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

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Systematic review of initial ART
Why do one?

- ART guidelines are based on serial assessment of individual randomized trials
- Systematic reviews
  - more data / power to identify predictors of ART success, to evaluate subpopulations 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 Weeks 96 and 144
  - predictors of efficacy after Week 48 unknown
**Systematic review of initial ART**

**Eligibility criteria and data sources**

- **Included new groups**
  - 1 January 2013 to 31 July 2017
  - prospective trial / cohort of initial ART regimen
  - ITT efficacy analysis (<50 cp/mL) ≥48 weeks
  - ≥20 subjects

- **Excluded groups**
  - indiscrete regimen (“2-NRTI” backbone allowed)
  - ART never recommended because of potency
  - directly-observed therapy

- **Data sources**
  - PubMed; trial registries (Cochrane, clinicaltrials.gov)
  - Conference abstracts, posters, slides (CROI, IAS, ICAAC, EACS, ID Week, Glasgow)
  - FDA product labels / medical reviews
  - CCO / NATAP

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**Analyses**

- Registered at PROSPERO (CRD42017079470)

- **Descriptive analyses**
  - treatment group = unit of analysis
  - heterogeneity assessed with $I^2$ statistic
  - bias assessments: sponsor, study phase, published, cohort, placebo, data completeness

- **Predictive analyses**
  - mixed-effect, meta-regression approach
    - forward, step-wise variable selection
    - year of study commencement excluded
    - non-significant variables or variables only significant on univariate analysis are not shown

- Performed with R meta-analysis package
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Efficacy: by study duration

- 67 new reports
- 141 new groups
- 37,875 new subjects

<table>
<thead>
<tr>
<th></th>
<th>All studies</th>
<th>Week 48</th>
<th>Week 96</th>
<th>Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups, n</td>
<td>354</td>
<td>351</td>
<td>145</td>
<td>48</td>
</tr>
<tr>
<td>Subjects, n</td>
<td>77,999</td>
<td>73,955</td>
<td>40,667</td>
<td>17,034</td>
</tr>
<tr>
<td>Follow-up, weeks (SD)</td>
<td>88 (38)</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>ART efficacy, % (SD)</td>
<td>67.7 (16.2)</td>
<td>71.3 (15.0)</td>
<td>63.5 (16.2)</td>
<td>61.8 (16.9)</td>
</tr>
</tbody>
</table>

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Efficacy: Weeks 48, 96 and 144

Year of commencement

- Week 48 (351 groups; 99.2%)
- Week 96 (145 groups; 41.0%)
- Week 144 (48 groups; 13.6%)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (%)</td>
<td>57.2%</td>
<td>68.8%</td>
<td>76.9%</td>
<td>83.8%</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Wk 48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td>51.6%</td>
<td>60.5%</td>
<td>64.8%</td>
<td>79.9%</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Wk 144</td>
<td>45.1%</td>
<td>54.5%</td>
<td>71.6%</td>
<td>77.1%</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
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Predictors of efficacy: backbone (week 48)

<table>
<thead>
<tr>
<th></th>
<th>TDF/TAF-FTC</th>
<th>ABC-3TC</th>
<th>AZT-d4T-ddi+</th>
<th>2 NRTIs</th>
<th>TDF-3TC</th>
<th>1 NRTI</th>
<th>No NRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (%)</td>
<td>78.0% (SD 11.9)</td>
<td>70.2% (SD 11.9)</td>
<td>59.2% (SD 12.4)</td>
<td>74.6% (SD 11.8)</td>
<td>76.9% (SD 12.1)</td>
<td>76.0% (SD 12.4)</td>
<td>73.0% (SD 12.1)</td>
</tr>
<tr>
<td>Ref.</td>
<td>-3.7%</td>
<td>-5.6%</td>
<td>0.0</td>
<td>-1.2%</td>
<td>-4.7%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.04</td>
<td>0.002</td>
<td>1.00</td>
<td>0.59</td>
<td>0.28</td>
<td>0.84</td>
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</tr>
</tbody>
</table>

- $r^2 = 35.7\%$, $p$-group = 0.02; also significant at Weeks 96 and 144

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Efficacy: TDF/TAF-FTC vs ABC-3TC (post-2005)

- Week 48
  - TDF/TAF-FTC: 78.2% (SD 9.4)
  - ABC-3TC: 76.3% (SD 9.4)
  - $\Delta = 1.9\%$ (95%CI -2.6, 6.4)
  - $p = 0.40$

- Week 96
  - TDF/TAF-FTC: 74.9% (SD 10.6)
  - ABC-3TC: 65.4% (SD 11.1)
  - $\Delta = 9.5\%$ (95%CI 2.7, 16.3)
  - $p = 0.006$
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Predictors of efficacy: ‘anchor’ class

<table>
<thead>
<tr>
<th></th>
<th>INSTI - other</th>
<th>NNRTI (145 groups)</th>
<th>PIr (120 groups)</th>
<th>INSTI (33 groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 48 – 144</td>
<td>-9.5%</td>
<td>70.6%</td>
<td>73.4%</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>-9.1%</td>
<td>61.8%</td>
<td>65.8%</td>
<td>81.1%</td>
</tr>
<tr>
<td></td>
<td>-8.6%</td>
<td>58.8%</td>
<td>63.4%</td>
<td>78.1%</td>
</tr>
<tr>
<td></td>
<td>-9.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-13.0%</td>
<td></td>
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<tr>
<td></td>
<td>-5.6%</td>
<td></td>
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<tr>
<td>Ref.</td>
<td></td>
<td>W48</td>
<td>W48</td>
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<td>Ref.</td>
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<td>W96</td>
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<td>W96</td>
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<tr>
<td>Ref.</td>
<td></td>
<td>W144</td>
<td>W144</td>
<td>W144</td>
</tr>
</tbody>
</table>

P-trend: Wk 48, <0.0001
Wk 96, 0.003
Wk 144, <0.0001

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Efficacy: INSTI ‘anchor’ + current NRTIs

Week 48
- TDF-FTC (n=16)
- TAF-FTC (n=7)
- ABC-3TC (n=7)
- 2 NRTIs (n=3)

Week 96

Week 144

Δ = -11.8%
Δ = -7.0%
Δ = -9.4%

P-trend:
Wk 48, <0.0001
Wk 96, 0.003
Wk 144, <0.0001
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Predictors of efficacy: ART dosing (week 48)

- Week 96: non-fasting ART + fewer pills per day
- Week 144: fewer pills per day

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Predictors of efficacy: genotyping (week 48)

- No significant effect observed at Weeks 96 or 144
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Predictors of efficacy Week 96: placebo

- No significant effect observed at Weeks 48 or 144

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Predictors of efficacy: patient variables

Baseline CD4 (week 48)
- $r^2 = 4.2\%$
- Adj. $\Delta = 2.2\% / 100$ cells
- (95%CI 1.0, 3.4)
- p-trend = 0.0003

Baseline age (week 144)
- $r^2 = 7.4\%$
- Adj. $\Delta = -1.0\% / \text{year}$
- (95%CI -1.8, -0.2)
- p-trend = 0.02
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Efficacy: subgroups

Phase 3 vs Phase 4

DHHS vs WHO

WHO: FTC vs 3TC

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Efficacy: viral load strata
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ART discontinuations

Conclusions

- Although initial ART efficacy continues to improve, >20% of post-2010 subjects on INSTI-based ART failed over 144 weeks
- Simpler dosing better (insufficient STR data)
- Phase 3 studies over-estimate real-world efficacy
- Few clinical reasons identified for ART failure
- Rate of ART discontinuation for virological failure has not declined in over 20 years
- Insufficient data at Weeks 96 and 144 – potential for bias
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**Implications for WHO ART guidelines**

- De-list EFV and AZT as ‘preferred’ drugs for initial ART
- Promote pre-ART genotyping (as well as viral load testing)
- TDF-3TC-EVF ‘similar’ to TDF-FTC-EVF at Week 48; ‘similarity’ at Weeks 96 and 144 uncertain

http://apps.who.int/iris/bitstream/handle/10665/273129/WHO-CDS-HIV-18.19-eng.pdf?ua=1

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