Kirby Institute

Treatment as prevention – where to next?

Defining individual benefit of treatment

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Kirby Institute

Defining individual benefit of treatment

Individual benefits are important

When to start cART?

Long term suppression of HIV replication

ARV dose reduction to increase access

When to start cART?

US guidelines now recommend cART independent of CD4+ cell count. Recommendation is reinforced by preventive impact of treatment.

Study	CD4+ strata (cells/mm^3)	RH (deferred vs immediate - 95% CIs)	
		AIDS/death	All-cause mortality
NA-ACCORD	<500 vs. >500	n/a	1.94 (1.37, 2.79)
	<350 vs. 351-500	n/a	1.69 (1.26, 2.26)
When to Start	351-450 vs. 451-550	0.99 (0.76, 1.29)	0.93 (0.60, 1.44)
	251-350 vs. 351-450	1.28 (1.04, 1.57)	1.13 (0.80, 1.60)
CASCADE Collaboration	<500 cs. 500-799	0.91 (0.56, 1.49)	0.98 (0.47, 2.04)
	<350 vs. 350-499	1.33 (0.88, 2.04)	1.96 (1.25, 3.03)
HIV-CAUSAL	<350 cs. 351-500	1.38 (1.23, 1.56)	1.01 (0.84, 1.22)

Defining individual benefit of treatment

When to start cART?

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm^3

Early ART Group

Initiate ART immediately following randomization

N=2,300 (300 >35 years old)

Deferred ART Group

Defer ART until the CD4+ count declines to < 350 cells/mm^3 or AIDS develops

N=2,300 (300 >35 years old)

When to start cART?

Characteristic	
Number (number with forms)	4190 (4136)
% female	25.0
Mean age (SD)	36 (10)
Asian	9.0
Black	27.0
Other	64.0
Heterosexual	58.5
Homosexual	37.0
Median CD4+ cell count	648 (582, 756)
Median plasma HIV RNA	4.1 (3.5, 4.3)
Hep B%	3.0
Hep C%	3.8

When to start cART?

Primary endpoint is a composite of AIDS/serious non-AIDS/death – require accrual of 271 confirmed events

Estimate completion of recruitment in December 2013

Estimate completion of follow-up in December 2016

Funding from US NIH (multiple institutes), NH&MRC, DoHA, and multiple other national research agencies.

Long term suppression of HIV replication

Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study

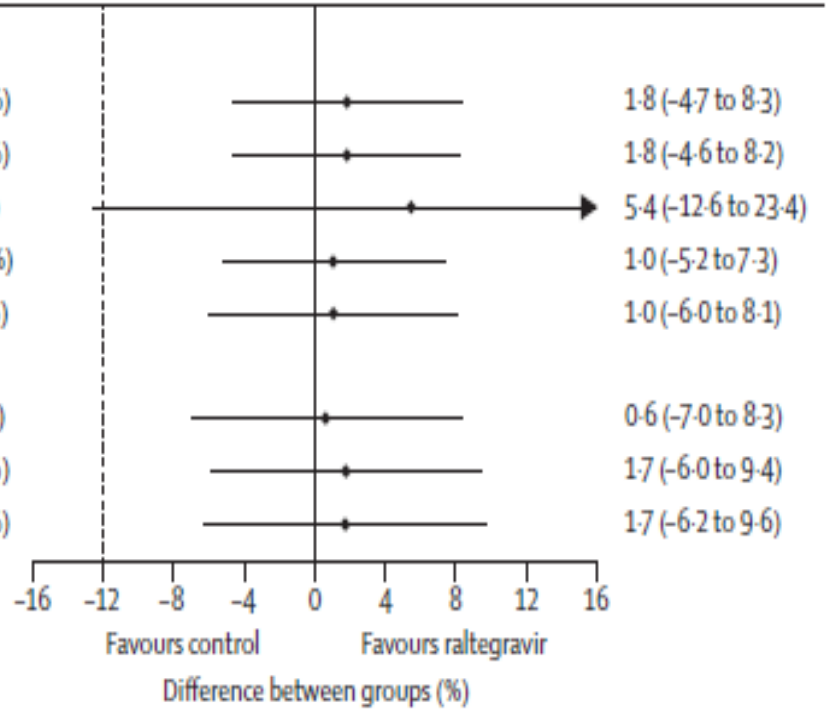
SECOND-LINE Study Group*

Lancet 2013; 381: 2091–99

Long term suppression of HIV replication

First adequately powered RCT comparing regimens of second line therapy.

	Control group	Raltegravir group	Difference (95% CI)
Plasma viral load <200 copies/mL			
Modified intention-to-treat (primary outcome)	219/271 (80·8%)	223/270 (82·6%)	1·8 (−4·7 to 8·3)
Baseline viral load ≤100 000 copies per mL*	188/219 (85·8%)	184/210 (87·6%)	1·8 (−4·6 to 8·2)
Baseline viral load >100 000 copies per mL*	31/52 (59·6%)	39/60 (65·0%)	5·4 (−12·6 to 23·4)
Per protocol	211/249 (84·7%)	211/246 (85·8%)	1·0 (−5·2 to 7·3)
Non-completer classed as failure†	208/271 (76·8%)	210/270 (77·8%)	1·0 (−6·0 to 8·1)
Plasma viral load <50 copies per mL			
Modified intention to treat	191/271 (70·5%)	192/270 (71·1%)	0·6 (−7·0 to 8·3)
Per protocol	183/249 (73·5%)	185/246 (75·2%)	1·7 (−6·0 to 9·4)
Non-completer classed as failure†	180/271 (66·4%)	184/270 (68·1%)	1·7 (−6·2 to 9·6)



Long term suppression of HIV replication

A novel regimen of cART containing two new classes of ARV is attractive in patients with failure using standard first line therapy.

Does not require HIV drug resistance testing.

Trial continues with 2nd year of follow-up likely to be reported in late 2013.

ARV dose reduction to increase access

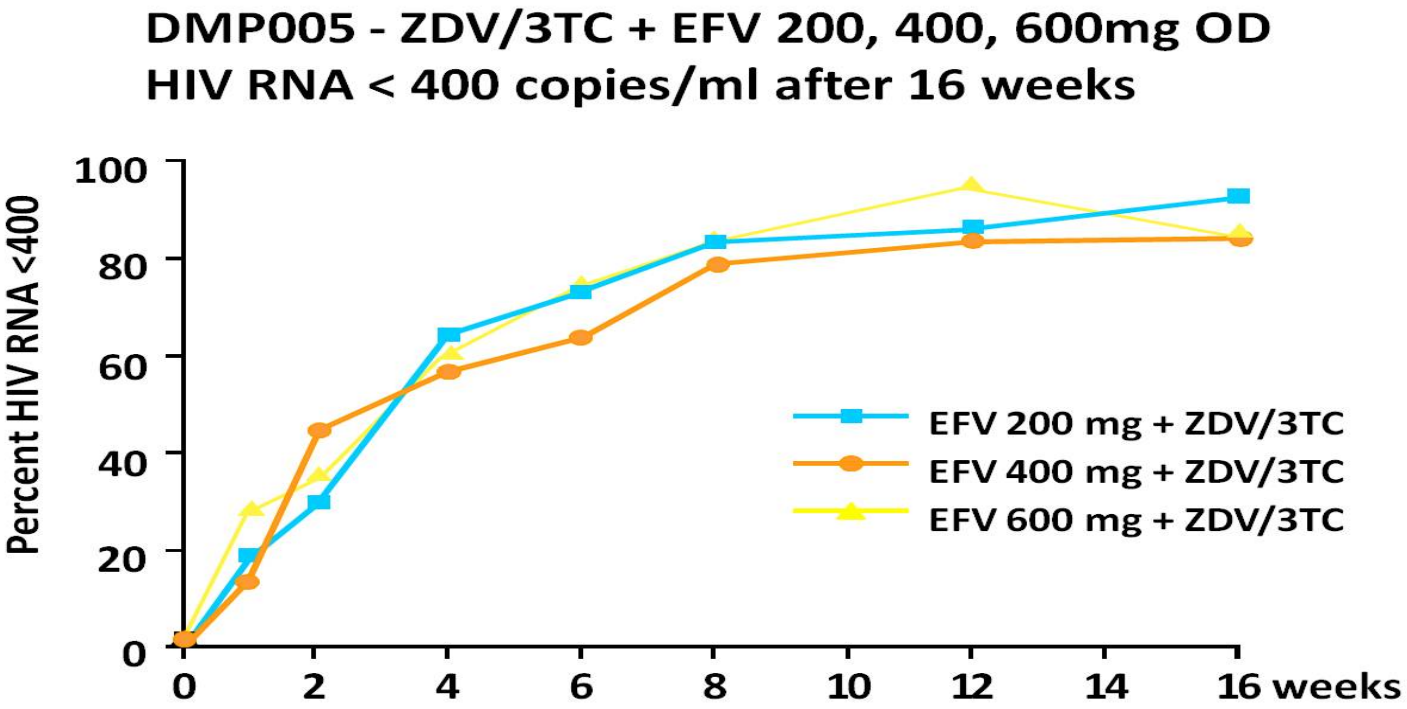
cART is expensive. In settings where cART is provided through public sector roll out programs, these costs are often limiting.

Costs have fallen considerably for selected drugs under the influence of competitive pricing and generic manufacturers coupled with new synthetic processes.

Further reductions in price are unlikely.

Dose reduction is a plausible and testable means of reducing drug costs.

ARV dose reduction to increase access



EFV 200 mg N =	32	34	34	30	29	32	31
EFV 400 mg N =	31	31	33	28	30	28	28
EFV 600 mg N =	32	29	32	28	30	27	28

Haas et al. 5th CROI 1998. Abstract 698

ARV dose reduction to increase access

Encore1

Intervention

I. TDF/FTC + 600mg EFV od

II. TDF/FTC + 400mg EFV od

Hypothesis

that reduced dose EFV + 2N(t)RTI regimen is non-inferior to the standard dose regimen in therapy-naïve patients - proportion of participants with HIV-1 RNA <200 copies/mL at 48 weeks

Patient population

630 therapy-naïve HIV-infected adults

Randomisation

1:1 (400mg:600mg), stratified by clinical site and screening plasma HIV-1 RNA > or ≤ 100,000 copies/mL

ARV dose reduction to increase access

region	% total
Africa	33%
Asia	31%
Australia and Europe	17%
Latin America	19%

ARV dose reduction to increase access

Characteristic	EFV 400mg N=321	EFV 600mg N=309	Total N=630
Male, n (%)	221 (68.8)	206 (66.5)	427 (67.7)
Mean age in years (SD)	36.1 (10.0)	35.8 (10.0)	36.0 (10.0)
Ethnicity, n (%)			
African	118 (36.8)	116 (37.4)	234 (37.1)
Asian	106 (33.0)	103 (33.2)	209 (33.1)
Caucasian	97 (30.2)	90 (29.0)	187 (29.6)
ATSI	0 (0.0)	1 (0.3)	1 (0.2)
CDC category A, n (%)	264 (82.2)	265 (85.8)	529 (84.0)
pVL copies/mL, n (%)			
<100,000	214 (66.7)	202 (64.4)	416 (66.0)
≥100,000	107 (33.3)	107 (34.6)	214 (34.0)
Median pVL in $\log_{10}$ copies/mL (IQR)	4.76 (0.84)	4.73 (0.90)	4.75 (0.88)
100 < CD4+ T cells/µL ≤ 350, n (%)	244 (76)	224 (72)	468 (74)
Mean CD4+ T cells/µL (SD)	273 (97)	272 (101)	273 (99)

Defining individual benefit of treatment

TasP will require an extensive expansion of treatment around the world and in places where resources are already limited.

START will define whether individuals gain benefit (avoid harms) from earlier use of cART.

2nd Line provides evidence to guide treatment recommendations aimed at long term suppression of HIV replication

ENCORE1 may provide a means to expand treatment programs at reduced costs – thereby expanding access.

Defining individual benefit of treatment

New work

Further opportunities for dose reduction – atazanavir and darunavir

Drug interactions – EFV and rifampicin

New drugs - dolutegravir

Defining individual benefit of treatment

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