Dolutegravir plus two nucleoside reverse transcriptase inhibitors versus efavirenz plus two nucleoside reverse transcriptase inhibitors as initial antiretroviral therapy for people with HIV: a systematic review

George W. Rutherford, M.D., A.M.
Hacsi Horváth, M.A.

Global Health Sciences
University of California, San Francisco
Cochrane Infectious Disease Group

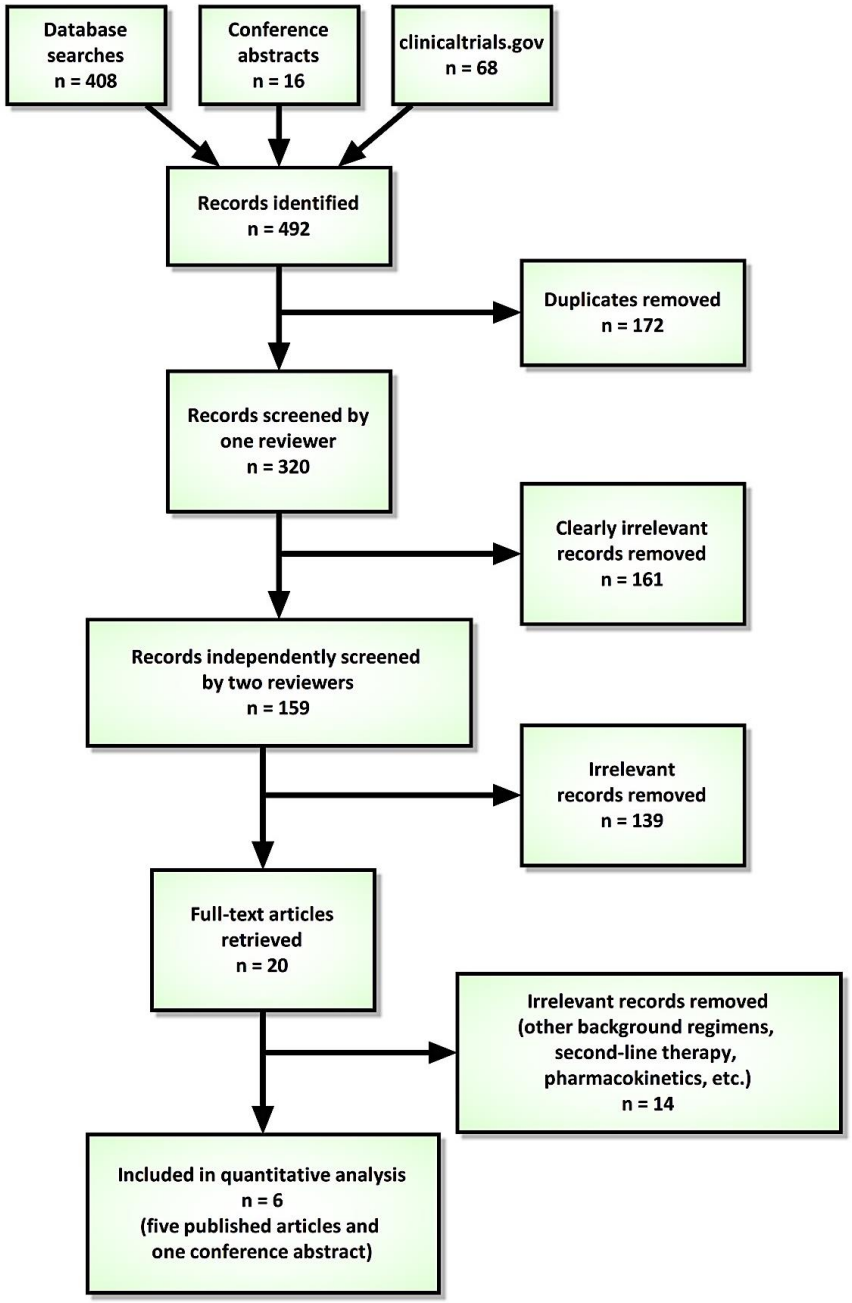
UCSF
University of California
San Francisco
advancing health worldwide

Background

- Current WHO guidelines recommend TDF+XTC+EFV as first-line therapy for HIV infection in all group except neonates
- BHVIA, EACS and US DHHS guidelines all recommend DTG + 2 NRTIs for first-line therapy (among others)
- We conducted a systematic review comparing TDF+XTC+EFV to DTG + 2 NRTIs

Methods

- We used standard Cochrane Collaboration methods to identify eligible studies
- Inclusion criteria: RCTs in HIV-1-infected patients who were ART naïve at entry
- Compared EFV + 2 NRTIs to DTG + 2 NRTIs
- Outcomes were clinical progression, death, viral suppression to non-detectable levels, discontinuation of therapy, immunologic recovery, acquired resistance and Grade III and IV severe adverse reactions



Results

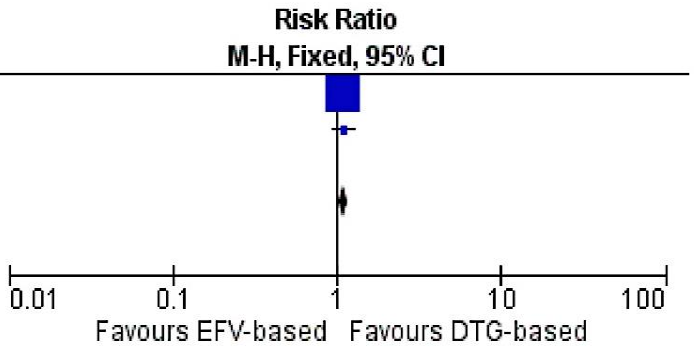
- Two trials
  - SPRING-1: 4-arm trial that compared DTG and either ABC+3TC or TDF+FTC to EFV + same NRTI combinations (N=101 for analysis)
  - SINGLE: DTG+ABC+3TC vs. EFV+ABC+3TC (N=833)
- Viral suppression to <50 copies/mL
  - 48 weeks RR=1.10, 95% CI 1.04-1.16 (both trials)
  - 96 weeks RR=1.12, 95% CI 1.04-1.21 (both trials)
  - 144 weeks RR=1.13, 95% CI 1.02-1.24 (SINGLE only)
- Discontinuation due to adverse events or death (SINGLE only)
  - RR=0.27, 955 CI 0.15-0.50 at 96 weeks
  - RR=0.28, 95% CI 0.16-0.48 at 144 weeks

Results

Viral suppression to <50 copies/mL at 48 weeks

Study or Subgroup	DTG-based regimen Events	Total	EFV-based regimen Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SINGLE	371	414	342	419	89.1%	1.10 [1.04, 1.16]
SPRING-1	46	51	41	50	10.9%	1.10 [0.94, 1.29]
Total (95% CI)		**465**		**469**	**100.0%**	**1.10 [1.04, 1.16]**
Total events	417		383			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.47 (P = 0.0005)



- No differences in mortality (2 deaths, both in EFV-containing arms)
- More robust immunologic recovery in DTG-containing arms (+57.9 cells/µL at 48 weeks, +42.2 at 96 weeks, +46.9 at 144 weeks)

Results

- No integrase inhibitor resistance at 96 weeks in either study but 10 instances of NRTI or NNRTI resistance at 96 weeks (RR =0.09, 95% CI 0.01-0.71)
- No differences in severe adverse events
- 34 patients on DTG+TDF+FTC from SPRING-1 had marginally higher levels of suppression than 431 patients on DTG+ABC+3TC from both trials (RR=1.08, 95% CI 1.01-1.16)

Author(s): George W. Rutherford, Hacsi Horvath
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Question: Should Dolutegravir 50 mg qd + two NRTIs vs Efavirenz 600 mg qd + two NRTIs be used for initial ART in people with HIV?
Settings: Australia, Belgium, Canada, France, Germany, Hungary, Italia, Netherlands, Romania, Spain, Russia, United Kingdom, United States
Bibliography: SINGLE trial (Walmsley 2013, Walmsley 2014, Walmsley 2015a, Walmsley 2015b); SPRING-1 trial (van Lunzen 2012, Stellbrink 2015)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dolutegravir 50 mg qd + two NRTIs	Efavirenz 600 mg qd + two NRTIsa	Relative (95% CI)	Absolute		
Viral suppression to non-detectable (<50 copies/mL) at 48 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	see footnote[4]	417/465 (89.7%)	383/469 (81.7%)	RR 1.1 (1.04 to 1.16)	82 more per 1000 (from 33 more to 131 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Viral suppression to non-detectable (<50 copies/mL) at 96 weeks												
2	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	see footnote[4]	376/465 (80.9%)	338/469 (72.1%)	RR 1.12 (1.04 to 1.21)	86 more per 1000 (from 29 more to 151 more)	⊕⊕⊕O MODERATE	CRITICAL
Viral suppression to non-detectable (<50 copies/mL) at 144 weeks												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	see footnote[4]	294/414 (71%)	264/419 (63%)	RR 1.13 (1.02 to 1.24)	82 more per 1000 (from 13 more to 151 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality at 48 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	see footnote[4]	0/465 (0%)	2/469 (0.43%)	RR 0.2 (0.01 to 4.2)	3 fewer per 1000 (from 4 fewer to 14 more)	⊕⊕OO LOW	CRITICAL

Conclusions

- There is high-quality evidence of virologic and immunologic benefits of DTG-containing therapy at 44 weeks and moderate-quality evidence of benefit at 96 weeks
- There were no DTG mutations in any trial
- A subanalysis suggested a minor benefit in viral suppression with DTG+TDF+FTC compared to DTG+ABC+3TC
- DTG as first-line therapy should be considered for next round of WHO guidelines