THE UNIVERSITY of ADELAIDE

When are 2 drugs better than 3?

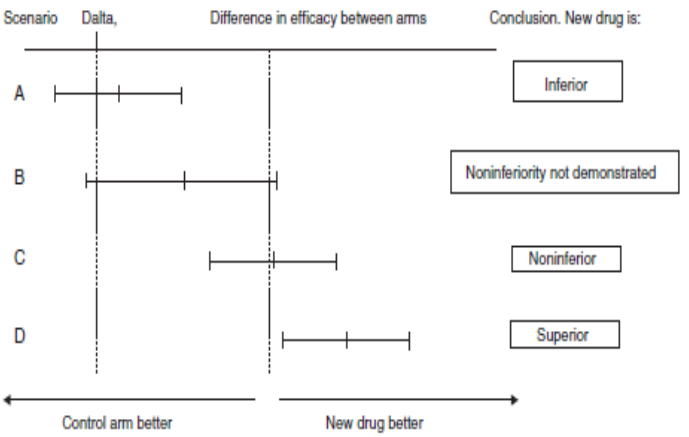
Mark Boyd MD, FRACP

Disclosures

- Gilead – grants, honoraria
- Janssen-Cilag – honoraria
- Merck – grants, honoraria
- ViiV Healthcare – honoraria

When are 2 drugs better than 3?

or



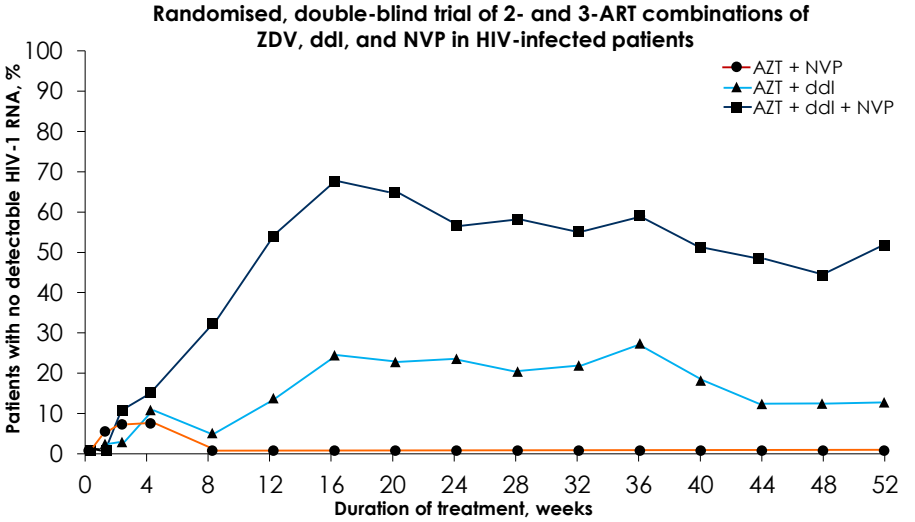
….when are 2 drugs as good as 3?

Hill A and Sabin C. AIDS 2008;22:913-21.

Rationale for evaluating dual therapy

- First principles
  - *'primum non nocere'*
  - use only as much drug as you need
- Maximise tolerability/minimise toxicity
- Reduce pill burden/optimise adherence
- Maximise quality of life
  - 'the 4th 90'
- Spare drug classes and individual drugs for later
  - ART needs to support a normal life expectancy
- Reduce cost

INCAS: Dual ART vs triple ART
Virological suppression (<20 c/mL) at Week 52



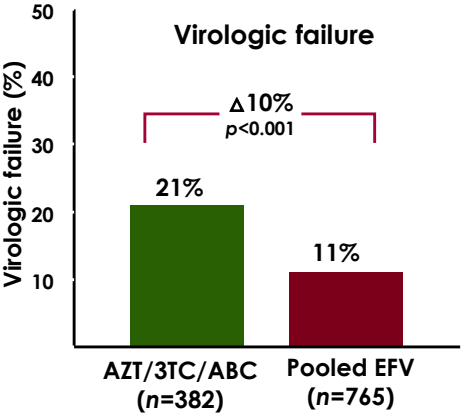
ART, antiretroviral therapy; ddI, didanosine; NVP, nevirapine; ZDV, zidovudine.

Montaner J, et al. JAMA 1998;279:930–7

ACTG 5095
Triple NRTIs vs 2 class ART

AZT/3TC/ABC v AZT/3TC/EFV +/- ABC

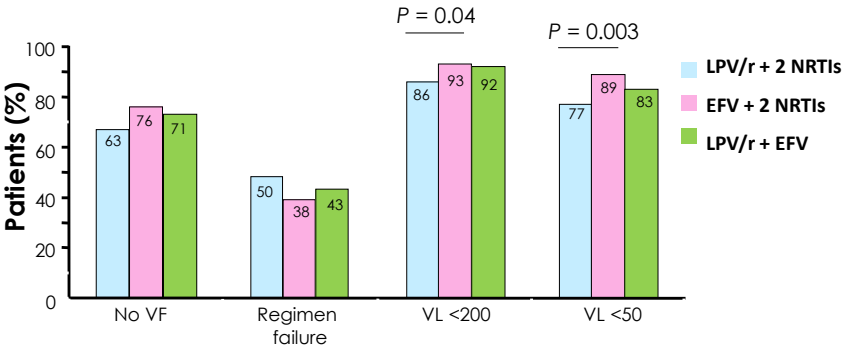
- % with VL <50 c/mL at week 48:
  - triple NRTI: 61%
  - pooled EFV arms: 83%
- Time to VF shorter for triple NRTI regardless of baseline VL:
  - <100K, p=0.001
  - >100K, p<0.001
- Post-hoc analysis: TTVF following VL suppression at least once:
  - to <200 c/mL, p<0.001
  - to <50 c/mL, p=0.08



ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; EFV, efavirenz; NRTI, nucleoside reverse transcriptase inhibitor; TTVF, total time to virologic failure; VF, virologic failure; VL, viral load; 3TC, lamivudine.

Gulick RM, et al. NEJM 2004;350:1850–61.

ACTG 5142: Efficacy at W96 (ITT)



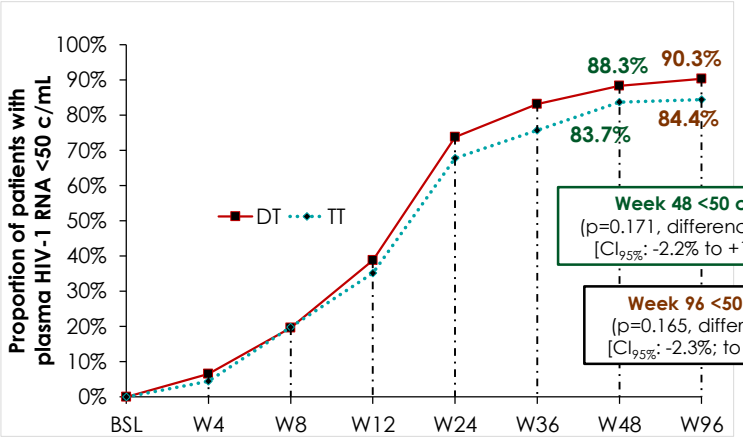
- EFV + 2 NRTI not superior to EFV + LPV/r
- EFV + LPV/r associated with more adverse metabolic profiles
- EFV + LPV/r associated with a greater degree of resistance at VF

Riddler S, et al. NEJM 2008;358:2095–106.

GARDEL

Dual therapy (2 class) versus triple therapy (2 class)

LPV/r + 3TC vs PV/r + 2N(t)RTI

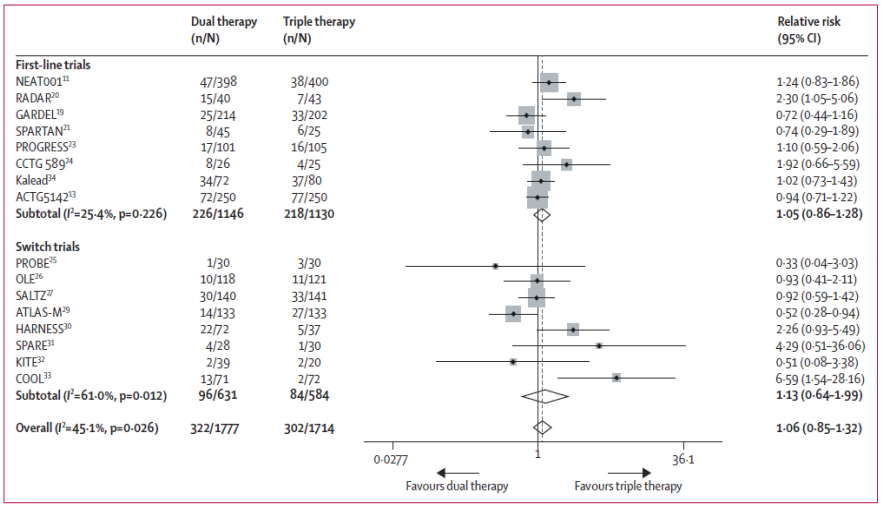


DT, dual therapy; LPV/r, lopinavir/ritonavir; N(t)RTI, nucleotide reverse transcriptase inhibitor; TT, triple therapy; 3TC, lamivudine.

Rolón MJ. EACS 2015, Barcelona. PS10/4.

Are 2 drugs as good as 3 drugs?

Systematic review and meta-analysis



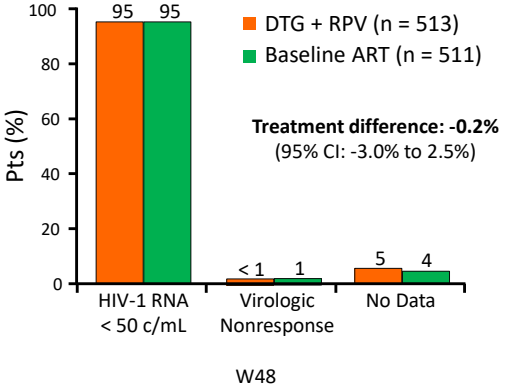
	Dual therapy (n/N)	Triple therapy (n/N)	Relative risk (95% CI)
First-line trials			
NEAT001[11]	47/398	38/400	1·24 (0·83–1·86)
RADAR[20]	15/40	7/43	2·30 (1·05–5·06)
GARDEL[19]	25/214	33/202	0·72 (0·44–1·16)
SPARTAN[21]	8/45	6/25	0·74 (0·29–1·89)
PROGRESS[23]	17/101	16/105	1·10 (0·59–2·06)
CCTG 589[24]	8/26	4/25	1·92 (0·66–5·59)
Kalead[34]	34/72	37/80	1·02 (0·73–1·43)
ACTG5142[13]	72/250	77/250	0·94 (0·71–1·22)
Subtotal (I^2=25·4%, p=0·226)	**226/1146**	**218/1130**	**1·05 (0·86–1·28)**
Switch trials			
PROBE[25]	1/30	3/30	0·33 (0·04–3·03)
OLE[26]	10/118	11/121	0·93 (0·41–2·11)
SALTZ[27]	30/140	33/141	0·92 (0·59–1·42)
ATLAS-M[29]	14/133	27/133	0·52 (0·28–0·94)
HARNESS[30]	22/72	5/37	2·26 (0·93–5·49)
SPARE[31]	4/28	1/30	4·29 (0·51–36·06)
KITE[32]	2/39	2/20	0·51 (0·08–3·38)
COOL[33]	13/71	2/72	6·59 (1·54–28·16)
Subtotal (I^2=61·0%, p=0·012)	**96/631**	**84/584**	**1·13 (0·64–1·99)**
Overall (I^2=45·1%, p=0·026)	**322/1777**	**302/1714**	**1·06 (0·85–1·32)**

Figure 3: Meta-analysis of the primary virological outcome by trial type (first-line and switch studies), excluding maraviroc trials

Achhra A, et al Lancet HIV 2016

SWORD

Switch from suppressive ART to DTG + RPV* dual ART non-inferior to continued ART at W48



Llibre JM, et al. CROI 2017. Oral abstract 44LB.

PADDLE

DTG + 3TC dual ART in ART-naïve PLHIV with CD4+ >200 cells/µL and VL <100,000 c/mL

Viral load values at baseline and weeks 48, 60, 72, 84 and 96 (copies/mL).

Patient Nr.	BSL	W. 48	W. 60	W.72	W. 84	W. 96
HIV-1 Viral load (copies/mL)						
01	10,909	<50	<50	<50	<50	<50
02	10,233	<50	<50	<50	<50	<50
03	151,569	<50	<50	<50	55/<50*	<50
04	148,370	<50	<50	<50	<50	<50
05	20,544	<50	<50	<50	<50	<50
06	14,499	<50	<50	<50	<50	<50
07	18,597	<50	<50	<50	<50	<50
08	24,368	<50	<50	<50	<50	<50
09	10,832	Discontinuation at visit W. 48 due to SAE				
10	7,978	<50	<50	<50	<50	<50
11	273,676	<50	<50	<50	<50	70/<50*
12	64,103	<50	<50	<50	<50	<50
13	33,829	<50	<50	<50	<50	<50
14	15,151	<50	<50	<50	<50	<50
15	23,400	<50	<50	<50	<50	<50
16	3,910	<50	<50	<50	<50	<50
17	25,828	<50	<50	<50	<50	<50
18	73,069	<50	<50	<50	<50	<50
19	106,320	Discontinuation at visit W. 48 due to protocol-defined virological failure				
20	7,368	<50	<50	<50	<50	<50

*Two patients required retest of viral load due to blips. VL retests were <50 copies/mL

Cahn P, et al. IAS July 2017

ACTG A5353: a pilot study of DTG+3TC for initial treatment of PLH with HIV RNA <500,000 c/mL

Primary Outcome: FDA Snapshot at Week 24

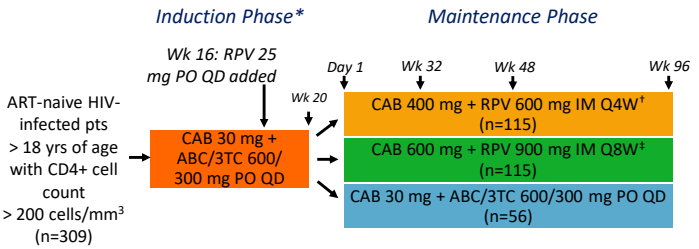
	Baseline HIV-1 RNA		
	> 100,000 cpm n=37	≤ 100,000 cpm n=83	Total N=120
Virologic success HIV-1 RNA < 50 cpm [95% CI]	**33 (89%) [75%,97%]**	**75 (90%) [82%,96%]**	**10 8 (90%) [83%,95%]**
Virologic non-success	**3 (8%)**	**2 (2%)**	**5 (4%)**
HIV-1 RNA ≥ 50 cpm	3	0	3
Discontinued study treatment for other reasons while HIV RNA ≥ 50*	0	2	2
No virologic data in window	**1 (3%)**	**6 (7%)**	**7 (6%)**
Discontinued study treatment for other reasons #	1	5	6
On study but missing data in window	0	1	1

** Poor adherence; # Lost to follow-up, pregnancy*

Taiwo B, et al. IAS Paris 2017

LATTE-2: Cabotegravir IM + Rilpivirine IM for long-acting maintenance ART

- Multicenter, open-label, randomized phase IIb study
  - Cabotegravir: InSTI formulated as an oral tablet and for long-acting IM injection



*Pts with HIV-1 RNA < 50 copies/mL from Wks 16-20 continued to maintenance phase. †CAB loading dose at Day

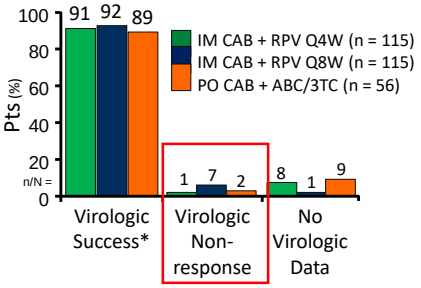
‡CAB loading doses at Day 1 and Wk 4.

- Injections were 2-3 mL, IM (gluteal region), provider administered

Margolis D et al. Lancet 2017;390:1499-1510.

LATTE-2: efficacy and safety through maintenance Week 48

- Virologic efficacy of Q4W/Q8W im therapy similar to oral therapy



*HIV-1 RNA < 50 copies/mL.

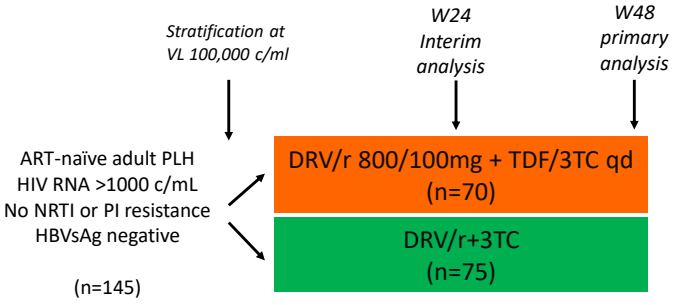
- 99% of ISRs for pts receiving injectable therapy grade 1 (82%) or 2 (17%); none grade 4
  - Most frequent ISRs: pain (67%), nodules (7%), swelling (6%)
  - 2/230 pts (< 1%) withdrew for ISRs (both in Q8W arm)
- AEs leading to withdrawal
  - Pooled Q4W/Q8W IM arms, 4%
  - PO arm, 2%

Phase III maintenance trials (ATLAS and FLAIR) enrolling using the q4W dosing interval

Margolis D et al. Lancet 2017;390:1499-1510.

ANDES
DRV/r + TDF/3TC v DRV/r + 3TC

- Phase 4, randomized, open-label, multicenter trial 48 week trial with a week 24 interim analysis



Seud O,et al. IAS Paris 2017; Abstract MOAB0106LB.

ANDES
DRV/r + TDF/3TC v DRV/r + 3TC

W24 interim analysis

Patients with VL<400 c/mL at week 24

	DT	TT	Difference (95% CI)
ITT snapshot (n=145)	71/75 (95%)	68/70 (97%)	-2.5% (-7.9; 2.9)
On treatment (n=140)	71/71 (100%)	68/69 (99%)	1.4% (-0.9, 3.8)
Discontinuations	4*	1**	
Virological failure	0	1	

*Withdraw consent (1) ,SAE (1), LTFU (1) , RASH (1)
** LTFU

Seud O,et al. IAS Paris 2017; Abstract MOAB0106LB.

Conclusions

- Is it time to change the language of ART?
  - should we drop 'triple therapy' from the lexicon
- Evidence exists that optimal outcomes will result from dual class (2 drug/3 drug) combinations that are potent, tolerable, non-toxic and convenient
- More research is needed
  - long term safety and efficacy

Acknowledgments

- David Cooper
- Cal Cohen
- Pedro Cahn
- Jean-michel Molina

THE UNIVERSITY of ADELAIDE