Tuberculosis in the Swiss HIV Cohort Study

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Outline

• HIV/AIDS
• The Swiss HIV Cohort Study
• Diagnostic tools: TST and IGRA
• Treatment challenges
- HIV/AIDS
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- Treatment challenges
A global view of HIV infection:
33 million people living with HIV/AIDS in 2007
• TB is the third most common AIDS-defining disease in Switzerland\(^1\)

• Increased risk of primary progressive disease and reactivation of latent TB

• Low sensitivity of tuberculin skin testing

• Treatment challenging (immune reconstitution syndrome, drug-drug interactions)

\(^1\) www.bag.admin.ch
The bulk of CD4 T cell depletion that leads to AIDS occurs over the 10 year period of chronic infection.
Cumulative probability of AIDS or death by initial CD4+ cell count

ART-CC, May et al, AIDS 2007
cART dramatically improves life expectancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design Type</th>
<th>Comparison</th>
<th>Decrease Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996 Delta</td>
<td>RCT</td>
<td>AZT vs dual ART</td>
<td>30</td>
</tr>
<tr>
<td>1996 ACTG 175</td>
<td>RCT</td>
<td>AZT vs dual ART</td>
<td>50</td>
</tr>
<tr>
<td>1997 ACTG 320</td>
<td>RCT</td>
<td>Dual vs HAART</td>
<td>70 – 80</td>
</tr>
<tr>
<td>1997 SHCS</td>
<td>OS</td>
<td>No HAART vs HAART</td>
<td>86</td>
</tr>
<tr>
<td>1998 HOPS</td>
<td>OS</td>
<td>No HAART vs HAART</td>
<td></td>
</tr>
<tr>
<td>2003 EUROSIDA</td>
<td>OS</td>
<td>96/97 HAART vs 98-02 HAART</td>
<td></td>
</tr>
<tr>
<td>2005 SHCS</td>
<td>OS</td>
<td>No HAART vs HAART</td>
<td></td>
</tr>
<tr>
<td>2007 Danish Coh.</td>
<td>OS</td>
<td>HIV versus non HIV</td>
<td></td>
</tr>
</tbody>
</table>

**2008**

20 year old: another 43 years life prolongation with cART ≈ normal life expectancy (?), The ART-CC, 2008, The Lancet

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The Swiss HIV Cohort Study

- Prospective enrollment of HIV-infected individuals aged >16 years
- >15,000 individuals included
- 70% of all AIDS cases in Switzerland
- Every 6 months data collection (clinical and laboratory parameters)
- TST performed in the first 2 years after enrollment

www.shcs.ch
Tuberculosis in the SHCS

Introduction of cART

Year

Number of patients
0 1000 2000 3000 4000 5000 6000 7000 8000

TB prevalence%
0 1 2 3 4 5 6 7 8 9

Prevalence of TB
Annually followed Patients

SHCS, Data on file
## Tuberculosis in the SHCS

### Characteristics of 477 HIV-infected individuals with active tuberculosis between 1988-2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>34 (29-40)</td>
</tr>
<tr>
<td>Males</td>
<td>66%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57%</td>
</tr>
<tr>
<td>Black</td>
<td>36%</td>
</tr>
<tr>
<td>Asian</td>
<td>6%</td>
</tr>
<tr>
<td>Transmission risk</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>20%</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>46%</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>30%</td>
</tr>
<tr>
<td>Prior AIDS-defining condition</td>
<td>18%</td>
</tr>
<tr>
<td>Median CD4 T-cell count (IQR)</td>
<td>291 (136-440)</td>
</tr>
</tbody>
</table>

SHCS, Data on file
Survival after Tuberculosis

Survival

Months after TB

Survival

0.00
0.25
0.50
0.75
1.00

0
3
6
9
12

TB before 1996
TB after 1996

p<0.001

477 patients at risk

SHCS, Data on file
Tuberculosis in Europe: The EuroSIDA Study

Incidence of TB after starting cART

IeDEA, ART-CC
Brinkhof MW, Clin Infect Dis, 2007
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Tuberculin Skin Testing

Elzi et al., Clin Infect Dis, 2007
Reactivation of latent TB

Diagram showing the proportion of patients without TB over follow-up months for different regions:
- Low-risk countries
- Medium-risk countries
- Sub-Saharan Africa

Key:
- No. of patients at risk:
  - Sub-Saharan Africa: 608, 391, 271, 170, 103, 37
  - Low-risk countries: 4506, 3548, 2786, 2101, 1417, 662
  - Medium-risk countries: 388, 284, 212, 158, 92, 27
Reactivation of latent TB

No. of patients at risk:
- Missing TST result: 1636, 1009, 689, 461, 226, 87
- Negative TST result: 3680, 3078, 2473, 1898, 1343, 628
- Positive TST result with no preventive therapy: 233, 176, 137, 97, 65, 22
- Positive TST result with preventive therapy: 140, 123, 84, 55, 32, 17

Follow-up, months: 0, 20, 40, 60, 80, 100
Reactivation of latent TB

Elzi et al., Clin Infect Dis, 2007
Patients and methods:

• Retrospective analysis of 64 HIV-infected individuals who developed TB after enrollment in the SHCS

• IGRA (T Spot-TB®) performed using frozen lymphocytes stored at a median of 3 months before active TB was diagnosed

• Comparison with TST

Elzi et al, SHCS, manuscript in preparation
Results:

Characteristics of 64 HIV-infected individuals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>35 (31-42)</td>
</tr>
<tr>
<td>Males</td>
<td>64%</td>
</tr>
<tr>
<td>Non-white ethnicity</td>
<td>54%</td>
</tr>
<tr>
<td>Prior AIDS-defining condition</td>
<td>18%</td>
</tr>
<tr>
<td>Median CD4 cell count (IQR)</td>
<td>223 (103-339)</td>
</tr>
</tbody>
</table>

IGRA (T Spot-TB®)

- Positive: 39%
- Indeterminate: 33%

Sensitivity of T Spot-TB®: 58%* (43-74)
Sensitivity of TST: 50% (35-65)

*if indeterminate results excluded
Interferon-gamma releasing assay

In 32 HIV-infected individuals with results of both tests:

Concordance between IGRA and TST in only 56% of individuals
Kappa 0.122 (p=0.246)

If IGRA and TST combined: sensitivity 66% (95% CI 51-80%)

Both tests negative in 25%
Multivariate analysis (adj. for CD4, age, ethnicity, prior AIDS, cART): older age associated with higher risk of having both tests negative (OR 3.2, 95% CI 1.2-8.3, p=0.02, per 10 years older)
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Treatment of HIV/Tuberculosis

• WHEN TO START?
  Immune Reconstitution Syndrome

• WHAT TO START?
  Drug-drug interactions
Immune Reconstitution Inflammatory Syndrome (IRIS) Incidence 3-25%

**Before ART**
- Advanced disease
- High pathogen endemicity

**After ART initiation**
- ART early initiation
- VL decrease
- CD4 increase

Threshold clinical disease

Pathogen +++
- CD4 very low

Pathogen (+)
- Pathogen specific immunity \(\approx\) inflammation
- CD4 function and increase +++

Tuberculosis-associated IRIS
Start ART rather earlier than too late

Retrospective study, 160 pts
Baseline CD4 68 cells/µl
ART start after 105 d (median)
IRIS in 12%

- Immediate TB treatment
- postpone ART if HIV allows
- NSAID (BIII) and/or prednison (CIII)
  1 mg/kg/d; reduce after 1-2 wks

Risk of Tb-associated IRIS +++ with early ART and low CD4-T-cells, but most cases self-limiting! (2 deaths due to IRIS)

1 Very similar results

Pozniak et al., AIDS 1992; Lawn et al., AIDS 2007,

1Murdoch DM, AIDS 2008
A5164: Immediate versus deferred ART
Time to AIDS progression or death

Better CD4 increase, non significantly different VL results
Less clinical progression

Adapted from Andrew Zolopa. CROI 2008; abstract 142
NIH DHHS Guidelines

Recommended timing of initiation of cART in treatment-naive patients with active TB disease according to CD4 cell counts

- CD4 <100  ART after 2 weeks
- CD4 =100–200  ART after 8 weeks
- CD4 =200–350  ART after 8 weeks*
- CD4 >350  ART after 8-24 weeks or after end of TB treatment*

* Individual evaluation

Rifabutin is the preferred rifamycin in HIV-infected patients with active TB due to its lower risk of drug interactions with cART (AII)

Compiled from Benson et al at http://aidsinfo.nih.gov/guidelines/ 2008
Acknowledgements

• All HIV-infected individuals participating in the Swiss HIV Cohort Study

• Manuel Battegay

• The members of the Swiss HIV Cohort Study are:


www.shcs.ch