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.
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

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
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

Comparison of Kaplan-Meier Survival Estimates by Treatment Group

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 Bicanic¹, J Jarvis¹,2,3, A Loyse, A Jackson¹, C Muzoora⁶, D Wilson⁶, C van der Horst⁴, R Wood², G Meintjes³ and T Harrison¹

¹St. George’s University of London, London, UK; ²Desmond Tutu HIV Centre, University of Cape Town, South Africa; ³Institute of Tropical Medicine, Antwerp, Belgium

Fig 1a. Survival of SA cohort (n=262)

Fig 1b. Survival of SA cohort (n=170 starting ART), split by median time to ART (tART)

Fig 1c. Causes of death over time SA cohort

Fig 1d. Non-CM causes of death S

- bacteremia/septicae
- bacterial pneumonia
- TB
- malignancy (KS, lymphoma)
- Infection-non-specific
- ART toxicity
- IRIS non CM
- diarrhoea/wasting
- medical, non HIV
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.
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 Charalambousa, Alison D. Grantb, Craig Innesa, Christopher J. Hoffmannac, Rob Dowdeswelld, Jan Pienaar, Katherine L. Fieldingb and Gavin J. Churchyarda,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.
Schéma : 4 stratégies

30 mois

ARV : début sur critères OMS

ARV : début sur critères OMS

ARV : début précoce

ARV : début précoce

+ INH

Essai TEMPRANO, Cote d’Ivoire
Performance of QuantiFERON-TB Gold for Detecting TB in HIV+ Adults in Sub-Saharan Africa

M Kabran1, A Inwoley1, RD Moh1,2, A Badje1,2, J Lecarrou3, F Bohoussou1,2, D Gabillard3, S Eholié1, X Anglaret3, 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

Survival Probability

0 0.70 0.75 0.80 0.85 0.90 0.95 1.00

0 2 4 6 8 10 12 14 16 18 20 22 24

Mos after Randomization

Integrated therapy
Sequential therapy

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

661 patients randomisés

- ARV précoce (2 sem) (n = 332)
  - 282 culture + BK
  - 38 culture –
  - 12 culture + MNT*

- ARV différé (8 sem) (n = 329)
  - 294 culture + BK
  - 31 culture –
  - 4 culture + MNT*

- Les patients inclus dans l’essai sont très immunodéprimés (médiane des lymphocytes CD4 = 25/mm³ 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)

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

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

Blanc FX, IAC 2010, Abs. THLBB106
Study of immediate vs. early ART to reduce AIDS and death in HIV+ patients with CD4+ cells <250 cells/mm³ and confirmed or suspected TB

**Arm 1**
Immediate ART

N=405
(2 weeks after TB treatment)

TMP/SMX + TDF/FTC/EFV at 2 weeks post TB Tx

**Arm 2**
Early ART

N=401
(8-12 weeks after TB treatment)

TMP/SMX + TDF/FTC/EFV at 8-12 weeks post TB Tx
## ACTG 5221: Results

<table>
<thead>
<tr>
<th></th>
<th>Immediate ART</th>
<th>Early ART</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB diagnosis confirmed</td>
<td>46%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Median ART Start Time</td>
<td>10 days</td>
<td>70 days</td>
<td></td>
</tr>
<tr>
<td>Experienced AIDS or death by week 48</td>
<td>12.9%</td>
<td>16.1%</td>
<td>p=0.45</td>
</tr>
<tr>
<td>Experienced AIDS or death by W48 with ≤ 50 cells/mm³ (n=285)</td>
<td>15.5%</td>
<td>26.6%</td>
<td>p=0.02</td>
</tr>
<tr>
<td>&gt;50 cells/mm³ (n=521)</td>
<td>11.5%</td>
<td>10.3%</td>
<td>p=0.67</td>
</tr>
</tbody>
</table>

Havlir D, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 38.
Essai STRIDE : quand débuter les ARV après le début des anti-tuberculeux ? (2)

Proportion avec nouvel événement sida/décès

<table>
<thead>
<tr>
<th></th>
<th>Trt ARV immédiat</th>
<th>Trt ARV différé</th>
<th>IC 95 % de la ≠</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tous les patients</td>
<td>12,9 %</td>
<td>16,1 %</td>
<td>- 1,8 ; 8,1</td>
<td>0,45</td>
</tr>
<tr>
<td>CD4 &lt; 50/mm³</td>
<td>15,5 %</td>
<td>26,6 %</td>
<td>1,5 ; 20,5</td>
<td>0,02</td>
</tr>
<tr>
<td>CD4 ≥ 50/mm³</td>
<td>11,5 %</td>
<td>10,3 %</td>
<td>- 6,7 ; 4,3</td>
<td>0,67</td>
</tr>
</tbody>
</table>

116 événements chez 806 patients

N à risque
- Immédiat : 405, 368, 346, 341, 335, 324, 226
- Différé : 401, 371, 342, 329, 325, 318, 218

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/mm³
- 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/mm³

No discernable differences in AIDS/death
SAPiT: Kaplan-Meier Curve for AIDS or Death in Patients with CD4 <50 cells/mm³

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/mm³) et sida ou décès chez les patients avec CD4 < 50/mm³ dans STRIDE et SAPIT

<table>
<thead>
<tr>
<th>Essai</th>
<th>CD4 &lt; 50/mm³</th>
<th>CD4 &gt; 50/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMELIA</td>
<td>75 %</td>
<td></td>
</tr>
<tr>
<td>STRIDE</td>
<td></td>
<td>42 %</td>
</tr>
<tr>
<td>SAPIT</td>
<td></td>
<td>68 %</td>
</tr>
</tbody>
</table>

Décès ou sida chez les patients avec CD4 > 50/mm³ dans STRIDE et SAPIT

<table>
<thead>
<tr>
<th>Essai</th>
<th>CD4 &gt; 50/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRIDE</td>
<td>67 %</td>
</tr>
<tr>
<td>SAPIT</td>
<td>34 %</td>
</tr>
</tbody>
</table>

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/mm³

- Traitement ARV immédiat
- Traitement ARV différé

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

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

Communications  19h30 - 21h15

- Objectifs de l’Atelier:
  Adapter, Diffuser et Appliquer les recommandations OMS 2010 (5 min.)  
  S. EHOUE - PM GIRARD
- Stratégies antirétrovirales (20 min.)  
  S. EHOUE, 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, Thai 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