HIV Antiretroviral Drug Regimens and Lung Function Decline in Early HIV Infection

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Conflicts of Interest

• Study funded by NIH

• GlaxoSmithKline consulting (2018)
## Rationale

| 1990 rank | Global  
| Both sexes, All ages, Deaths per 100,000 | 2017 rank |
|-----------|-------------------------------------------------|-----------|
| 1 Ischemic heart disease | 1 Ischemic heart disease | 3 COPD |
| 2 Stroke | 2 Stroke | |
| 3 Lower respiratory infect | 4 Lower respiratory infect | 5 Alzheimer's disease |
| 4 Neonatal disorders | 5 Alzheimer's disease | 6 Lung cancer |
| 5 COPD | 3 COPD | |
| 6 Diarrheal diseases | |

Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis

Jean Joel Bigna, Angeladine Malaha Kenne, Serra Lem Asangbeh, Aurelie T Sibetcheu

Lancet Glob Health 2018; 6: e193–202
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- Inflammation
- Oxidative stress
- Respiratory microbiota
- Viral persistence
- Pneumonia / Respiratory Infections?
- ART
Rationale

Table 2. Studies examining effects of antiretroviral therapy on risk of chronic obstructive pulmonary disease among patients with HIV infection. All studies adjusted for smoking variables.

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>On ART (n)</th>
<th>No ART (n)</th>
<th>Design</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>George [11]</td>
<td>USA, single center</td>
<td>195</td>
<td>20</td>
<td>Cross-sectional study</td>
<td>ART use associated with lower FEV₁/FVC ratio in linear regression analysis (β coefficient = -3.2; p = 0.04).</td>
</tr>
<tr>
<td>Gingo [12]</td>
<td>USA, single center</td>
<td>134</td>
<td>33</td>
<td>Cross-sectional study</td>
<td>ART use with higher odds COPD (OR 6.22; 95% CI: 1.19–32.43).</td>
</tr>
<tr>
<td>Crothers [22*]</td>
<td>USA, national healthcare system database</td>
<td>∼21 700</td>
<td>∼11 700</td>
<td>Prospective, administrative data analysis</td>
<td>ART use with lower incident COPD without smoking adjustment (incidence rate ratio [IRR] 0.90; 95% CI: 0.82–0.99). Smoking adjustment resulted in wider CI (RR 0.93; 95% CI: 0.73–1.18).</td>
</tr>
<tr>
<td>Drummond [25*]</td>
<td>USA, single center</td>
<td>169</td>
<td>134</td>
<td>Cross-sectional study</td>
<td>ART use not associated with COPD (OR 0.60; 95% CI: 0.29–1.22). However, viral load at least 200 000 copies/ml associated with COPD (OR 3.41; 95% CI: 1.24–9.39).</td>
</tr>
<tr>
<td>Drummond [10***]</td>
<td>USA, single center</td>
<td>172</td>
<td>144</td>
<td>Prospective, observational cohort</td>
<td>ART use not associated with differences in FEV₁ rate of decline. However, viral load at least 75 000 copies/ml associated with faster rate of FEV₁ decline compared with viral load less than 75 000 copies/ml (69 ml/year faster decline; 95% CI: 15.3–123.0 ml/year; p = 0.012).</td>
</tr>
<tr>
<td>Maseddu [14]</td>
<td>Italy, single center</td>
<td>87</td>
<td>24</td>
<td>Cross-sectional study</td>
<td>ART not associated with COPD, but CI very wide (OR 0.59; 95% CI: 0.06–5.93).</td>
</tr>
</tbody>
</table>

HIV(+) patients with CD4+ counts >500 cells/mm³
\[ n = 4,685 \]

### Strategic Timing of AntiRetroviral Therapy (START) Trial

#### Main Trial
- **Immediate ART group**
  - Initiate ART immediately following randomization
  - \[ n = 518 \]

#### Ancillary Study
- **Deferred ART group**
  - Defer ART until CD4+ count declines to < 350 cells/mm³ or AIDS develops
  - \[ n = 508 \]

*Baseline + Annual*

- **Spirometry**

Main trial study procedures,
Primary Outcome: Lung Function Decline

FEV$_1$: Forced expiratory volume in 1 second

Normal: (-25 to -30 mL/yr)

COPD = (-50 to -60 mL/yr)
Previously Published Main RCT Results

<table>
<thead>
<tr>
<th></th>
<th>FEV₁ slope (95% CI), mL/year</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline smokers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate ART (n=135)</td>
<td>-32.9 (-58.5 to -7.4)</td>
<td>--</td>
</tr>
<tr>
<td>Deferred ART (n=155)</td>
<td>-29.7 (-54.3 to -5.0)</td>
<td>--</td>
</tr>
<tr>
<td>Difference</td>
<td>-3.3 (-38.8 to 32.2)</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Baseline non-smokers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate ART (n=383)</td>
<td>-27.8 (-44.2 to -11.4)</td>
<td>--</td>
</tr>
<tr>
<td>Deferred ART (n=353)</td>
<td>-22.2 (-39.6 to -4.9)</td>
<td>--</td>
</tr>
<tr>
<td>Difference</td>
<td>-5.6 (-29.4 to 18.3)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Pooled analysis adjusted for baseline smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate ART (n=518)</td>
<td>-29.1 (-42.9 to -15.4)</td>
<td>--</td>
</tr>
<tr>
<td>Deferred ART (n=508)</td>
<td>-24.5 (-38.6 to -10.3)</td>
<td>--</td>
</tr>
<tr>
<td>Difference</td>
<td>-4.7 (-24.4 to 15.1)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Pooled analysis adjusted for smoking status at each study visit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate ART (n=518)</td>
<td>-28.8 (-42.6 to -14.9)</td>
<td>--</td>
</tr>
<tr>
<td>Deferred ART (n=508)</td>
<td>-23.6 (-37.8 to -9.3)</td>
<td>--</td>
</tr>
<tr>
<td>Difference</td>
<td>-5.2 (-25.1 to 14.6)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Data are from groups of patients randomly assigned to either immediate or deferred ART initiation. ART=antineprotoviral therapy.

Table 2: Primary outcome of FEV₁ slope comparisons

Current Analysis

• **Secondary analysis of relationship between ART regimen and FEV$_1$ slope**

• Analysable ART regimens: NNRTI, PI, INSTI
  - All on dual-NRTI (88% TDF/FTC; 7% ZDV/3TC; 4%ABC/3TC)
  - Includes both immediate and deferred ART strategies

• Through all of follow-up
  - Unblinding May 2015
  - Follow-up through Dec 2016
FEV\textsubscript{1} Slopes, mL/year (95% CI)

\begin{itemize}
  \item NNRTI (n=643) \hspace{0.5cm} \text{15.4 mL/year (}-6.8 \text{ to } +37.5 \text{ mL/year}) \hspace{0.5cm} p=0.17
  \item PI (n=128) \hspace{0.5cm} \text{39.8 mL/year (}-21.0 \text{ to } -58.6 \text{ mL/year}) \hspace{0.5cm} p=0.53
  \item INSTI (n=82) \hspace{0.5cm} \text{24.5 mL/year (}-12.7 \text{ to } -36.2 \text{ mL/year}) \hspace{0.5cm} p=0.27
\end{itemize}

FEV\textsubscript{1} Slope Differences, mL/year (95% CI and p-value)
NNRTI (n=643)

PI (n=128)

INSTI (n=82)

FEV$_1$ Slopes, mL/year
(95% CI)

FEV$_1$ Slope Differences, mL/year
(95% CI and p-value)

-24.5 (-12.7 to -36.2)

-28.7 (-22.7 to -34.8)

-4.3 mL/year
(-17.5 to +8.9 mL/year)
p=0.53

11.1 mL/year
(-8.6 to +30.8 mL/year)
p=0.27

-39.8 (-21.0 to -58.6)

-24.5 (-12.7 to -36.2)

-28.7 (-22.7 to -34.8)
FEV₁ SLOPES, mL/year (95% CI)

**NNRTI** (n=643)
-28.7 (-22.7 to -34.8)

**PI** (n=128)
-24.5 (-12.7 to -36.2)

**INSTI** (n=82)
-39.8 (-21.0 to -58.6)

FEV₁ SLOPE DIFFERENCES, mL/year (95% CI AND p-VALUE)

- **NNRTI** (n=643)
  - Slope: -28.7 mL/year
  - (95% CI: -22.7 to -34.8)
  - p-value: 0.53

- **PI** (n=128)
  - Slope: -24.5 mL/year
  - (95% CI: -12.7 to -36.2)
  - p-value: 0.17

- **INSTI** (n=82)
  - Slope: -39.8 mL/year
  - (95% CI: -21.0 to -58.6)
  - p-value: N/A

- **NNRTI** vs. **PI**
  - Difference: 15.4 mL/year
  - (95% CI: -6.8 to +37.5 mL/year)
  - p-value: 0.17

- **NNRTI** vs. **INSTI**
  - Difference: -4.3 mL/year
  - (95% CI: -17.5 to +8.9 mL/year)
  - p-value: 0.53

- **PI** vs. **INSTI**
  - Difference: 11.1 mL/year
  - (95% CI: -8.6 to +30.8 mL/year)
  - p-value: 0.27
INSTI (n=82)

-39.8 mL/year
(-21.0 to -58.6)

PI (n=128)

-24.5 mL/year
(-12.7 to -36.2)

NNRTI (n=643)

-28.7 mL/year
(-22.7 to -34.8)

FEV₁ Slopes, mL/year (95% CI)

FEV₁ Slope Differences, mL/year (95% CI and p-value)

15.4 mL/year
(-6.8 to +37.5 mL/year)
p=0.17

11.1 mL/year
(-8.6 to +30.8 mL/year)
p=0.27

-4.3 mL/year
(-17.5 to +8.9 mL/year)
p=0.53
Conclusions

• Lung function decline is similar for NNRTI and PI drugs
  • Both in the range of normal age-related FEV$_1$ decline.

• More data are needed to assess the potential effects of INSTIs on lung function decline.

Thank you to the 1,026 START Pulmonary Substudy participants