ART Guidelines Session - ASHM 2015

What to Start: A look from the Australian perspective

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Disclosures

Benefit to institution:

- Bristol-Myers Squibb – clinical trial PI
- Gilead – clinical trial PI, advisory board, grants
- Merck – clinical trial PI
- ViiV Healthcare – clinical trial PI, advisory board

NRTI backbone	3rd drug	DHHS April 2015	DHHS May 2014
Tenofovir/Emtricitabine	Raltegravir	Recommended	Recommended
	Dolutegravir	Recommended	Recommended
	Elvitegravir/cobicistat	Recommended	Recommended
	Atazanavir/ritonavir	Alternative	Recommended
	Atazanavir/cobicistat	Alternative	No comment
	Darunavir/ritonavir	Recommended	Recommended
	Darunavir/cobicistat	Alternative	No comment
	Lopinavir/ritonavir	Other	Alternative
	Efavirenz	Alternative	Recommended
	Nevirapine	Not recommended	Not recommended
	Rilpivirine	Alternative#	Recommended*
	Maraviroc	Not recommended	Not recommended
Abacavir/Lamivudine	Raltegravir	Other	Alternative
	Dolutegravir	Recommended	Recommended
	Atazanavir/ritonavir	Other*	Recommended*
	Atazanavir/cobicistat	Other*	No comment
	Darunavir/ritonavir	Alternative	Alternative
	Darunavir/cobicistat	Alternative	No comment
	Lopinavir/ritonavir	Other	Alternative
	Efavirenz	Other*	Recommended*
	Nevirapine	Not recommended	Not recommended
	Rilpivirine	Not recommended	Not recommended
	Maraviroc	Not recommended	Not recommended
NRTI sparing/limiting (when TDF or ABC can't be used)			
Raltegravir + Darunavir/ritonavir		Other*	No comment
Raltegravir + Lopinavir/ritonavir		No comment	No comment
Lamivudine + Lopinavir/ritonavir		Other	No comment
Notes		* Only if pre-ART HIV RNA <100,000 c/ml # Only if pre-ART <100,000 c/ml and CD4 > 200	* Only if pre-ART HIV RNA <100,000 c/ml

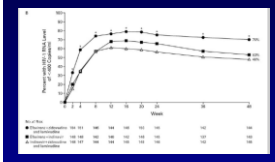
NRTI backbone	3rd drug	DHHS April 2015	DHHS May 2014
Tenofovir/Emtricitabine			
	Atazanavir/ritonavir	Alternative	Recommended
	Efavirenz	Alternative	Recommended
	Rilpivirine	Alternative#	Recommended*
Abacavir/Lamivudine			
	Atazanavir/ritonavir	Other*	Recommended*
	Efavirenz	Other*	Recommended*
Notes		* Only if pre-ART HIV RNA <100,000 c/ml # Only if pre-ART <100,000 c/ml and CD4 > 200	* Only if pre-ART HIV RNA <100,000 c/ml

Adapted from http://arv.ashm.org.au/images/WhatAntiretroviralTreatmentStart_UpdateSep2014.pdf

DHHS Category Changes

- Recommended, Alternative, Not recommended
- New Category → 'Other'
  - Comparing with Recommended and Alternative may have:
    - Decreased efficacy or supporting data,
    - Increased toxicity, pill burden or potential drug interactions
- 'Alternative' or 'other' regimen may be preferred for some patients
  - Table 7 (F-6 to F-8) or arv.ashm.org.au
    - Details different clinical scenarios or patient preferences and their impact on regimen choice

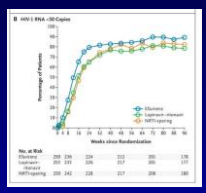
EFV vs IDV[1]



Intention to Treat at 48 weeks
EFV 70%
IDV 48%

1 NEJM 1999 341:1865-1873
2 NEJM 2008 358:2095-2106

EFV vs LPV/r[2]



On Treatment at 96 weeks
EFV 89%
LPV/r 77%

Time to regimen failure (EFV vs LPV/r)
HR 0.75 (95% CI 0.57-0.98)

EFV vs NVP Lancet 2004; 363:1253-1263

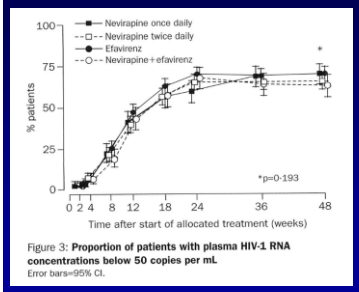


Figure 3: **Proportion of patients with plasma HIV-1 RNA concentrations below 50 copies per mL**
Error bars=95% CI.

ITT - Difference between NVP BD and EFV daily 5.9% (95% CI -0.9 - 12.8)

2 deaths attributed to NVP

Equivalence if 95% CI of the difference was within 10% of zero

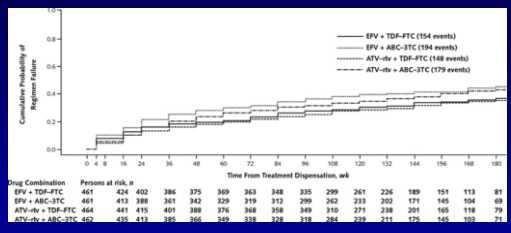
"..we could not show equivalence"

But conclude 'similar efficacy and recommended for first line treatment' (in 2004)

On treatment outcomes in figure

EFV vs ATV/r Ann Intern Med 2011;154:445-456

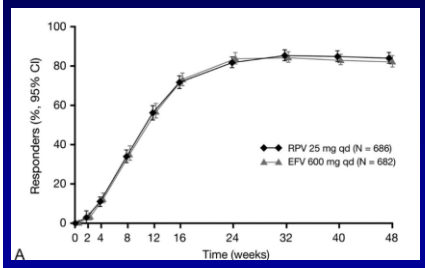
(ACTG 5202)



1º virological efficacy similar for ATV/r and EFV, not differing by NRTI backbone

Hazard ratios for time to virologic failure (EFV as reference):
1.13 for ABC/3TC (95% CI 0.82-1.56) and 1.01 for TDF/FTC (95% CI 0.70-1.46)

EFV vs RPV JAIDS 2012; 60:33-42
(Combined ECHO and THRIVE)



Intention to treat at 48 weeks

EFV 82% (561/682)

RPV 84% (578/686)

Difference of 2.0% (95% CI -2.0-6.0%)

EFV vs RPV JAIDS 2012; 60:33-42

Baseline HIV RNA	< 100,000 c/mL		> 100,000 c/mL	
	Rilpivirine (n=368)	Efavirenz (n=330)	Rilpivirine (n=318)	Efavirenz (n=352)
Virological Failure	15 (4%)	10 (3%)	47 (15%)	22 (6%)
Discontinuation	22 (6%)	43 (13%)	26 (8%)	46 (13%)

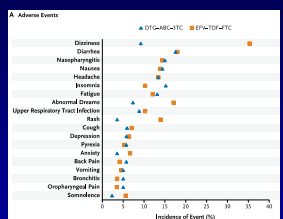
Treatment-related AEs ≥ Grade 2	Rilpivirine (n=686)	Efavirenz (n=682)
Rash	7 (1%)	56 (8%)
Dizziness	4 (1%)	43 (6%)
Abnormal dreams/nightmares	9 (1%)	25 (4%)
Headache	11 (2%)	15 (2%)
Insomnia	12 (2%)	16 (2%)

EFV adverse events

	EVG/COBI/FTC/TDF group (n=348)	EFV/FTC/TDF group (n=352)
Diarrhoea	80 (23%)	66 (19%)
Nausea*	72 (21%)	48 (14%)
Fatigue	40 (11%)	45 (13%)
Upper respiratory infection	48 (14%)	38 (11%)
Dizziness†	23 (7%)	86 (24%)
Headache	49 (14%)	34 (10%)
Abnormal dreams†	53 (15%)	95 (27%)
Insomnia‡	30 (9%)	49 (14%)
Depression	33 (9%)	39 (11%)
Rash§	22 (6%)	43 (12%)

Data are n (%). p>0·05 unless otherwise stated. Groups compared with Fisher's exact test. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz. *p=0·016. †p<0·001. ‡p=0·031. §p=0·005.

Table 4: Adverse events in ≥10% of patients in either group



Lancet 2012; 379:2439-2448

N Engl J Med 2013; 369:1807-1818

EFV and Suicidality

- Meta-analysis of 4 randomised ACTG studies comparing EFV-containing to EFV-free regimens[1]
- Suicidal ideation or attempted or completed suicide in EFV regimens had HR 2.28 [95% CI 1.27-4.10]; p=.006
- Attempted or completed suicide HR was 2.58 [CI 0.94 to 7.06]; p=.065
- 32% participants had a psychiatric history

1 Ann Intern Med 2014 Aug 19;161(4):308

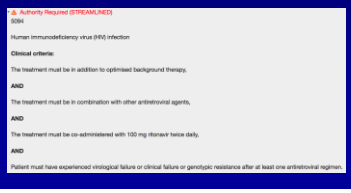
EFV and Suicidality

- Observational studies don't show same increased risk[1,2]
  - D:A:D. 675 of 4420 deaths had suicide or psychiatric condition reported as the underlying or associated cause of death
  - FDA adverse event reporting system. 457 reports of ideation, attempt and completed suicide on ART
- No association with EFV use
- May reflect appropriate prescribing to people at risk of suicide

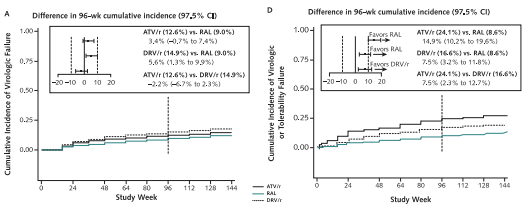
1 JIAS 2014; 17(4 Suppl 3):19512 2 JIAS 2014; 17:19214

Protease Inhibitors

- TDF/FTC + ritonavir boosted DRV is the only non-InSTI based regimen recommended for initial therapy in this update
- DRV not currently reimbursed for initial therapy in Australia


Authority Required (STREAMLINED)
9094
Human immunodeficiency virus (HIV) infection
Clinical criteria:
The treatment must be in addition to optimised background therapy,
AND
The treatment must be in combination with other antiretroviral agents,
AND
The treatment must be co-administered with 100 mg ritonavir twice daily,
AND
Patient must have experienced virological failure or clinical failure or genotypic resistance after at least one antiretroviral regimen.

ACTG 5257 – VF and combined VF and Tolerability endpoint

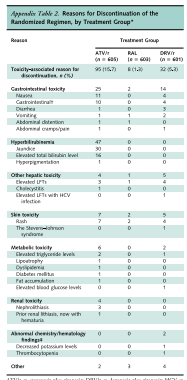


Ann Intern Med 2014; 161:461-471

ACTG 5257 – AEs and Reasons for Treatment Discontinuation

Table 3. Grade 2 or Higher Adverse Effects Occurring in ≥5% of Participants, by Treatment Group

Adverse Effect	ATV/r				DRV/r			
	Grade, n*			Total, n (%)	Grade, n*			Total, n (%)
	2	3	4		2	3	4	
Diarrhea	35	11	0	46 (7.6)	46	6	0	52 (8.6)
Nausea	36	8	1	45 (7.4)	29	12	0	41 (6.8)
Vomiting	22	7	1	30 (5.0)	21	11	0	32 (5.3)
Abdominal pain	13	17	1	31 (5.1)	13	14	2	29 (4.8)
Headache	23	10	2	35 (5.8)	30	12	2	44 (7.3)
Pain in extremity	27	14	1	42 (6.9)	18	13	1	32 (5.3)
Arthralgia	17	8	0	25 (4.1)	13	14	1	28 (4.7)
Back pain	14	4	0	18 (3.0)	9	12	0	21 (3.5)
Fatigue	32	6	1	39 (6.4)	26	7	0	33 (5.5)
Cough	33	9	0	42 (6.9)	31	5	0	36 (6.0)
Dyspnea	16	9	1	26 (4.3)	8	14	1	23 (3.8)
Pyrexia	16	9	1	26 (4.3)	18	7	2	27(4.5)
Elevated blood bilirubin level†	22	217	47	286 (47.2)	0	4	0	4 (<1.2)
Decreased blood phosphorus level‡	3	30	1	34 (5.6)	2	35	0	37 (6.2)
Elevated blood glucose level§	11	15	0	26 (4.3)	15	11	1	27 (4.5)

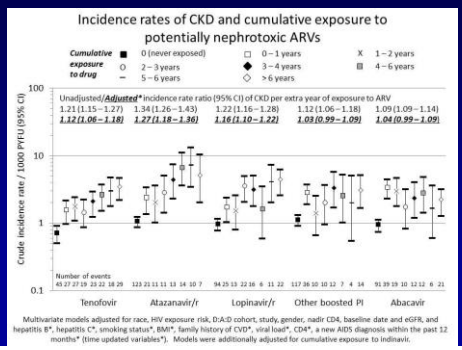

Appendix Table 2. Reasons for Discontinuation of the Randomized Regimen, by Treatment Group*

Reason	Treatment Group		
	ATV/r (n = 605)	RAL (n = 603)	DRV/r (n = 601)
Toxicity-associated reason for discontinuation, n (%)	95 (15.7)	47 (7.8)	32 (5.3)
Gastrointestinal toxicity	25	2	14
Nausea	11	0	4
Gastrointestinal†	10	0	4
Diarrhea	1	0	3
Vomiting	1	1	2
Abdominal distention	1	1	0
Abdominal cramps/pain	1	0	1
Hyperbilirubinemia	47	0	0
Jaundice	30	0	0
Elevated total bilirubin level	16	0	0
Hyperpigmentation	1	0	0
Other hepatic toxicity	4	1	5
Elevated LFTs	3	1	4
Cholecystitis	1	0	0
Elevated LFTs with HCV infection	0	0	1
Skin toxicity	7	2	5
Rash	7	2	4
The Stevens–Johnson syndrome	0	0	1
Metabolic toxicity	6	0	2
Elevated triglyceride levels	2	0	1
Lipodystrophy	1	0	0
Diabetes mellitus	1	0	0
Fat accumulation	1	0	0
Elevated blood glucose levels	0	0	1
Renal toxicity	4	0	0
Nephrolithiasis	3	0	0
Prior renal lithiasis, now with hematuria	1	0	0
Abnormal chemistry/hematology findings‡	0	0	2
Decreased potassium levels	0	0	1
Thrombocytopenia	0	0	1
Other	2	2	4

ATV/r = atazanavir plus ritonavir; DRV/r = darunavir plus ritonavir; HCV = hepatitis C virus; LFT = liver function test; RAL = raltegravir.
* All values are numbers unless otherwise noted.
† Severed vesicles.
‡ Excluding LFTs.

Ann Intern Med 2014; 161:461-471

D:A:D Data. CROI 2015 Abstract #142



Multivariate models adjusted for race, HIV exposure risk, D:A:D cohort, study, gender, nadir CD4, baseline date and eGFR, and hepatitis B*, hepatitis C*, smoking status*, BMI*, family history of CVD*, viral load*, CD4*, a new AIDS diagnosis within the past 12 months* (time updated variables*). Models were additionally adjusted for cumulative exposure to Indinavir.

Conclusions

- Decreased number of DHHS recommended regimens (EFV, RPV, ATV/r left recommended category)
- Not always in line with PBS
- 'Alternative' or 'other' regimen may be preferred for some patients
  - Different clinical scenarios, patient preferences