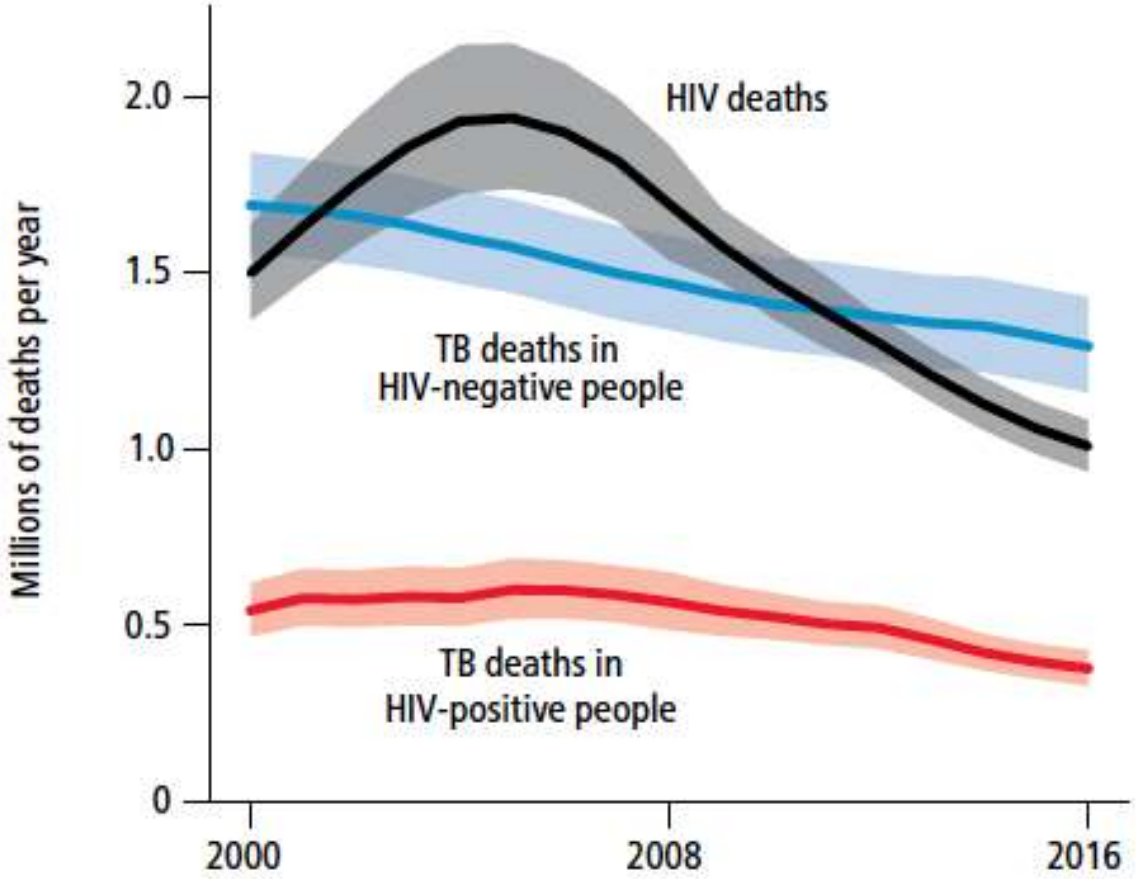
World Health Organization

WHO Global tuberculosis report 2017

Mortalité liée à la tuberculose et au VIH, 2000-2016

Global trends in the estimated number of deaths caused by TB and HIV (in millions), 2000–2016.[a,b]
Shaded areas represent uncertainty intervals.

World Health Organization

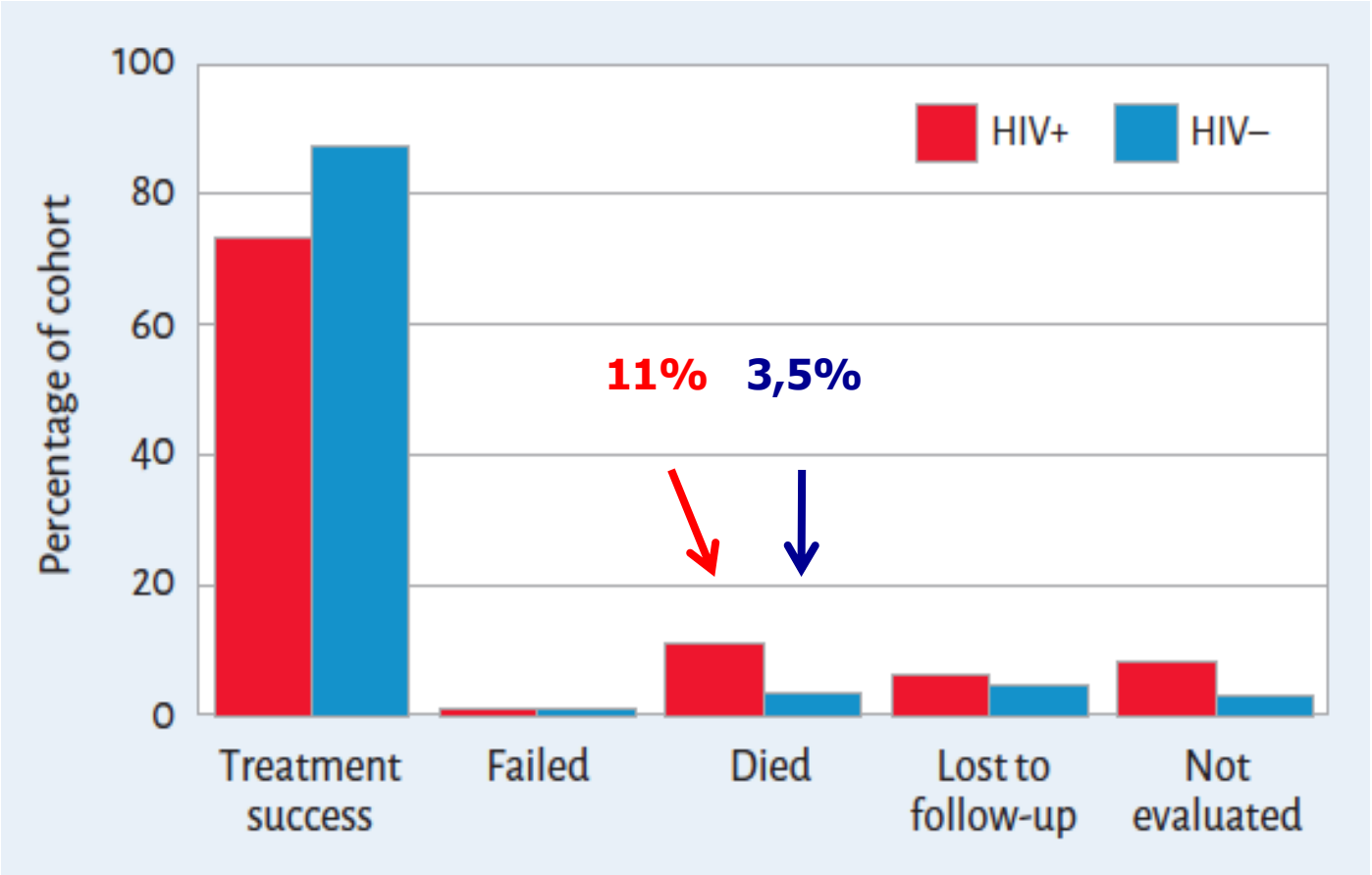


WHO Global tuberculosis report 2017

Devenir de cohortes de patients tuberculeux

Données 2013

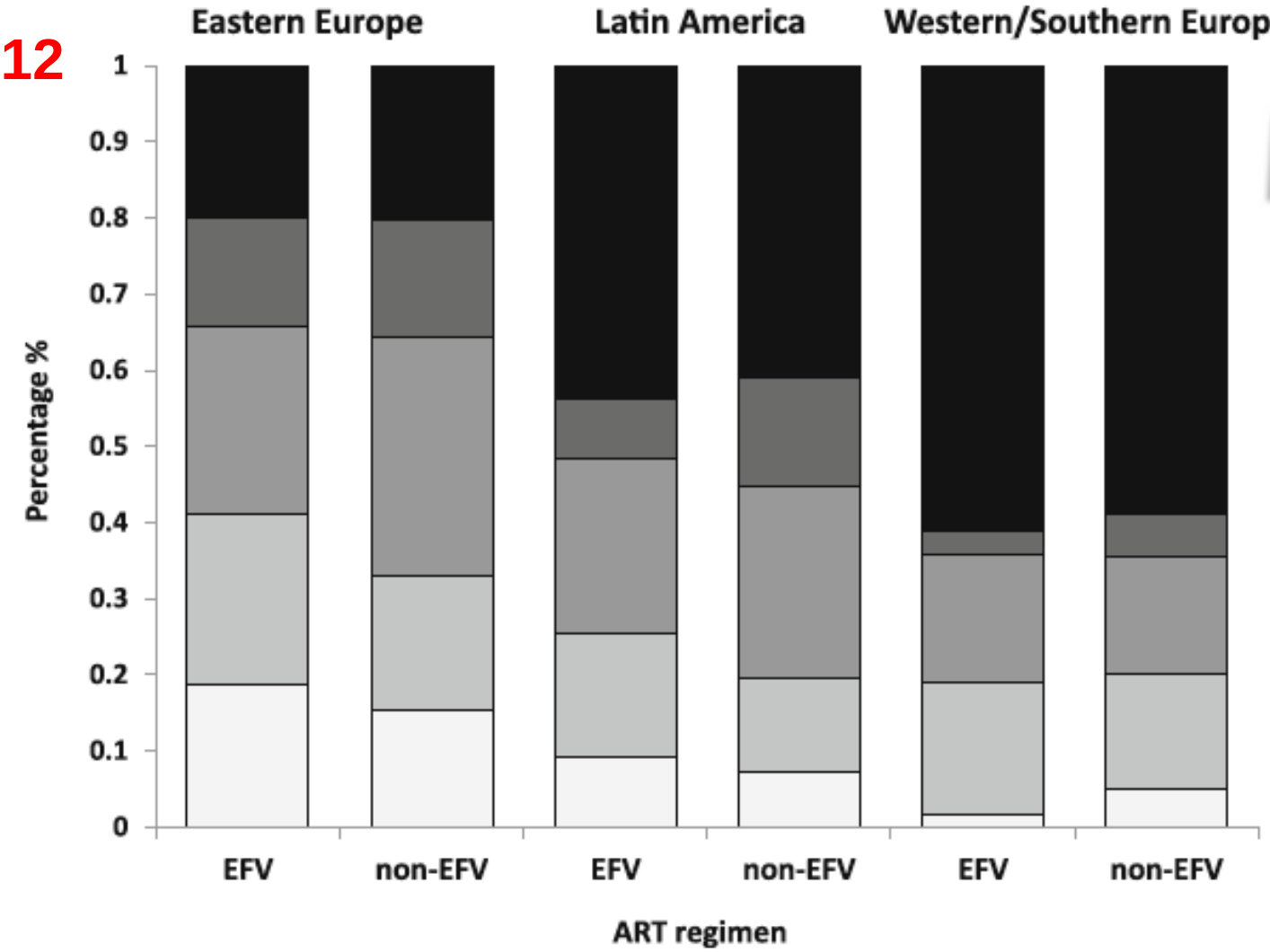
World Health Organization



WHO Global tuberculosis report 2015

Devenir de cohortes de patients VIH+ tuberculeux

M12

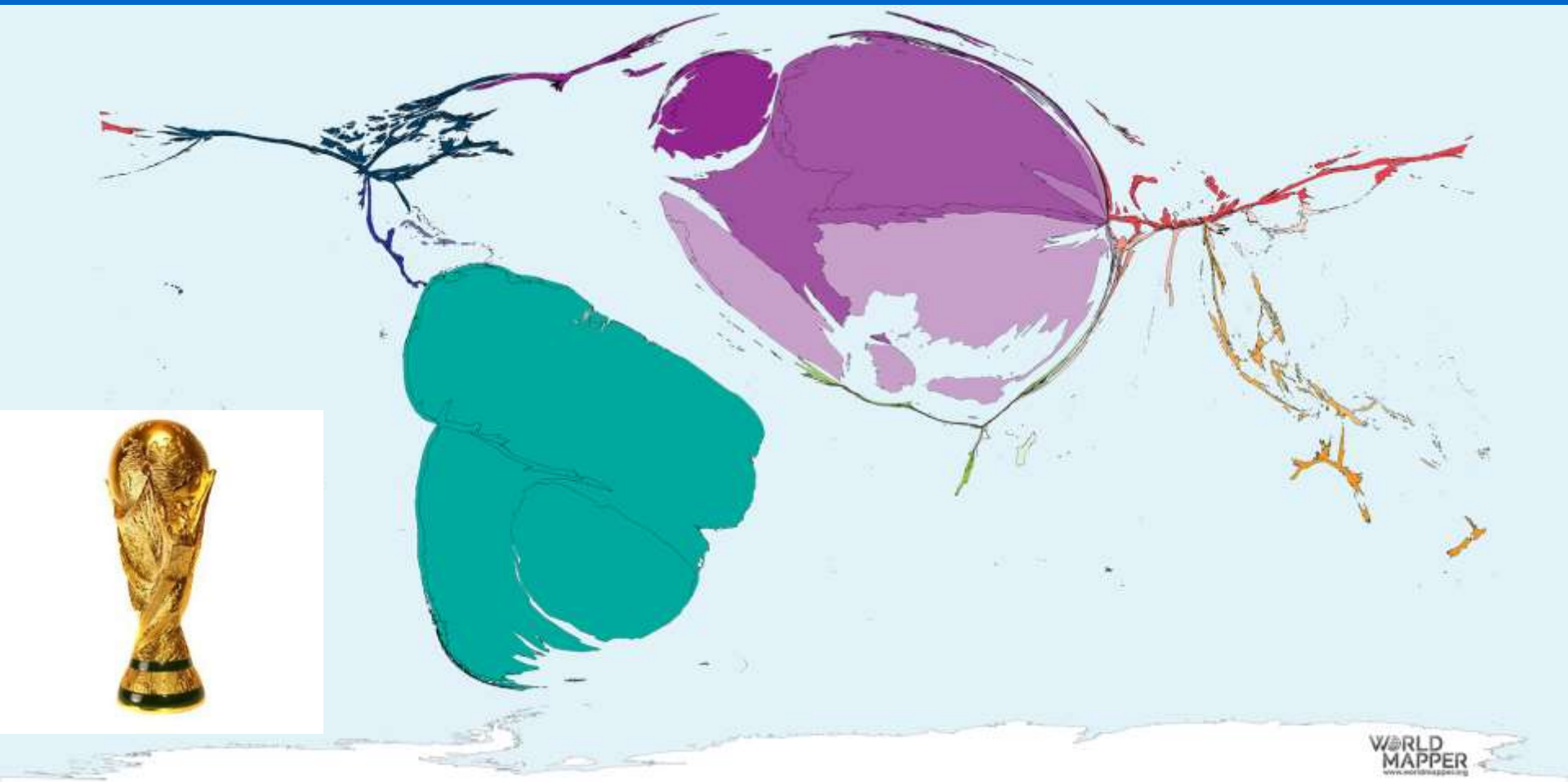


BMC

Undetectable:
VL<400 copies/ml

Caro-Vega *et al. BMC Infectious Diseases* (2018) 18:191

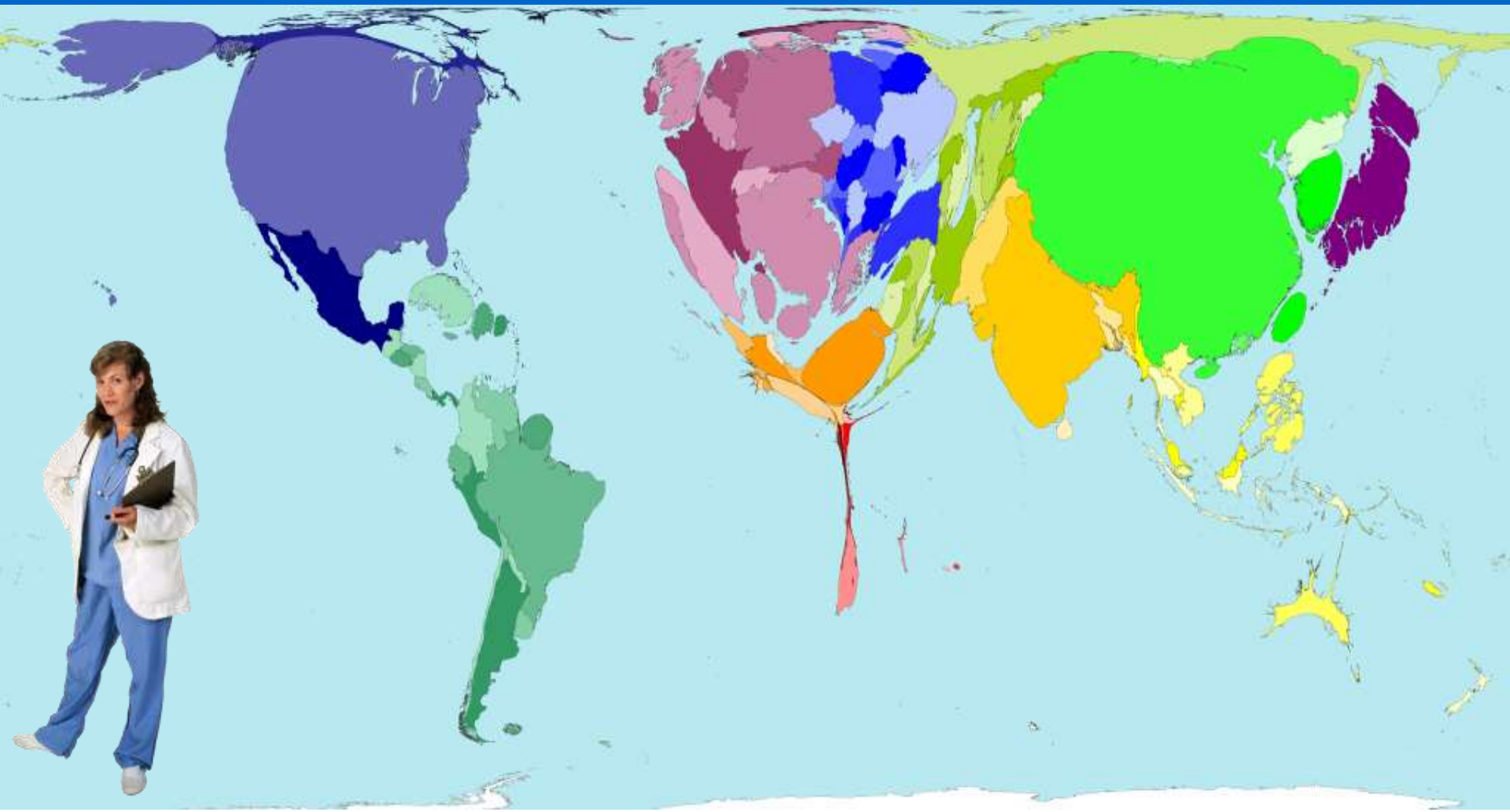
Dans quel type de monde vivons-nous ???



VAINQUEURS DE LA COUPE DU MONDE DE FOOTBALL (1930-2014)

https://worldmapper.org/maps/football-world-cup-wins-1930t2014/

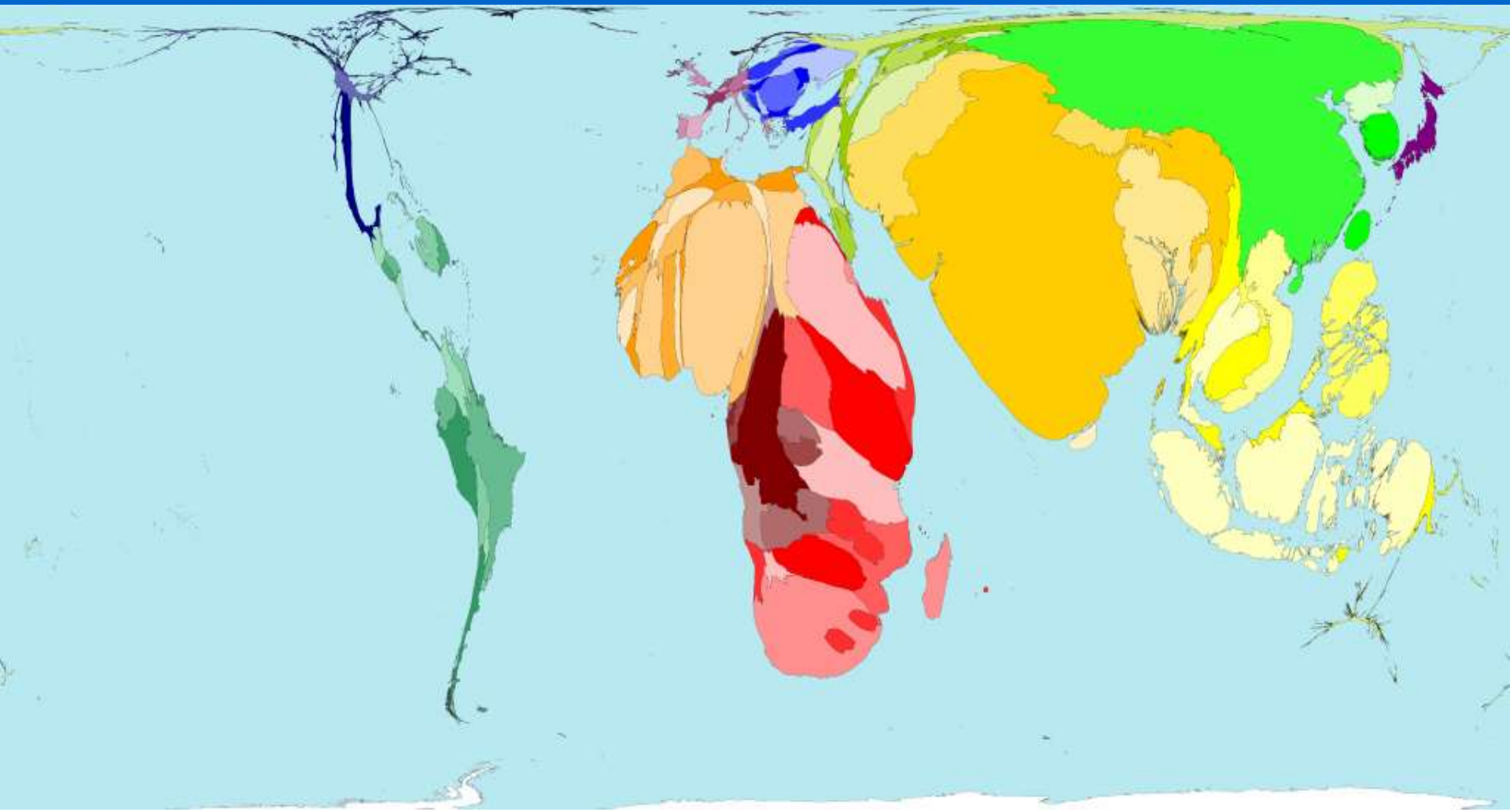
Dans quel type de monde vivons-nous ???



DENSITÉ MÉDICALE

Territory size shows the proportion of all physicians (doctors) that work in that territory (map #219, worldmapper.org)

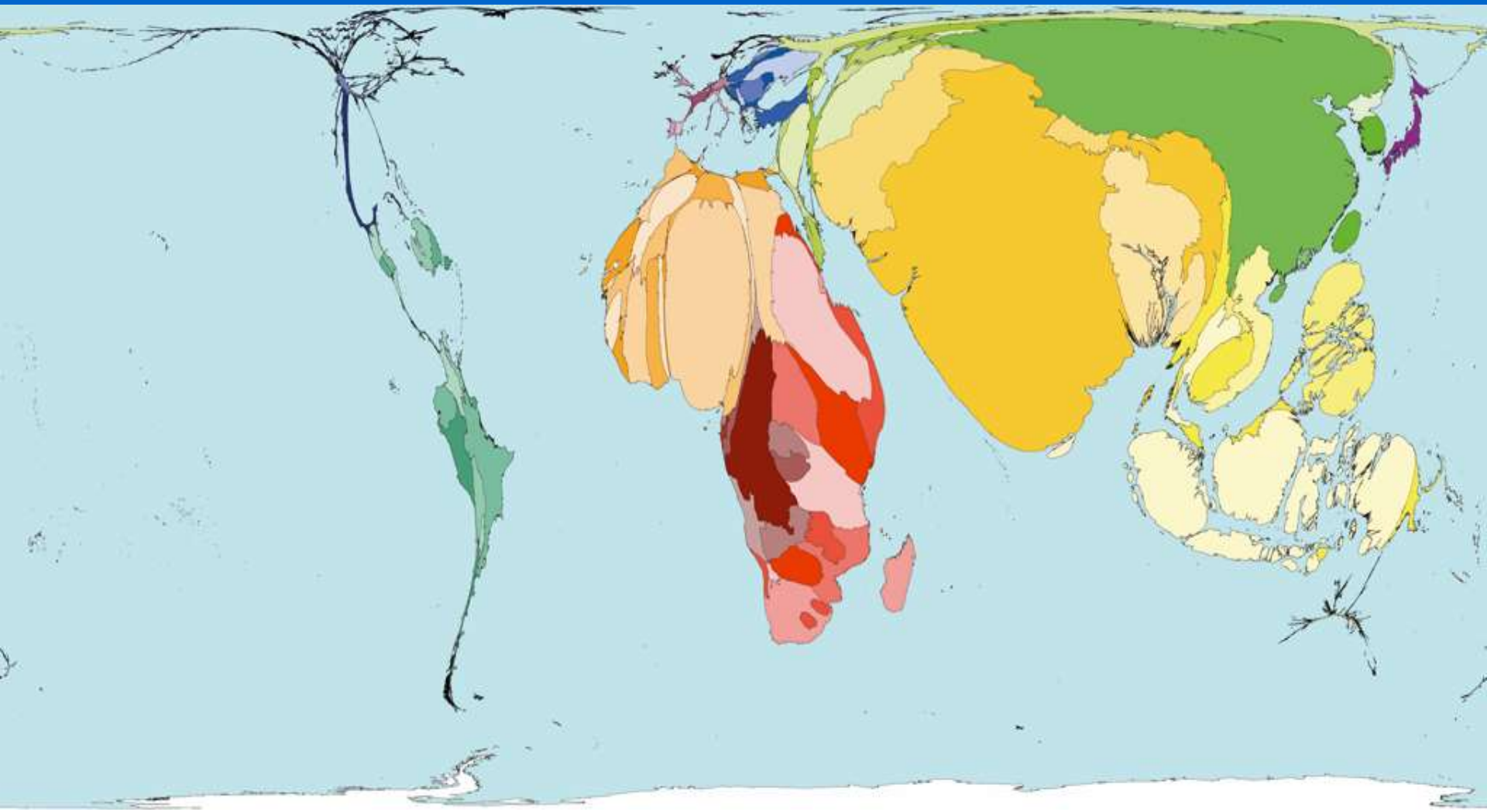
Dans quel type de monde vivons-nous ???



CAS DE TUBERCULOSE

Territory size shows the proportion of worldwide tuberculosis cases found there (map #228, worldmapper.org)

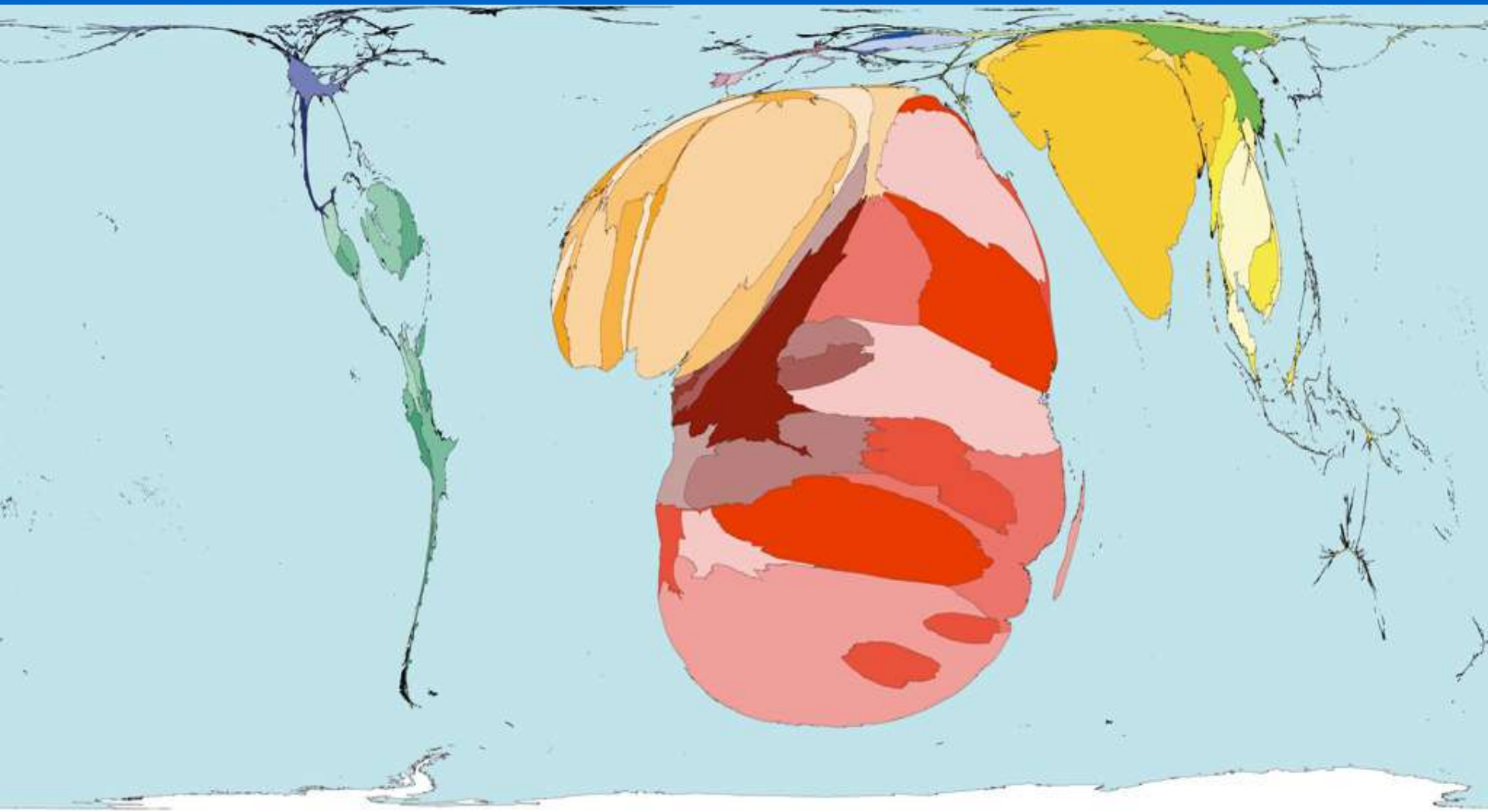
Dans quel type de monde vivons-nous ???



DÉCÈS LIÉS À LA TUBERCULOSE

Territories are sized in proportion to the absolute number of people who died from TB in one year (map #373, worldmapper.org)

Dans quel type de monde vivons-nous ???



DÉCÈS LIÉS AU VIH/SIDA

Territories are sized in proportion to the absolute number of people who died from HIV/AIDS in one year (map #374, worldmapper.org)

La tuberculose dans le monde où nous vivons

- **Mortalité importante liée à la tuberculose chez les PVVIH, notamment en Afrique sub-saharienne**
- **Autres formes d'immunodépression : également concernées +++**
- **Comment améliorer la prise en charge de la tuberculose chez les patients immunodéprimés ?**
  - **En réduisant le risque du passage de l'infection à la maladie**
  - **En améliorant le diagnostic (particularités de l'imagerie, nouveaux tests…)**
  - **En discutant de nouvelles modalités de traitement**
- **Exemple de la transplantation d'organe solide…**

Imagerie de ransplantés

20 TB pulm. ch il (1990-2015)

HRC	Lung zone
Ground-glass attenuation w	per lobes (in 50.0%)
Cavitation and centrilobula pattern	per lobes (in 66.6%)
Mediastinal lymph node enl	N/A
Miliary nodules	Random
All	N/A

Table 3. Chest X-ray and chest CT findings in kidney transplant recipients.

Finding	X-ray	CT	n	%
Ground-glass opacity/ consolidations	0	9	9	9.38
Cavitation/tree-in-bud pattern	5	29	34	35.4
Mediastinal lymph node enlargement	6	8	14	14.6
Miliary pattern	1	22	23	24
Pleural effusion	11	5	16	16.7
Total	23	73	96	100

*Data are expressed as n (%).

Table 2. Chest X-ray and chest CT findings in lung transplant recipients.

Finding	X-ray	CT	n	%
Ground-glass opacity/ consolidations	1	9	10	18.9
Cavitation/tree-in-bud pattern	24	11	35	66.0
Mediastinal lymph node enlargement	0	4	4	7.5
Miliary pattern	0	2	2	3.8
Pleural effusion	2	0	2	3.8
Total	27	26	53	100

Table 4. Chest X-ray and chest CT findings in liver transplant recipients.

Finding	X-ray	CT	n	%
Ground-glass opacity/ consolidations	0	1	1	1.4
Cavitation/tree-in-bud pattern	0	47	47	67.2
Mediastinal lymph node enlargement	0	10	10	14.3
Miliary pattern	0	12	12	17.1
Total	0	70	70	100

J Bras Pneumol. 2018;44(2):161-166

Tuberculose chez les patients transplantés

- Revue de la littérature 1998-2016
- 187 études
- 2082 cas de TB après transplantation d'organe solide
- Asie : n=72; Europe : n=66; Etats-Unis : n=25
- 1719 transplantés rénaux
- 253 transplantés hépatiques
- 77 transplantés cardiaques
- 25 transplantés pulmonaires
- 8 transplantés rein-pancréas

Clinical Transplantation. 2018;e13259.

Tuberculose chez les patients transplantés

- Transplantés rénaux : incidence de TB = 1,69%
- Transplantés hépatiques : incidence de TB = 1,33%

- TB transmise par le donneur : 23 cas, dont 10 après greffe pulmonaire; 5 décès, dont 3 liés à la TB.
- Temps médian post-greffe : 3 mois (extrêmes : 0,2-29).

- Mortalité de la TB chez les patients transplantés : 18,84%

Clinical Transplantation. 2018;e13259.

Tuberculose chez les patients transplantés

- **Réactivation d'une ITL : mécanisme de loin le + fréquent**
- **40% des cas durant les 12 mois suivant la greffe**
- **Seuls 36/140 (26%) patients ont reçu une chimioprophylaxie par isoniazide, dont 20 après la transplantation**

Clinical Transplantation. 2018;e13259.

Isoniazid versus no treatment for preventing post solid organ transplant tuberculosis

Patient or population: kidney transplant recipients
Settings: hospital
Intervention: isoniazid versus no treatment

Cochrane Library
Cochrane Database of Systematic Reviews

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Isoniazid				
Tuberculosis Follow-up: 2 to 4 years	Study population		RR 0.35 (0.14 to 0.89)	558 (3)	⊕⊕⊕○ moderate[1]	All studies conducted in kidney transplant population
	159 per 1000	45 per 1000 (22 to 86)				
	Moderate					
	259 per 1000	80 per 1000 (40 to 149)				
INH hepatotoxicity Jaundice, elevated bilirubin, elevated liver enzymes Follow-up: 2 to 4 years	Study population		RR 1.59 (1.06 to 2.40)	558 (3)	⊕⊕⊕○ moderate[2]	Almost all reported hepatotoxicity (45/47) were from one study which had high prevalence of patients with hepatitis B and C infection
	58 per 1000	145 per 1000 (70 to 277)				
	Moderate					
	0 per 1000	0 per 1000 (0 to 0)				
All-cause mortality Follow-up: 2 to 4 years	Study population		RR 1.39 (0.7 to 2.78)	558 (3)	⊕⊕○○ low[2,3]	One of the three studies (largest study) reported no mortality

Adamu B, Abdu A, Abba AA, Borodo MM, Tleyjeh IM.
Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis.
Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD008597.

Summary of main results

A statistically significant lower risk of developing TB was reported among kidney transplant recipients who received anti-TB prophylaxis (isoniazid). However, liver dysfunction was statistically significant among participants who received anti-TB prophylaxis compared with people in the control groups. Most reported liver dysfunction was mild and transient; 45/47 events were reported by Vikrant 2005 which included a significant proportion (~25%) of participants with hepatitis B or C infection. Sensitivity analysis excluding this study yielded no statistically significant difference in the incidence of anti-TB drug hepatotoxicity.

All-cause mortality was not significantly different between those who received anti-TB prophylaxis and those who did not.

Adamu B, Abdu A, Abba AA, Borodo MM, Tleyjeh IM.
Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis.
Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD008597.

Haut Conseil de la Santé Publique

Enquête autour d'un cas de tuberculose

Recommandations pratiques

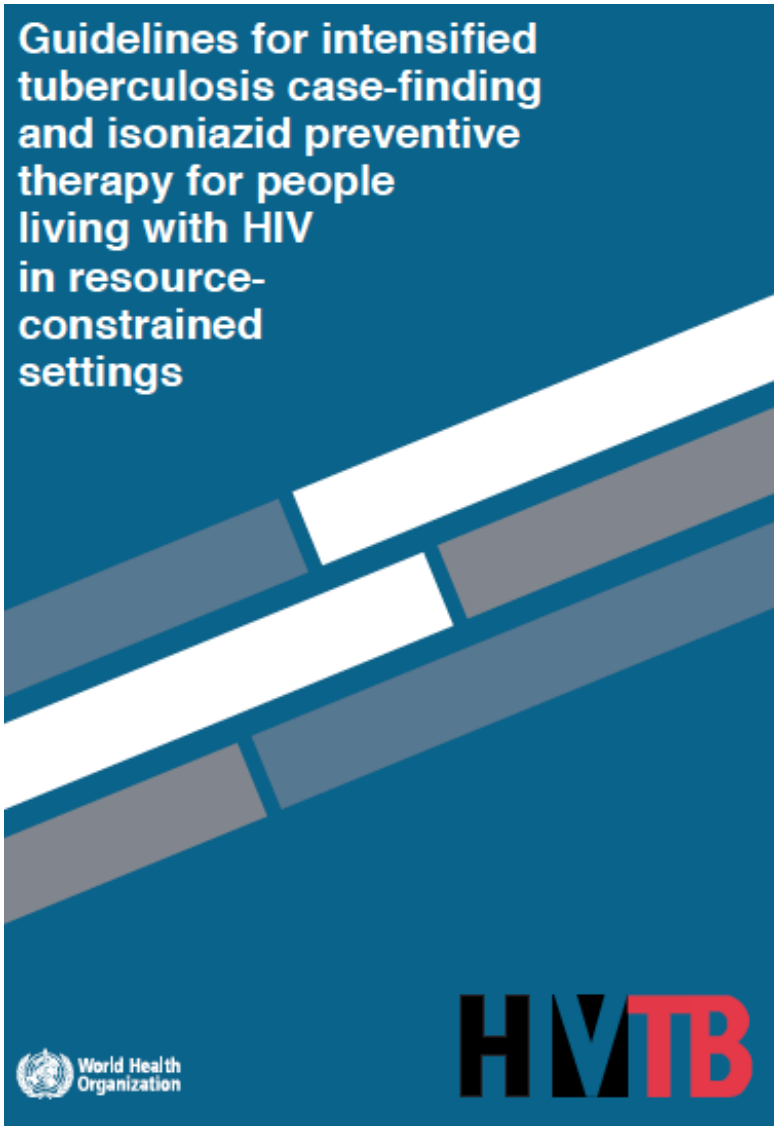
Collection
Avis et Rapports

Tableau 1 – Conditions augmentant le risque de progression vers la tuberculose maladie à partir d'une ITL
(Adaptation du tableau 2 de : Erkens CGM, *et al.* [3])

Conditions augmentant le risque de tuberculose maladie	Odds ratio ou Risque relatif
Déficit immunitaire avéré	
Infection à VIH	50-110
Sida	110-170
Greffe d'organe solide avec traitement immunosuppresseur	20-74
Traitement par anti-TNF-alpha	1,5-17
Corticostéroïdes >10 mg d'équivalent prednisone/jour pendant > 2-4 semaines [4]	4-9
Néoplasie	4-8
Hémopathie maligne (leucémie, lymphome)	16
Cancer de la tête, cou ou poumon	2,5-6,3
Autres situations	
Gastrectomie	2,5
Anastomose jéjuno-iléale	27 - 63
Silicose	30
Insuffisance rénale chronique / hémodialyse	10-25
Diabète sucré	2-3,6
Consommation de tabac	2-3
Consommation excessive d'alcool	3
Déficit pondéral	2,0-2,6
Age $\leq$ 5 ans	2-5

Note : Degré de preuves de niveau B ou C en général. TNF : le risque relatif (RR) ajusté concernant les corticostéroïdes pour le risque de tuberculose maladie n'a pas été établi de façon concluante. Le tableau a été adapté et mis à jour en se basant sur plusieurs sources

Chimioprophylaxie par isoniazide (IPT)



Réunion à Genève :
25-27 Jan. 2010

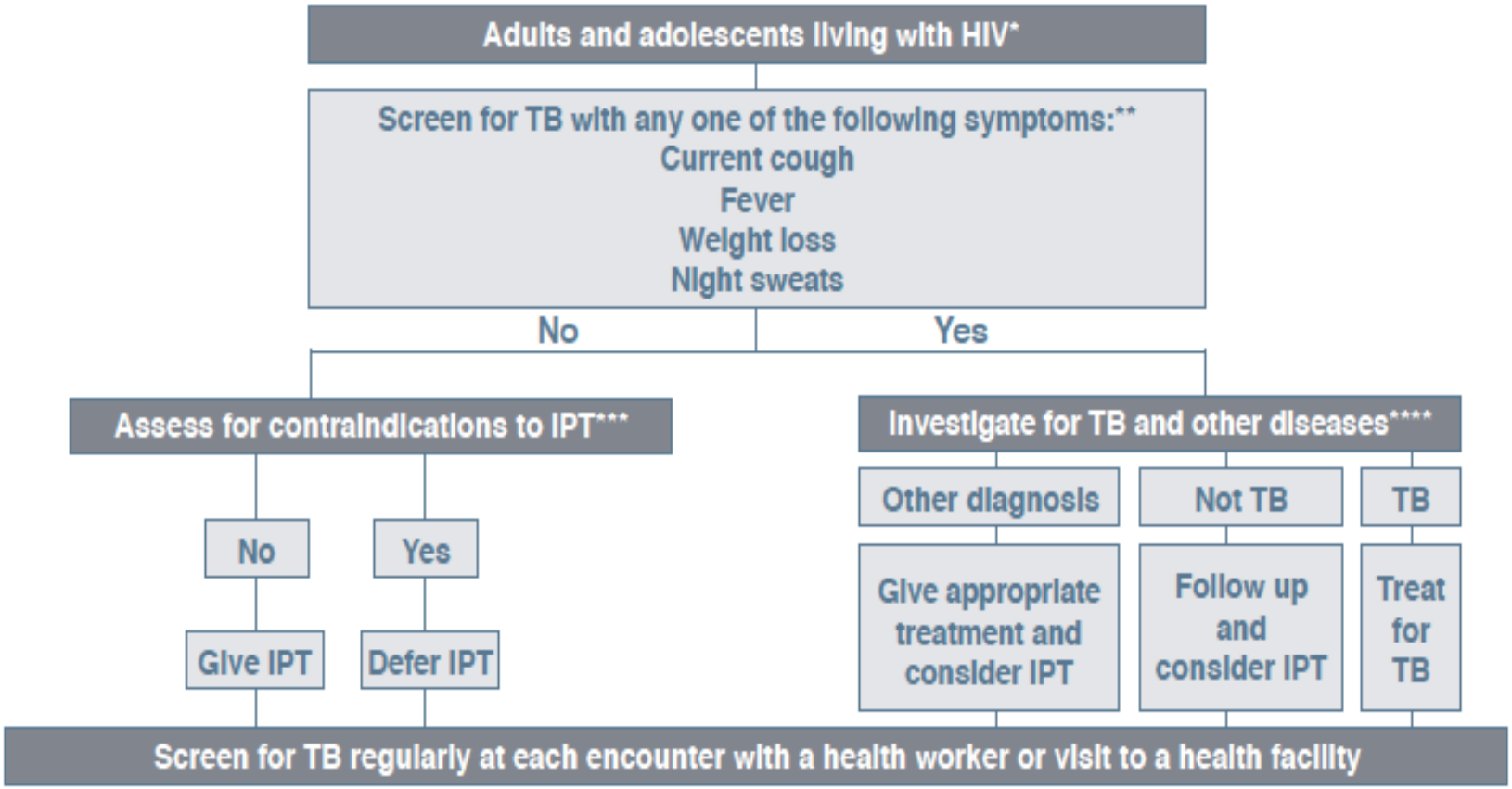
12 recommandations clés

7 pour les adultes
5 pour les enfants

World Health Organization

Dépistage de la TB avant de décider si IPT ou non

2.2.7 Figure 1. Algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



Recommandations OMS sur l'IPT en pays du Sud

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

Recommandations OMS sur l'IPT en pays du Sud

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

Essais publiés depuis les recommandations OMS

Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial

Molebogeng X Rangaka, Robert J Wilkinson, Andrew Boulle, Judith R Glynn, Katherine Fielding, Gilles van Cutsem, Katalin A Wilkinson, Rene Goliath, Shaheed Mathee, Eric Goemaere, Gary Maartens

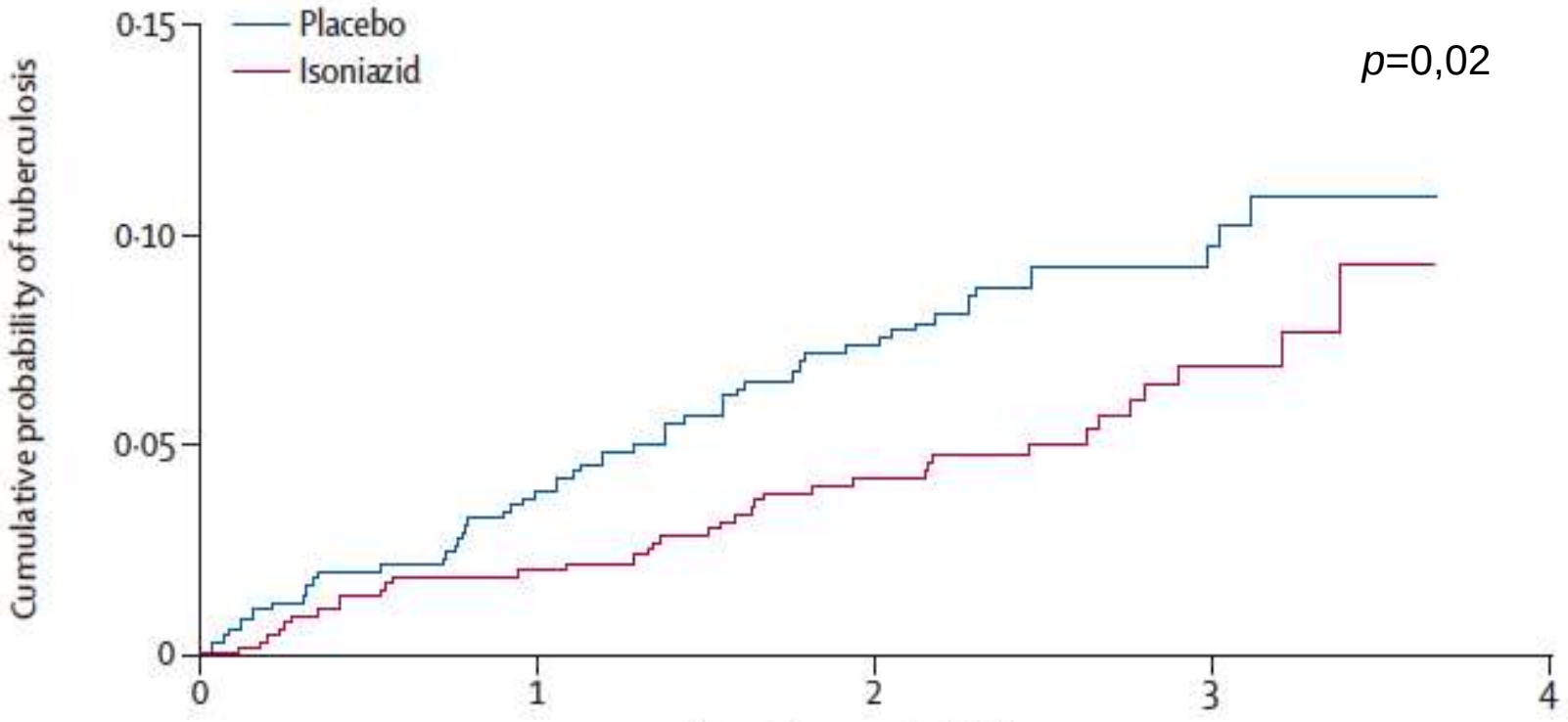
Lancet 2014; 384: 682–90

- Une clinique ARV en Afrique du Sud (Cape Town)
- Adultes recrutés entre janv. 2008 et sept. 2011
- TB maladie éliminée d'emblée (interrog. puis 2 crachats pour ex. direct et culture)
- **Randomisation entre 12 mois d'INH ou de placebo**
- **Critère de jugement principal : développement d'une TB active**
- Critères secondaires : temps jusqu'au décès; risque de développer des effets indésirables liés aux médicaments

	Placebo (n=667)	Isoniazid (n=662)	Total (n=1329)
Median age (years)	34 (29–40)	34 (30–40)	34 (30–40)
Women	498 (75%)	500 (76%)	998 (75%)
Established on ART	490 (74%)	462 (70%)	952 (72%)
Median days on ART, on- ART	330 (137–727)	394 (139–889)	357 (139–798)
Median days on ART, start- ART	14 (4–20)	14 (4–25)	14 (4–25)
Median CD4 count (cells per mm^3)*	214 (154–355)	218 (150–373)	216 (152–360)
Previous tuberculosis†	271 (41%)	289 (44%)	560 (43%)
TST			
Positive (≥5 mm)	202 (30%)	190 (29%)	392 (30%)
Negative (<5 mm)	283 (42%)	269 (41%)	552 (42%)
Unknown	182 (27%)	203 (31%)	385 (29%)
IGRA			
Positive	205 (31%)	184 (28%)	389 (29%)
Negative	261 (39%)	274 (41%)	535 (40%)
Indeterminate	38 (6%)	36 (5%)	74 (6%)
Unknown	163 (24%)	168 (25%)	331 (25%)
Discordant or concordant TST/IGRA pairs			
TST+/IGRA+	119 (18%)	115 (17%)	234 (18%)
TST–/IGRA–	190 (29%)	198 (30%)	388 (29%)
TST+/IGRA–	73 (11%)	66 (10%)	139 (11%)
TST–/IGRA+	64 (10%)	54 (8%)	118 (9%)
Unknown	221 (33%)	229 (35%)	450 (34%)

Lancet 2014; 384: 682–90

Critère de jugement principal



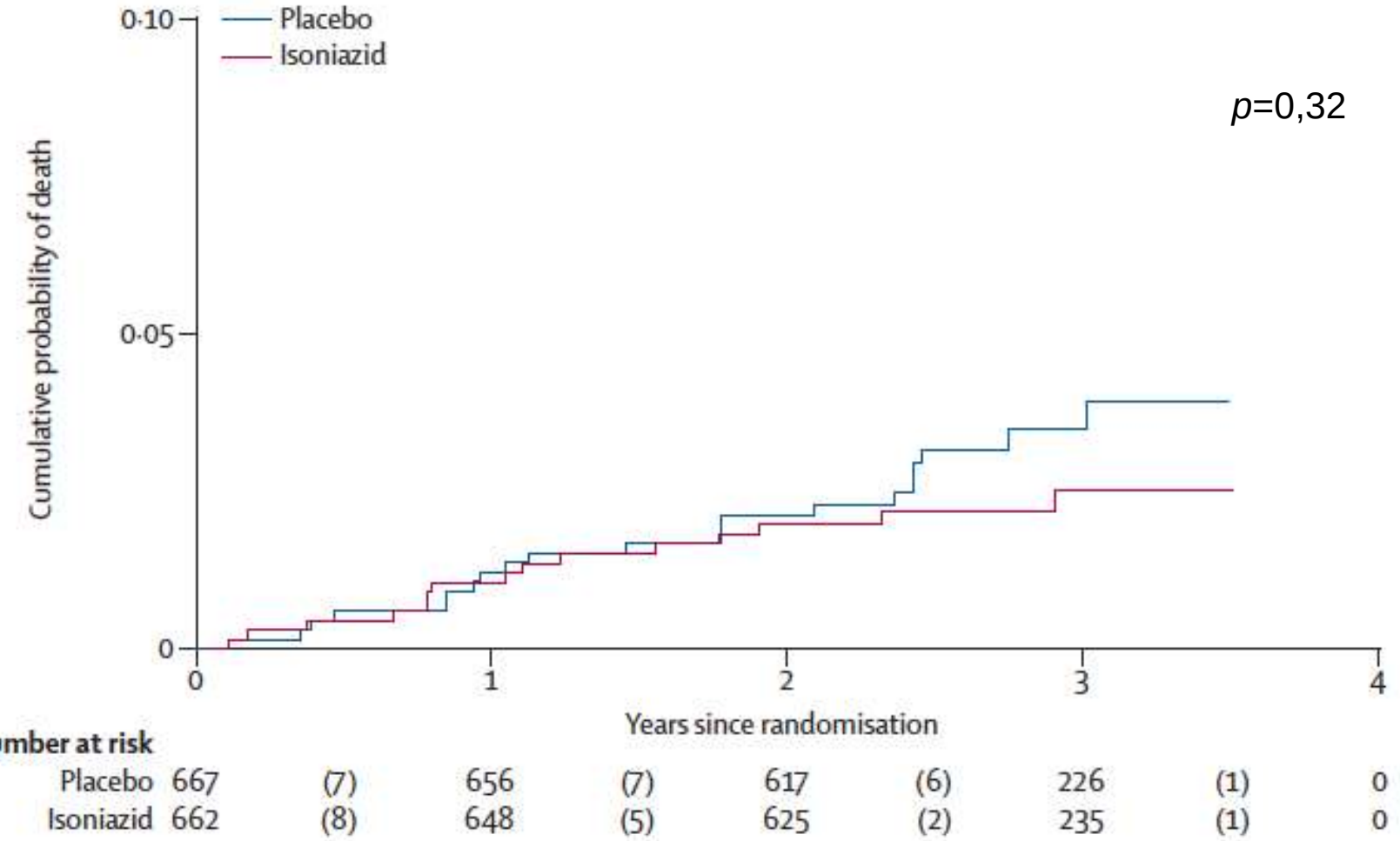
p=0,02

Number at risk

Placebo	667	(25)	601	(21)	521	(10)	181	(2)	0
Isoniazid	662	(13)	609	(13)	539	(9)	195	(2)	0

Lancet 2014; 384: 682–90

Critère de jugement secondaire



p=0,32

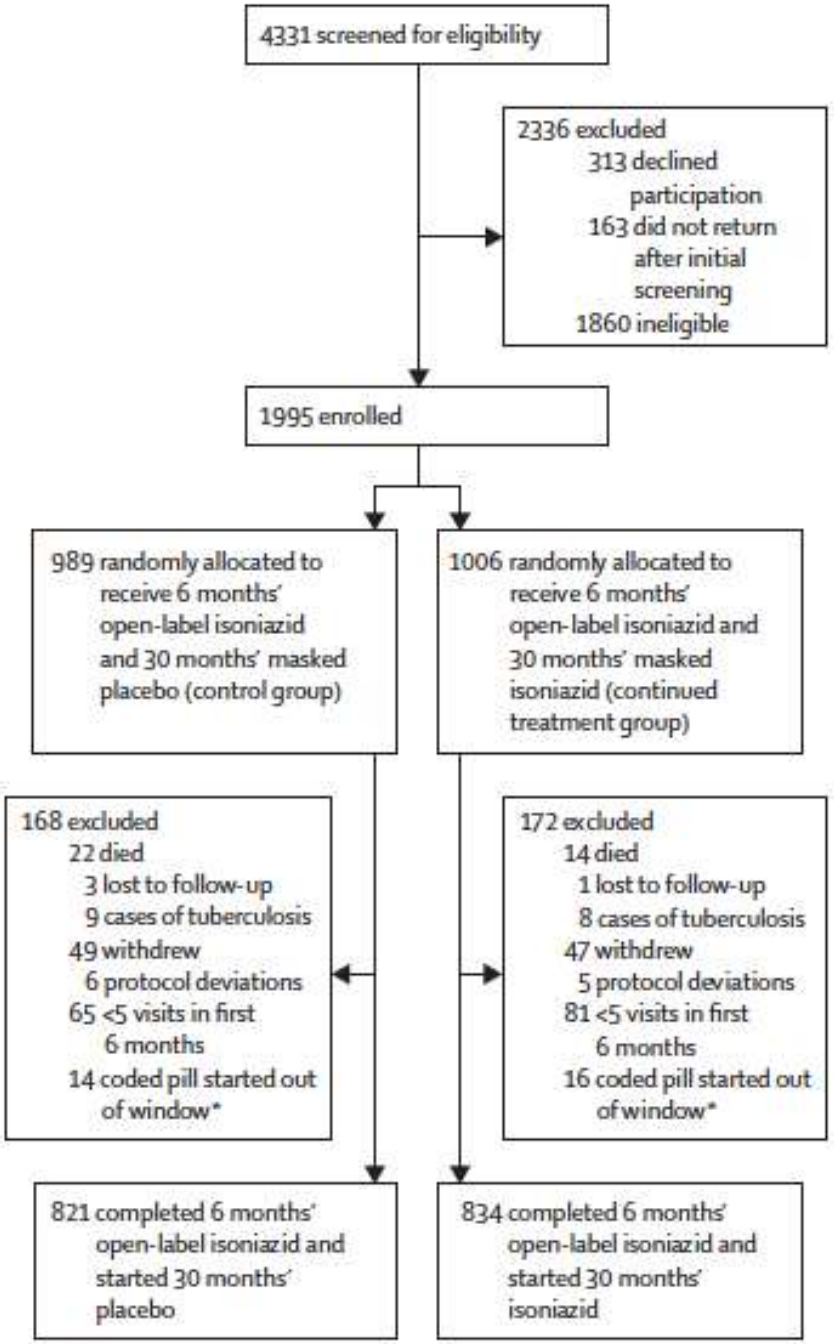
Lancet 2014; 384: 682–90

Essais publiés depuis les recommandations OMS

6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

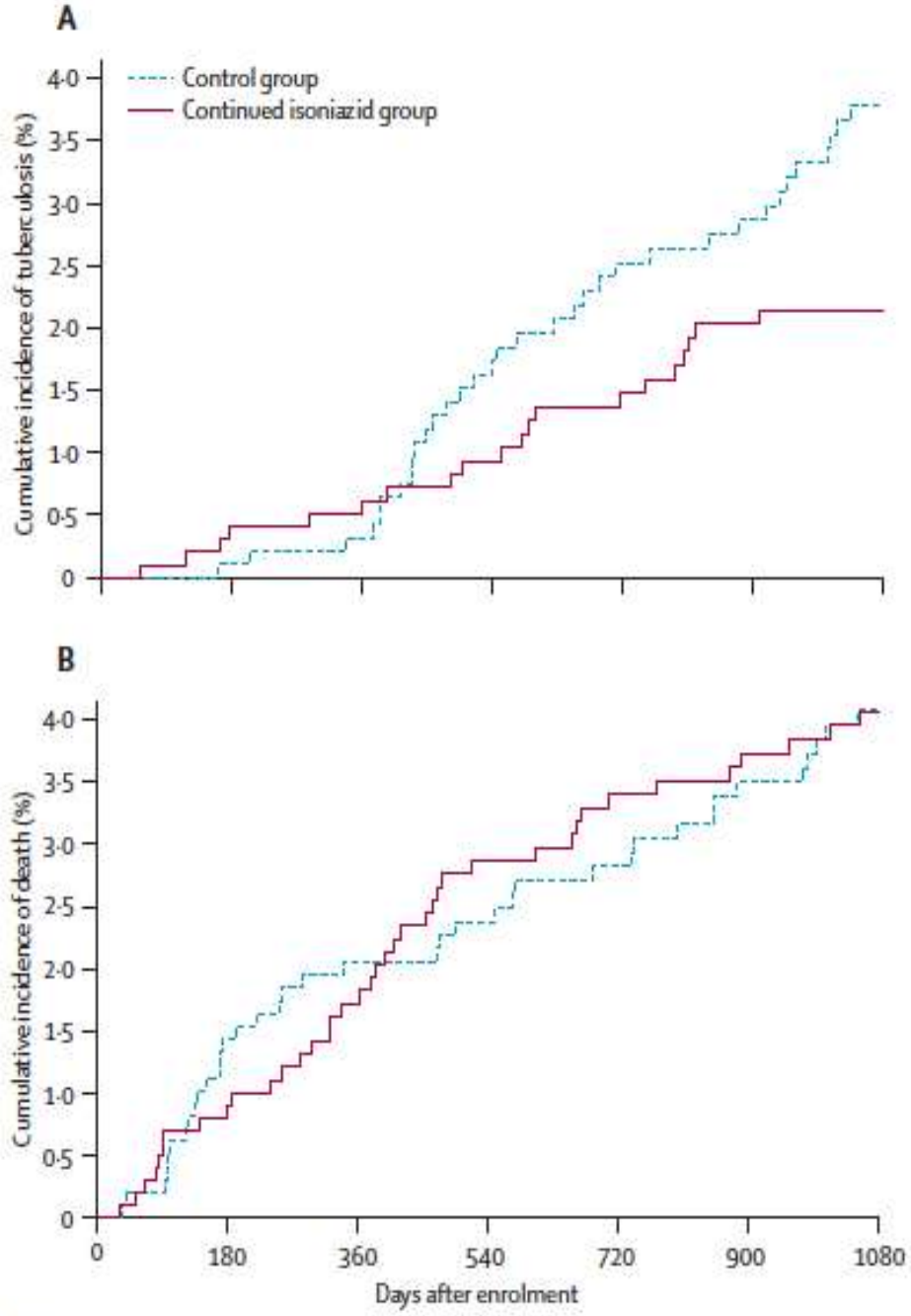
Taraz Samandari, Tefera B Agizew, Samba Nyirenda, Zegabriel Tedla, Thabisa Sibanda, Nong Shang, Barudi Mosimaneotsile, Oaitse I Motsamai, Lorna Bozeman, Margarett K Davis, Elizabeth A Talbot, Themba L Moeti, Howard J Moffat, Peter H Kilmarx, Kenneth G Castro, Charles D Wells

Samandari T. *et al.*, *Lancet* 2011; 377(9777): 1588-98



Samandari T. *et al.*, *Lancet* 2011; 377(9777): 1588-98

Résultat principal



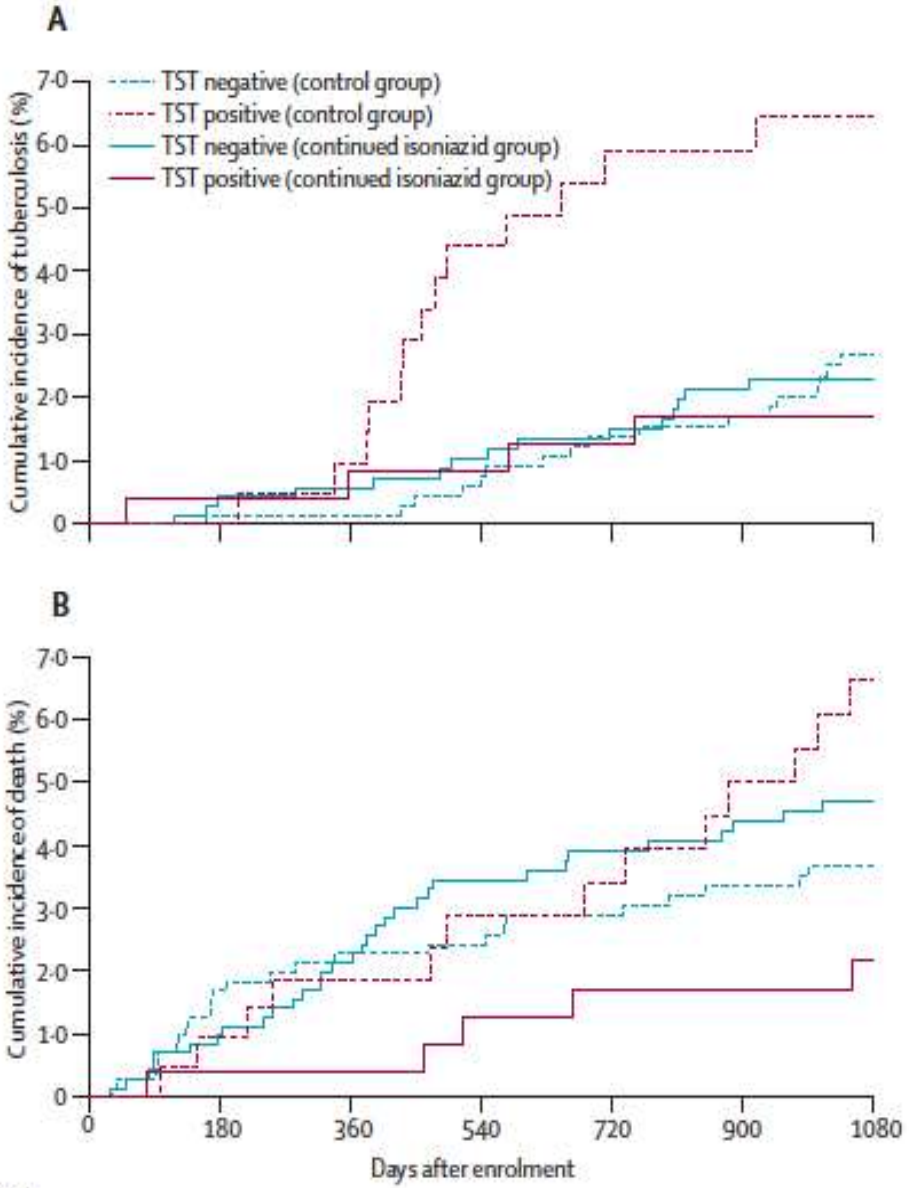
Number at risk						
Control group	989	962	921	891	865	846
Continued isoniazid group	1006	983	949	920	891	866

Incidence TB

Incidence décès

Samandari T. *et al.*,
Lancet 2011; 377(9777): 1588-98

Analyse en fonction du résultat de l'IDR initiale



Number at risk						
TST negative (control group)	729	704	672	656	637	623
TST positive (control group)	216	214	206	192	185	180
TST negative (continued isoniazid group)	722	706	681	658	637	617
TST positive (continued isoniazid group)	252	246	237	231	226	222

Samandari T. *et al.*,
Lancet 2011; 377(9777): 1588-98

Essais publiés depuis les recommandations OMS

Effets de l'IPT sur la mortalité

Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial

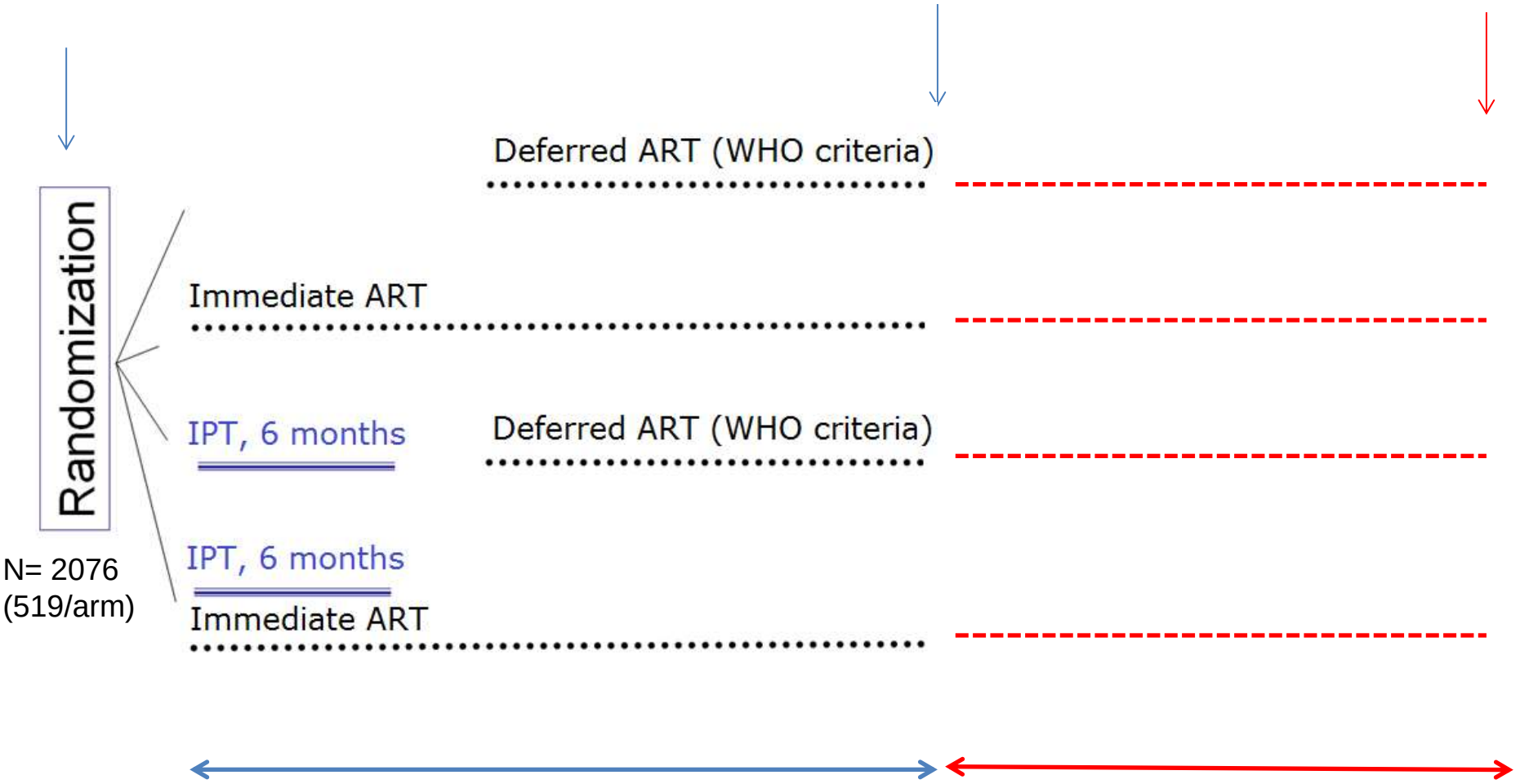
Anani Badje, Raoul Moh, Delphine Gabillard, Calixte Guéhi, Mathieu Kabran, Jean-Baptiste Ntakpé, Jérôme Le Carrou, Gérard M Kouame, Eric Ouattara, Eugène Messou, Amani Anzian, Albert Minga, Joachim Gnokoro, Patrice Gouesse, Arlette Emieme, Thomas-d'Aquin Toni, Cyprien Rabe, Baba Sidibé, Gustave Nzunetu, Lambert Dohoun, Abo Yao, Synali Kamagate, Solange Amon, Amadou-Barenson Kouame, Aboli Koua, Emmanuel Kouamé, Marcelle Daligou, Denise Hawerlander, Simplice Ackoundzé, Serge Koule, Jonas Séri, Alex Ani, Fassery Dembélé, Fatoumata Koné, Mykayila Oyebi, Nathalie Mbakop, Oyewole Makaila, Carolle Babatunde, Nathaniel Babatunde, Gisèle Bleoué, Mireille Tchoutedjem, Alain-Claude Kouadio, Ghislaine Sena, Sahinou-Yediga Yededji, Sophie Karcher, Christine Rouzioux, Abo Kouame, Rodrigue Assi, Alima Bakayoko, Serge K Domoua, Nina Deschamps, Kakou Aka, Thérèse N'Dri-Yoman, Roger Salamon, Valérie Journot, Hughes Ahibo, Timothée Ouassa, Hervé Menan, André Inwoley, Christine Danel, Serge P Eholié*, Xavier Anglaret*, on behalf of the Temprano ANRS 12136 Study Group†*

***Lancet Glob Health* 2017;**
5: e1080–89

Eligibility
- **CD4<800/mm³**
- **no WHO criteria for starting ART**

Primary outcome
Severe morbidity

Primary outcome
Death



30 months

Temprano ANRS 12136

Temprano Study Group, NEJM 2015

Post Temprano

(until last participant reached 30 months)

Baseline characteristics (N=2056)

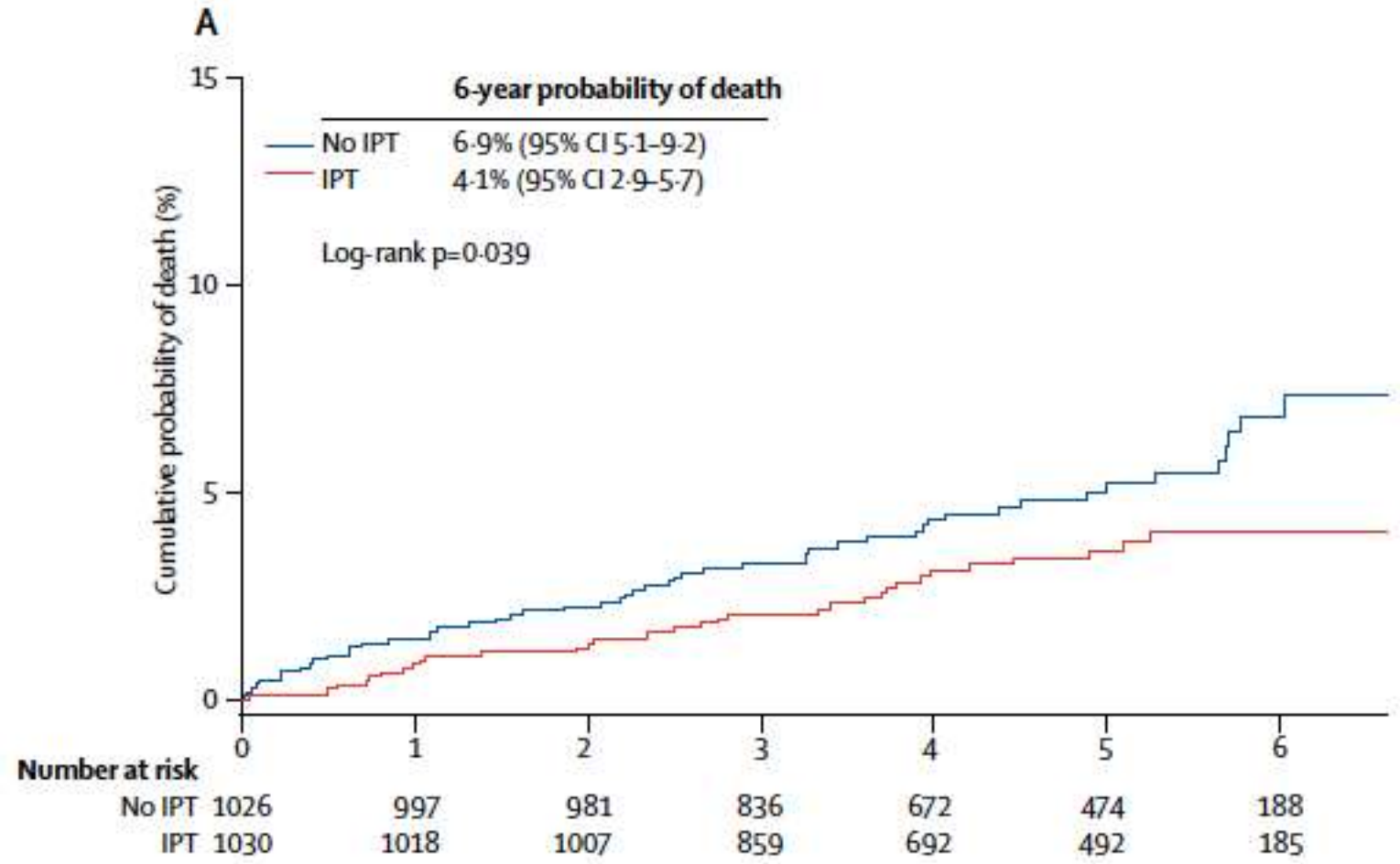
	No IPT N=1026	IPT N=1030
Age, years, median (IQR)	35 (30-41)	35 (30-42)
Female, n (%)	807 (79%)	807 (78%)
Body mass index, kg/m², median	22.6	22.3
CD4 count/*mm³*		
≥ 500	426 (42%)	423 (41%)
< 500	603 (58%)	604(59%)
Plasma HIV-1 RNA, log_{10}copies/ml, median	4.7	4.7
Past history of tuberculosis, n (%)	33 (3%)	28 (3%)
Positive IGRA for tuberculosis, n (%) *	173 (36%)	164 (34%)

No significant difference between strategies for all characteristics

* QuantiFERON-TB-Gold test, performed in the first 966 participants in Temprano

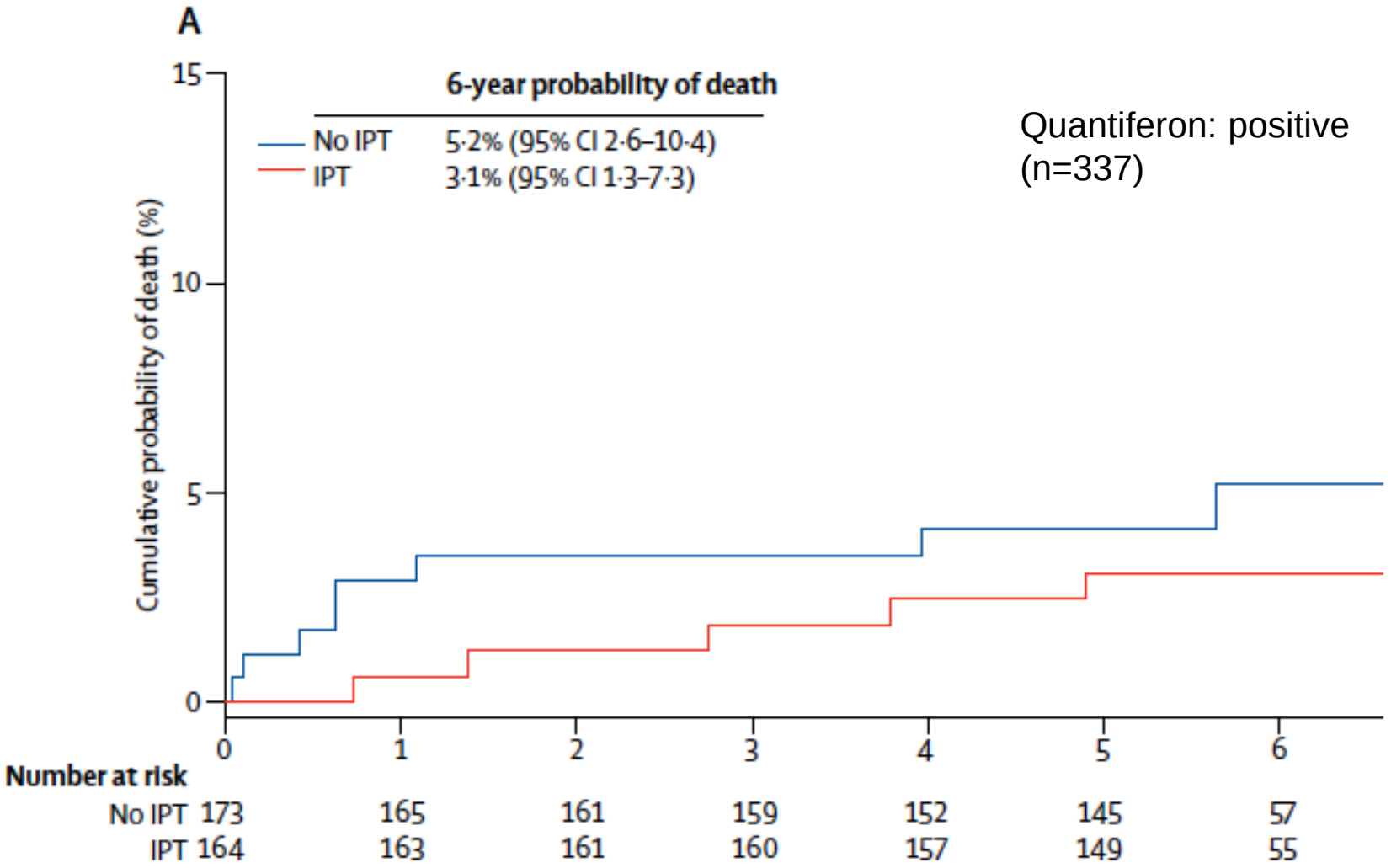
Lancet Glob Health 2017; 5: e1080–89

Effets de l'IPT sur la mortalité



Lancet Glob Health 2017; 5: e1080–89

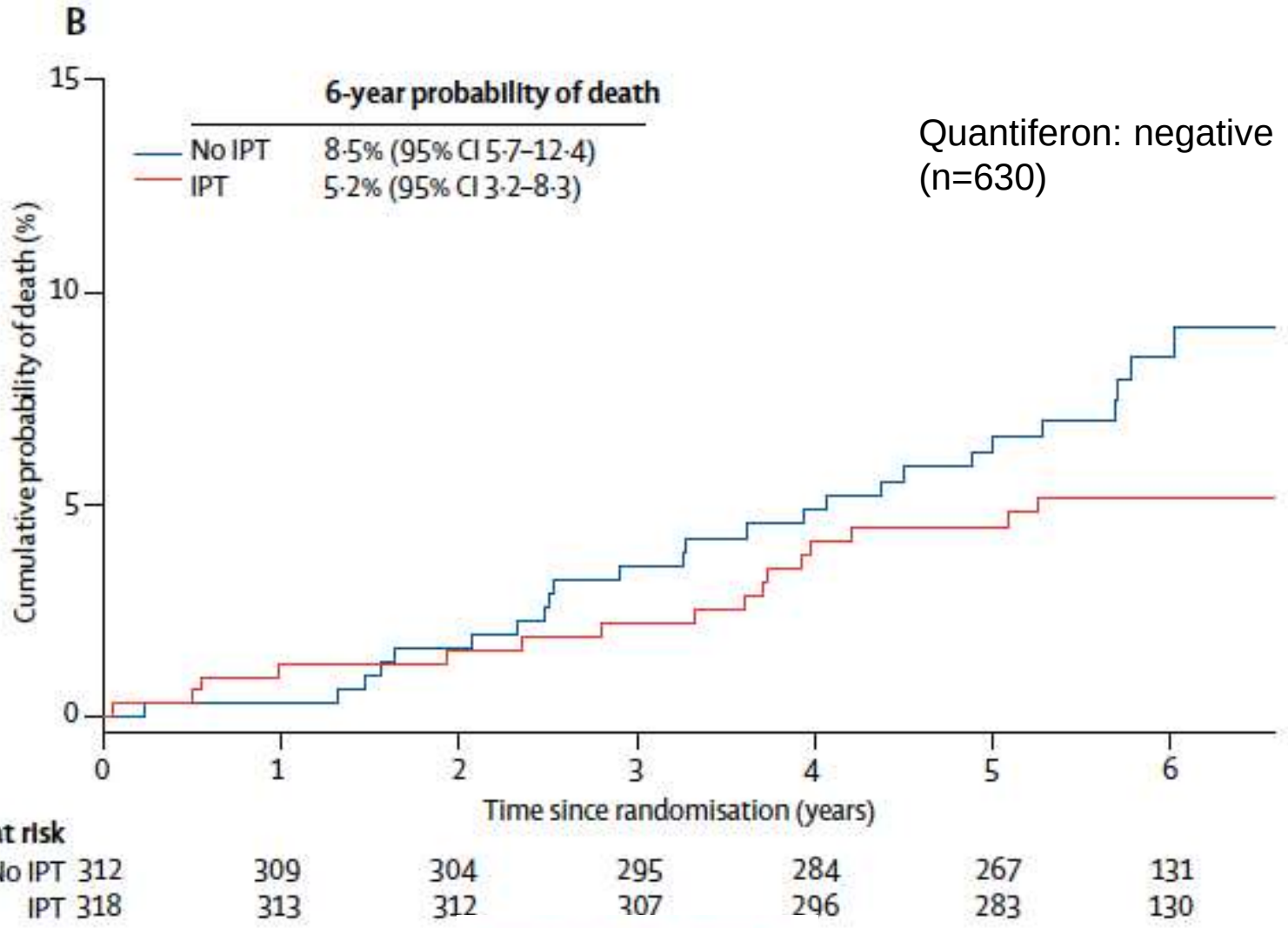
Effets de l'IPT sur la mortalité



Quantiferon: positive (n=337)

Lancet Glob Health 2017; 5: e1080–89

Effets de l'IPT sur la mortalité



Quantiferon: negative (n=630)

Lancet Glob Health 2017; 5: e1080–89

Association between IPT and outcomes (multivariate analysis), N=2056

	N	n	Rate /100 PY	HR*	95% CI	*p*
Death						
No IPT	1026	52	1.1			
IPT	1030	34	0.7	**0.63**	**(0.41-0.97)**	*0.04*
Death or LTFU						
No IPT	1026	162	3.5			
IPT	1030	131	2.7	**0.78**	**(0.62-0.98)**	*0.03*

* Hazard Ratio (adjusted for: immediate/deffered ART, and study center)

Lancet Glob Health 2017; 5: e1080–89

Conclusion de l'essai TEMPRANO (ANRS 12136)

In conclusion, in these African HIV-infected adults with high CD4 cell counts, 6 months of IPT led to a 37% decrease in mortality, independently of baseline CD4 cell count and with no significant evidence for an interaction between IPT and ART. 6 months of IPT should be proposed to all adults who start ART at any CD4 cell count and have no evidence of active tuberculosis in sub-Saharan Africa, regardless of IGRA or TST status.[34,35]

Lancet Glob Health 2017;
5: e1080–89

IPT: une partie seulement de la chimioprophylaxie

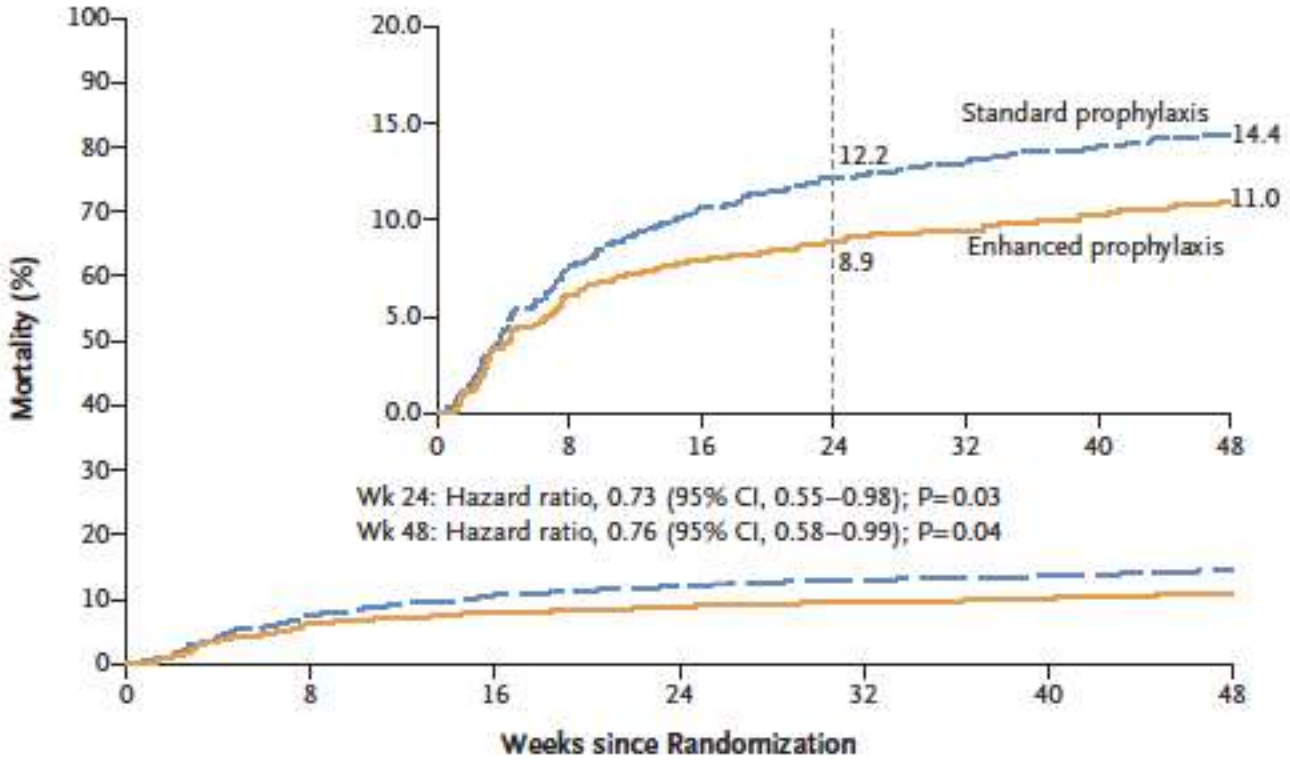
REALITY trial (NEJM 2017)

- Juin 2013 - Avril 2015
- 8 centres
- Ouganda, Zimbabwe, Malawi, Kenya
- VIH/, naïfs d'ARVs
- CD4<100/mm3
- Instauration des ARV puis
- Prophylaxie 'standard' (*n*=899) *vs.* 'améliorée' (*n*=906) :
    - albendazole 400 mg dose unique
    - azithromycine 500 mg/j pendant 5 jours
    - fluconazole 100 mg/j pendant 12 semaines
    - cotrimoxazole + INH + pyridoxine pendant 12 semaines

N Engl J Med 2017;377:233-45.
DOI: 10.1056/NEJMoa1615822

Essai REALITY (NEJM 2017)

A Overall Mortality

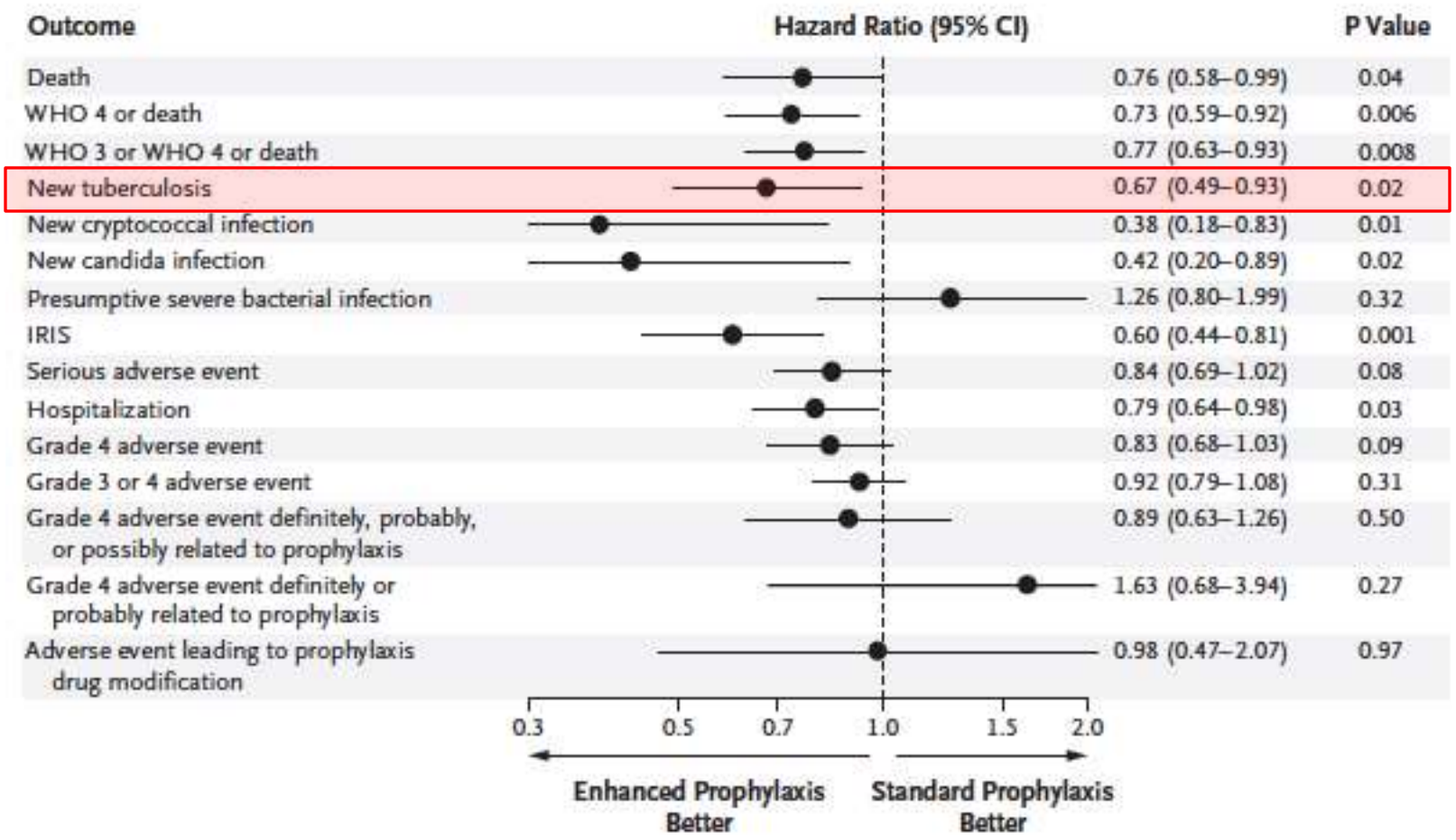


No. at Risk (no. of deaths)

Standard prophylaxis	899 (67)	816 (27)	786 (13)	768 (7)	754 (7)	739 (6)	637
Enhanced prophylaxis	906 (55)	839 (16)	817 (8)	807 (6)	797 (6)	787 (7)	689

N Engl J Med 2017;377:233-45.
DOI: 10.1056/NEJMoa1615822

Essai REALITY (NEJM 2017)



N Engl J Med 2017;377:233-45.
DOI: 10.1056/NEJMoa1615822

Recommandations européennes ERS/ECDC

Standard 16 (changed)

Persons with HIV co-infection who, after careful evaluation, have a positive test (TST and/or IGRAs) for presumed latent infection with *M. tuberculosis* but do not have active tuberculosis should be offered preventive treatment.

EU specific requirements

As HIV co-infection is known to increase the probability of developing active TB disease upon infection, HIV-seropositive persons who have been in contact with an index case harbouring an MDR-TB strain should initially undergo an individual risk assessment. Regular clinical monitoring and follow-up should be provided for those with evidence of latent infection [100].

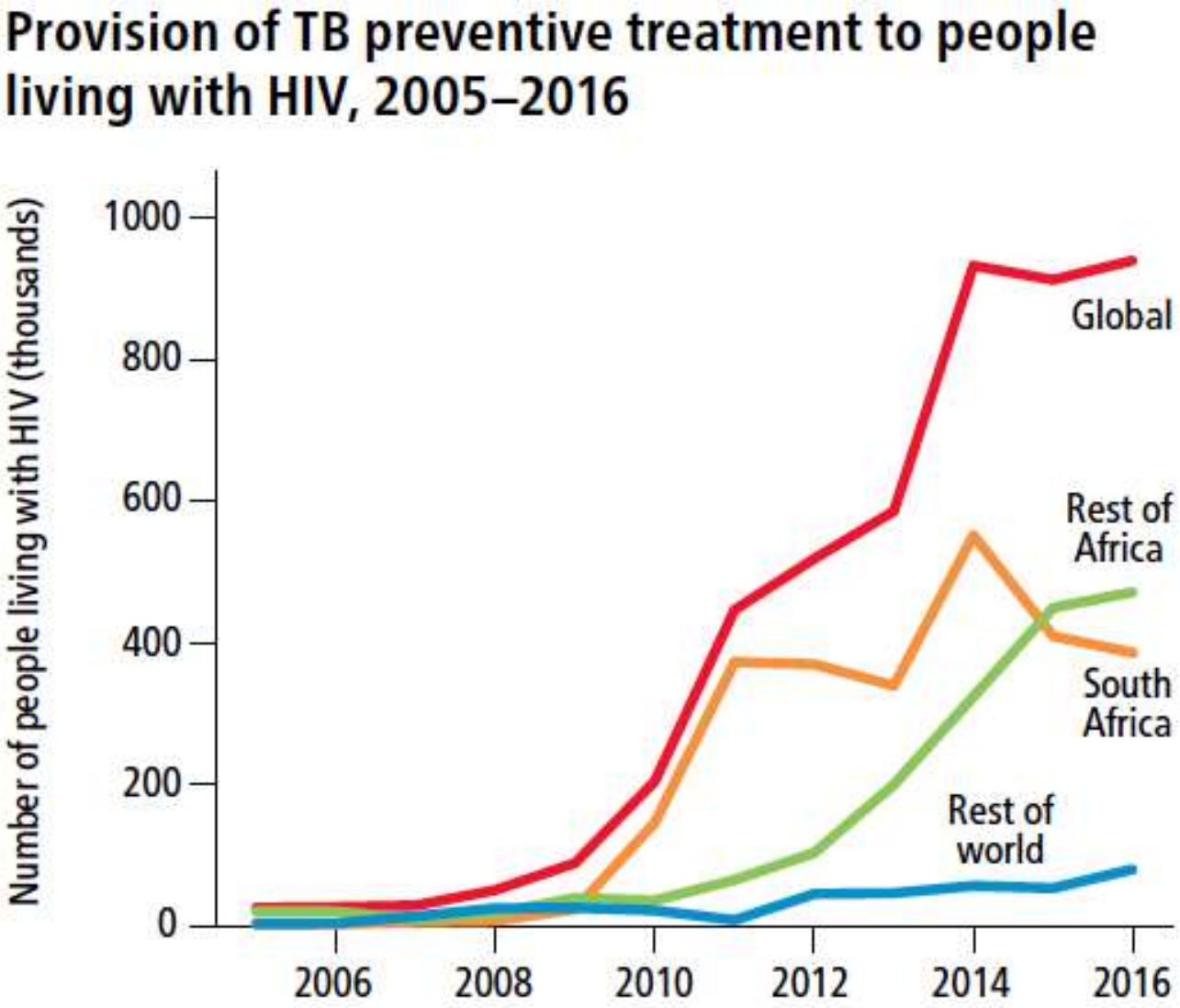
Preventive treatment should take into account the drug resistance pattern of the source case, the CD4 count and the use of antiretroviral treatment. Preventive treatment should be provided with 6-month isoniazid, or 9-month isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or 3–4-month isoniazid plus rifampicin, or 3–4-month rifampicin alone [31, 101]. Rifampicin- and rifapentine-containing regimens should be prescribed with caution to people living with HIV who are on antiretroviral treatment due to potential drug-to-drug interactions [31, 32].

Eur Respir J 2018; 51: 1702678

Chimioprophylaxie par INH chez les PVVIH

- **Efficacité démontrée chez les VIH+ comme chez les VIH-**
- **Effet sur la mortalité enfin démontré (TEMPRANO)**
- **Recommandations OMS 2010 et grandes études publiées**
- **Volonté politique de généraliser cette pratique ?**
- **Mise en œuvre à grande échelle → réduction de l'incidence TB**

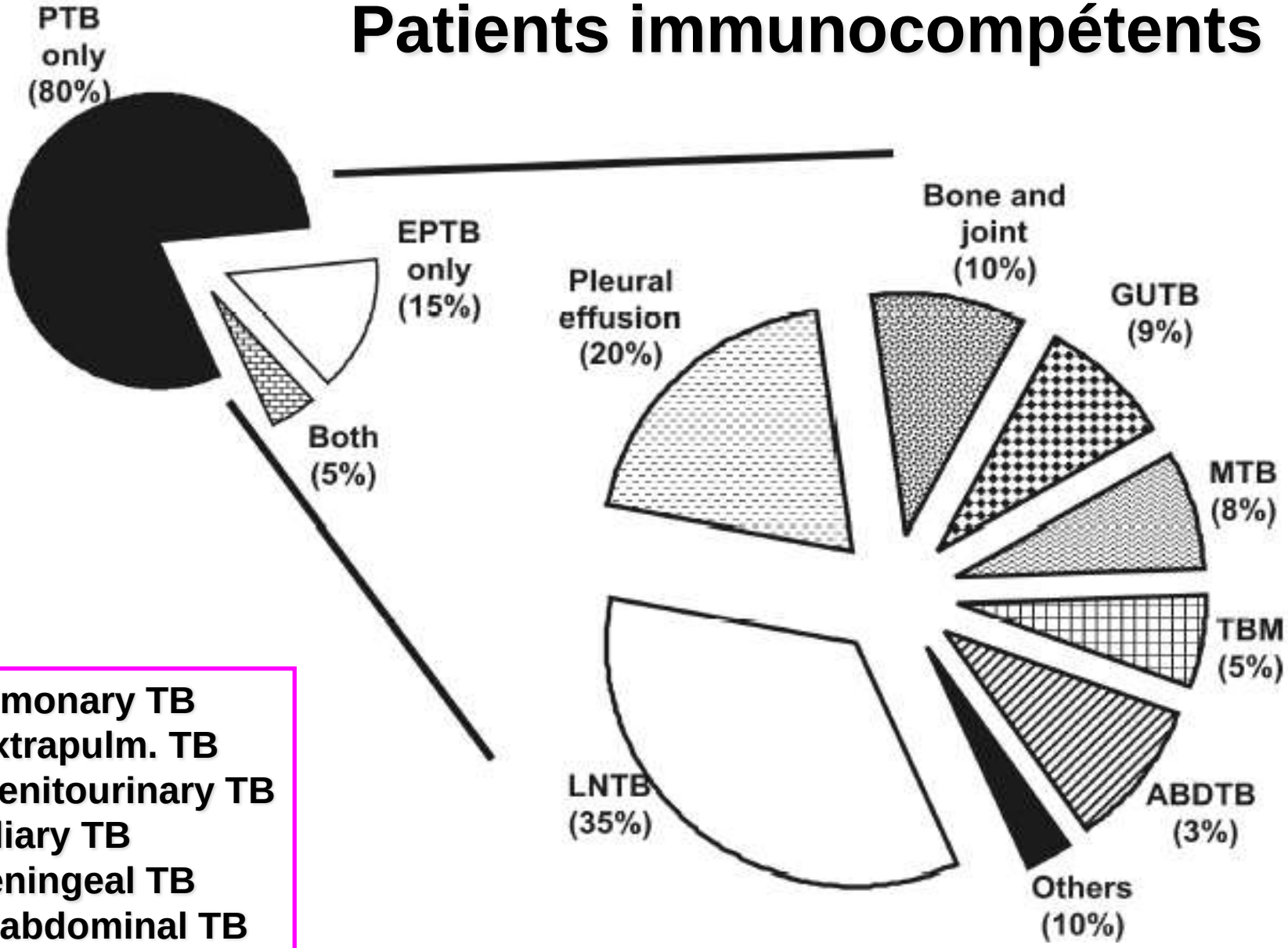
Développement de l'IPT au niveau mondial



Global tuberculosis report 2017

World Health Organization

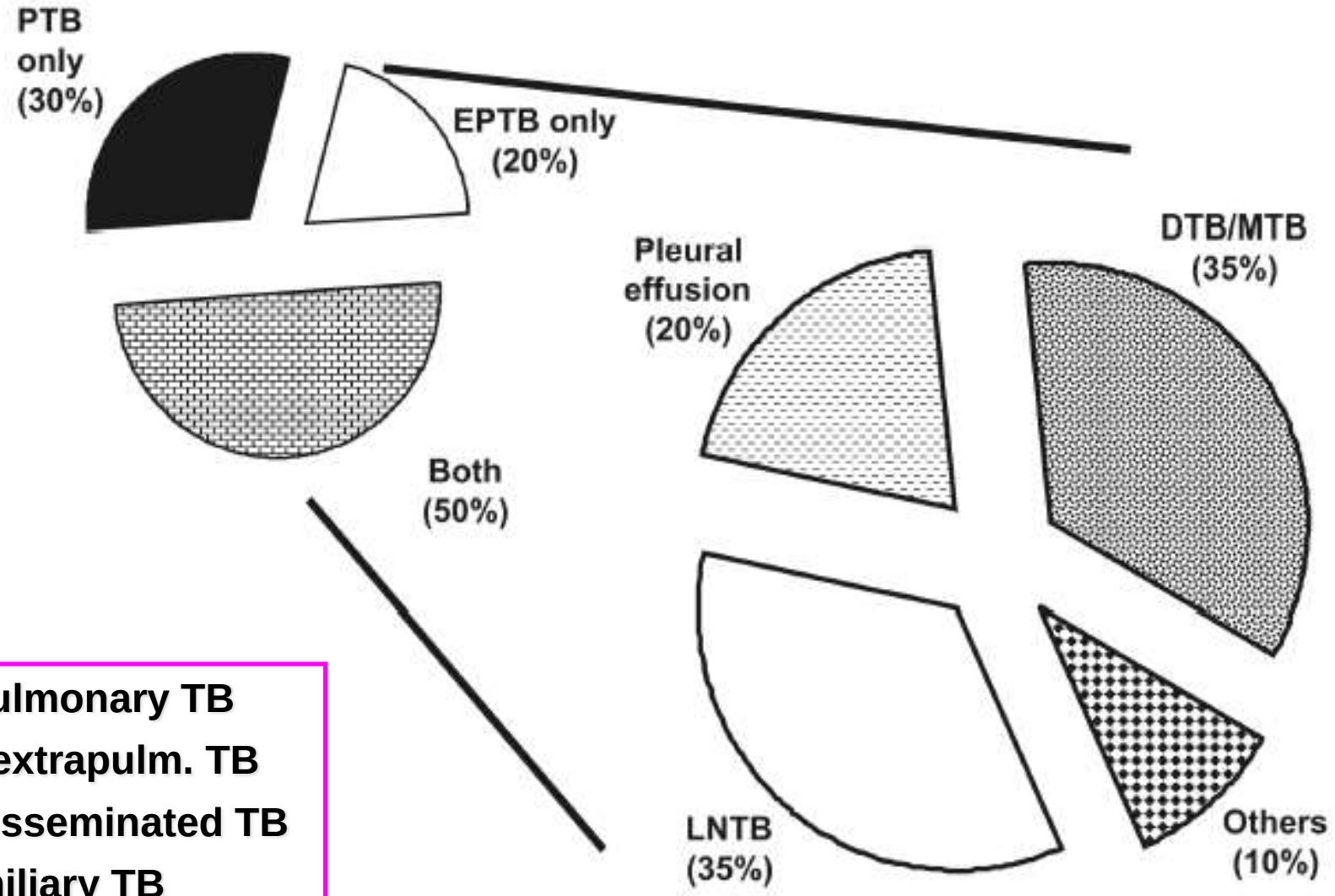
Patients immunocompétents



PTB: pulmonary TB
EPTB: extrapulm. TB
GUTB: genitourinary TB
MTB: miliary TB
TBM: meningeal TB
ABDTB: abdominal TB

Sharma et al., Indian J Med Res 2005

Patients infectés par le VIH



PTB: pulmonary TB

EPTB: extrapulm. TB

DTB: disseminated TB

MTB: miliary TB

LNTB: lymph node TB

Sharma et al., Indian J Med Res 2005

Tuberculose pulmonaire : présentation selon CD4

Ouganda : 873 cas de TB pulm. chez des patients VIH+ comparées à 1 141 cas chez des patients VIH- (rétrospective)

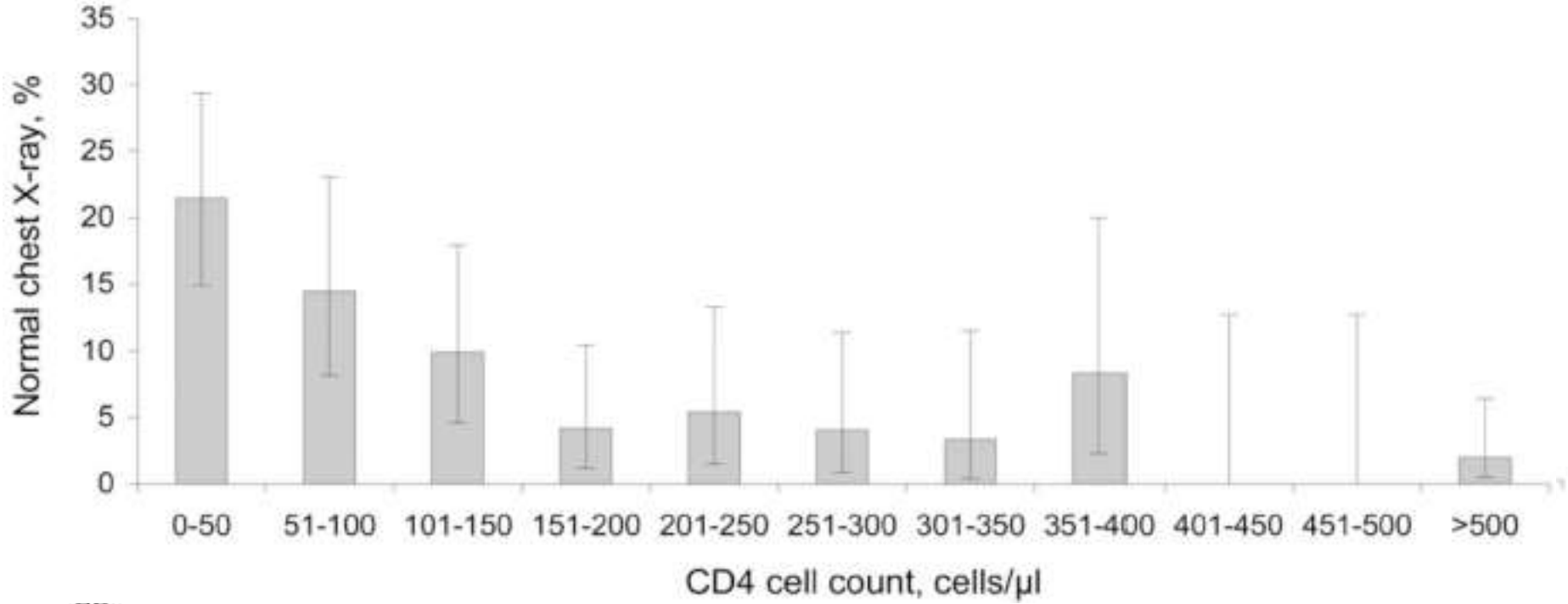
Quand CD4 < 50, 21% de radiographies thoraciques normales *vs.* 2% si CD4 > 500

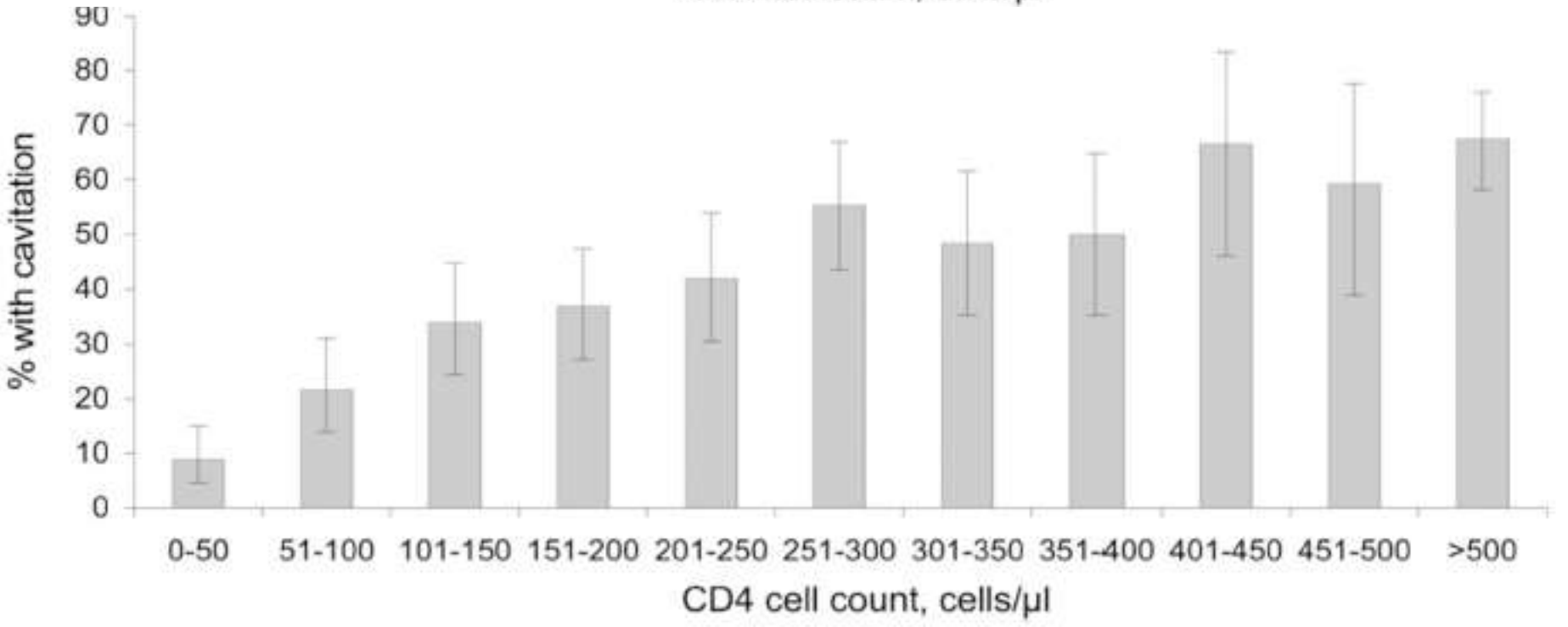
Pas de différence entre VIH- et VIH+ pour :

- les miliaires ou les pleurésies si CD4 > 100,
- les Rx normales ou les fibroses pulm. si CD4 > 150,
- les adénopathies si CD4 > 250,
- les lésions excavées ou des lobes sup. si CD4 > 300.

23% des patients co-infectés avec CD4 < 50 *vs.*1% avec CD4 > 500 étaient BAAR- (*p* < 0.001).

Int J Tuberc Lung Dis 2010; 14(10): 1295-1302


Normal chest X-ray, %
35
30
25
20
15
10
5
0
0-50
51-100
101-150
151-200
201-250
251-300
301-350
351-400
401-450
451-500
>500
CD4 cell count, cells/µl


% with cavitation
90
80
70
60
50
40
30
20
10
0
0-50
51-100
101-150
151-200
201-250
251-300
301-350
351-400
401-450
451-500
>500
CD4 cell count, cells/µl

Diagnostic de la TB chez les PVVIH sévèrement ID

- Diagnostic difficile car :
  - moins de formes bacillifères
  - plus de localisations extra-pulmonaires
  - présentation clinique et radiologique trompeuse

- Mais des outils diagnostiques existent…

- **Exemple de la détection du lipoarabinomannane urinaire et de l'Xpert Ultra**

Outils diagnostiques

Technologies in early development[a]

Volatile organic compounds
- BreathLink, Menssana Research, USA
- Prototype breath analyzer device, Next Dimensions Technology, USA

Molecular technologies
- Alere Q, Alere, USA
- B-SMART, LabCorp, USA
- Gendrive MTB/RIF ID, Epistem, UK
- LATE-PCR, Brandeis University, USA
- GeneXpert XDR cartridge, Cepheid, USA
- TruArray MDR-TB, Akkoni, USA
- INFINITIMTB Assay, AutoGenomics, USA

Culture-based technologies
- BNP Middlebrook, NanoLogix, USA
- MDR-XDR TB Color Test, FIND, Switzerland/Imperial College, UK
- TREK Sensititre MYCOTB MIC plate, Trek Diagnostic Systems/Thermo Fisher Scientific, USA

Other technologies
- TB Rapid Screen, Global BioDiagnostics, USA
- TBDx, Signature Mapping Medical Sciences, USA

Evaluated by WHO but not yet endorsed due to insufficient evidence

Molecular technologies
- TB LAMP, Eiken, Japan
- Genotype MTBDRsl, Hain Lifescience, Germany

On the market but evidence for use not yet submitted to WHO for evaluation

Molecular technologies
- iCubate System, iCubate, USA
- TB drug resistance array, Capital Bio, China
- EasyNAT TB Diagnostic kit, Ustar Biotechnologies, China
- Truelab/Truenat MTB, Molbio/bigtec Diagnostics, India

Non-molecular technologies
- Alere Determine TB-LAM, Alere, USA

Technologies endorsed by WHO

Molecular technologies
- Xpert MTB/RIF[b]
- Line probe assays (acid-fast bacilli smear-positive sputum specimens or culture-positive specimens)

Microscopy
- Ziehl-Neelsen and fluorescence microscopy methods

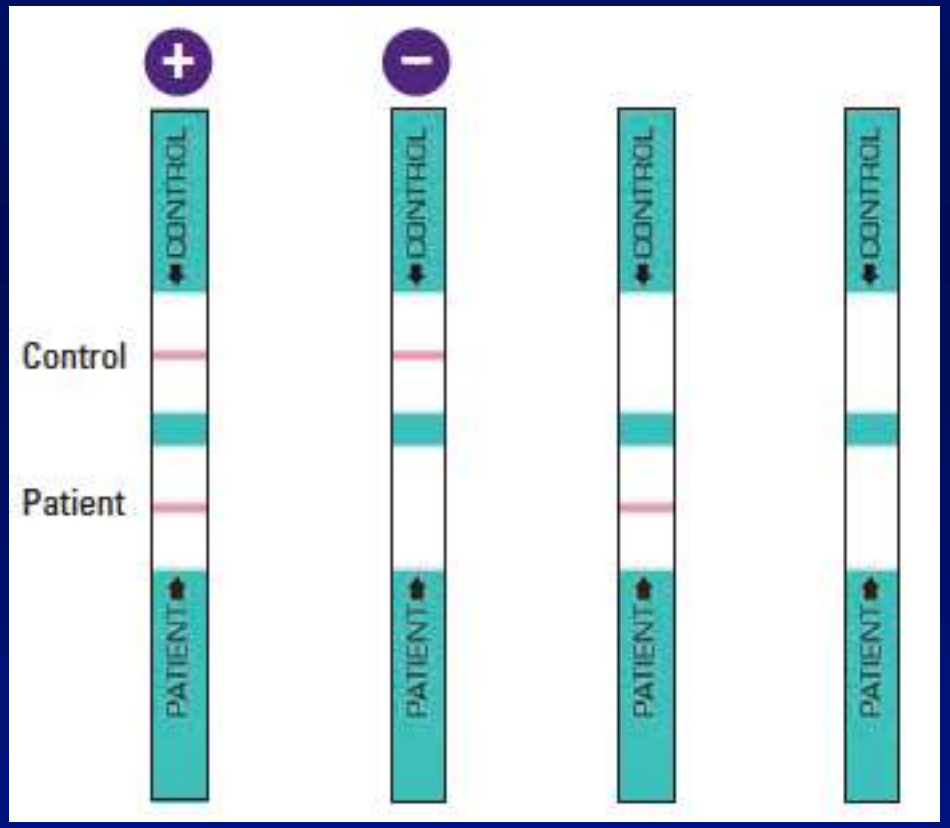
Culture-based technologies
- Commercial liquid culture systems and rapid speciation
- Non-commercial culture and drug susceptibility testing methods

World Health Organization

LAM urinaire: aide au diagnostic ?

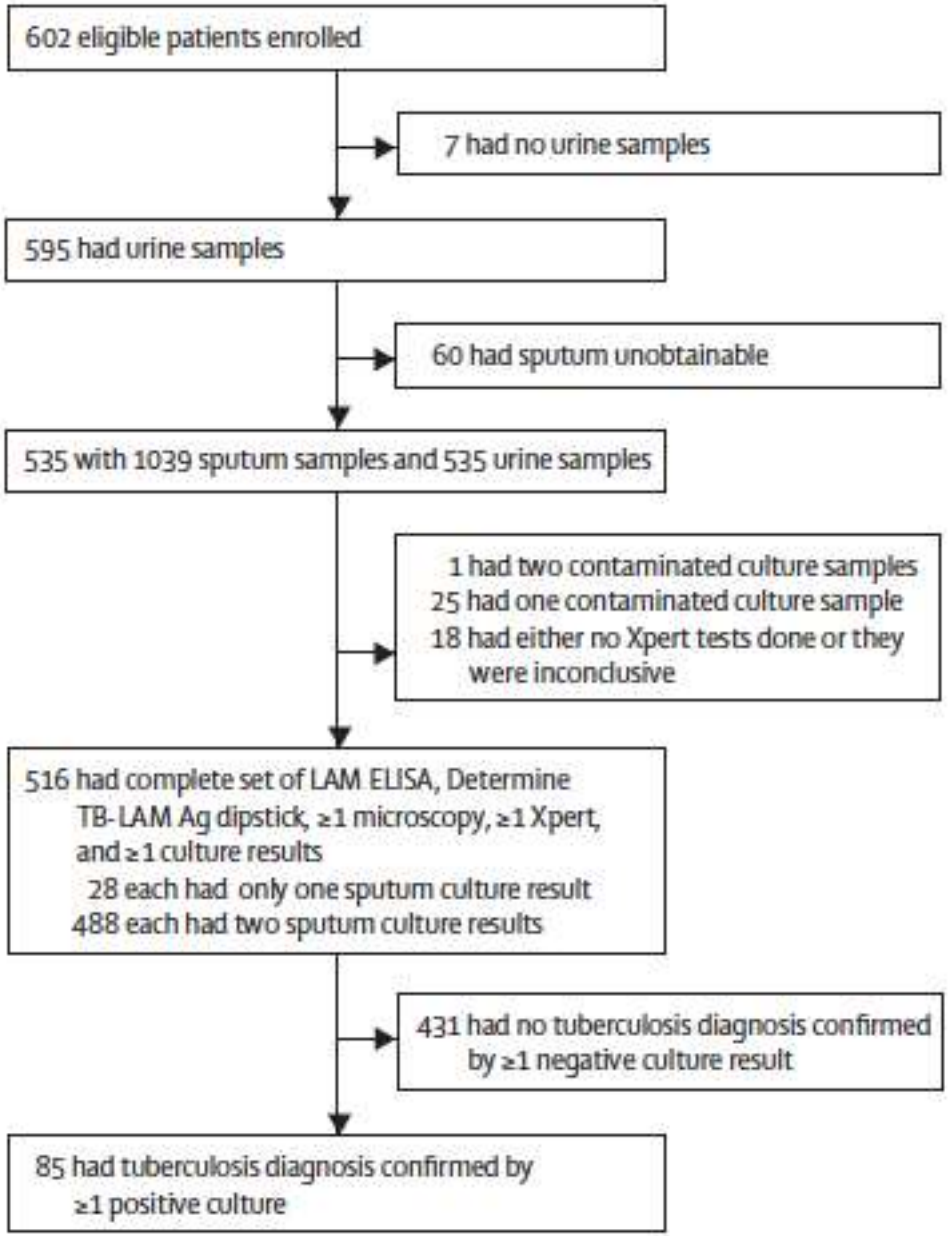
• Bandelette Determine® TB-LAM Ag fonctionnant comme un test de grossesse. Déposer un échantillon d'urine et attendre 25 minutes pour lire le résultat !

LAM : lipoarabinomannane



Source : *http://www.alere.co.uk/microbiology/coming-soon-new-determiner-tb-lam-ag-283/product-listing.htm*

LAM urinaire: aide au diagnostic ?



www.thelancet.com/infection Published online October 18, 2011 DOI:10.1016/S1473-3099(11)70251-1

New strategy #1: urine LAM + Xpert MTB/RIF?

	Sputum AFB		TB ELISA		Determine TB-LAM		Determine TB-LAM and sputum AFB		Xpert MTB/RIF (1 sample)		Determine TB-LAM and Xpert MTB/RIF	
	Positive	Sensitivity	Positive	Sensitivity	Positive	Sensitivity	Positive	Sensitivity	Positive	Sensitivity	Positive	Sensitivity
All (n=85)	24	28·2% (19·0–39·0)	23	27·1% (18·0–37·8)	24	28·2% (19·0–39·0)	37	43·5% (32·8–54·7)	49	57·6% (46·4–68·3)	52	61·2% (50·0–71·6)
<50 cells per μL (n=18)	6	33·3% (13·3–59·0)	11	61·1% (35·7–82·7)	12	66·7% (41·0–86·7)	13	72·2% (46·5–90·3)	13	72·2% (46·5–90·3)	15	83·3% (58·6–96·4)
<100 cells per μL (n=29)	10	34·5% (17·9–54·3)	14	48·3% (29·4–67·5)	15	51·7% (32·5–70·6)	19	65·5% (45·7–82·1)	22	75·9% (56·5–89·7)	24	82·8% (64·2–94·2)
<150 cells per μL (n=46)	16	34·8% (21·4–50·2)	20	43·5% (28·9–58·9)	21	45·7% (30·9–61·0)	27	58·7% (43·2–73·0)	33	71·7% (56·5–84·0)	35	76·1% (61·2–87·4)
<200 cells per μL (n=59)	18	30·5% (19·2–43·9)	21	35·6% (23·6–49·1)	23	39·0% (26·5–52·6)	31	52·5% (39·1–65·7)	37	62·7% (49·1–75·0)	40	67·8% (54·4–79·4)
≥200 cells per μL (n=25)	6	24·0% (9·4–45·1)	2	8·0% (1·0–26·0)	1	4·0% (0·1–20·4)	6	24·0% (9·4–45·1)	11	44·0% (24·4–65·1)	11	44·0% (24·4–65·1)

84 patients stratified by CD4 cell count. Data are number and sensitivity (95% CI). AFB=acid-fast bacilli. LAM=lipoarabinomannan. MTB/RIF=Mycobacterium tuberculosis/rifampicin.

Table 2: Sensitivity of the different diagnostic assays for all patients with tuberculosis and for those stratified by CD4 cell count

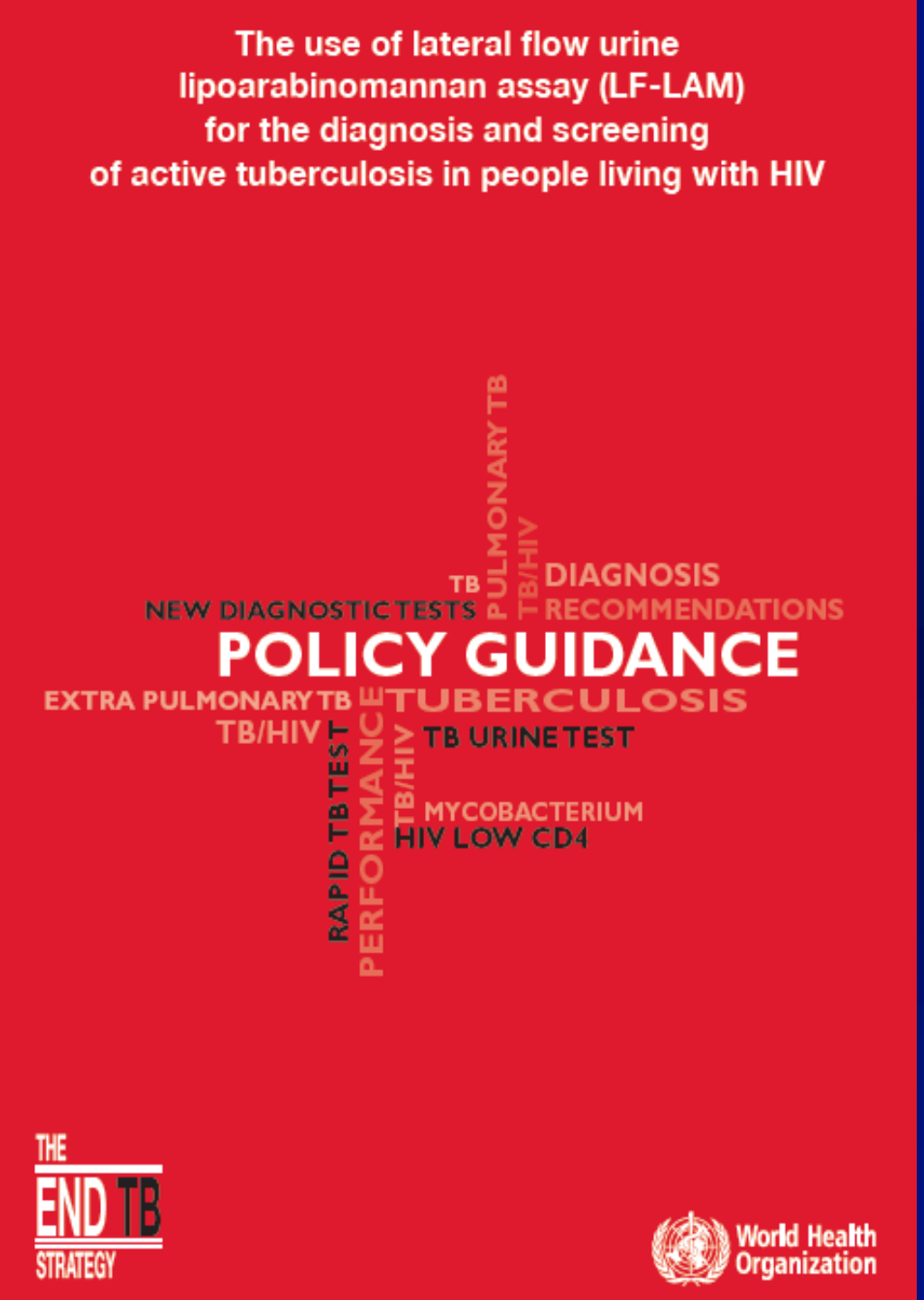
	Sputum AFB		ELISA		Determine TB-LAM		Determine TB-LAM and sputum AFB		Xpert MTB/RIF (1 sample)		Determine TB-LAM and Xpert MTB/RIF	
	Negative	Specificity	Negative	Specificity	Negative	Specificity	Negative	Specificity	Negative	Specificity	Negative	Specificity
All (n=431)	430	99·8% (98·7–100)	423	98·1% (96·4–99·2)	425	98·6% (97·0–99·5)	424	98·4% (96·7–99·3)	427	99·1% (97·6–99·7)	421	97·7% (95·8–98·9)

Data are number and sensitivity (95% CI). AFB=acid-fast bacilli. TB=tuberculosis. LAM=lipoarabinomannan. MTB/RIF=Mycobacterium tuberculosis/rifampicin.

Table 3: Specificity of the different diagnostic assays for all patients with tuberculosis whose cultures were negative

www.thelancet.com/infection Published online October 18, 2011 DOI:10.1016/S1473-3099(11)70251-1

OMS et LAM urinaire



OMS et LAM urinaire

WHO's policy recommendations

Policy Recommendations for the use of the lateral flow urine lipoarabinomannan (LF-LAM) assay

1. **Except as specifically described below for persons with HIV infection with low CD4 counts or who are seriously ill**[2], LF-LAM **should not be used** for the diagnosis of TB **(strong recommendation, low quality of evidence)**.

2. LF-LAM **may be used** to assist in the diagnosis of TB **in HIV positive** adult *in-patients* with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/µL, or HIV positive patients who are seriously ill[2] regardless of CD4 count or with unknown CD4 count **(conditional recommendation; low quality of evidence)**.

Remarks

a. This recommendation also applies to HIV positive adult *out-patients* with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/µL, or HIV positive patients who are seriously ill[2] regardless of CD4 count or with unknown CD4 count, based on the generalisation of data from in-patients.

b. This recommendation also applies to HIV positive children with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalisation of data from adults while acknowledging very limited data and concern regarding low specificity of the LF-LAM assay in children.

3. LF-LAM **should not be used** as a screening test for TB. **(strong recommendation, low quality of evidence)**.

Avenir : LAM urinaire + Xpert MTB/RIF ?

OPEN ACCESS Freely available online

Le Cap (Afrique du Sud)

PLoS one

The Diagnostic Accuracy of Urine-Based Xpert MTB/RIF in HIV-Infected Hospitalized Patients Who Are Smear-Negative or Sputum Scarce

Jonathan G. Peter[1], Grant Theron[1], Tapuwa E. Muchinga[1], Ureshnie Govender[1], Keertan Dheda[1,2,3]*

1 Lung Infection and Immunity Unit, Division of Pulmonology & UCT Lung Institute, Department of Medicine, University of Cape Town, Cape Town, South Africa, 2 Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa, 3 Department of Infection, University College London Medical School, London, United Kingdom

- Etude préliminaire réalisée chez 281 patients.
- 116/242 prélèvements + en culture.
- LAM urinaire + Xpert MTB/RIF sur des urines chez des patients avec peu de crachats : meilleure sensibilité qu'avec l'Xpert MTB/RIF seul (p=0.03)

→ sensibilité MTB/RIF + LAM ELISA = 70% (IC 95% : 48-85)

→ sensibilité MTB/RIF seul = 40% (IC95%: 22-61)

Diagnostic test(s)	All *m.tb* culture positive	Only sputum-scarce non-sputum *m.tb* culture positive	HIV-infected patients with CD4 count >200 cells/ml	HIV-infected patients with CD4 count ≤200 cells/ml	Random sample of *m.tb* culture negative patients[§]
	(N = 113)	(N = 20)	(N = 26)	(N = 78)	(N = 62)
	Sensitivity (%)	Sensitivity (%)	Sensitivity (%)	Sensitivity (%)	Specificity (%)
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
	n/N	n/N	n/N	n/N	n/N
Sputum smear microscopy	52[#3]		58[#6 #7]	50[#8]	100
	(43–61)	N/A	(39–75)	(39–61)	(94–100)
	59/113		15/26	39/78	62/62
Urine MTB/RIF	48[#1]	40[#5]	31[#7 *1]	54[#9 *1]	98[#11]
	(39–57)	(22–61)	(17–50)	(43–65)	(95–100)
	54/113	8/20	8/26	42/78	61/62
Urine LAM ELISA	58[#4]	60	27[*2]	69[#8 *2]	89[#11]
	(49–67)	(39–78)	(14–46)	(58–78)	(81–97)
	65/112	12/20	7/26	53/77	55/62
Urine LAM strip test (grade 2 cut-point)	48[#2]	45	27[#6 *3]	56[#10 *3]	85
	(39–57)	(26–66)	(14–46)	(45–67)	(77–94)
	55/113	9/20	7/26	44/78	53/62
Urine LAM ELISA followed by urine MTB/RIF (performed if LAM ELISA negative)	68[#1 #2]	70[#5]	38[*4]	79[#9 #10 *4]	89
	(60–77)	(48–85)	(20–57)	(71–88)	(81–97)
	77/113	14/20	10/26	62/78	55/62
Urine LAM ELISA combined with smear microscopy	74[#3 #4]		58[*5]	80[*5]	89
	(65–82)	N/A	(39–77)	(71–88)	(81–97)
	83/113		15/26	62/78	55/62

Xpert MTB/RIF ou Xpert Ultra ?

	Minsk, Belarus (N=121)	Vitoria, Brazil (N=128)	Cape Town, South Africa (N=152)	Zheng-zhou, China (N=101)	Tbilisi, Georgia (N=372)	Johannesburg, South Africa (N=234)	Nairobi, Kenya (N=135)	Mumbai, India (N=213)	New Delhi, India (N=116)	Kampala, Uganda (N=181)	All participants (N=1753)
Demographic or clinical characteristics											
Age, years	42 (28–56)	50 (37–59)	41 (34–49)	47 (34–57)	45 (33–57)	34 (30–43)	33 (26–44)	31 (23–45)	30 (21–45)	30 (26–39)	38 (28–50)
Female sex	50/121 (41%)	47/128 (37%)	89/152 (59%)	25/101 (25%)	105/372 (28%)	87/234 (37%)	66/135 (49%)	110/213 (52%)	50/116 (43%)	65/181 (36%)	694/1753 (40%)
HIV infection	7/8 (≤4%*)	7/128 (5%)	87/152 (57%)	0/101	7/13 (≤4·0%*)	157/214 (73%†)	78/135 (58%)	8/10 (≤4%*)	7/54 (≤4%*)	83/181 (46%)	441/996 (25%*)
History of tuberculosis‡	5/48 (10%)	10/128 (8%)	59/150 (39%)	1/133 (3%)	95/348 (27%)	55/234 (24%)	20/135 (15%)	7/64 (11%)§	28/115 (24%)	15/181 (8%)	295/1436 (21%)§

	Tuberculosis detection*				
	Sensitivity: all culture-positive (95% CI; n/N)	Sensitivity: smear-negative (95% CI; n/N)	Sensitivity: HIV-negative (95% CI; n/N)‡	Sensitivity: HIV-positive (95% CI; n/N)‡	Specificity (95% CI; n/N)
Xpert	83% (79 to 86; 383/462)	46% (37 to 55; 63/137)§	90% (84 to 94; 143/159)	77% (68 to 84; 88/155)	98% (97 to 99; 960/977)
Xpert Ultra	88% (85 to 91; 408/462)	63% (54 to 71; 86/137)§	91% (86 to 95; 145/159)	90% (83 to 95; 103/115)	96% (94 to 97; 934/977)
Difference (Xpert Ultra minus Xpert)	5·4% (3·3 to 8·0; 25/162)	17% (10 to 24; 23/137)	1·3% (–1·8 to 4·9; 2/159)	13% (6·4 to 21; 15/115)	–2·7% (–3·9 to –1·7; 36/977)
Non-inferiority margin	Not predefined	–7%	Not predefined	Not predefined	Not predefined

Lancet Infect Dis 2018; 18: 76–84

Mais que se passe-t-il si on débute les ARV sans avoir diagnostiqué la tuberculose ?

- Prospective trial of 1,771 HIV-infected patients with CD4 <200 cells/µl or a prior AIDS-defining illness
- **TB incidence and mortality: maximal during the first 3 months following ART initiation**

Table 2. Tuberculosis incidence and mortality rates during follow-up as number per 100 person-years along with 95% confidence interval and number of events (*n*), broken down by timing of event.

	0–3 months	3–6 months	6–12 months	12–24 months	>24 months
Confirmed/probable TB	8.42 (6.07–11.67) *n* = 36	3.24 (1.88–5.58) *n* = 13	1.98 (1.17–3.34) *n* = 14	2.21 (1.48–3.30) *n* = 24	1.95 (1.26–3.02) *n* = 20
TB – all events	19.88 (16.05–24.6) *n* = 84	8.75 (6.25–12.25) *n* = 34	6.06 (4.46–8.23) *n* = 41	5.50 (5.23–7.14) *n* = 56	4.11 (3.00–5.62) *n* = 39
Death	16.89 (13.42–21.24) *n* = 73	8.29 (5.92–11.60) *n* = 34	5.78 (4.27–7.82) *n* = 42	3.54 (2.60–4.83) *n* = 40	1.75 (1.12–2.75) *n* = 19

AIDS 2010, **24**:1849–1855

Mais que se passe-t-il si on débute les ARV sans avoir diagnostiqué la tuberculose ?

- High prevalence of TB at ART initiation ➔ 20 - 25%
- High incidence of TB after ART initiation ➔ 10 - 20%
- Majority of cases occur early after ART initiation

  ➔ Prevalent TB, present at baseline but **UNDIAGNOSED**, so **UNTREATED!**

Undiagnosed TB in patients starting ART may result in morbidity during early ART because of:

- Unmasking of TB by ART
- IRIS-associated mortality
- TB transmission to other patients in crowded clinics

ANRS 12290 STATIS

Systematic empirical vs. Test-guided Anti-tuberculosis Treatment Impact in Severely immunosuppressed HIV-infected adults initiating antiretroviral therapy with CD4 cell counts <100/mm^3

STATIS design

Screening
- CD4 <100/mm3
- ART naïve
- Age ≥18 yrs
- HIV-1 positive
- No TB treatment <5 years
- No ongoing IPT

Pre-inclusion
- No overt evidence of TB
- Able to start ART immediately

Inclusion
- CD4 <100/mm3 (confirmation)
- Absence of non-inclusion criteria

Primary endpoint at *Week 24:*
All-cause mortality and invasive bacterial infections (composite)

End of follow-up
Week 48

Arm 1 (525 patients)

Extensive TB screening
Xpert MTB/RIF
Urine LAM
Chest X-ray

- **No TB** → ART — *Search for active TB if symptomatic at anytime*
- **TB** → TB treatment; ART

Arm 2 (525 patients)

Systematic TB treatment
Chest X-ray

→ TB treatment; ART

Day 0
Inclusion/randomization

7 days | 3 days

Informed consent signature

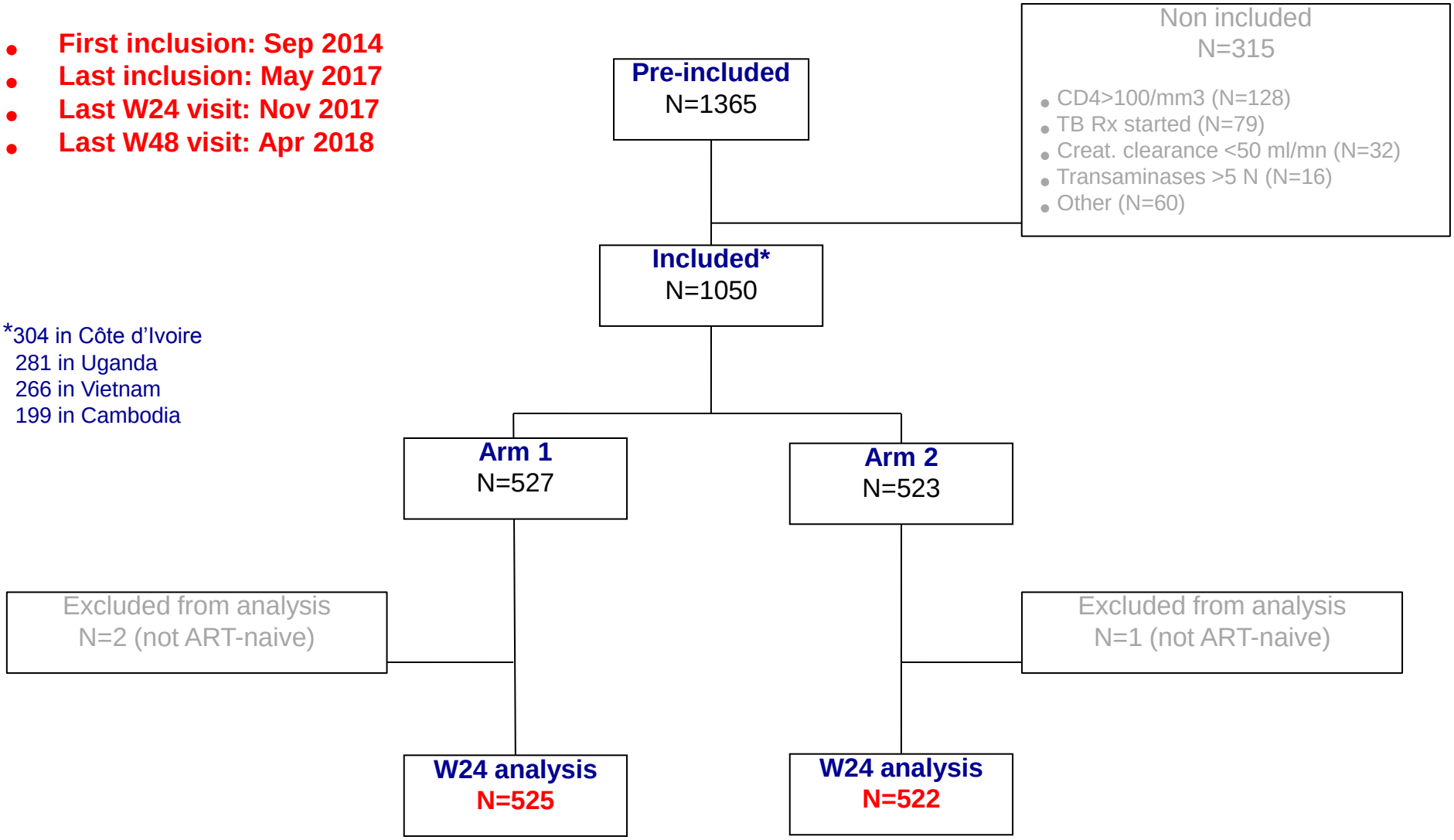
W2 W4 W8 W12 W16 W20 **W24** W36 W48

INTERVENTION

Cambodia, Vietnam
Ivory Coast, Uganda

Flow chart

- **First inclusion: Sep 2014**
- **Last inclusion: May 2017**
- **Last W24 visit: Nov 2017**
- **Last W48 visit: Apr 2018**



*304 in Côte d'Ivoire
281 in Uganda
266 in Vietnam
199 in Cambodia

Baseline characteristics

	Arm 1 (n=525)	Arm 2 (n=522)
Women, n (%)	**221 (42)**	**215 (41)**
Age, median (IQR)	**35 (29-41)**	**35 (29-41)**
Karnofsky perform. score ≥80%, n (%)	**497 (95)**	**494 (95)**
Body mass index, median (IQR)	**19.6 (17.9-21.9)**	**19.7 (17.8-21.9)**
CD4/mm^3, median (IQR)	**28 (12-56)**	**32 (13-55)**
CD4<50/mm^3, n (%)	**370 (70)**	**370 (71)**
HIV-RNA, $\log_{10}$ copies/ml, median (IQR)	**5.5 (5.2-5.8)**	**5.4 (5.1-5.8)**
Hemoglobin, g/dl, median (IQR)	**11.5 (9.9-13.4)**	**11.7 (9.9-13.2)**
Positive plasma HBs Ag, n (%)	**47 (9.0)**	**48 (9.2)**

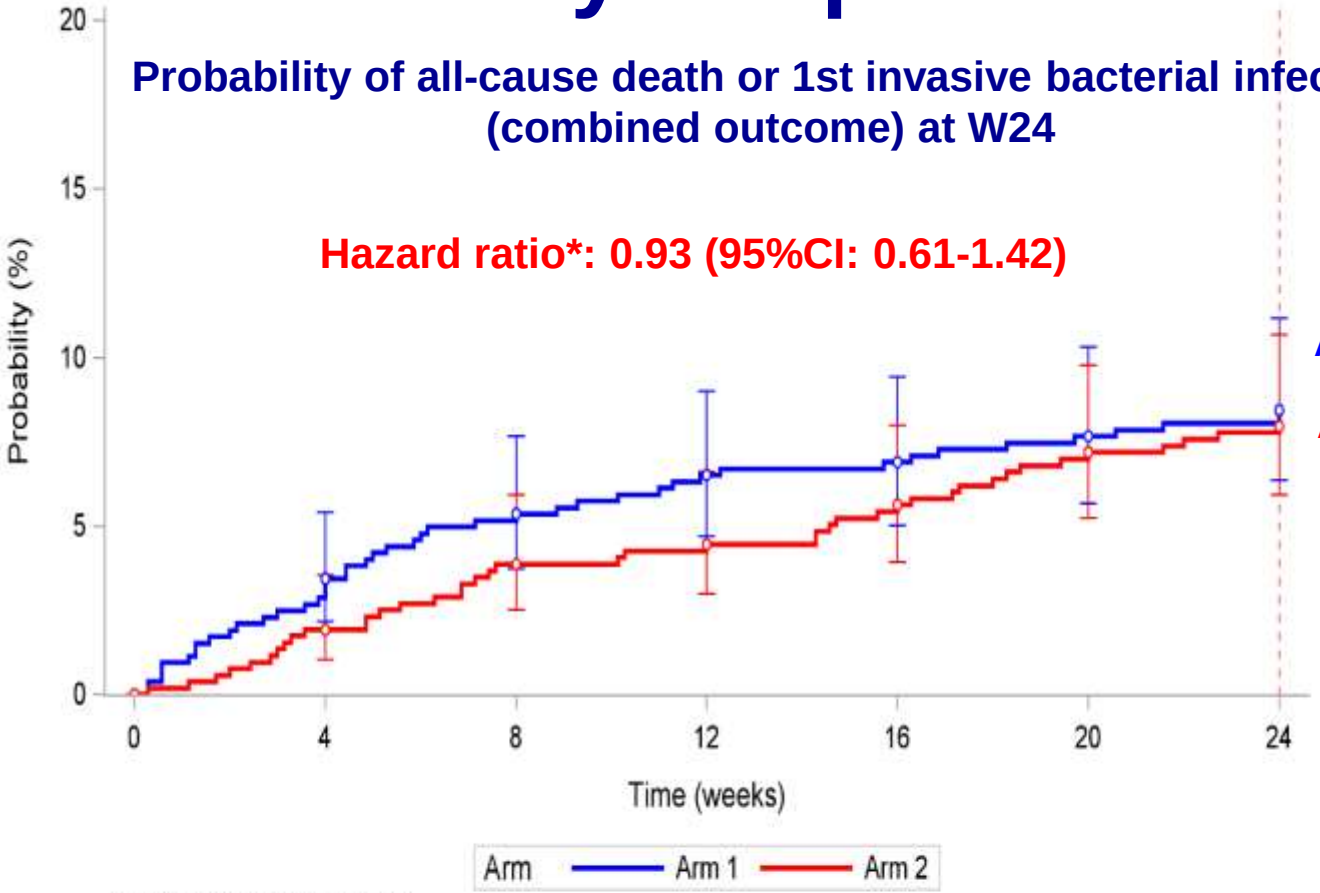
Follow-up characteristics

	Arm 1 (n=525)	Arm 2 (n=522)
Status at Week 24		
Active follow-up, n (%)	**468 (89.1)**	**471 (90.2)**
Lost to follow-up / consent withdrawal, n (%)	**21 (4.0)**	**18 (3.5)**
Dead, n (%)	**36 (6.9)**	**33 (6.3)**
Anti-TB treatment initiated, n (%)	**86 (16.4)**	**521 (99.8)**
ART initiated, n (%)	**523 (99.6)**	**510 (97.7)**

Primary endpoint

Probability of all-cause death or 1st invasive bacterial infection (combined outcome) at W24

Hazard ratio*: 0.93 (95%CI: 0.61-1.42)



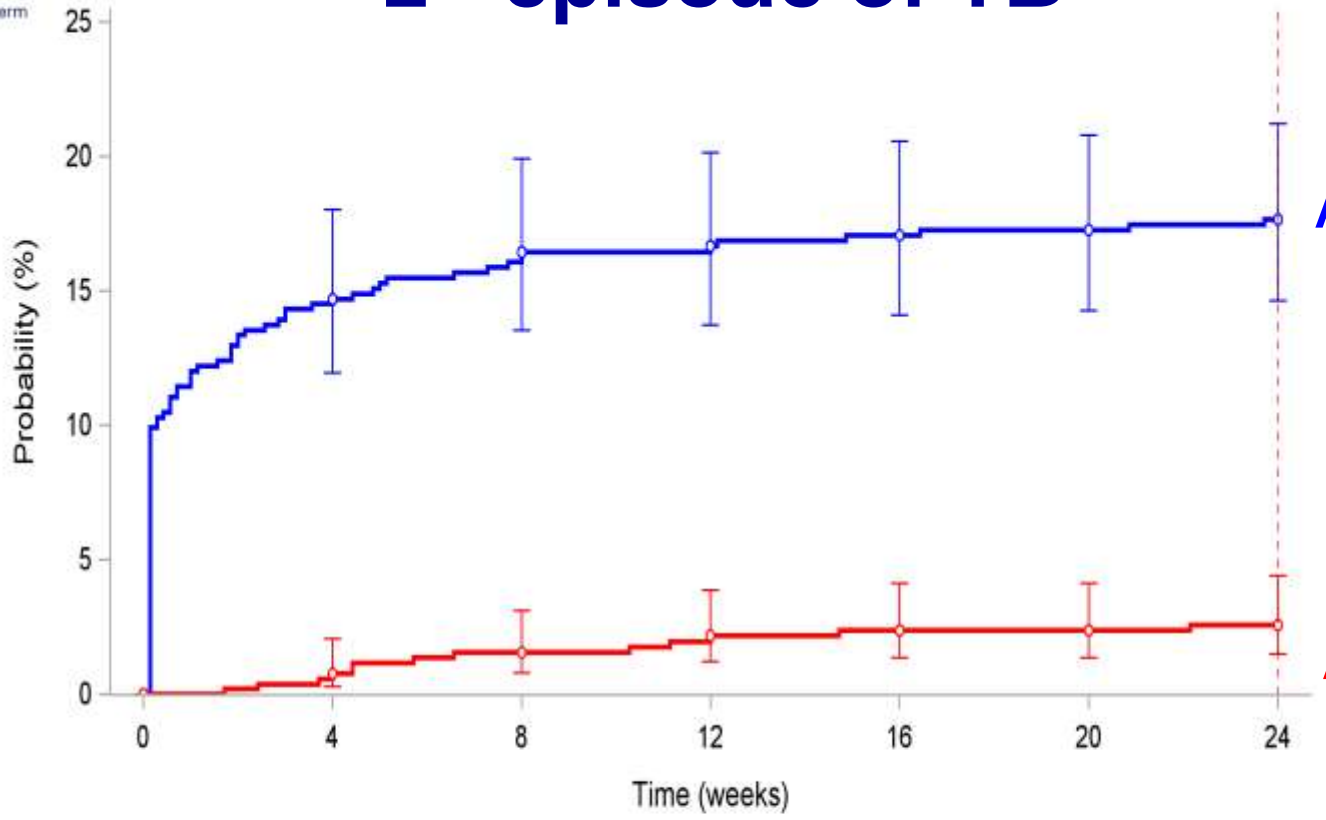
Arm 1 = 8.4%

Arm 2 = 8.0%

Number of Subjects at Risk							
Arm 1	525	504	493	486	484	480	473
Arm 2	522	507	495	492	484	475	470
Number of events							
Arm 1	0	18	28	34	36	40	44
Arm 2	0	10	20	23	29	37	41
Probability of events							
Arm 1	0.00	3.44	5.35	6.51	6.89	7.66	8.43
Arm 2	0.00	1.93	3.87	4.45	5.62	7.18	7.96

*** Adjusted for country and baseline CD4 count (< or ≥50/mm^3)**

1st episode of TB



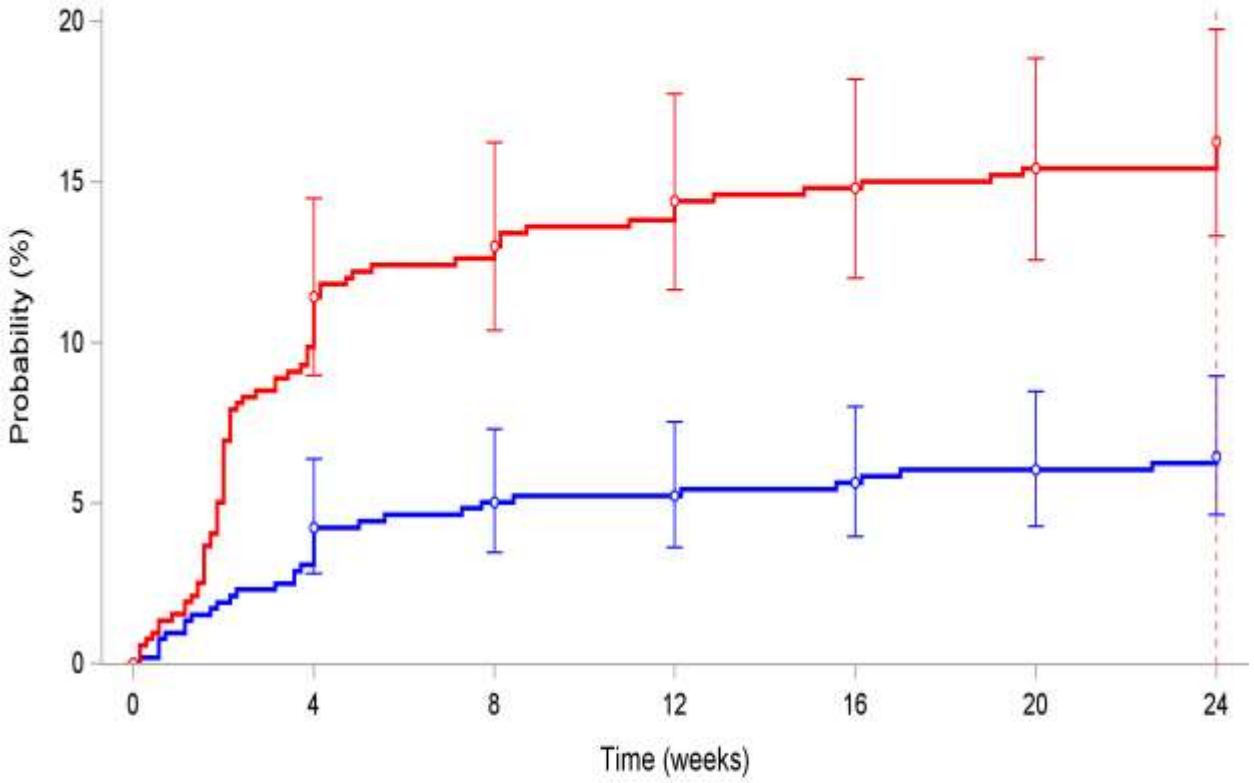
Arm 1 = 17.7%

Arm 2 = 2.6%

Number of Subjects at Risk							
Arm 1	525	440	427	418	416	413	408
Arm 2	522	506	491	485	476	470	467
Number of events							
Arm 1	0	77	86	87	89	90	92
Arm 2	0	4	8	11	12	12	13
Probability of events							
Arm 1	0.00	14.70	16.46	16.66	17.05	17.25	17.66
Arm 2	0.00	0.78	1.57	2.17	2.37	2.37	2.58

1st episode of grade 3-4 drug-related toxicity

HR: 2.70 (95%CI: 1.80-4.04)



Arm 2 = 16.3%

Arm 1 = 6.5%

Number of Subjects at Risk							
Arm 1	525	490	478	469	465	462	456
Arm 2	522	453	436	427	418	409	403
Number of events							
Arm 1	0	22	26	27	29	31	33
Arm 2	0	59	67	74	76	79	83
Probability of events							
Arm 1	0.00	4.24	5.03	5.23	5.63	6.04	6.45
Arm 2	0.00	11.43	13.00	14.40	14.81	15.42	16.25

En guise de conclusion…

- **Tuberculose : évidemment plus grave chez l'immunodéprimé → mortalité +++**
- Diagnostic : nouveaux outils (LAM urinaire, Xpert…)
- Particularités d'imagerie à connaître, notamment au niveau pulmonaire (greffés ≠ VIH)
- Traitement antituberculeux empirique : souvent fait, non validé
- Intensification du traitement antituberculeux : études en cours et à venir
- **Importance +++ de la chimioprophylaxie : bénéfice démontré, y compris en terme de mortalité**

In memoriam

Professor Stephen D Lawn, 1966–2016

département hospitalo-universitaire
DHU 2020
médecine personnalisée des maladies chroniques

Merci pour votre attention

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