The effect of antiretroviral therapy on chest radiograph appearance in HIV-associated pulmonary tuberculosis

Clare van Halsema, Violet Chihota, Tom Gorsuch, James Lewis, Elizabeth George, Katherine Fielding, Gavin Churchyard, Alison Grant

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Background

- Clinical features of tuberculosis (TB) vary with the degree of HIV-associated immunosuppression (CD4 count)

- Positive sputum smears and lung cavitation are associated with TB transmission

- We have previously shown that combination antiretroviral therapy (cART) does not affect the proportion smear positive, independently of CD4 count\(^1\)

- The effect of cART on lung cavitation, independent of CD4 count, is unknown and relevant to TB control

\(^1\)van Halsema et al, CROI 2010, abstract P-126
Aim

• To examine the effect of cART on chest radiograph (CXR) appearance, particularly cavitation, as a marker of TB infectiousness
Setting

• TB case notification rates
  2450 – 3000/100,000/year in 2008

• High HIV prevalence (around 29%) on background of high TB incidence due to silicosis

• Thibela TB was a cluster-randomised trial of a mass TB prevention intervention

• TB screening and community-wide isoniazid preventive therapy were delivered in intervention clusters

Thibela TB study design

Baseline TB prevalence survey

Enrolment in intervention clusters

Nine months to complete IPT in intervention clusters

12 months measurement period for primary outcome

Final TB prevalence survey

Data extraction from medical records for all incident TB episodes in intervention and control clusters throughout study

Adapted from Fielding et al, Contemp Clin Trials 2011
Methods

• Cross-sectional analysis of TB episodes from 2004-9

• CXRs read by investigators masked to HIV and cART status

• Analysis included individuals with:
  – Known HIV and cART status
  – Pulmonary +/- disseminated or extrapulmonary disease
  – Sputum smear and/or *M. tuberculosis* culture positive
  – Available CXR within 2 months of TB treatment start

• Those on cART <=90 days analysed separately in view of possible immune reconstitution inflammatory syndrome
Results: numbers included

- 5957 TB episodes from 5858 individuals
- HIV status established for 2741/5858 (47%)
- HIV and cART status established for 1589/5858 (27%)
- 1086/1589 (68%) had pulmonary disease (125/1086 [12%] also disseminated or extrapulmonary)
- 533/1086 (49%) had available CXR
- 4 smear and culture negative
- 24 CXR taken >2/12 from TB treatment start
- 495 included in analysis
## Results: study group characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number(^1) (% of 495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>481/494 (97%)</td>
</tr>
<tr>
<td>Median age</td>
<td>43 years (IQR 38, 48)</td>
</tr>
<tr>
<td>Living in hostel/informal housing</td>
<td>343/492 (71%)</td>
</tr>
<tr>
<td>First TB episode</td>
<td>318/487 (65%)</td>
</tr>
<tr>
<td>Sputum smear positive</td>
<td>370 (75%)</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> culture positive</td>
<td>385/423 (91%)</td>
</tr>
</tbody>
</table>

\(^1\)Denominator given where some data missing  \(^2\)IQR = interquartile range
### Results: HIV and cART status

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Median CD4 count (cells/µl; IQR(^1); number with known CD4 count)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-negative</td>
<td>156</td>
<td>-</td>
</tr>
<tr>
<td>HIV-positive not on cART</td>
<td>224</td>
<td>139* (76, 220; n=201)</td>
</tr>
<tr>
<td>HIV-positive on cART &lt;=90 days</td>
<td>28</td>
<td>187 (90, 339; n=26)</td>
</tr>
<tr>
<td>HIV-positive on cART &gt;90 days</td>
<td>87</td>
<td>219* (125, 333; n=80)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>495</td>
<td>149 (86, 263; n=307)</td>
</tr>
</tbody>
</table>

*Difference in CD4 distribution between those on cART >90 days versus not on cART: p<0.002 by Kruskal-Wallis test

\(^1\)IQR = interquartile range
Results: sputum smear status

- Proportions smear-positive, regardless of cART status, varied non-linearly with CD4 count among HIV-positive individuals ($\chi^2$ p=0.01)
Results: Bacillary density and cavitation

<table>
<thead>
<tr>
<th>Cavitation</th>
<th>Smear grade: number (% of row total)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Scanty+</td>
</tr>
<tr>
<td>No</td>
<td>85 (31)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Yes</td>
<td>35 (16)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>120 (25)</td>
<td>7 (1)</td>
</tr>
</tbody>
</table>

- Cavitation is associated with higher sputum bacillary density (chi² p<0.001)
Results: lung cavitation

Comparing HIV-positive on cART >90 days vs. not on cART, odds ratio (OR) for cavitation 1.85 (1.11-3.09); p=0.02

Cavitation linearly associated with CD4 count: OR for cavitation 1.61 (1.27-2.06) for each increase in CD4 category (p<0.001)
# Results: multivariable analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>Number of TB episodes included</th>
<th>OR for lung cavitation On cART &gt;90 days vs. off cART</th>
<th>p-value&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>cART status (unadjusted)</td>
<td>311</td>
<td>1.85 (1.11-3.09)</td>
<td>0.02</td>
</tr>
<tr>
<td>cART status, adjusted for CD4</td>
<td>281</td>
<td>1.66 (0.95-2.91)</td>
<td>0.08</td>
</tr>
<tr>
<td>cART status, adjusted for CD4, age, episode type&lt;sup&gt;1&lt;/sup&gt;</td>
<td>259</td>
<td>1.50 (0.82-2.72)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

- cART not associated with lung cavitation after adjustment in multivariable model

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<sup>1</sup>Episode type = First or subsequent TB episode for that individual  
<sup>2</sup>p-values from Wald test in multivariable model
Study limitations

• Observational study with possible bias
  – HIV testing in those with more severe disease
  – cART used in group with specific characteristics
  – Missing data possibly associated with HIV-related outcomes

• Gold mining workforce with particular characteristics, eg silicosis, but internal comparisons still valid and relevant to other settings

• Some variation in timing of CD4, CXR, smear measurement could affect estimation of ORs
Conclusions

• High proportions smear positive in lowest CD4 stratum

• cART use was not associated with lung cavitation after adjustment for CD4 count

• Overall, cART is likely to increase infectiousness of TB through CD4 recovery

• This has implications for TB control in high HIV-prevalence areas, including nosocomial settings

• Data may be of use in modelling the impact of widespread cART use on TB transmission
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