Histoire naturelle de la tuberculose / VIH

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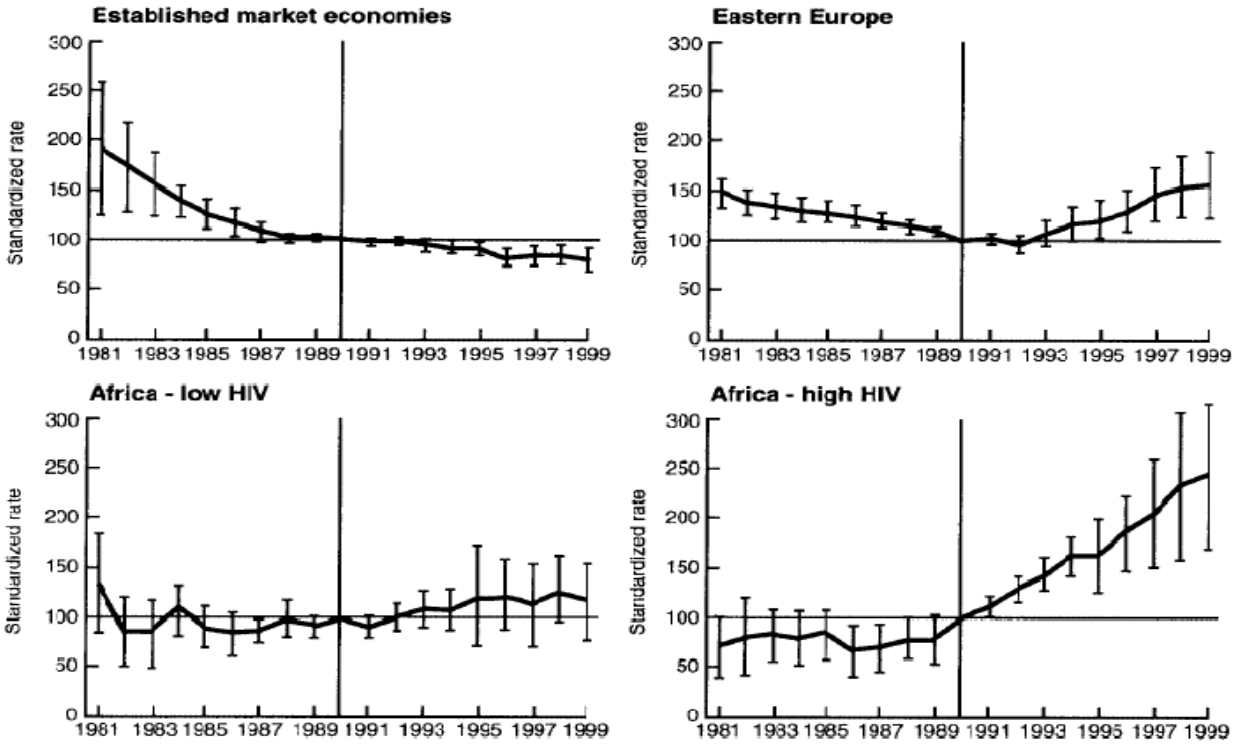
Symposium TB/VIH Pasteur
28/03/11

Plan

1) Evolution initiale en l'absence de trithérapie
2) Modification de l'histoire naturelle depuis l'ère des trithérapies
3) Qu'en est-il dans l'ère « post HAART » et stratégies aux vues de l'histoire naturelle TB/VIH

Données OMS dans les années 80



Données OMS depuis 1990

- Incidence TBx3 depuis 1990 dans les pays à forte prévalence VIH
- Prévalence globale TB : 32% pop (1,86 Milliard)
- 2008 :
  - incidence de la tuberculose : 9.4 M
  - Incidence TB/VIH: 1.4 M, soit 15% VIH+
  - 1.8 M de décès dont 0.52 M chez VIH +
  - 22% connaissaient leur statut VIH, dont 45% en Afrique, 0.1 M ont reçu HAART
  - 9 pays d'Afrique S concentrent 50% cas TB/VIH

Relation TB/VIH : exemple en Afrique du Sud

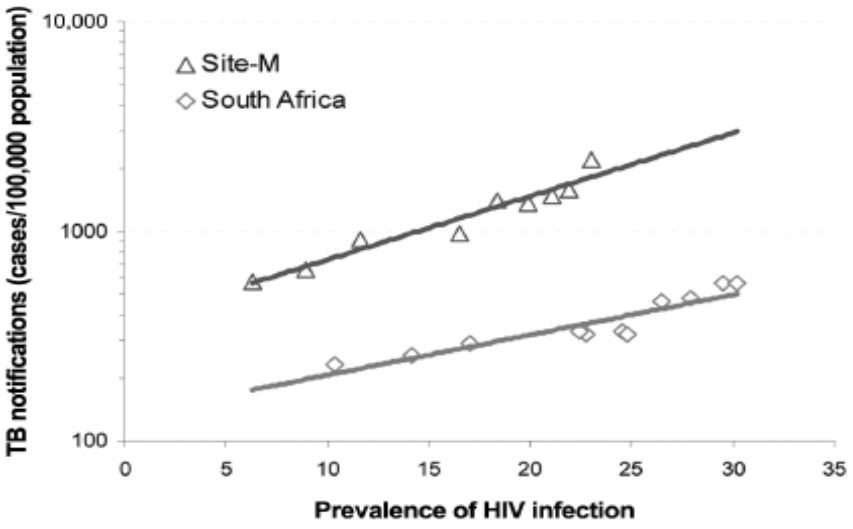


Figure 3. The relationship between tuberculosis (TB) notification rates and seroprevalence of HIV infection in the South African population *(diamonds)* and the population at Site-M *(triangles)*, with exponential regression lines for South African data during 1990–2005 (R^2, 0.8461) and for Site-M data during 1996–2005 (R^2, 0.9376).

TB and HIV in an Area of Hyperendemicity • CID 2010:50 (Suppl 3) • S211

Linda-Gail Bekker[1,2] and Robin Wood[1,2]

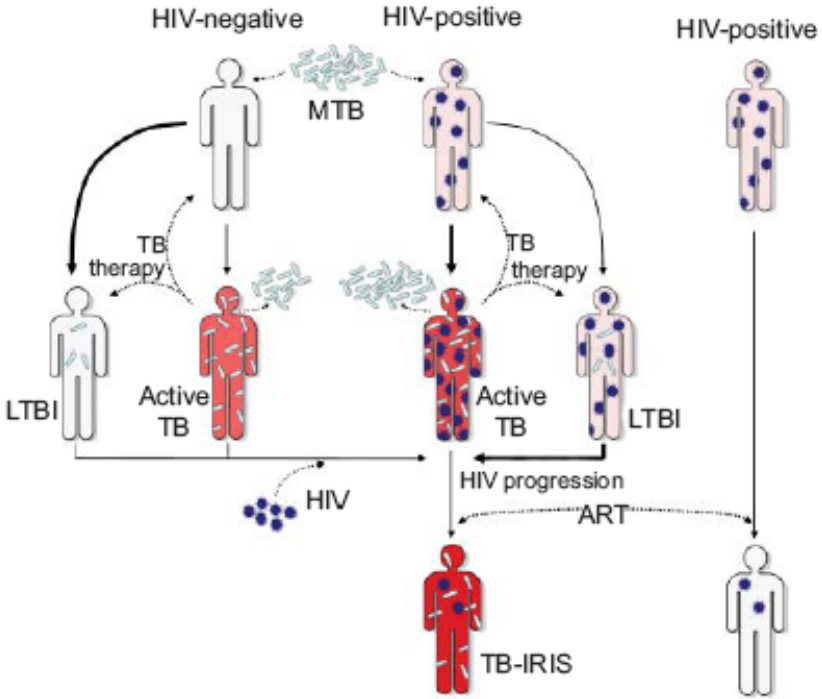
Histoire naturelle tuberculose VIH

Passage de TB latente à TB maladie :

- 5-10% après PIT chez VIH-

- 10% / an en zone d'endémie chez VIH+

M. SESTER ET AL.
Eur Respir J 2010; 36: 1242–1247



Données générales

- Plus de réactivations :
  - incidence de TB x2 dès la 1ère année de séroconversion, puis ↑ /ans (P. Sonnenberg, JID 2005)

- Plus de réinfections chez les VIH+ :
  - HR : 2.4 après ttt TB complété (P. Sonnenberg, Lancet 2005)
  - 2.2/100PA (A.C. Crampin, AIDS 2010)

High Rates of Recurrence in HIV-Infected and HIV-Uninfected Patients with Tuberculosis

Judith R. Glynn,[1] Jill Murray,[3,4] Andre Bester,[6] Gill Nelson,[3,4] Stuart Shearer,[5] and Pam Sonnenberg[2]

The Journal of Infectious Diseases 2010;201:704–711

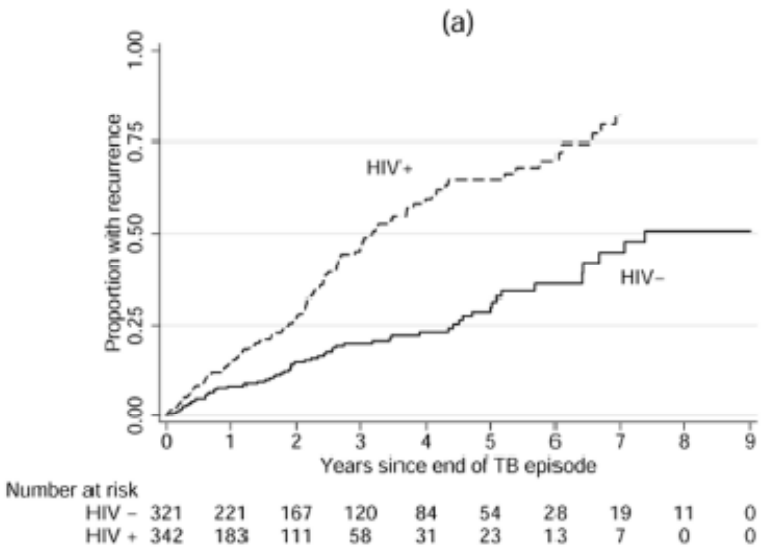


Table 3. Rates of New Tuberculosis (as Estimated Elsewhere [13]) and Recurrent Tuberculosis (as Estimated in This Study), by Human Immunodeficiency Virus (HIV) Status

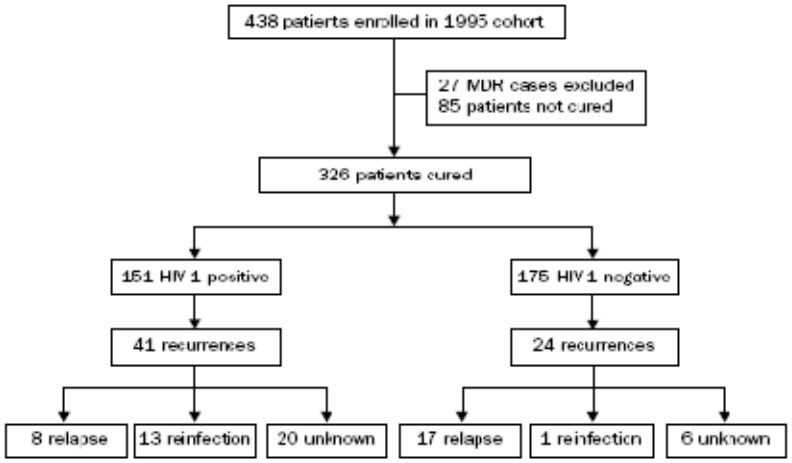
Episode	HIV-negative cases per 100 PYAR (95% CI)	HIV-positive cases per 100 PYAR (95% CI)
Incicence of new pulmonary tuberculosis		
Overall	0.75 (0.67–0.84)	3.7 (3.3–4.1)
In 2003/2004	1.2 (0.89–1.7)	8.4 (6.2–11.2)
≥10 years after seroconversion to HIV		10.0 (6.5–15.5)
Recurrence		
Overall	7.7 (6.1–9.8)	19.7 (16.4–23.7)
Estimated recurrence due to reinfecton[a]	4.3 (2.2–8.3)	24.4 (17.2–34.8)

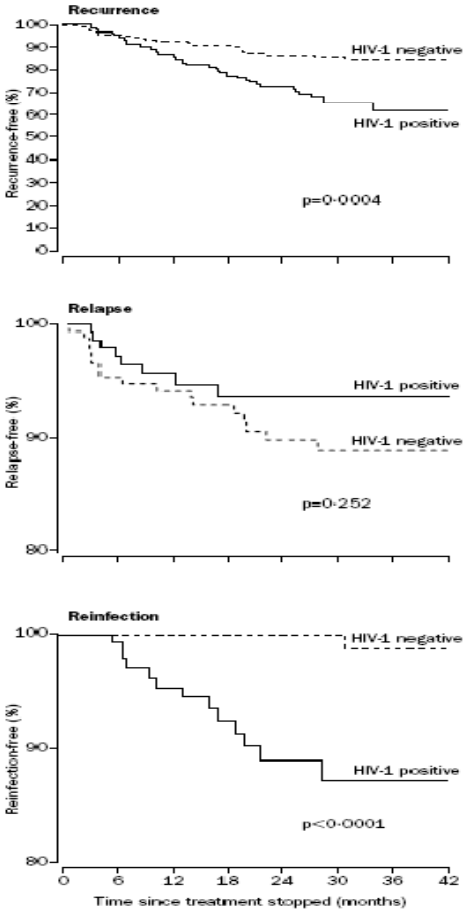
[a] Pulmonary tuberculosis, ony 1 previous episode, cure recorded, >2 years follow-up.

HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers

Pamela Scnnenberg, Jill Murray, Judith R Glynn, Stuart Shearer, Bupe Kambashi, Peter Godfrey-Faussett

Lancet 2001; **358:** 1687–93





Numbers at risk

HIV-1 negative	175	160	146	131	106	84	34	34
HIV-1 positive	151	131	104	87	66	39	15	15

Figure 2: **Kaplan-Meier curves**
Showing risk of recurrence, relapse, and reinfection in 151 HIV-1-positive and 175 HIV-1-negative tuberculosis patients.

Recurrent TB: relapse or reinfection? The effect of HIV in a general population cohort in Malawi

AIDS. 2010 January 28

Amelia C. Crampin[1,2], J. Nimrod Mwaungulu[1], Frank D. Mwaungulu[1], D. Totah Mwafulirwa[1], Kondwani Munthali[1], Sian Floyd[2], Paul EM Fine[2], and Judith R Glynn[2]

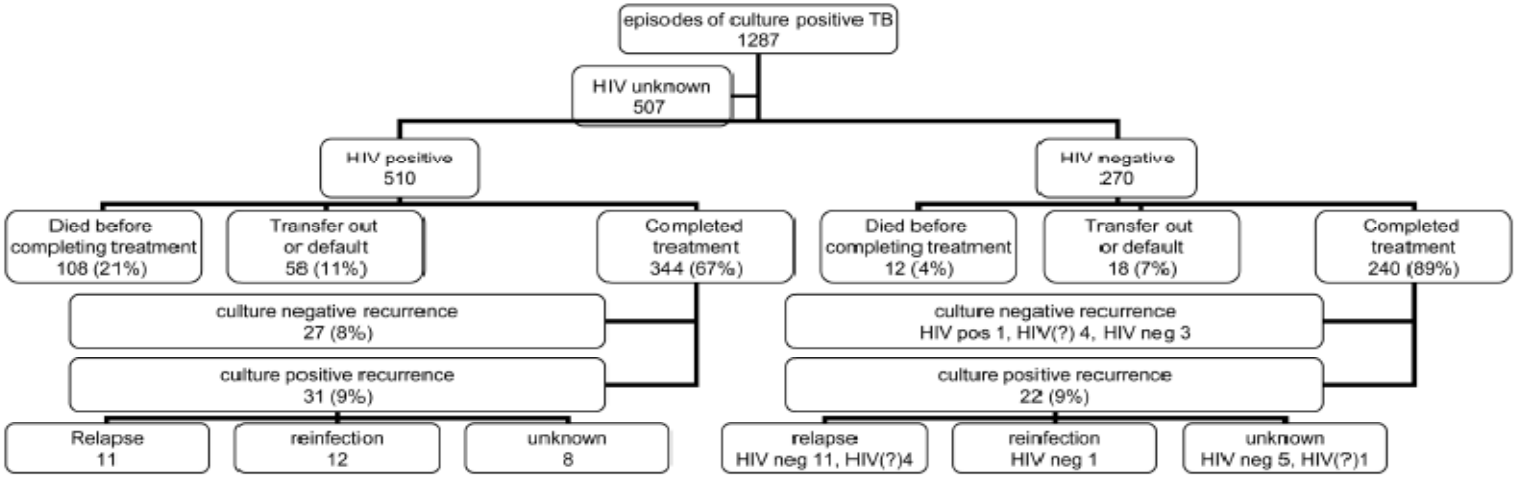


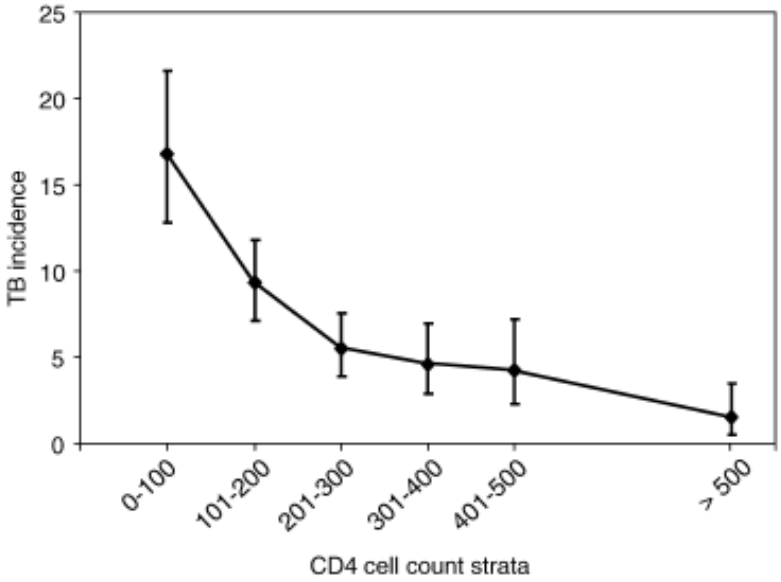
Figure 1.
Outcome of episodes of culture positive tuberculosis

Incidence TB chez VIH+ augmente avec l'aggravation du déficit imunitaire et est déjà visible dès CD4<500/mm3

Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa

Stephen D. Lawn[a,b], Landon Myer[c,d], David Edwards[a], Linda-Gail Bekker[a] and Robin Wood[a]

AIDS 2009, **23**:1717–1725



CD4 count stratum	No. of incident TB cases	Person-years of observation (PYO)	Rate per 100 PYO (95%CI)
≤ 100	59	352.0	16.76 (12.76-21.62)
101-200	65	701.2	9.27 (7.15-11.82)
201-300	38	693.7	5.48 (3.88-7.52)
301-400	23	499.1	4.61 (2.92-6.91)
401-500	13	307.1	4.23 (2.25-7.24)
> 500	5	334.2	1.50 (0.49-3.49)

Diagnostic de TB + difficile chez VIH+

- > 50% d'examens directs négatifs à un stade avancé (Mugusi 2006, Lawson Sc J I D 2008, Bruchfeld Sc J I D 2002)
- Formes associées à la multi R et XDR
- Plus de formes extra-pulmonaires disséminées ou à Rx thorax N avec l'abaissement des CD4 (Jones BE ARRD 93, Perronne C presse med 88, Harries AD 1998)

Formes cliniques de TB chez VIH+

Tuberculosis in HIV-infected persons in the context of wide availability of highly active antiretroviral therapy

E. Girardi*, G. Antonucci#, P. Vanacore*, F. Palmieri#, A. Matteelli¶, E. Iemoli+, S. Carradori§, B. Salassa[f], M. Bruna Pasticci**, M.C. Raviglione##, G. Ippolito*, and the GISTA–SIMIT Study Group

Eur Respir J 2004; 24: 11–17

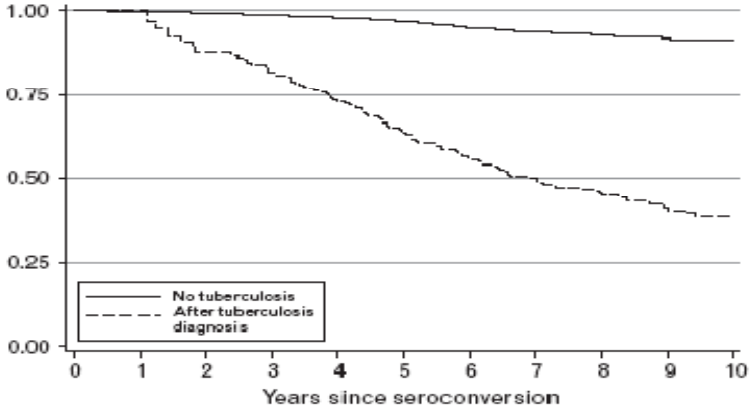
Table 3. – Localisation of tuberculosis (TB) and chest radiograph pattern in patients with pulmonary involvement by antiretroviral therapy at the time of diagnosis of TB

	Antiretroviral therapy at the time of diagnosis of TB	
	Yes	No
Patients n	82	189
Localisation of TB		
Pulmonary	50 (61.0)	100 (52.9)
Pulmonary+extrapulmonary	15 (18.3)	54 (28.6)
Extrapulmonary	17 (20.7)	35 (18.5)
Chest radiograph pattern#		
Upper-lobe infiltrate/cavitation	16 (23.2)	45 (26.6)
Lower-lobe infiltrate	9 (13.0)	24 (14.2)
Pleural effusion	8 (11.6)	18 (10.7)
Miliary/interstitial	16 (23.2)	36 (21.3)
Other	20 (29.0)	46 (27.2)

Data are presented as n (%). #: among 216 patients with pulmonary involvement and available results of chest radiograph.

Mortalité accrue

- tuberculose : marqueur de progression du VIH (J.R. Glynn AIDS 2010)



NoTB	1574	1599	1326	1074	880	635	430	263	144	52
AfterTB	23	51	87	112	112	111	83	72	43	27

Fig. 1. Survival after an episode of tuberculosis compared with survival in those without tuberculosis among 1950 HIV-positive men (adjusted to age 25–29 years at seroconversion). The numbers being followed at each stage are shown.

- En l'absence de ttt approprié : 90% VIH+ décèdent qq mois après avoir contracté TB

Complications thérapeutiques liées à la coinfection :

- Intéractions médicamenteuses
- Effets secondaires cumulés
- IRIS
- MultiR aux antituberculeux

Tenofovir DF/Emtricitabine and Efavirenz in HIV infected patients treated for tuberculosis : Results from the ANRS 129 BKVIR Trial

O.Lortholary, C.Roussillon, M-L. Chaix, N.Veziris, G.Breton, O.Patey, E.Caumes,T.May, J-M. Molina,G.Chene,and the ANRS 129 BKVIR Trial Group

Poster ICAAC 2010

TB à l'ère des trithérapies : HAART : un des meilleurs moyens de prévention de la tuberculose?

1) Évolution TB pré et post HAART : baisse 70% risque TB sous HAART et baisse de la mortalité de 64 à 95%

Girardi E, Antonucci G, Vanacore P, *et al.* Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. *AIDS* 2000; 14: 1985–1991.

Jones JL, Hanson DL, Dworkin MS, DeCock KM. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *Int J Tuberc Lung Dis* 2000; 4: 1026–1031.

Santoro-Lopes G, de Pinho AM, Harrison LH, Schechter M. Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. *Clin Infect Dis* 2002; 34: 543–546.

Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002; 359: 2059–2064.

Evolution de l'incidence des IO sous HAART

The Changing Natural History of HIV Disease: Before and After the Introduction of Generic Antiretroviral Therapy in Southern India

N. Kumarasamy,[1] Suniti Solomon,[1] Sreekanth K. Chaguturu,[2] Anitha J. Cecelia,[1] Snigdha Vallabhaneni,[2] Timothy P. Flanigan,[2] and Kenneth H. Mayer[2]

Clinical Infectious Diseases 2005; 41:1525–8

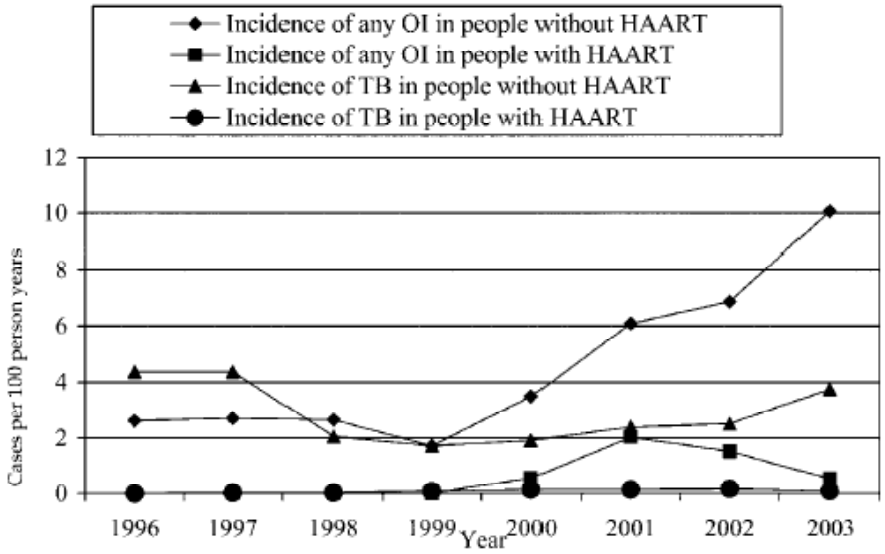


Figure 2. Incidence of opportunistic infection (OI) and tuberculosis (TB) among patients with and without HAART, 1996–2003.

2) Intérêt de HAART introduit précocément

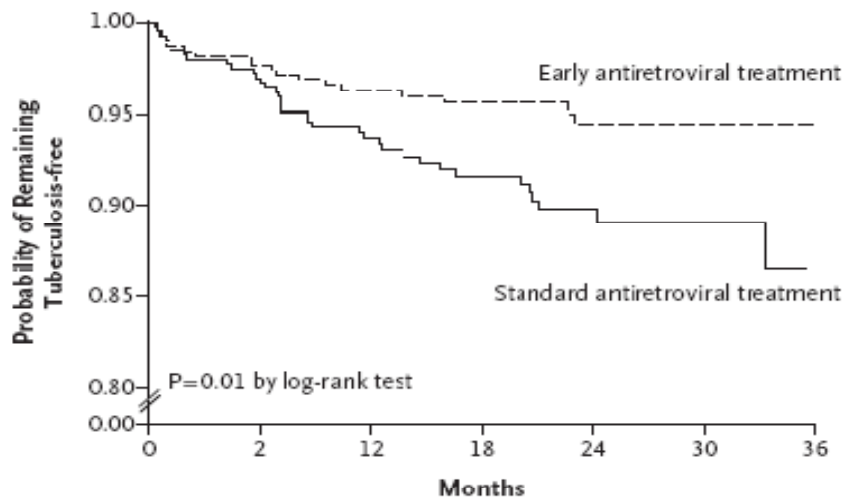
- CAMELIA trial : Press release 07/2010
  - 2006-2010 : 5 hôpitaux au Cambodge
  - 661 patients coinfectés, 72% avec CD4<50/mm3
  - 2 bras :
    - 332 patients J1 ARV= S2 ttt TB,
    - 329 patients J1 ARV= S8 ttt TB
  - Suivi jusqu'à M26 : baisse de 34% de mortalité dans le bras ttt précoce à S2 (p : 0.007)

2) Intérêt de HAART introduit précocément

Early versus Standard Antiretroviral Therapy
for HIV-Infected Adults in Haiti

Patrice Severe,

N ENGL J MED 363;3 NEJM.ORG JULY 15, 2010



No. at Risk				
Early treatment	380	302	140	20
Standard treat-ment	393	288	122	16

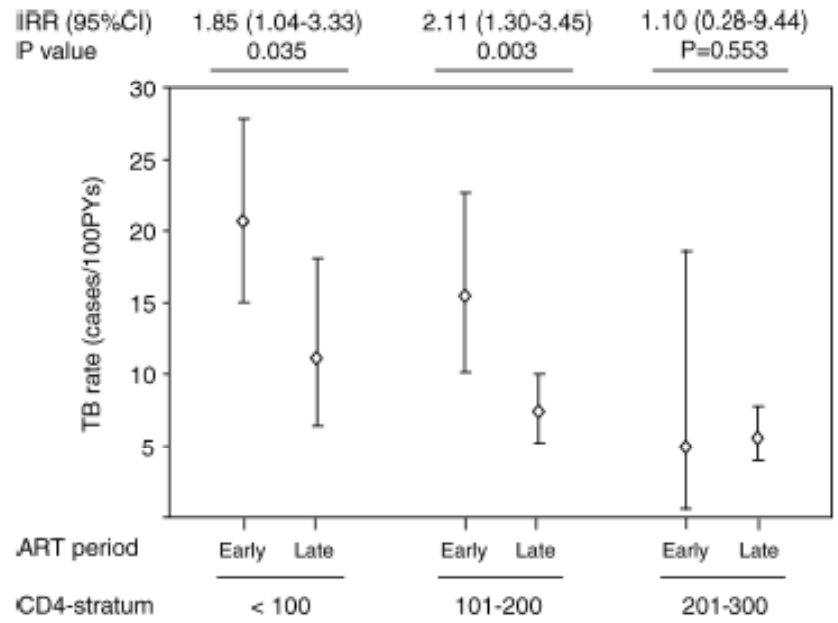
Figure 3. Kaplan–Meier Estimates of the Probability of Remaining Free from Active Tuberculosis in the Early-Treatment and Standard-Treatment Groups.

2) Intérêt de HAART mais associé à 1 dépistage précoce de la TB

Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa

Stephen D. Lawn[a,b], Landon Myer[c,d], David Edwards[a], Linda-Gail Bekker[a] and Robin Wood[a]

AIDS 2009, Vol 23 No 13



3) Intérêt d'un dépistage précoce

Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pretreatment screening strategy

Stephen D. Lawn[a,b], Katharina Kranzer[a,b], David J. Edwards[a], Matthew McNally[c], Linda-Gail Bekker[a] and Robin Wood[a]

AIDS 2010, **24**:1323–1328

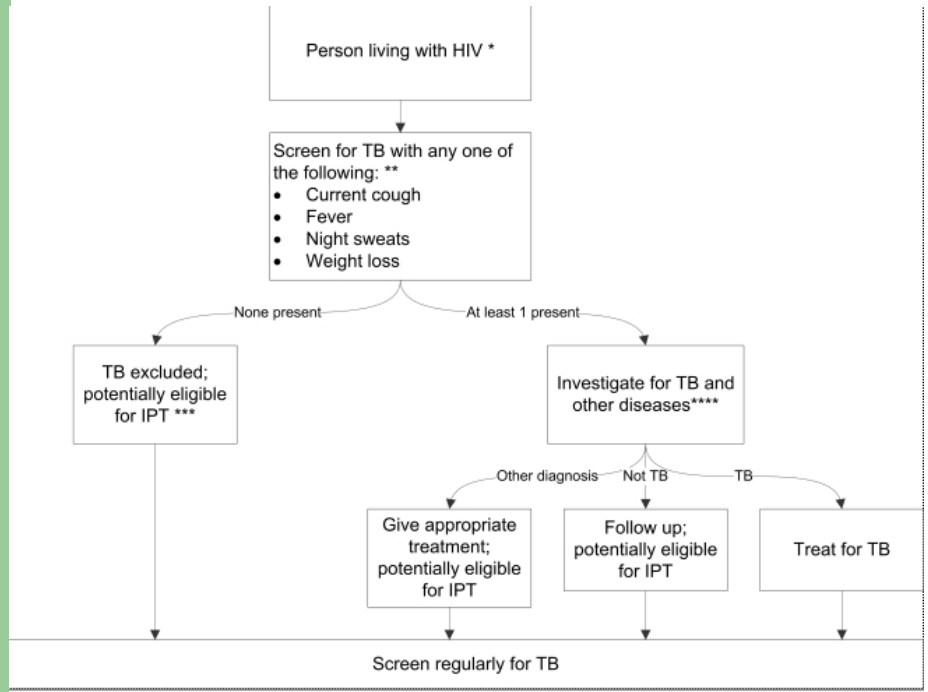
- 241 patients , médiane CD4 : 125/mm3, 83% ont débuté HAART
- TB diagnostiquée chez 87 (36%), 82% culture +,
- 87% des TB dépistées au départ, 13% pdt la 1ère année de HAART
- Incidence TB entre 0-4 mois =entre 5-12 mois (10.9 %PA vs 8.1)
- Baisse de 50% de l'incidence de TB dans 1ers mois sous HAART par dépistage systématique avec culture BK

3) Dépistage précoce possible par des données simples d'interrogatoire en zone de forte endémie VIH/TB

PLoS Med. 2011 Jan 18;8(1):e1000391.

Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies.

Haileyesus Getahun,1* Wanitchaya Kittikraisak,2 Charles M. Heilig,3 Elizabeth L. Corbett,4 Helen Ayles,4,5 Kevin P. Cain,3 Alison D. Grant,4 Gavin J. Churchyard,6 Michael Kimerling,7 Sarita Shah,8 Stephen D. Lawn,4,9 Robin Wood,9 Gary Maartens,10 Reuben Granich,1 Anand A. Date,3 and Jay K. Varma2,3



Sensibilité globale :78.9% [58.3%-90.9%],

Spécificité :49.6% [29.2%-70.1%]

Sensibilité dans cliniques : 90.1% [76.3%-96.2%]

Pas de dépistage de TB antérieur : 88.0% [76.1%-94.4%

VPN : 97.7% qd 5% prévalence TB/VIH

4) Traitement « IPT » dans les pays à ressources limitées

- Isoniazide pendant 6-9 mois :
  - réduit le risque de TB de 33% chez VIH+
  - de 64% chez VIH+ avec IDR +
  - avec un effet protecteur de 6 à 24 mois après l'arrêt de la prophylaxie

Int J Tuberc Lung Dis. 2009 Aug;13(8):927-35.

Isoniazid preventive therapy for people living with HIV: public health challenges and implementation issues.

Aït-Khaled N, Alarcon E, Bissell K, Boillot F, Caminero JA, Chiang CY, Clevenbergh P, Dlodlo R, Enarson DA, Enarson P, Ferroussier O, Fujiwara PI, Harries AD, Heldal E, Hinderaker SG, Kim SJ, Lienhardt C, Rieder HL, Rusen ID, Trébucq A, Van Deun A, Wilson N.

International Union Against Tuberculosis and Lung Disease, Paris, France.

Cochrane Database Syst Rev. 2010 Jan 20;(1):CD000171.

Treatment of latent tuberculosis infection in HIV infected persons.

Akolo C, Adetifa I, Shepperd S, Volmink J.

Department of Public Health, University of Oxford, Oxford, UK, OX3 7LF.

5) Vaccins efficaces ?

- Actuellement pas de données suffisantes

La tuberculose reste –t-elle un pb en post HAART dans les pays à ressources limitées?

(NIH, CID 2010)

- OUI

OMS 2009

FIGURE 1

Estimated TB incidence rates, by country, 2009

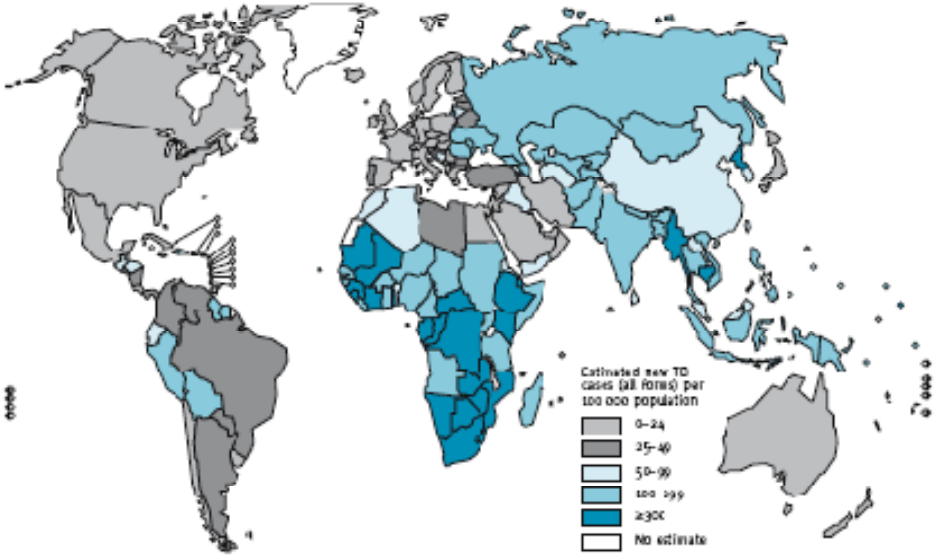
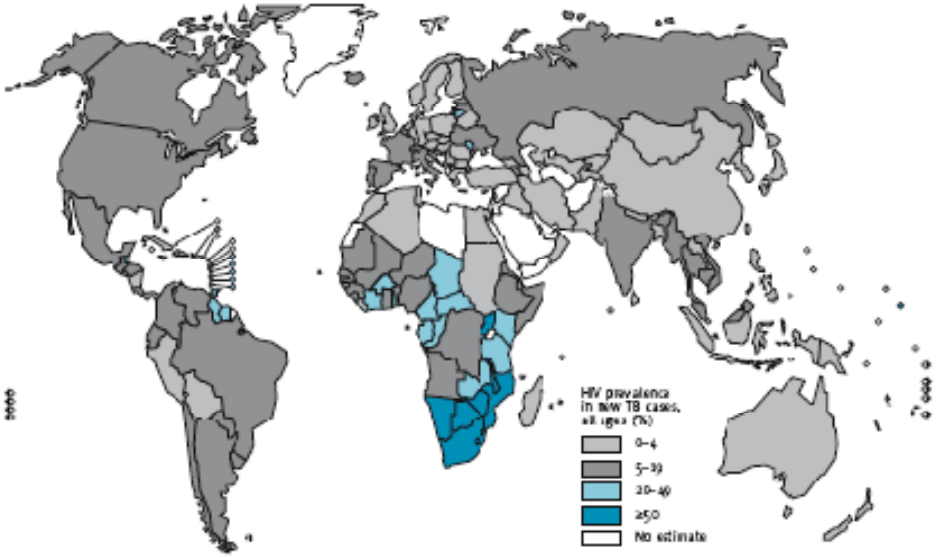


FIGURE 2

Estimated HIV prevalence in new TB cases, 2009



Evolution récente du dépistage TB et VIH, de la mise sous traitements préventif et HAART dans le monde

The HIV-associated tuberculosis epidemic—when will we act?

Anthony D Harries, Rony Zachariah, Elizabeth L Corbett, Stephen D Lawn, Ezio T Santos-Filho, Rhehab Chimzizi, Mark Harrington, Dermot Maher, Brian G Williams, Kevin M De Cock

Lancet 2010; 375: 1906–19

	Global Plan target for 2006	Country reports for 2006*	Global Plan target for 2007	Country reports for 2007*	Global Plan target for 2008	Country reports for 2008*
Number of HIV-infected people who were actively screened for tuberculosis	11 000 000	314 000 (2·9%)	14 000 000	630 000 (4·5%)	16 000 000	1 385 000 (8·7%)
Number of eligible HIV-infected people who were offered isoniazid preventive therapy	1 200 000	27 000 (2·3%)	1 500 000	29 000 (1·9%)	1 900 000	48 000 (2·5%)
Number of tuberculosis patients who were tested and counselled for HIV infection	1 600 000	687 000 (42·9%)	2 000 000	1 122 000 (56·1%)	2 300 000	1 374 000 (59·7%)
Number of HIV-positive tuberculosis patients who started co-trimoxazole treatment	500 000	147 000 (29·4%)	600 000	196 000 (32·7%)	700 000	229 000 (32·7%)
Number of HIV-positive tuberculosis patients who started antiretroviral treatment	220 000	66 000 (30·0%)	300 000	90 000 (30·0%)	300 000	109 000 (36·3%)

Adapted from WHO Global Tuberculosis Control 2009,[16] the Global Plan to Stop TB 2006–2015,[17] and WHO Global Tuberculosis Control.[18] *Numbers are rounded to nearest thousand; percentages are the proportion of the Global Plan target.

Table 1: Progress against collaborative tuberculosis and HIV targets in the Global Plan to Stop TB, 2006–2015

Résultats encourageants

- Augmentation du dépistage et de l’accessibilité aux IPT et ttt ARV
- Mais trop peu de patients bénéficient de HAART et ttt débuté le + souvent tardivement avec des CD4<150/mm3
- Prise de conscience de la nécessité d’une prise en charge commune tuberculose VIH

La tuberculose reste –t-elle un problème en post HAART dans les pays industrialisés?

- OUI
- NHS 2010 Update en Europe :
  - UK : 5.7% de coinfection sur les cas de TB entre 99-2003 et 8.3% en 2003
  - A Londres : estimation de 17-25% de co-infection
  - UK :en 2008 : proportion des VIH+ diagnostiqués avec des CD4<200/mm3 : 32%
  - En France : VIH+ de la cohorte FHDH/ANRS CO4, malgré la disponibilité des HAART, augmentation de l'incidence des cas de TB de 97 à 2007
  - Multi résistance aux anti TB dans les pays de l'Est

HIV-associated tuberculosis and immigration in a high-income country: incidence trends and risk factors in recent years

Sophie Abgrall[a,b,c], Pascal del Giudice[d], Giovanna Melica[e], Dominique Costagliola[a,b,f], on behalf of FHDH-ANRS CO4[1]

AIDS 2010, **24**:763–771

Table 2. Characteristics of the patients at diagnosis of tuberculosis in the French Hospital Database on HIV.

	Prevalent TB ($N = 932$)	Incident TB ($N = 1693$)	P
TB form [n (%)]			
Pulmonary	441 (47.3)	894 (52.8)	<0.0001
Extrapulmonary	372 (39.9)	678 (40.1)	
Both pulmonary and extrapulmonary	119 (12.8)	121 (7.1)	
Male sex [n (%)]	637 (68.4)	1071 (63.3)	0.0089
Transmission group [n (%)]			
Homosexual	73 (7.8)	274 (16.2)	<0.0001
Injecting drug use	80 (8.6)	299 (17.7)	
Heterosexual	656 (70.4)	943 (55.7)	
Other or unknown	123 (13.2)	177 (10.4)	
Age [years, median (IQR)]	37 (32–44)	39 (33–45)	0.0004
Period [n (%)]			
1997	69 (7.4)	152 (8.9)	<0.0001
1998–1999	199 (21.4)	251 (14.8)	
2000–2001	216 (23.2)	316 (18.7)	
2002–2003	211 (22.6)	339 (20.0)	
2004–2005	136 (14.6)	312 (18.4)	
2006–2007	85 (9.1)	242 (14.3)	
2008	16 (1.7)	81 (4.9)	
Region of birth [n (%)]			
France	380 (40.8)	1014 (59.9)	<0.0001
Sub-Saharan Africa	378 (40.6)	430 (25.4)	
Other	174 (18.6)	249 (14.7)	
Region of care [n (%)]			
Paris area	660 (70.8)	986 (58.2)	<0.0001
Southern France	51 (5.5)	164 (9.7)	
French West Indies	98 (10.5)	202 (11.9)	
Other/Reunion Island	123 (13.2)	341 (20.2)	
Previous AIDS [n (%)]	0 (0.0)	386 (22.8)	<0.0001
CD4 cell count [cells/μl, median (IQR)]	105 (39–214)	183 (77–346)	<0.0001
pVL [$\log_{10}$ copies/ml, median (IQR)]	5.19 (4.67–5.70)	4.28 (2.70–5.22)	<0.0001
ARV therapy [n (%)]			
Naive	932 (100.0)	522 (30.8)	<0.0001
NRTI mono/dual therapy	0 (0.0)	128 (7.6)	
cART	0 (0.0)	1043 (61.6)	

ARV, antiretroviral; cART, combined antiretroviral therapy; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; pVL, plasma viral load; TB, tuberculosis.

Conclusion

The HIV-associated tuberculosis epidemic—when will we act?

Anthony D Harries, Rony Zachariah, Elizabeth L Corbett, Stephen D Lawn, Ezio T Santos-Filho, Rhehab Chimzizi, Mark Harrington, Dermot Maher, Brian G Williams, Kevin M De Cock

Lancet 2010; 375: 1906–19

Prevention of Tuberculosis in People Living with HIV

Reuben Granich,[1] Christopher Akolo,[2] Christian Gunneberg,[2] Haileyesus Getahun,[2] Phoebe Williams,[1] and Brian Williams[4]

Clinical Infectious Diseases 2010; 50(S3):S215–S222

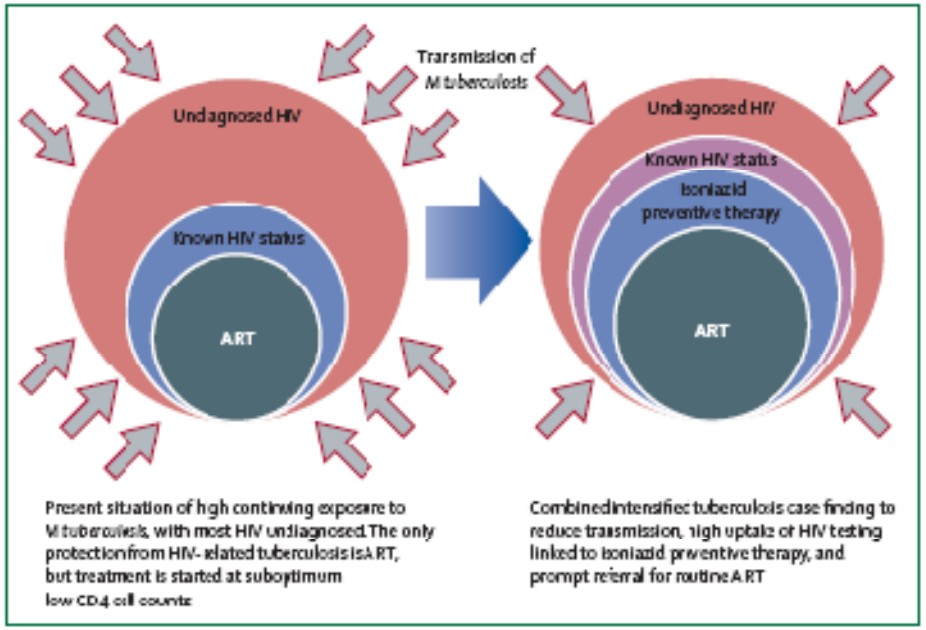


Figure: Combined effect of intensified tuberculosis case finding, HIV testing, isoniazid preventive therapy, and antiretroviral treatment (ART) on exposure and susceptibility to *Mycobacterium tuberculosis*
Arrows indicate amount of exposure to *M tuberculosis*.

Conclusion

- OMS :
  - 2008 : 1.8M DC de TB dont 29% coinfectés
  - 2008 : dépistage VIH : 22% statut VIH connu
  - 2007 : 7.3% (0.1M) des patients coinfectés sous HAART

- Baisse de morbi/mortalité TB nécessite :
  - Collaboration active des réseaux TB et VIH
  - Dépistage précoce des cas de TB avec amélioration des outils diagnostic
  - Dépistage précoce VIH et traitement HAART rapide+++ et prophylaxie par Bactrim
  - Ttt préventif INH en zone de forte endémie VIH/TB