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

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Introduction

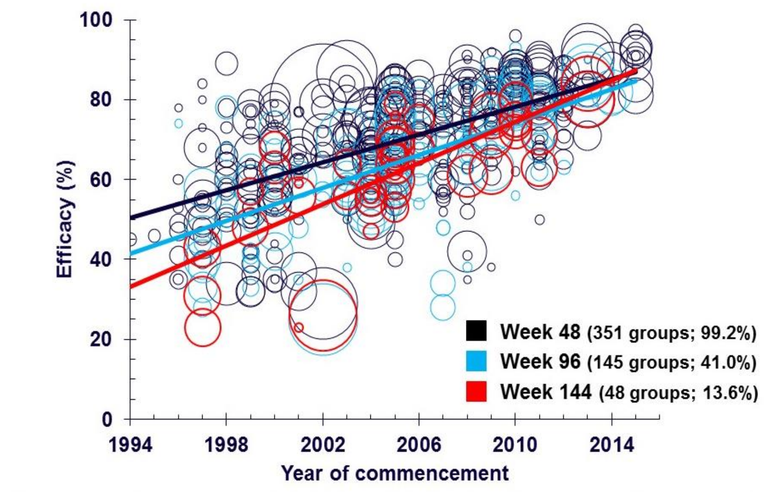
- ART guidelines based on serial assessment of individual RCTs
- Systematic reviews provide more data / power to identify predictors of ART success, to evaluate sub-populations and to identify data gaps
- Limitations of previous reviews
  - weeks 48, 96 and 144 "combined"
  - no evaluation of real-world 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

Results

Overall efficacy



Wk 48	57.2%	68.8%	76.9%	83.8%	p<0.001
Wk 96	51.6%	60.5%	64.8%	79.9%	p<0.001
Wk 144	45.1%	54.5%	71.6%	77.1%	p<0.001

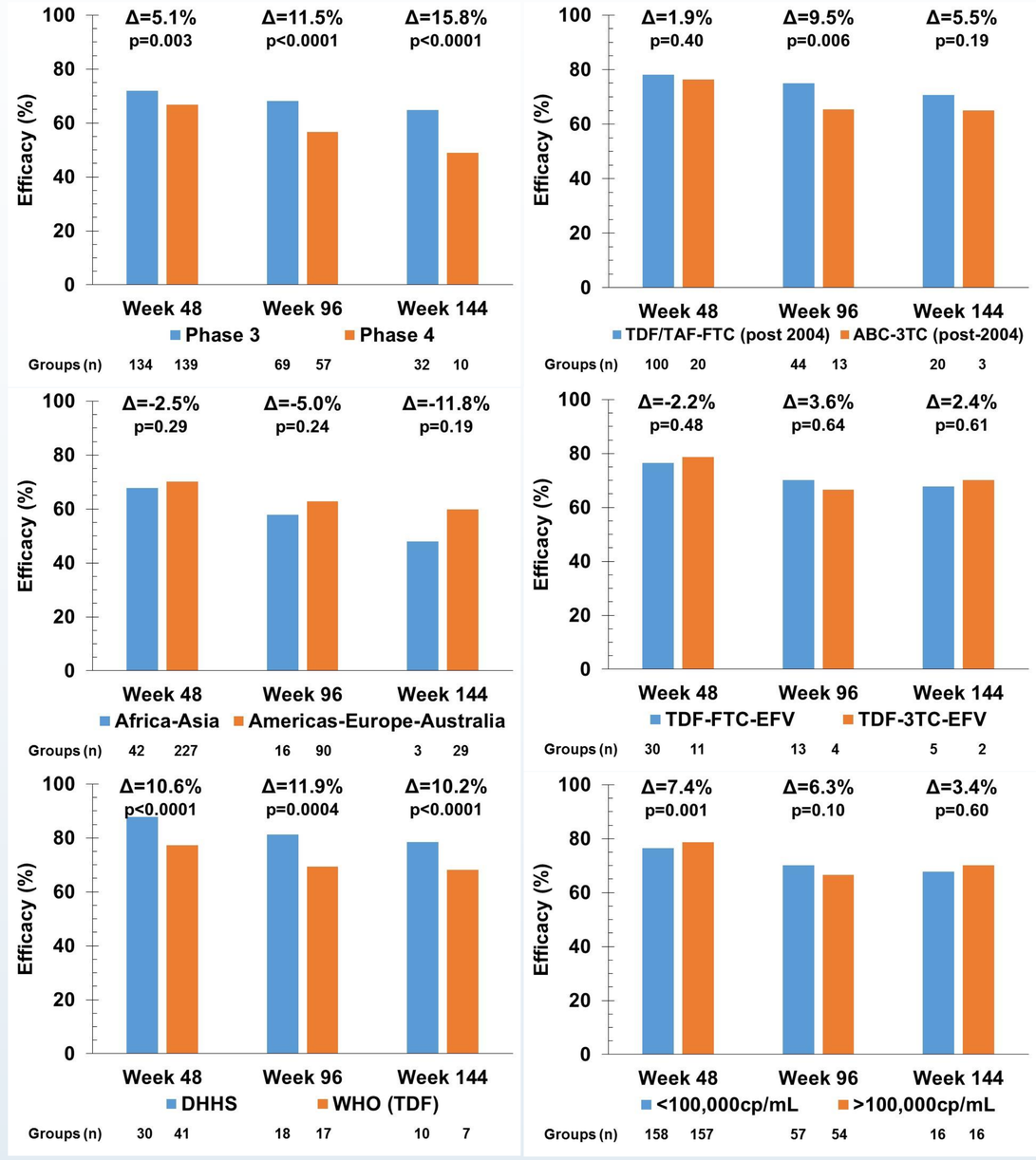
- Only 41% of groups had follow-up to Week 96, and only 13% to Week 144

Predictors of greater efficacy on multivariable analysis

Baseline variables	Predictors		
	Week 48	Week 96	Week 144
Design			
placebo used	+5.2%	+6.3%	+17.0%
phase 3 vs. 4	+6.1%	+4.9%	+15.8%
randomised	x	x	+8.7%
Eligibility			
genotyping	+4.3%	x	x
no CD4 restriction	+8.0%	+6.3%	+10.5%
Pre-ART			
higher CD4 (per 100 cells)	+2.2%	+0.5%	+0.8%
younger age (/yr)	x	x	+1.0%
ART			
1 dose/day (vs. 2)	+3.4%	+8.7%	+11.4%
non-fasting ART	x	x	x
less pills / day	x	x	x
TDF/TAF-FTC (vs. other NRTIs)	x	x	x
INSTI (vs rPI or NNRTI)	≥+9.3%	≥+9.0%	≥+5.6%

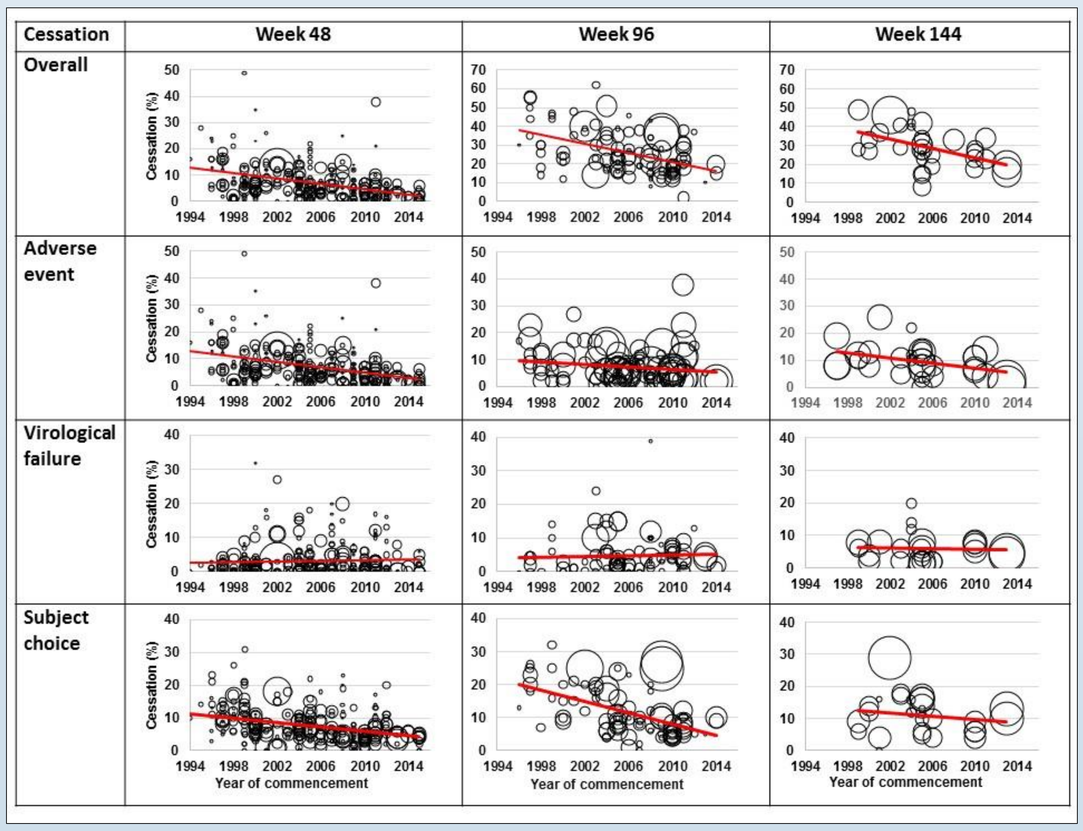
Not significant
Univariate significance
Significant in multivariate analysis, but not after exclusion of studies without HL-B*5701 screening
Significant in multivariate analysis (adjusted value)

Efficacy by subgroups



ART cessation

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



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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