Success and failure of initial ART in adults: an updated systematic review from 1994 to 2017
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Introduction

- ART guidelines based on serial assessment of individual RCTs
- Systematic reviews provide more data / power to identify predictors of ART success, to evaluate sub-populations and to identify data gaps
- Limitations of previous reviews
  - weeks 48, 96 and 144 “combined”
  - no evaluation of real-world efficacy (high vs. LMIC countries; phase 4 vs. phase 3)
  - limited data on INSTIs and Wks 96 and 144
- predictors of efficacy after Week 48 not known

Methods

- Included groups
  - 1994 to 31 July 2017
  - prospective trial cohort of initial ART regimen
  - ITT efficacy analysis (<50 cp/mL) ≥48 to 144 weeks
  - ≥20 subjects
- Excluded: indiscrete regimens (“2-NRTI” backbone allowed), ART never recommended, and observed ART
- Data: PubMed; Cochrane registry, clinicaltrials.gov; Conference abstracts, posters, slides (CROI, IAS, ICAAC, ID Week, Glasgow); FDA product labels; CCO / NATAP websites
- Registered at PROSPERO (CRD42017079470)
- Descriptive analyses
  - ART group = unit of analysis
  - bias assessments: sponsor, study phase, published, cohort, placebo, data completeness
- Predictive analyses by mixed-effect, meta-regression and forward, step-wise variable selection
  - year of study commencement excluded
- R meta-analysis package

Baseline variables

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Week 48</th>
<th>Week 96</th>
<th>Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design placebo used</td>
<td>+5.2%</td>
<td>+6.3%</td>
<td>+17.0%</td>
</tr>
<tr>
<td>phase 3 vs. 4 randomised</td>
<td>+6.1%</td>
<td>+4.9%</td>
<td>+15.8%</td>
</tr>
<tr>
<td>Eligibility genotyping</td>
<td>+4.3%</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>no CD4 restriction</td>
<td>+8.0%</td>
<td>+6.3%</td>
<td>+10.5%</td>
</tr>
<tr>
<td>Pre-ART higher CD4 (per 100 cells)</td>
<td>+2.2%</td>
<td>+0.5%</td>
<td>+0.8%</td>
</tr>
<tr>
<td>younger age (yr)</td>
<td>x</td>
<td>x</td>
<td>+1.0%</td>
</tr>
<tr>
<td>ART 1 dose/day (vs. 2) non-fasting ART</td>
<td>+3.4%</td>
<td>+0.7%</td>
<td>+11.4%</td>
</tr>
<tr>
<td>less pills / day</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>TDF/TAF-FTC (vs. other NRTIs)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>INSTI (vs rPI or NNRTI)</td>
<td>2≥0.3%</td>
<td>≥9.0%</td>
<td>≥5.6%</td>
</tr>
</tbody>
</table>

Conclusions

- >20% of post-2010 subjects failed INSTI-based ART over 144 weeks
- Simpler dosing better (insufficient data regarding STRs)
- Phase 3 studies progressively over-estimate real-world efficacy
- Few clinical reasons identified for ART failure
- Rate of ART cessation for virological failure unchanged in >20 years
- Insufficient data at Weeks 96 and 144 – potential for bias

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ART cessation

- Cessation overall, for adverse events and for subject choice all declined over time, but did not decline for virological failure