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

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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

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

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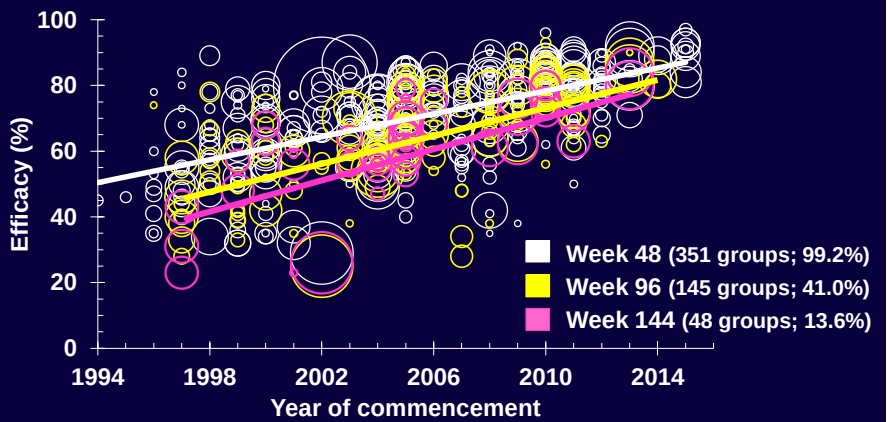
Efficacy: Weeks 48, 96 and 144



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

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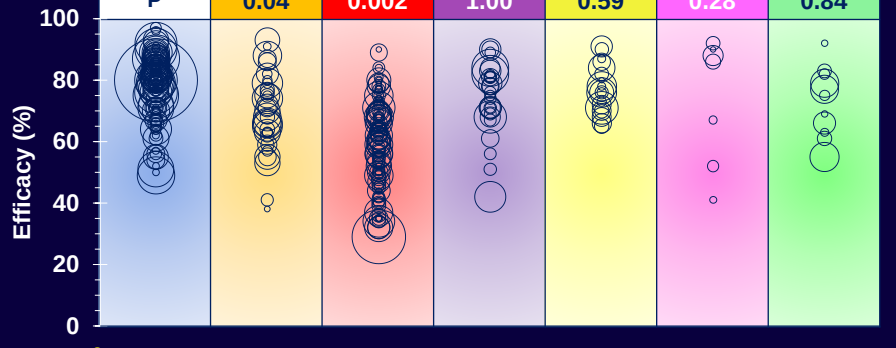
Predictors of efficacy: backbone (week 48)

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



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

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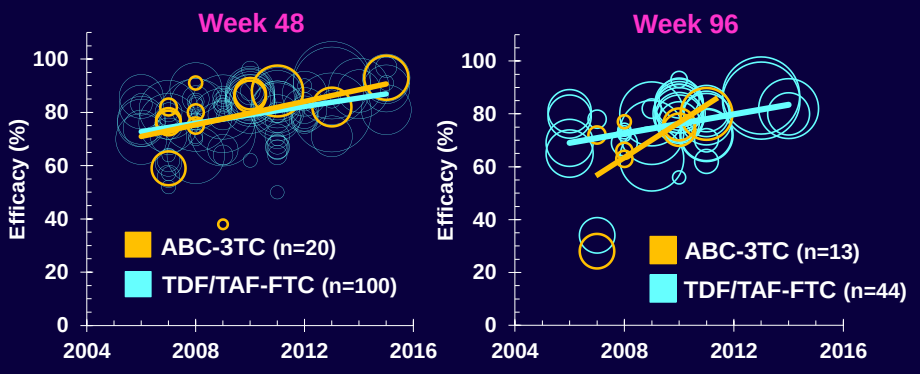
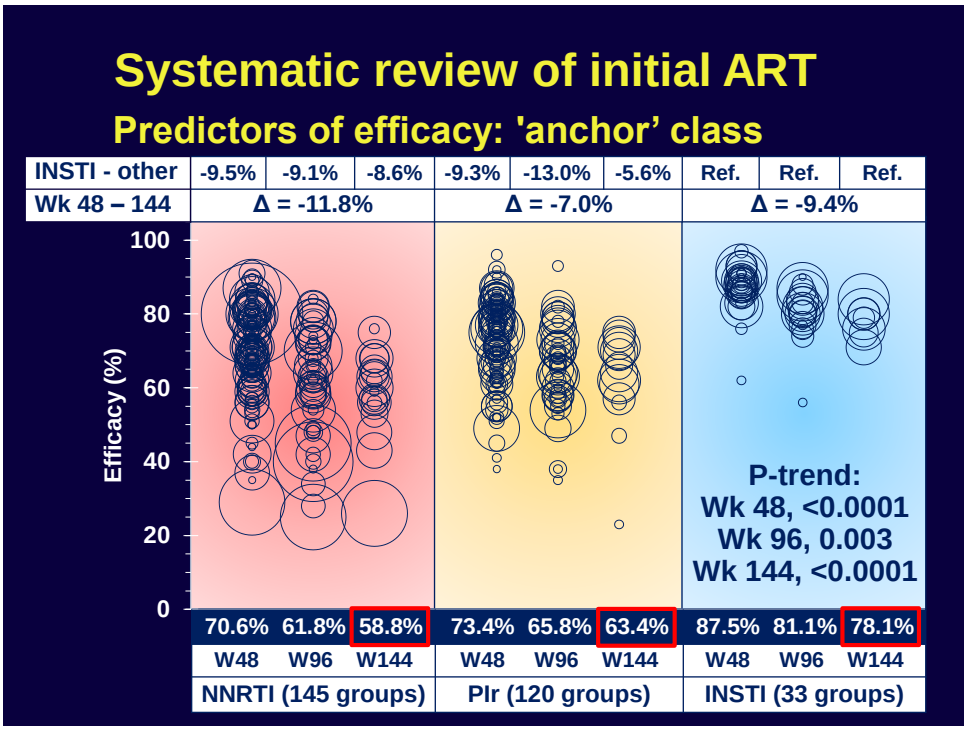
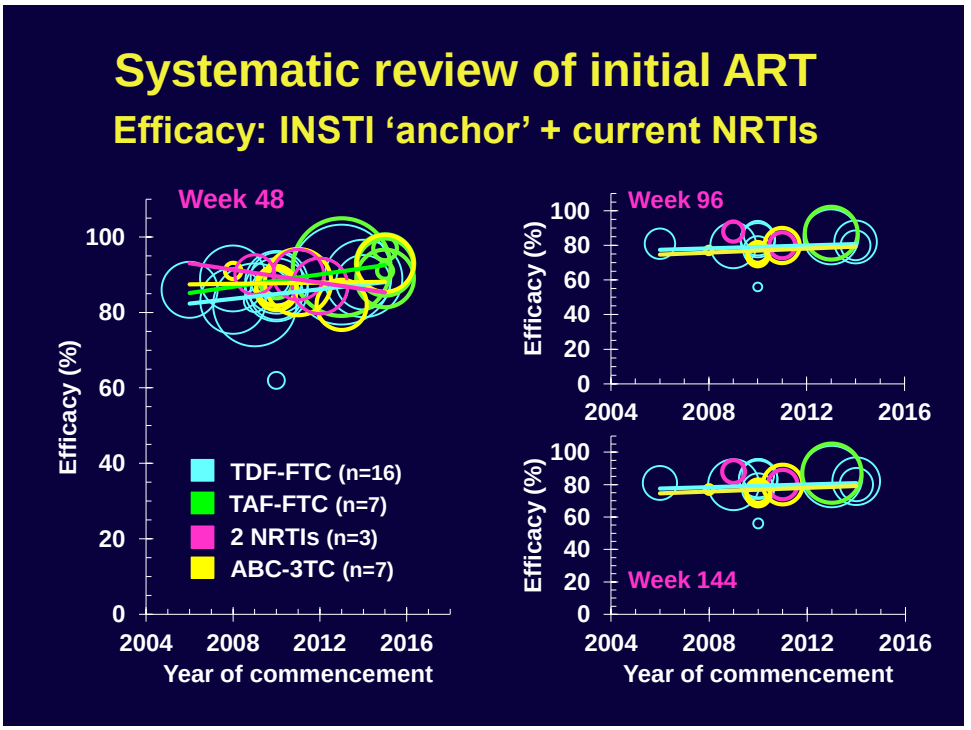
Efficacy: TDF/TAF-FTC vs ABC-3TC (post-2005)



TDF/TAF-FTC	ABC-3TC
78.2% (SD 9.4)	76.3% (SD 9.4)
Δ = 1.9% (95%CI -2.6, 6.4) p = 0.40	

TDF/TAF-FTC	ABC-3TC
74.9% (SD 10.6)	65.4% (SD 11.1)
Δ = 9.5% (95%CI 2.7, 16.3) p = 0.006	


Systematic review of initial ART
Predictors of efficacy: 'anchor' class
INSTI - other
-9.5% -9.1% -8.6%
-9.3% -13.0% -5.6%
Ref. Ref. Ref.
Wk 48 – 144
Δ = -11.8%
Δ = -7.0%
Δ = -9.4%
Efficacy (%)
100
80
60
40
20
0
P-trend:
Wk 48, <0.0001
Wk 96, 0.003
Wk 144, <0.0001
70.6% 61.8% 58.8%
73.4% 65.8% 63.4%
87.5% 81.1% 78.1%
W48 W96 W144
W48 W96 W144
W48 W96 W144
NNRTI (145 groups)
PIr (120 groups)
INSTI (33 groups)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Efficacy: INSTI 'anchor' + current NRTIs
Week 48
Efficacy (%)
100
80
60
40
20
0
TDF-FTC (n=16)
TAF-FTC (n=7)
2 NRTIs (n=3)
ABC-3TC (n=7)
2004 2008 2012 2016
Year of commencement
Week 96
Week 144
Efficacy (%)
2004 2008 2012 2016
Year of commencement

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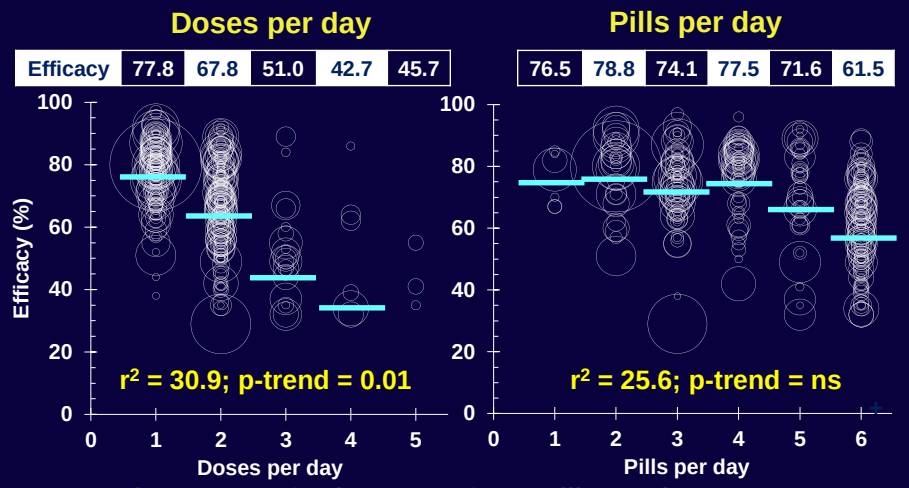
Predictors of efficacy: ART dosing (week 48)



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

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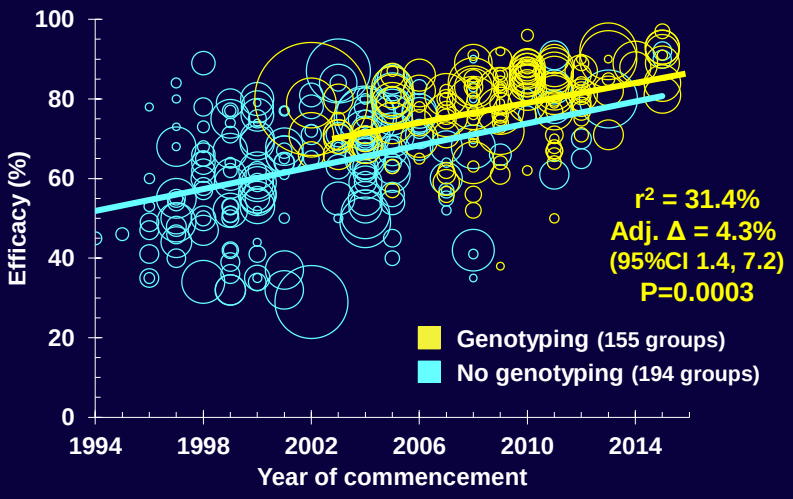
Predictors of efficacy: genotyping (week 48)



- **No significant effect observed at Weeks 96 or 144**

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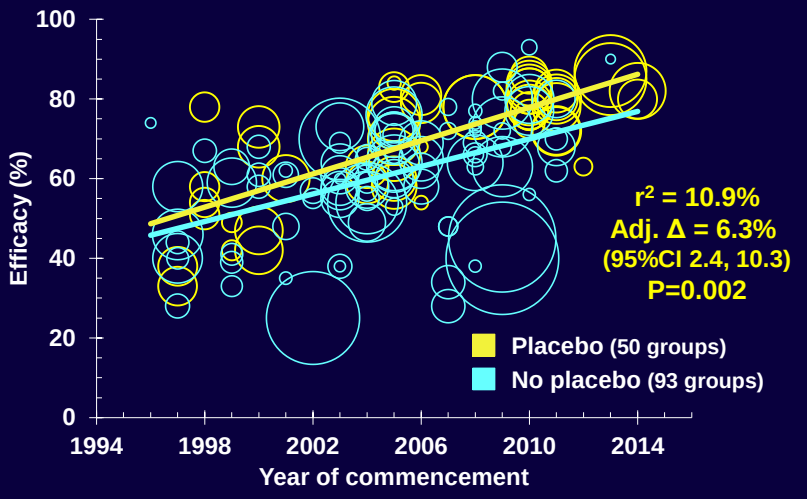
Predictors of efficacy Week 96: placebo



- No significant effect observed at Weeks 48 or 144

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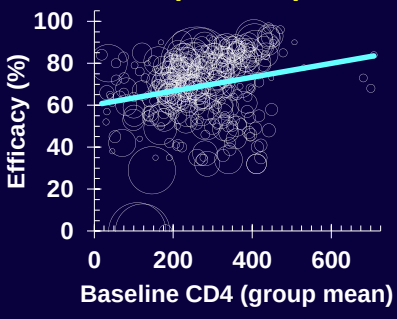
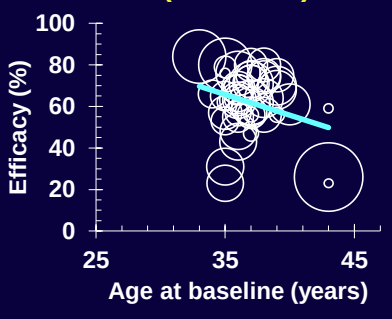
Predictors of efficacy: patient variables

Baseline CD4 (week 48)



r^2 = 4.2%
Adj. Δ = 2.2% / 100 cells
(95%CI 1.0, 3.4)
p-trend = 0.0003

Baseline age (week 144)



r^2 = 7.4%
Adj. Δ = -1.0% / year
(95%CI -1.8, -0.2)
p-trend = 0.02

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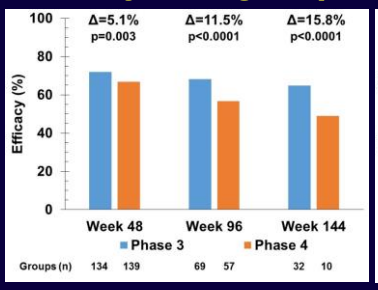
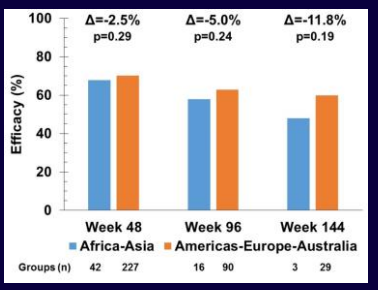
Efficacy: subgroups

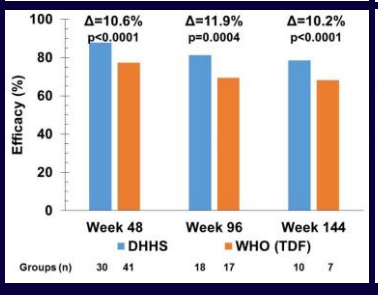
Phase 3 vs Phase 4

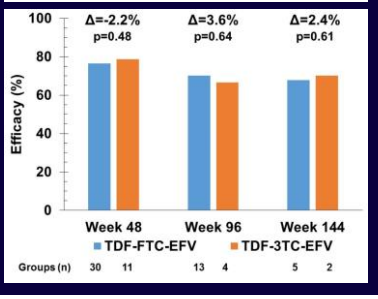




"LMIC" vs "HIC"

DHHS vs WHO





WHO: FTC vs 3TC

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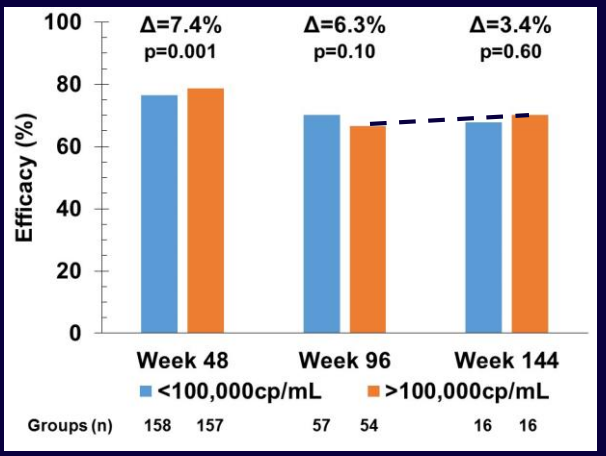
Efficacy: viral load strata



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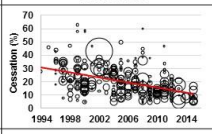
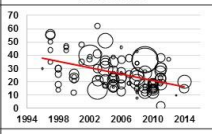
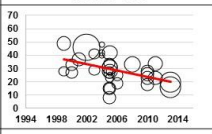
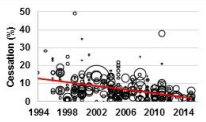
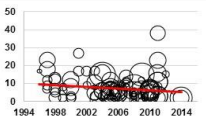
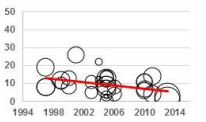
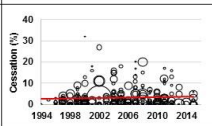
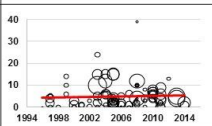
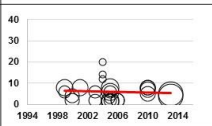
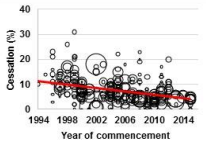
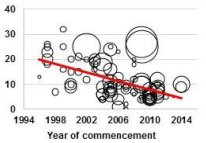
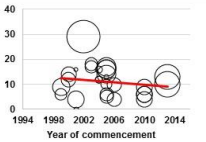
ART discontinuations

Cessation	Week 48	Week 96	Week 144
Overall			
Adverse event			
Virological failure			
Subject choice			

Cessation (%)

Year of commencement

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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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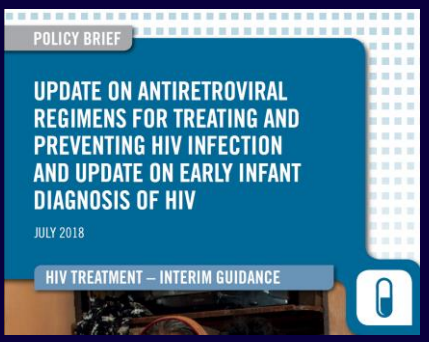
Implications for WHO ART guidelines

- De-list EFV and AZT as 'preferred' drugs for initial ART
- Promote pre-ART genotyping (as well as viral load testing)
- TDF-3TC-EFV 'similar' to TDF-FTC-EFV 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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- RR, SR and ZL declare no conflict of interest