We can’t treat ourselves out of the HIV epidemic

Gary Maartens
Clinical benefit of early ART:
Only one RCT informing when to start

Figure 2. Kaplan–Meier Estimates of Survival in the Early-Treatment and Standard-Treatment Groups.

NEJM 2010;363:257
Post hoc analysis HTPN 052

RCT to assess effect of ART on HIV transmission in serodiscordant couples

- CD4 350-550
- ART start immediate vs delayed (CD4 <250 twice)
- No difference in death
- Reduction in AIDS (HR 0.64 95%CI 0.43-0.96), mostly driven by TB
- Only 52/1763 received IPT
Incidence of OIs Cape Town: pre-ART era

TB ≥2-fold higher than HIV-
Cohorts of when to start ART

<table>
<thead>
<tr>
<th>Study</th>
<th>CD4 bands</th>
<th>Death</th>
<th>AIDS + death</th>
</tr>
</thead>
<tbody>
<tr>
<td>When to start</td>
<td>351-450 vs 451-550</td>
<td>0.93 (0.60, 1.44)</td>
<td>0.99 (0.76, 1.29)</td>
</tr>
<tr>
<td></td>
<td>251-350 vs 351-450</td>
<td>1.13 (0.80, 1.60)</td>
<td>1.28 (1.04, 1.57)</td>
</tr>
<tr>
<td>CASCADE</td>
<td>350-499 vs 500-799</td>
<td>0.98 (0.47, 2.04)</td>
<td>0.91 (0.56, 1.49)</td>
</tr>
<tr>
<td></td>
<td>200-349 vs 350-499</td>
<td>1.96 (1.25, 3.03)</td>
<td>1.33 (0.88, 2.04)</td>
</tr>
<tr>
<td>HIV-CAUSAL</td>
<td>200-350 vs 350-500</td>
<td>1.01 (0.84, 1.22)</td>
<td>1.38 (1.23, 1.56)</td>
</tr>
</tbody>
</table>

Lancet 2009; 373: 1352–63  
Arch Intern Med. 2011;171(17):1560  
Ann Intern Med. 2011;154:509-515  
Sabin AIDS 2013
ART tolerability

- HIV-related morbidity and ART side effects can both impair QoL
- Treating asymptomatic patients with high CD4 counts could worsen QoL
- Severe ART adverse drug reactions are rare with newer regimens, but unclear whether the very small clinical benefits with early ART outweigh risks
Healthcare costs

• Discounted 10 year costs SA public sector (Khayelitsha) $7,688
  $184,512 to prevent one case of AIDS (CASCADE NNT=48 for 5 years)
• Earlier ART would reduce TB incidence, but IPT is effective & much cheaper
• Donor funding has plateaued
• Reducing transmission will save healthcare costs, but need data to estimate NNT long term
Won’t all need ART soon?

CD4 count decline Cape Town

**TABLE 2. CD4 Cell Count Declines by CD4 Count Stratum**

<table>
<thead>
<tr>
<th>CD4 Cell Count Stratum (cells/μL)</th>
<th>CD4 Cell Count Decline (cells/μL) (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500</td>
<td>47.1 (40.0–54.2)</td>
</tr>
<tr>
<td>351–500</td>
<td>30.6 (23.4–37.8)</td>
</tr>
<tr>
<td>201–350</td>
<td>20.5 (13.7–27.3)</td>
</tr>
</tbody>
</table>

500 to 350 will take 3.97-6.41 years

750 to 500 will take 4.61-6.25 years
ART for preventing transmission

Observational studies of serodiscordant couples show ART ↓ transmission by 64%

HTPN 052 RCT in serodiscordant couples

96% (73-99%) reduction in transmission

Median follow up 1.7 yrs

RCTs of “test & treat” strategy underway

Cochrane Database Syst Rev. 2013 Apr 30;4:CD009153
“all models are wrong, but some are useful”

GEORGE BOX
Models of HIV in SA with test & treat

- Start universal test & treat (UTT) 2012 & scale up to 90% coverage by 2019
- Elimination = <1 per 1000 person years
- Model D: elimination reached in 2029 with UTT vs 2041 starting ART with CD4 <350
- Dropout rate of 8.5% in the first year of treatment and 1.5% in subsequent years ("rather optimistic"). Sensitivity analysis if dropout increased to 5% in subsequent years:
  Elimination UTT  2048 vs 2041 starting ART CD4 <350
Despite “rather optimistic” assumptions*:

“Although we show that the universal test & treat intervention proposed is highly cost-effective, the required number of health workers and financial resources for such a strategy far exceeds the current availability in South Africa.”

*LTFU 8.5% year 1 then 1%

90% tested and treated

90% transmission reduction with ART
Start ART CD4 >500 vs <350 in Africa

LTFU assumed 11.6% in 1st year, then 9.2% per year
↑ Mortality if withdrawal >1.2 fold higher on immediate ART

Antivir Ther 2013;18:45
SA retention in ART care

Figure 18: Adult remaining in care by year started ART (cohort)

Percentage adults remaining on ART by duration

Consequences of LTFU

- 42% resume ART within 3 years of defaulting
- 3-fold higher rate of failure & switching to 2nd line ART after defaulting
- Model of test & treat in Los Angeles estimates increasing primary ARV resistance

JAIDS 2010;55:e17–e23
Leisegang PLoS ONE 2013
CID 2013;56:1789
How many on ART are suppressed?

• Sample of 10% all adults in Masiphumelele, research site with high HIV testing and ART coverage

• 30.4% of those on ART had VL>1,500

• Community VL based on routine VL monitoring are over estimates
Conclusions

• Main clinical benefit of early ART is reducing TB, which IPT does very well
• Massive scale up needed to test & treat – donor funding plateau
• Models of test & treat sensitive to LTFU, which will likely worsen with implementation. This undermines transmission benefit & may increase long term mortality
• Community VL studies over estimated transmission benefit
• ↑ risk of resistance with ↑ ART use
• Need good evidence - RCT results pending, but need long term follow up to assess intervention
• When we are treating those who need it and retaining them in care test & treat could be considered