Solthis
SOLIDARITÉ THÉRAPEUTIQUE & INITIATIVES CONTRE LE SIDA

Infections opportunistes & tuberculose

Post-CROI « Pays du Sud »
Epicentre & Solthis
Jussieu, le 28 avril 2011

Pr Pierre-Marie Girard
Hôpital Saint-Antoine – IMEA

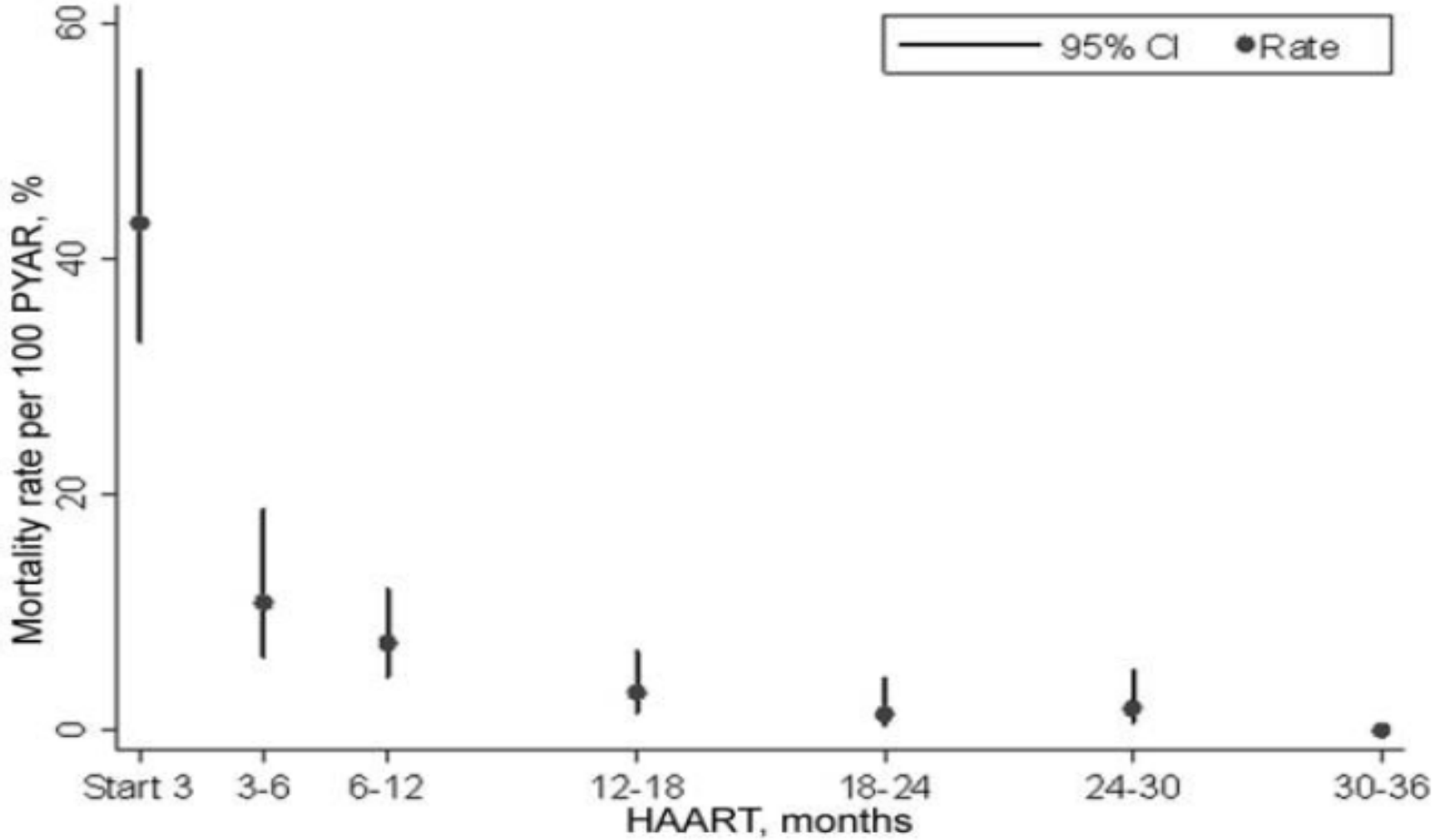


Figure 1. All-cause mortality incidence rates (95% confidence interval [CI]) during the first 36 months of antiretroviral treatment, showing highest rates per 100 person-years at risk (PYAR) during the first 3 months after highly active antiretroviral therapy (HAART) initiation.

Castelnuovo B et al, CID, 2009

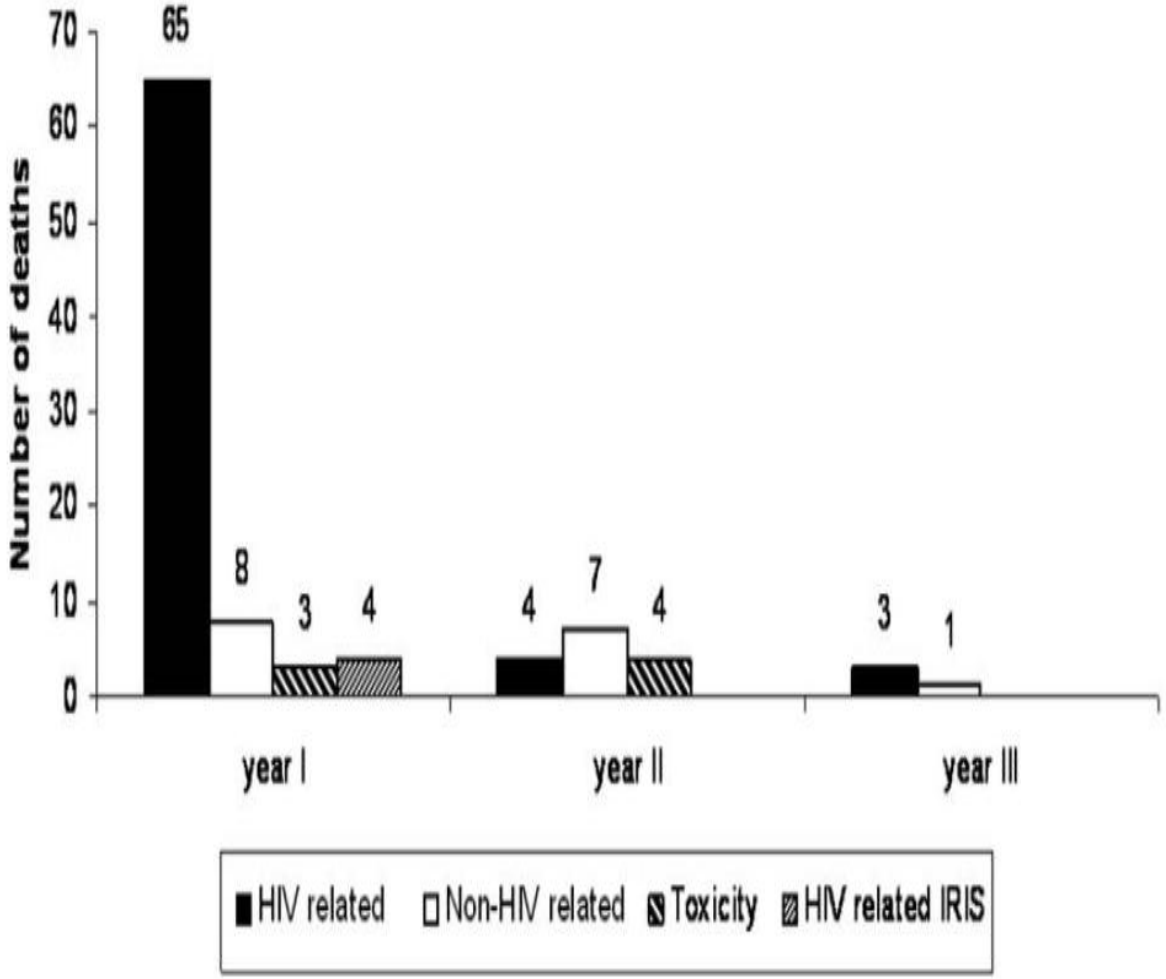
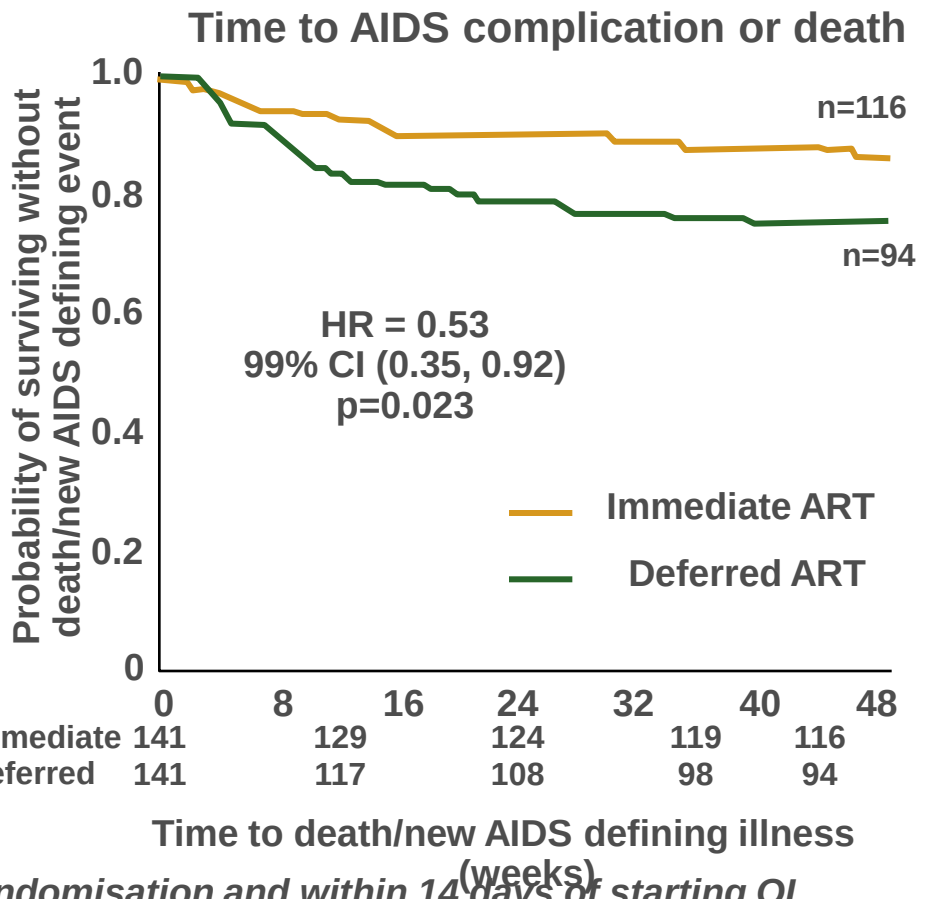


Figure 2. Cause-specific mortality during the first 3 years of antiretroviral treatment. HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome.

Castelnuovo B et al, CID, 2009

ACTG 5164: Immediate vs deferred HAART in patients with acute OIs*

- Immediate treatment group had reduced rate of AIDS progression or death (14.2%) compared with deferred treatment group (24.1%)
  - No differences in IRIS between arms (6% immediate vs 9% deferred)
  - The most common OIs were PCP (63%), Cryptococcus (12%), BI (12%)
- Patients with TB were ineligible



Immediate ART: initiation within 48h of randomisation and within 14 days of starting OI treatment

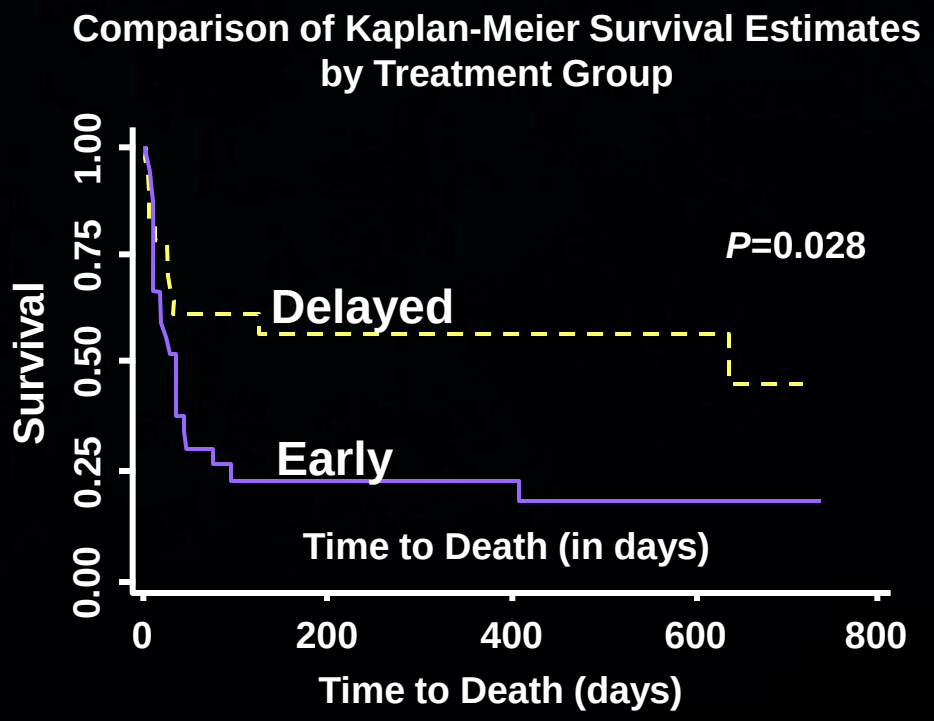
Deferred ART: initiation between weeks 4 and 32

*OIs = opportunistic infections excluding TB; IRIS = immune reconstitution inflammatory syndrome

Adapted from Zolopa AR *et al. PLoS One* 2009; 4 (5):e5575.

ART and Cryptococcal Meningitis: Zimbabwe

- Immediate vs. delayed (10 weeks) ART in Cryptococcal Meningitis (N=54)
  - Tx: Fluconazole 800 mg daily and d4T/3TC/NVP
  - No use of amphotericin or management of raised intracranial pressure
- Mortality: 87% immediate vs. 37% delayed (*P*=0.002)
  - Most deaths in immediate ART group occurred within the first month, possibly due to IRIS
  - Fluconazole-NVP drug interaction postulated



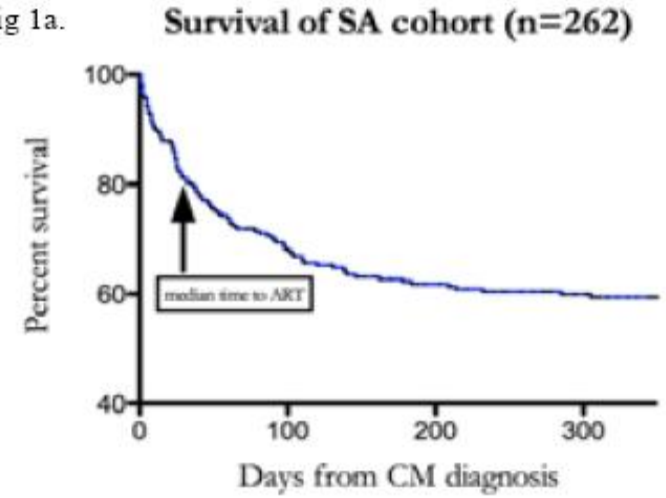
Makadzange A, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 36cLB.

Determinants of Acute Outcome and Long-term Survival in HIV-associated Cryptococcal Meningitis: Results from a Combined Cohort of 523 Patients

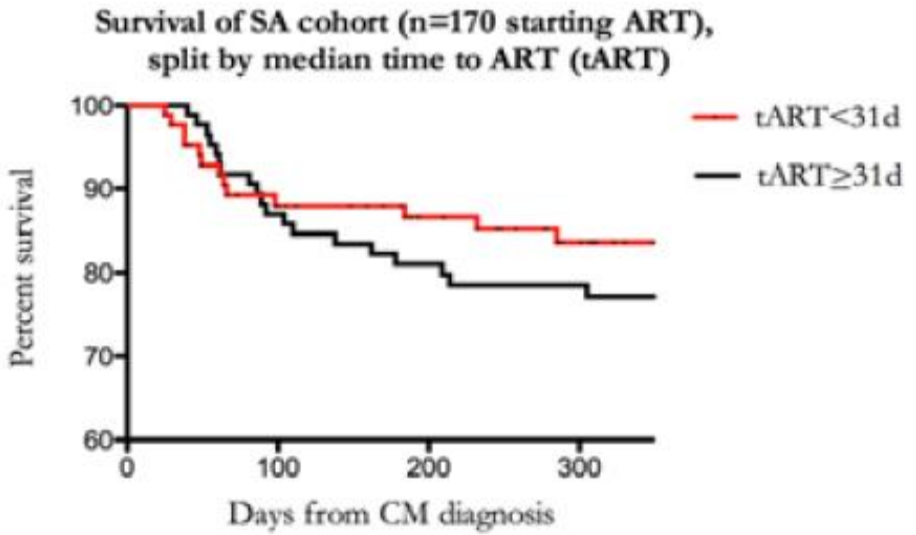
T Bicanic*[1], J Jarvis[1,2,3], A Loyse[1], A Jackson[4], C Muzoora[5], D Wilson[6], C van der Horst[4], R Wood[2], G Meintjes[3] and T Harrison[1]

St. George`s University of London, London, UK; [2]Desmond Tutu HIV Centre, University of Cape Town, South Africa; [3] Institute of

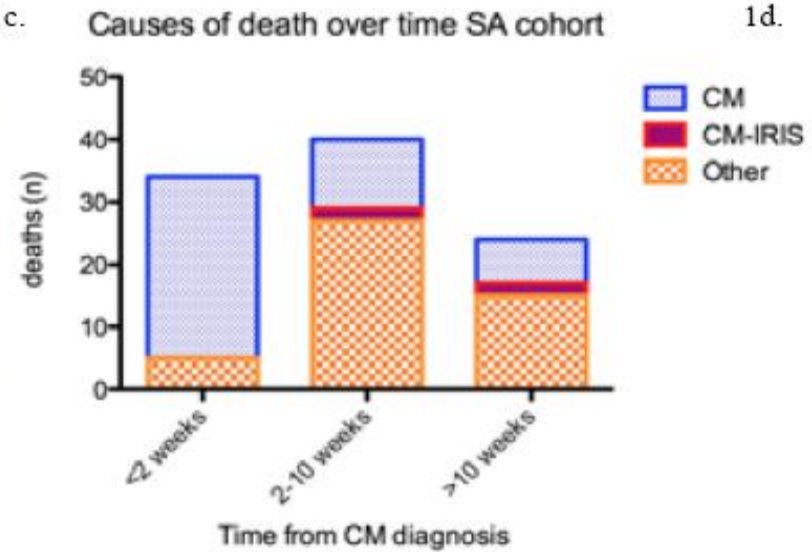
Fig 1a.



1b



1c.



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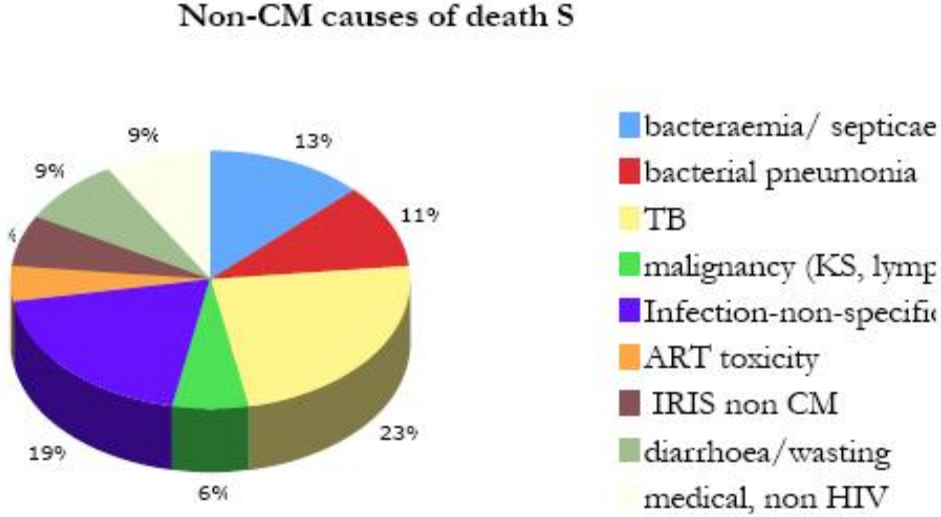


Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources

Stephen D Lawn, Robin Wood, Kevin M De Cock, Katharina Kranzer, James J Lewis, Gavin J Churchyard

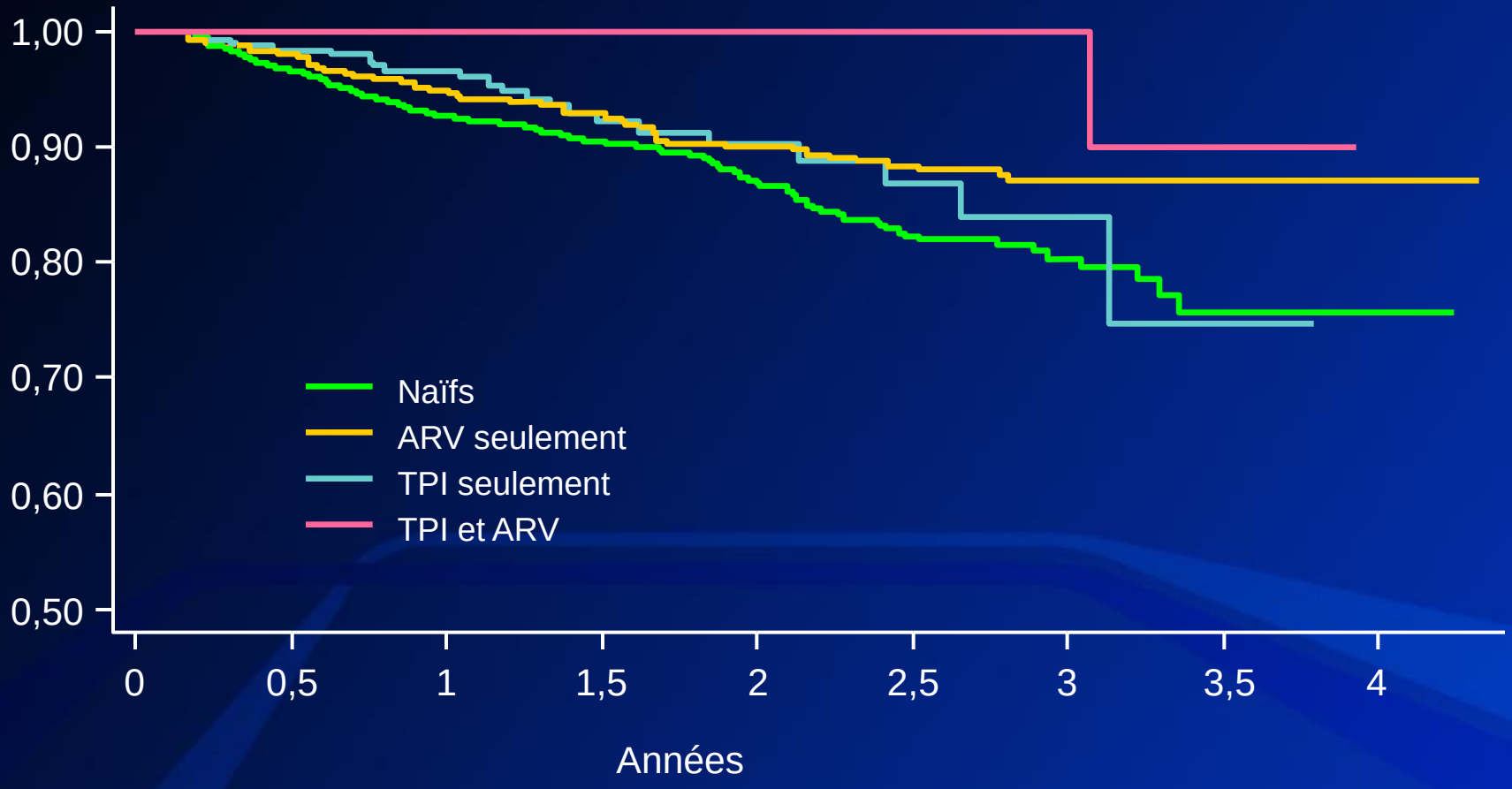
Antiretroviral therapy and isoniazid preventive therapy (IPT) are both effective interventions to prevent HIV-associated tuberculosis, but work via different mechanisms. We propose that these two interventions might best be used as complementary strategies at different stages of HIV progression. At relatively high CD4-cell counts, IPT reduces tuberculosis risk by 64% (95% CI 39–78%) in patients with positive tuberculin skin tests, and is the key tuberculosis preventive intervention before patients are eligible for antiretroviral therapy. However, at low CD4-cell counts, reliable exclusion of active tuberculosis is difficult, fewer patients are eligible for IPT, and waning immune function might limit the durability of its effect. In such patients, antiretroviral therapy is the primary intervention needed, reducing tuberculosis incidence by 67% (95% CI 61–73%). However, tuberculosis risk during long-term antiretroviral therapy remains several times higher than background, especially in those with poor immune recovery. Patients might therefore derive additional benefit from combined use of IPT and antiretroviral therapy to simultaneously treat mycobacterial infection and restore tuberculosis-specific immune function. For those first presenting with advanced immunodeficiency, we propose that concurrent IPT might best be delayed until completion of the first few months of antiretroviral therapy, when active tuberculosis can be more reliably excluded. Data from randomised controlled trials are needed to underpin further development of public-health policy.

Lancet Infect Dis 2010; 10: 489–98

Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa (S D Lawn MD, R Wood FCP, K Kranzer MRCP); Clinical Research Unit, Department of Infectious and Tropical Diseases (S D Lawn, K Kranzer, G J Churchyard PhD), and Infectious Disease Epidemiology Unit, Department of Epidemiology and Population Health

Prophylaxie de la tuberculose par isoniazide à l'ère des ARV

Estimations selon Kaplan-Meier de la probabilité de ne pas avoir de tuberculose



Golub JE et al., AIDS 2009;423:631-6

Association of isoniazid preventive therapy with lower early mortality in individuals on antiretroviral therapy in a workplace programme

Salome Charalambous[a], Alison D. Grant[b], Craig Innes[a], Christopher J. Hoffmann[a,c], Rob Dowdeswell[d], Jan Pienaar[e], Katherine L. Fielding[b] and Gavin J. Churchyard[a,b,f]

Objective: To describe the association between isoniazid preventive therapy (IPT) and mortality among individuals starting antiretroviral therapy (ART) in a workplace programme in South Africa where tuberculosis (TB) incidence is very high.

Methods: ART-naive individuals starting ART from January 2004 to December 2007 were followed for up to 12 months. Deaths were ascertained from clinic and human resource data. The association between IPT and mortality was assessed using Cox regression.

Results: A total of 3270 individuals were included (median age 45; 93% men; median baseline CD4 cell count 155 cells/μl (interquartile range 87–221); and 45% with WHO stage 3/4]. Nine hundred twenty-two (28%) individuals started IPT either prior to or within 3 months of starting ART. Individuals who started IPT tended to have less advanced HIV disease at ART initiation. Two hundred fifty-nine (7.9%) deaths were observed with overall mortality rate 8.9 per 100 person-years [95% confidence interval (CI) 7.9–10.6]. The unadjusted mortality rate was lower among those who received IPT compared with those who did not [3.7/100 vs. 11.1/100 person-years, respectively, hazard ratio 0.34 (95% CI 0.24–0.49)]; this association remained after adjustment for age, baseline CD4 cell count, baseline WHO stage, year of ART start, and individual company (hazard ratio 0.51, 95% CI 0.32–0.80). In sensitivity analyses restricted to those with no previous history of TB ($n = 3036$) or with no TB symptoms at ART initiation ($n = 2251$), IPT remained associated with reduced mortality [adjusted hazard ratios 0.51 (95% CI 0.32–0.81) and 0.48 (95% CI 0.24–0.96), respectively].

Conclusion: Mortality was lower among individuals receiving IPT with or prior to ART start. These results support routine use of IPT in conjunction with ART.

AIDS 2010, **24** (suppl 5):S5–S13

Schéma : 4 stratégies

Randomisation

ARV : début sur critères OMS

INH

ARV : début sur critères OMS

ARV : début précoce

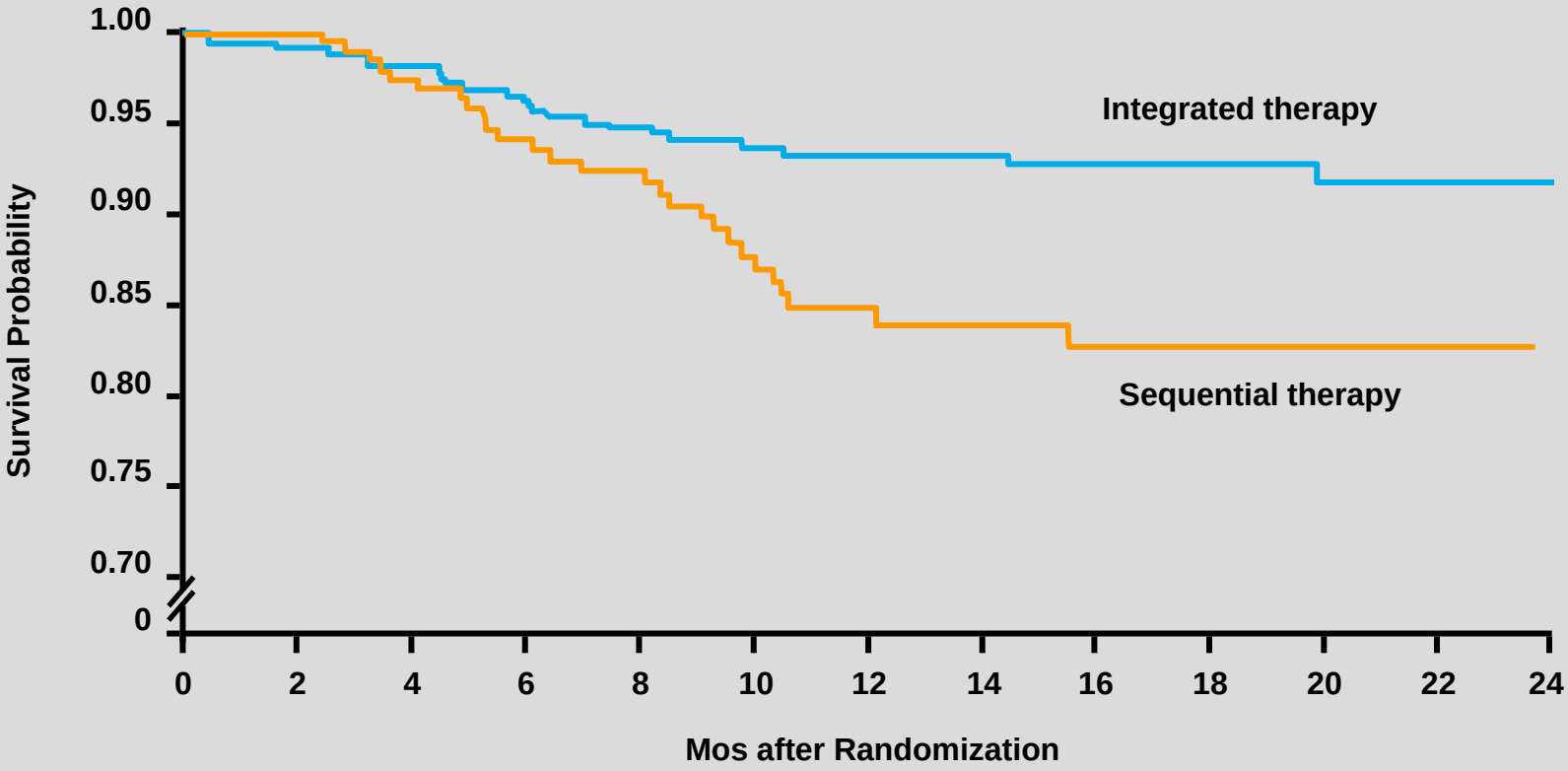
ARV : début précoce
+ INH

Performance of QuantiFERON-TB Gold for Detecting TB in HIV+ Adults in Sub-Saharan Africa

M Kabran[1], A Inwoley[1], RD Moh[1,2], A Badje[1,2], J Lecarrou[3], F Bohoussou[1,2], D Gabillard[3], S Eholié[1], X Anglaret[3], and Christine Danel*[1,2]CHU de Treichville, Abidjan, Côte d`Ivoire

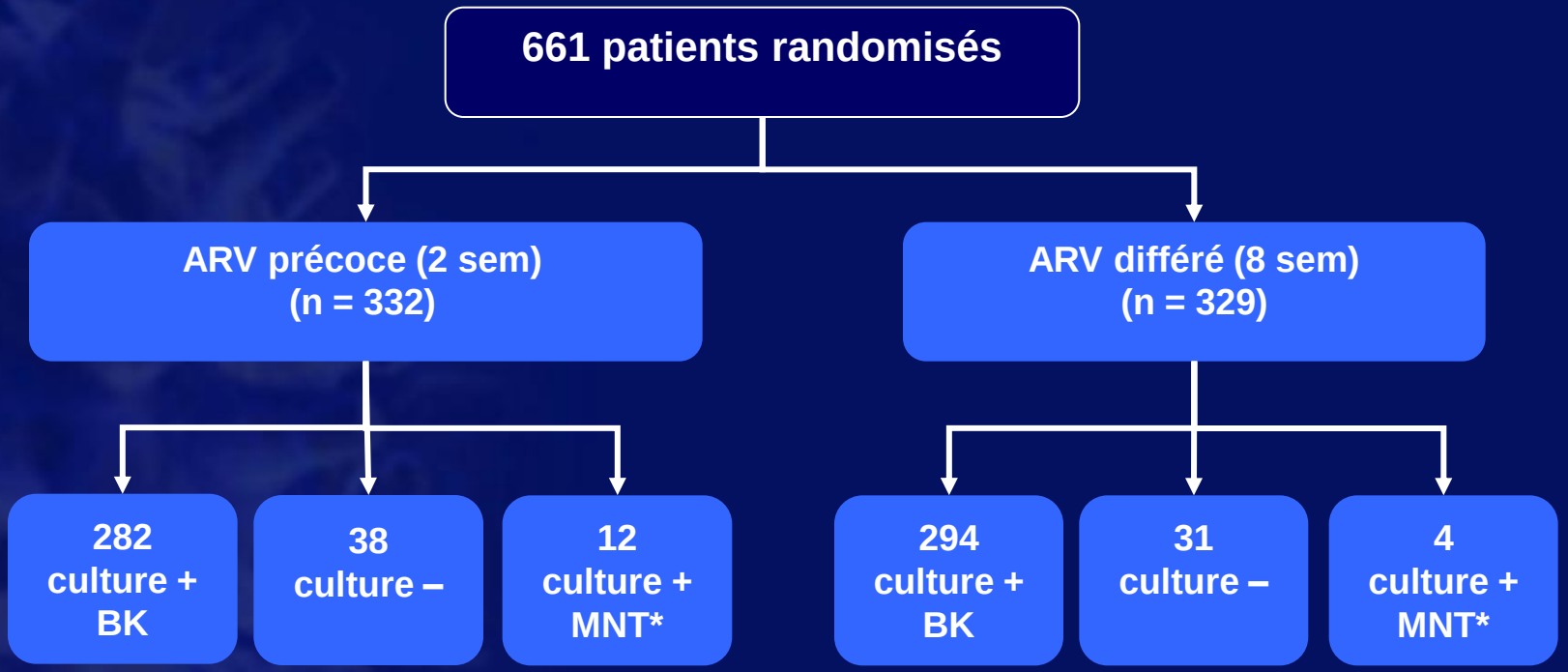
- Temprano N =976 pts/2000 CD4 386 (350-800). 26 TB
- The QFT-G specificity, sensitivity, positive predictive value and negative predictive value for the diagnosis of active TB were respectively 67.0%, 88.2%, 4.5%, and 99.7%
- These results confirm that in HIV-infected patients, positive QFT-G test **is not valid** for confirming the diagnosis of active TB, though negative QFT-G test can help rule out such diagnosis. Further phases of the study will examine the place of the test in identifying patients who might benefit from earlier ART initiation.

SAPiT: Reduced Survival Probability With Sequential vs Integrated TB Therapy



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

Essai CAMELIA : quand commencer les ARV après le début des anti-BK chez des patients VIH+ très immunodéprimés ? (2)



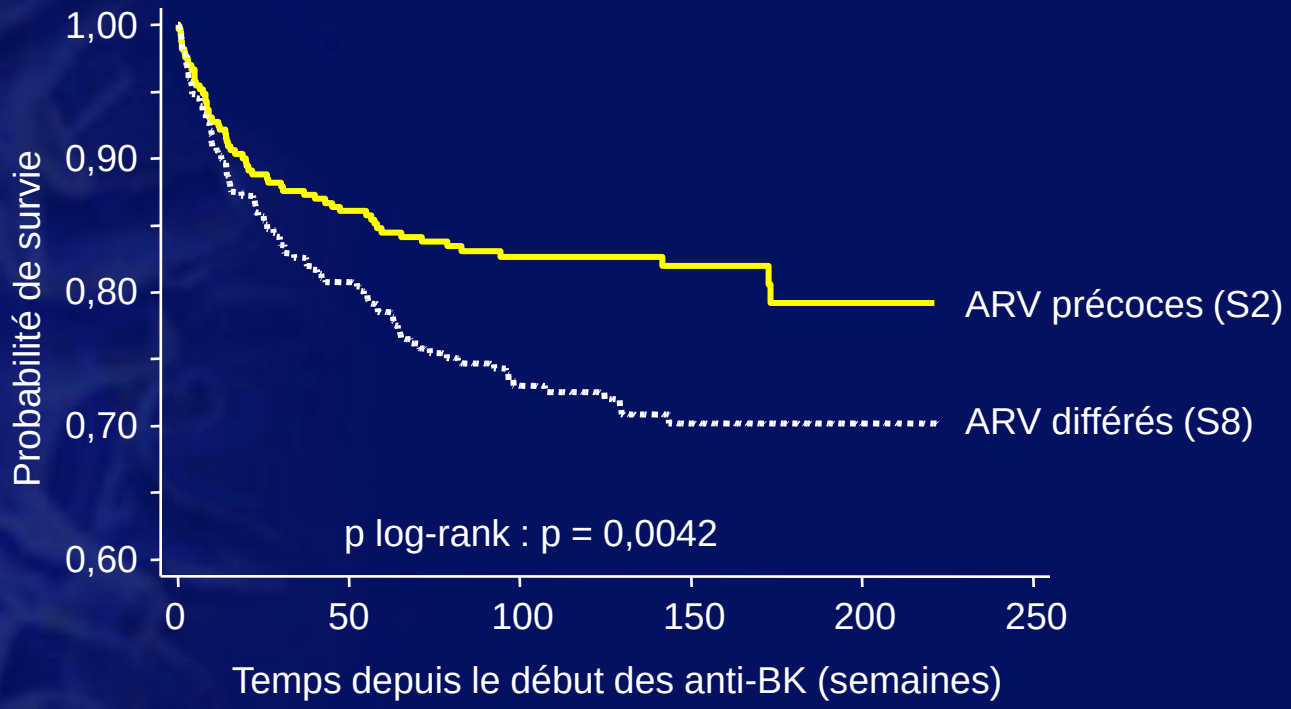
- Les patients inclus dans l'essai sont très immunodéprimés (médiane des lymphocytes CD4 = 25/mm^3 dans les 2 bras)
- Les caractéristiques des patients et de la maladie tuberculeuse sont les mêmes dans les 2 bras
  - 9 % de formes extrapulmonaires exclusives

* MNT : mycobactérie non tuberculeuse

Blanc FX, IAC 2010, Abs. THLBB106

Essai CAMELIA : quand commencer les ARV après le début des anti-BK chez des patients VIH+ très immunodéprimés ? (3)

- Résultat : critère principal de jugement (survie)



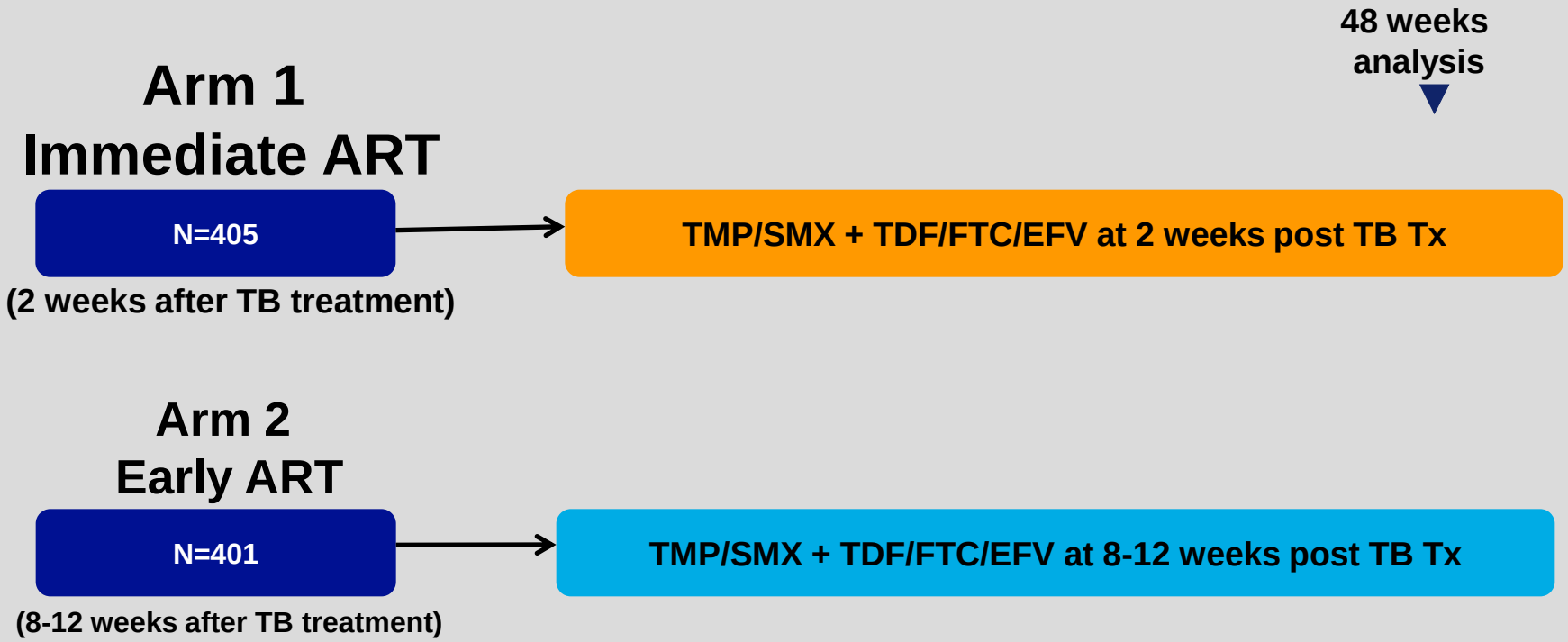
ARV	n	Décès	Durée de suivi*	Mortalité** (IC 95 %)	p
Précoce	332	59	712,4	8,28 (6,42-10,69)	0,002
Différé	329	90	653,7	13,77 (11,20-16,93)	

* en années-patient – ** pour 100 années-patient

Blanc FX, IAC 2010, Abs. THLBB106

ACTG 5221: Starting ART in Patients on TB Therapy

Study of immediate vs. early ART to reduce AIDS and death in HIV+ patients with CD4+ cells <250 cells/mm^3 and confirmed or suspected TB



Havlir D, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 38.

ACTG 5221: Results

	Immediate ART	Early ART	p value
TB diagnosis confirmed	46%	54%	
Median ART Start Time	10 days	70 days	
Experienced AIDS or death by week 48	12.9%	16.1%	p=0.45
Experienced AIDS or death by W48 with ≤ 50 cells/mm^3 (n=285)	15.5%	26.6%	p=0.02
>50cells/mm^3 (n=521)	11.5%	10.3%	p=0.67

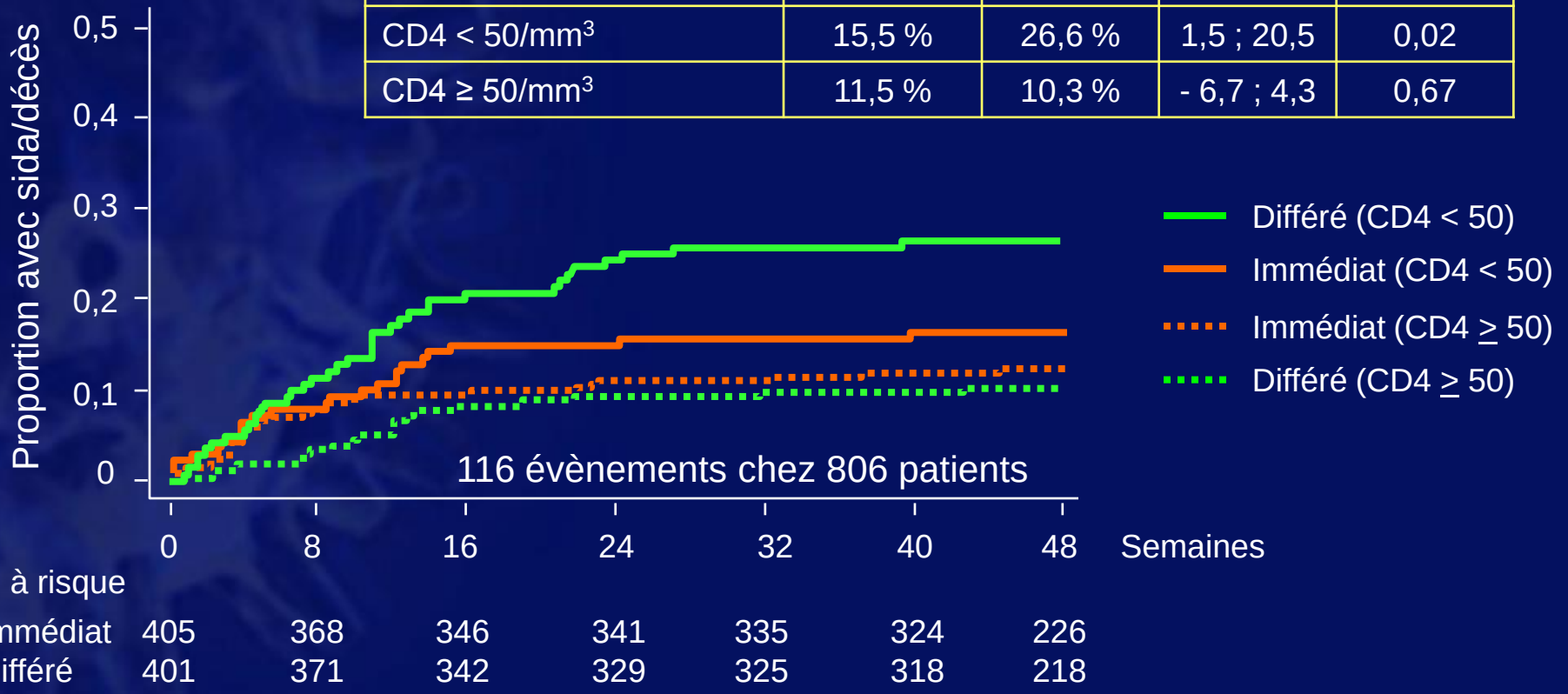
Havlir D, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 38.

le meilleur ...de la CROI 2011

Essai STRIDE : quand débuter les ARV après le début des anti-tuberculeux ? (2)

Proportion avec nouvel événement sida/décès

	Trt ARV immédiat	Trt ARV différé	IC 95 % de la ≠	p
Tous les patients	12,9 %	16,1 %	- 1,8 ; 8,1	0,45
CD4 < 50/mm^3	15,5 %	26,6 %	1,5 ; 20,5	0,02
CD4 ≥ 50/mm^3	11,5 %	10,3 %	- 6,7 ; 4,3	0,67



Havlir D, CROI 2011, Abs. 38

SAPiT: Optimal Timing of ART Relative to TB Treatment in Coinfected Patients

Patients enrolled in the Integrated Treatment Arm of the SAPiT Trial:

- **HIV-infected patients**
- **CD4+ < 500 cells/mm^3**
- **Smear-positive TB**

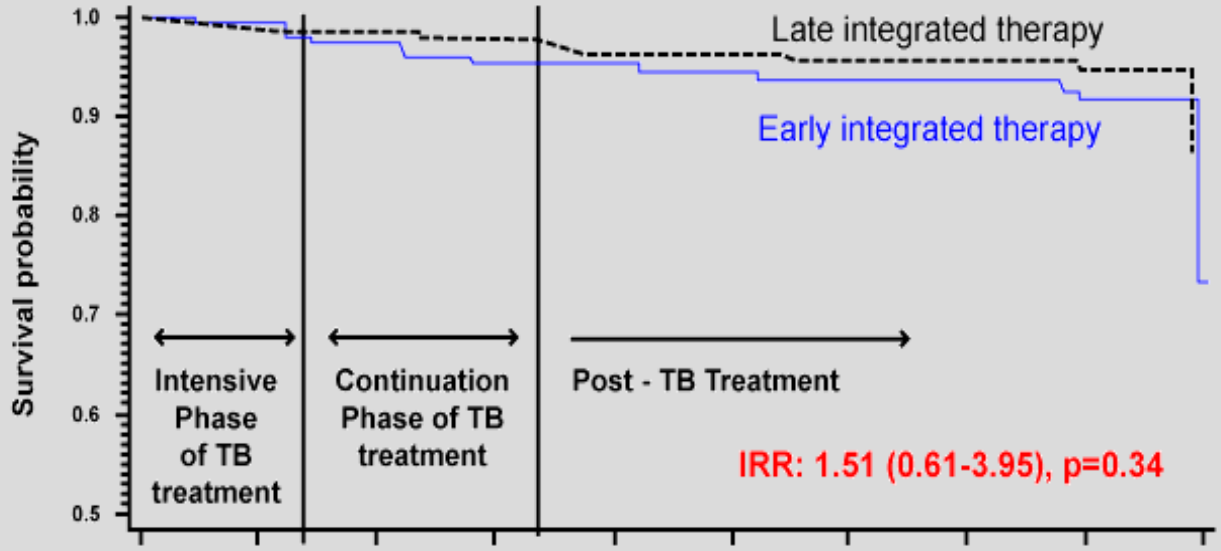
(n=642)

Early Treatment
Initiate ART within first 2 months of starting TB treatment
(n = 214)

Late Treatment
Initiate ART as soon as possible after 2 months of intensive TB treatment phase completed
(n = 215)

Karim S, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 39LB.

SAPiT: Kaplan-Meier Curve for AIDS or Death in Patients with CD4 ≥50 cells/mm^3

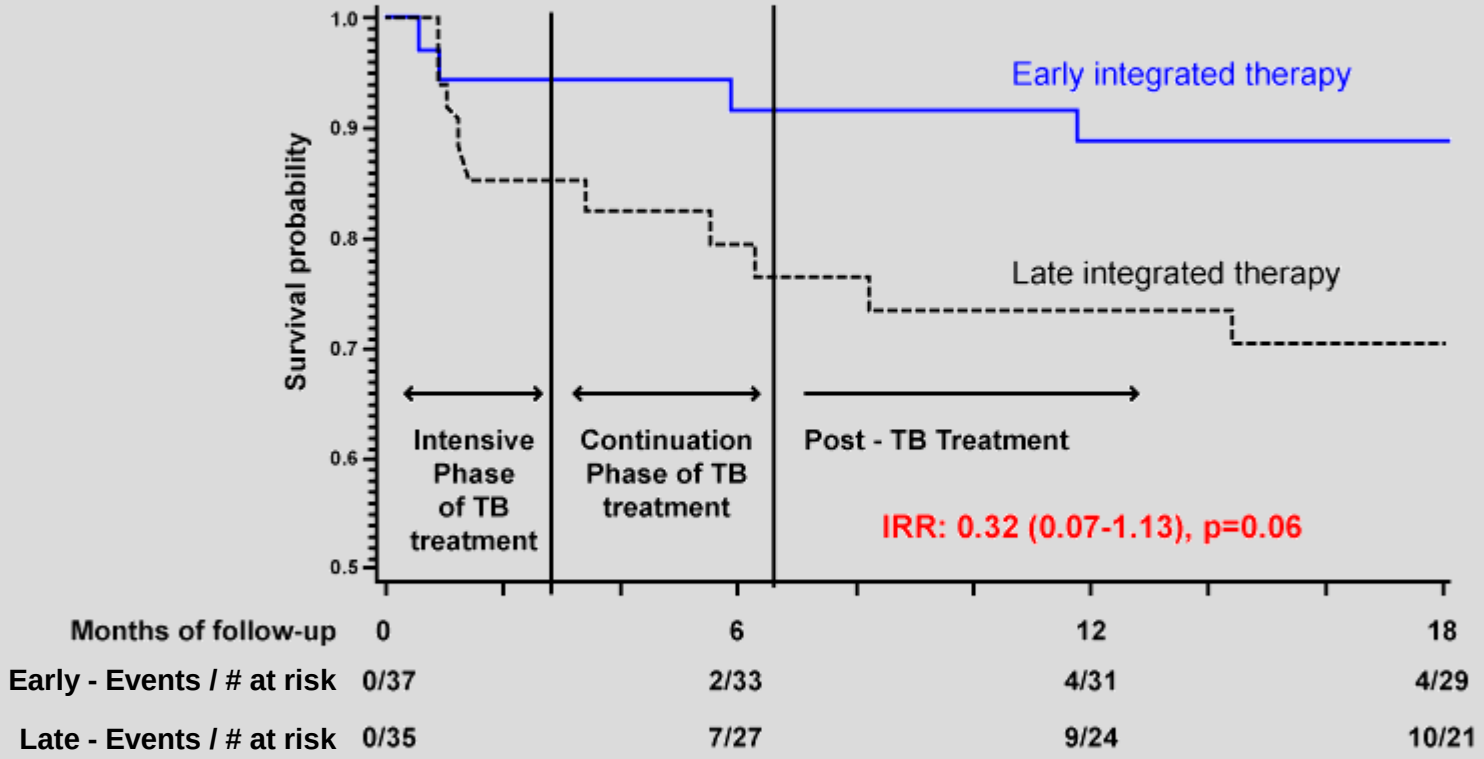


Months of follow-up	0	6	12	18
Early - Events / # at risk	0/177	8/149	10/137	14/121
Late - Events / # at risk	0/180	4/48	7/129	9/121

No discernable differences in AIDS/death

Karim S, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 39LB.

SAPiT: Kaplan-Meier Curve for AIDS or Death in Patients with CD4 <50 cells/mm^3

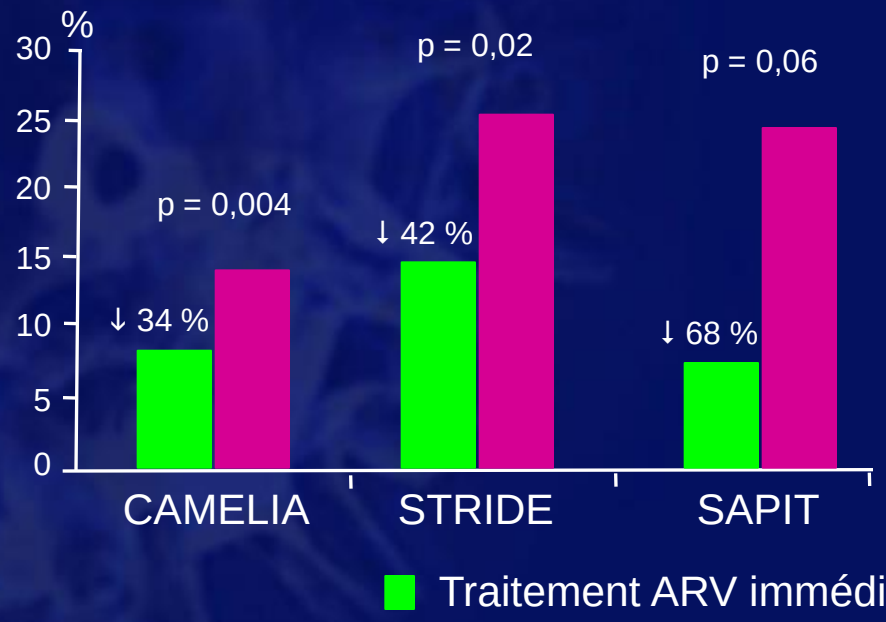


68% reduction of AIDS/death by starting ART Early (p=0.06)

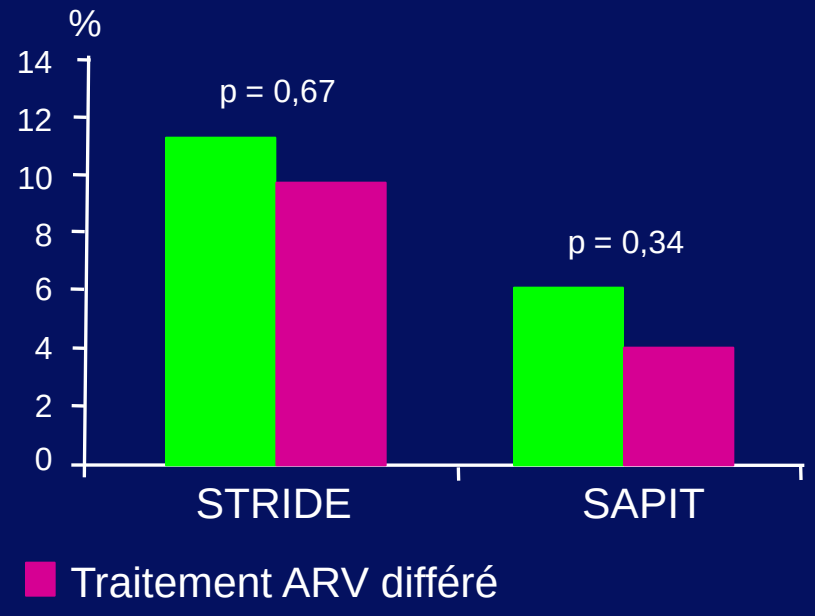
Karim S, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 39LB.

Quand débuter les ARV après le début des anti-TB ?

Décès dans l'essai CAMELIA (75 % des patients avec CD4 < 50/mm^3) et sida ou décès chez les patients avec CD4 < 50/mm^3 dans STRIDE et SAPIT



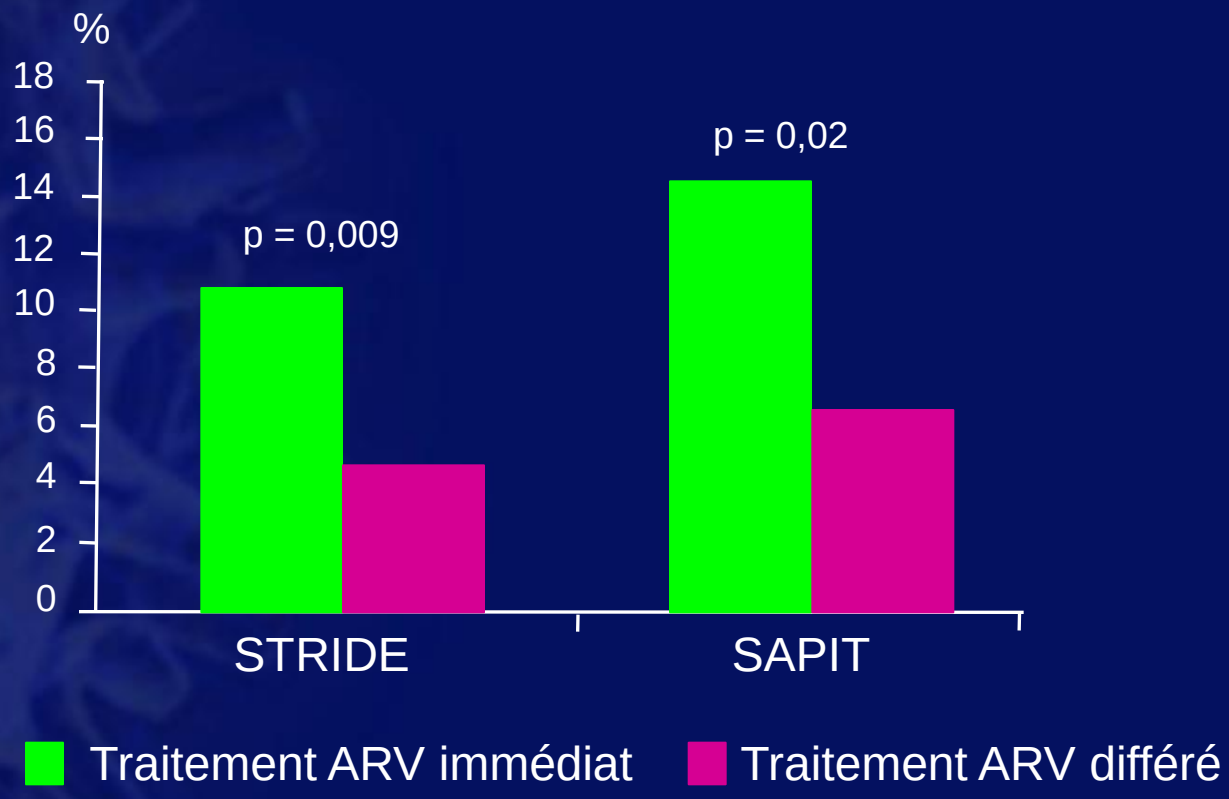
Décès ou sida chez les patients avec CD4 > 50/mm^3 dans STRIDE et SAPIT



Burman W, CROI 2011, Abs. 166 ; Havlir D, CROI 2011, Abs. 38 ; Abdool Karim S, CROI 2011, Abs. 39LB

Quand débuter les ARV après le début des anti-TB ? – Incidence des IRIS

Effet du moment de l'initiation du traitement ARV sur la survenue d'IRIS chez les patients avec CD4 > 50/mm^3



Burman W, CROI 2011, Abs. 166 ; Havlir D, CROI 2011, Abs. 38 ; Abdool Karim S, CROI 2011, Abs. 39LB

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SOLIDARITÉ THÉRAPEUTIQUE & INITIATIVES CONTRE LE SIDA

RESEARCH

Elephant-to-Human Transmission of Tuberculosis, 2009

Rendi Murphree, Jon V. Warkentin, John R. Dunn, William Schaffner, and Timothy F. Jones

In 2009, the Tennessee Department of Health received reports of 5 tuberculin skin test (TST) conversions among employees of an elephant refuge and isolation of *Mycobacterium tuberculosis* from a resident elephant. To determine the extent of the outbreak and identify risk factors for TST conversion, we conducted a cohort study and onsite assessment. Risk for conversion was increased

public, private, and nonprofit facilities. Among these, ≈12
of Asian and ≈2% of African elephants are thought to
infected with *M. tuberculosis* (*6*,*7*). Recommendations
detection and treatment of tuberculosis (TB) in elepha
exist (*8*). However, no standard definition exists for lat
TB in elephants, and no sound clinical criteria exist

Emerging Infecti Dis Mars 2011

Le Bon Usage des Antirétroviraux en Afrique :

Conclusions du 5e Atelier RESAPSI-IMEA sur les recommandations OMS 2010

Mardi 10 mai 2011

Auditorium du journal « Le Monde »
80, boulevard Auguste Blanqui – 75013 Paris
(Métro : Glacière – Parking Auguste Blanqui)

Organisé par RESAPSI et IMEA avec le soutien institutionnel des Laboratoires Boehringer Ingelheim

RESAPSI

IMEA

IRD
Institut de recherche pour le développement

Boehringer Ingelheim

Programme

Modérateurs
Sinata KOULLA SHIRO (Yaoundé) et Théodore NIYONGABO (Bujumbura)

Accueil à partir de 18h30

Communications 19h30 - 21h15

- Objectifs de l'Atelier :
  Adapter, Diffuser et Appliquer les recommandations OMS 2010 (5 min.) — *S. EHOLIE – PM GIRARD*
- Stratégies antirétrovirales (20 min.) — *S. EHOLIE, Abidjan*
- Nouvelles modalités de prévention de la transmission mère-enfant (20 min.) — *Ch. COURPOTIN, Paris*
- Diagnostic précoce et traitement de l'enfant infecté par le VIH (20 min.) — *M. AMORISSANI FOLQUET, Abidjan*
- Stratégies antirétrovirales et co-infections :
  Virus des Hépatites, Tuberculose (15 min.) — *K. LACOMBE, Paris*
- Suivi biologique sous antirétroviraux :
  Que nous disent les études Stratall, DART, Thaï PHPT-5 sur l'usage optimal des CD4 et/ou de la charge virale ? (15 min.) — *E. DELAPORTE, Montpellier*

Débat Comment mieux faire ? 21h15 - 22h

S. KOULLA SHIRO (Yaoundé) et T. NIYONGABO (Bujumbura),
R. LANDMAN (Paris), G. RAGUIN (Esther, Paris), Y. YAZDANPANAH (Tourcoing)

Cocktail dinatoire à l'issue de la réunion