New treatment strategies: Novelties in ART & strategy

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NRTI reducing therapy: new strategies

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Disclosures

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  - Gilead Sciences, Merck Sharp & Dohme, Bristol-Myers Squibb, ViiV Healthcare, Janssen, Johnson & Johnson, Boehringer Ingelheim and GlaxoSmithKline

Let's start with Betty…

- Jamaican female
- 50 years old
- HIV 2002
  - ✓ CD4 205 cells/mm^3 nadir
  - ✓ Now >700 cells/mm^3
  - ✓ HIV Wild type

PAST MEDICAL HISTORY

- Previous PCP
- Type 2 diabetes
- Hypercholesterolemia
- Hysterectomy for fibroids

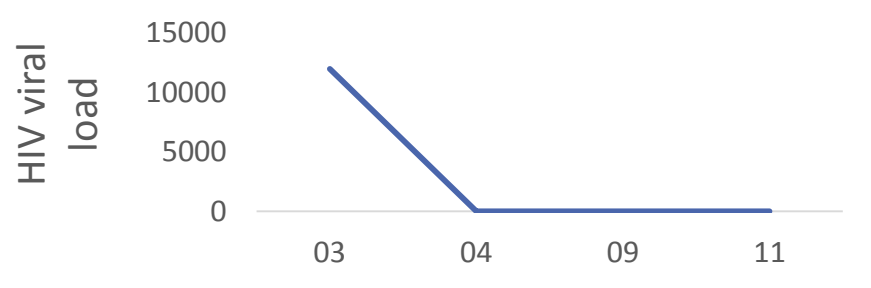
Drug History

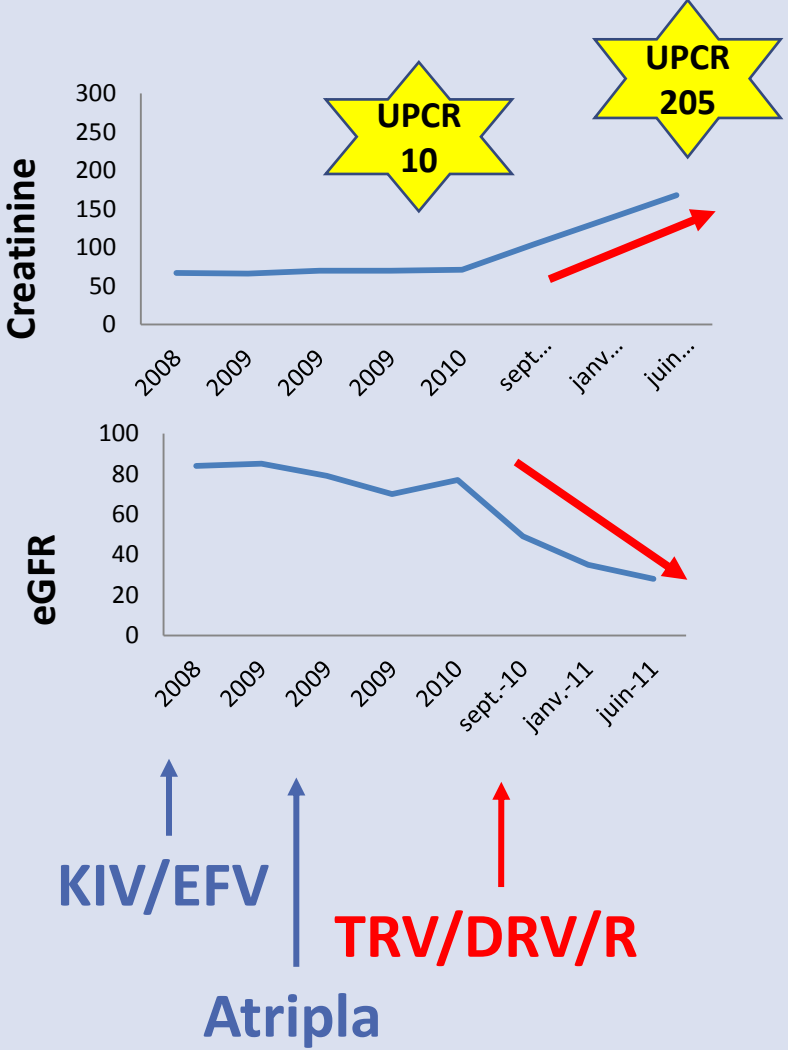
- Metformin 1g bd
- Gliclazide 80mg od
- Atorvastatin 10mg
- Enalapril 10mg
- Lansoprazole 30mg

ARV History

2004 2009 2010

KIV/EFV Atripla TRV/DRV/R




UPCR 10
UPCR 205
Creatinine
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250
200
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janv...
juin...
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janv.-11
juin-11
KIV/EFV
TRV/DRV/R
Atripla

Guidelines for ART use in naïve patients

	EACS European AIDS Clinical Society		IAS	British HIV Association BHIVA
2 NRTI + 3rd drug	✓	✓	✓	✓
1 NRTI + 2nd drug	When TAF, TDF or ABC cannot be used, consider LPV/r + 3TC only if HBsAg-negative	When TAF, TDF or ABC cannot be used, consider LPV/r +3TC (BID)	2-drug regimens recommended only in **rare situations** in which patient cannot take TAF, TDF or ABC	**Recommend against** the use of PI-based dual ART with a single NNRTI, NRTI or CCR5 receptor antagonist
No NRTI	**Alternative** only if TAF, TDF and ABC cannot be used: suggest RAL (BID) + DRV/r only if VL < 100,000 copies/mL, CD4 >200 cells/mm^3 and HBsAg-negative	**Alternative** only if TAF, TDF and ABC cannot be used: RAL (BID) + DRV/r if VL < 100,000 copies/mL and CD4 > 200 cells/mm^3 PI/r monotherapy **not recommended**	2-drug regimens recommended only in **rare situations** in which patient cannot take TAF, TDF or ABC	Alternative only if TAF, TDF and ABC cannot be used: RAL (BID) + DRV/r if VL < 100,000 copies/mL and CD4 > 200 cells/mm^3 PI/r monotherapy **not recommended**

NRTI, nucleoside reverse-transcriptase inhibitors; CCR, chemokine receptor; BC, abacavir; DRV, darunavir; r, ritonavir; PI, protease inhibitors; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; 3TC, lamivudine; HBsAg; hepatitis B surface antigen; NNRTI, non-nucleoside reverse-transcriptase inhibitors

1. European AIDS Clinical Society. Guidelines. Version 8.1 2016; 2 Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. July 2016; 3 Huldrych et al. JAMA 2016;316:191-210; 4 British HIV Association. Guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy. 2015 2016 interim update)

Guidelines for ART maintenance

	EACS European AIDS Clinical Society		IAS	British HIV Association BHIVA
2 NRTI + 3rd drug	✓	✓	✓	✓
1 NRTI + 2nd drug	Consider PI/r + 3TC if no PI resistance, VL < 50 c/mL ≥ 6/12 and no chronic HBV co-infection. 1 NRTI plus NNRTI, or unboosted PI, or RAL are **not recommended**	PI/r + 3TC can be an option when the use of TDF, TAF or ABC is contraindicated or not desirable. **Insufficient data** exists to support use of DTG + 3TC or FTC	Induction maintenance strategies (3- to 2-drug switch) **not currently recommended**	Suggest 3TC + PI/r or PI/c as an **alternative** to triple ART if VL suppressed
No NRTI	DRV/r or DRV/c (QD), LPV/r (BID) might be an option for **certain patient populations**§, if no PI resistance, VL < 50 c/mL ≥ 6/12 and no chronic HBV co-infection	PI/r monotherapy not recommended. DRV/r + RAL has not been explored. ATV/r + RAL **not recommended**	Induction maintenance strategies (3- to 2-drug switch) **not currently recommended**	PI monotherapy **not recommended**

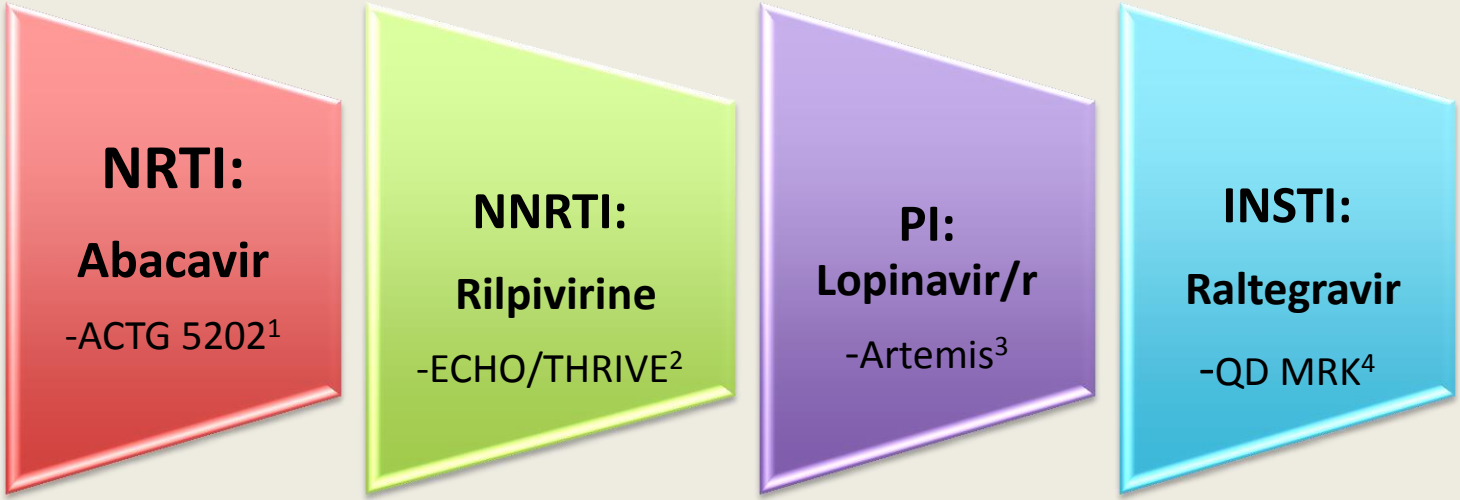
§ NRTI intolerance, recreational drug users with frequent interruptions of cART

c, cobicistat

1. European AIDS Clinical Society. Guidelines. Version 8.1 2016; 2. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. July 2016; 3. Huldrych et al. JAMA 2016;316:191-210; 4. British HIV Association. Guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy. 2015 (2016 interim update).

Efficacy

Efficacy: those VL > 100,000c/ml do worse

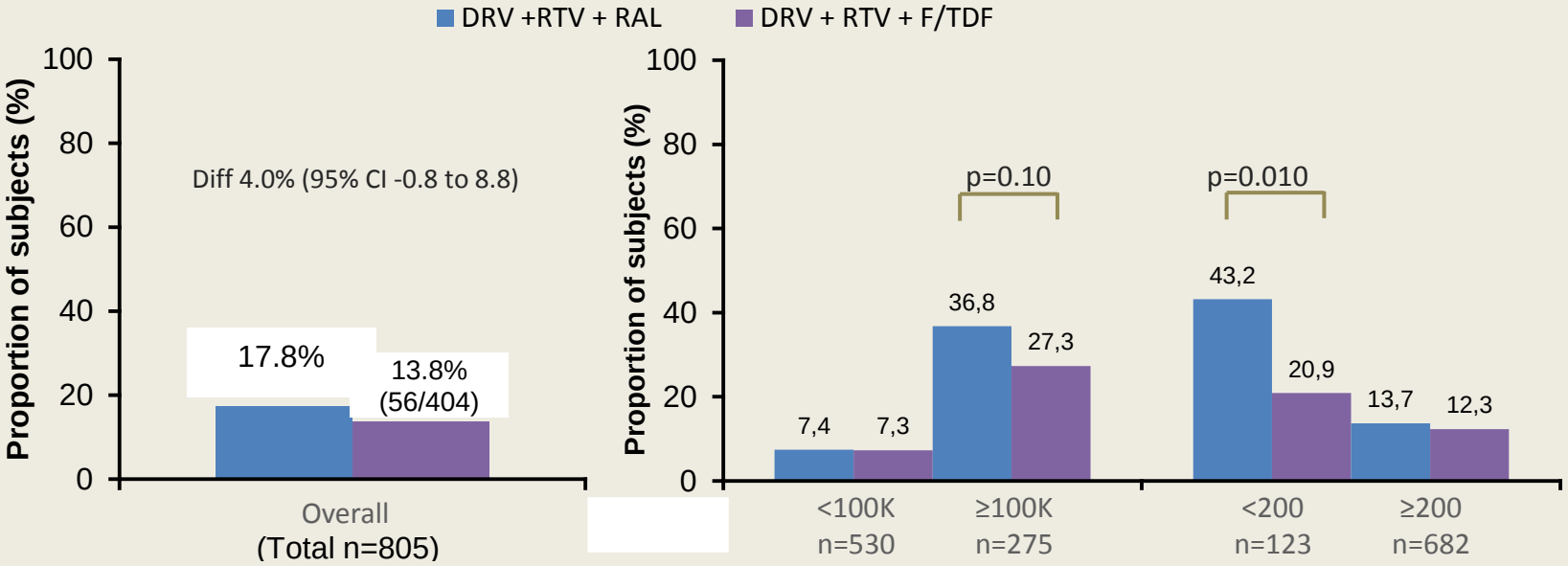


1. ACTG 5202: Daar E *et al. Ann Intern Med*. 2011;154:445-456.
2. ECHO/THRIVE: Rimsky L *et al. J Acquir Immune Defic Syndr* 2012;59:39–46
3. Artemis: Ortiz R *et al. AIDS*. 2008;22:1389-1397. 2. Mills A, et al. AIDS. 2009;23:1679-1688
4. QDMRK: Eron J *et al. Lancet Infect Dis*. 2011;11:907-915. 2. Krishna R, et al. EACS 2013, Abstract PE10/17

NEAT 001: DRV + RTV + RAL *vs* DRV + RTV + F/TDF

Primary endpoint

Regimen failure at Week 96, by baseline characteristic (ITT analysis)



- Treatment-emergent resistance was seen in 6/29 (RAL + DRV + RTV) vs 0/13 (F/TDF + DRV + RTV) individuals with available genotype at failure

1. Raffi F *et al. Lancet* 2014; 384:1942-51
2. Raffi F *et al. CROI* 2014. Boston, MA. #84LB

NRTI-reducing studies in ART-naïve patients

Strategy	Study	N	Reducing regimen	Design
PI/r + INSTI	NEAT 001 †	805	DRV + RTV + RAL	Randomised, open-label, multicentre, non-inferiority study
	RADAR †	85	DRV + RTV + RAL	Randomised, open-label study
	PROGRESS †	206	LPV/r + RAL	Randomised, open-label, multicentre study
	SPARTAN †	94	ATV * + RAL	Randomised, open-label, multicentre, non-comparative pilot study
	ACTG5262	112	DRV + RTV + RAL	Single-arm, open-label, multicentre study
PI/r + 3TC	GARDEL	217	LPV/r + 3TC	Randomised, controlled, open-label, non-inferiority study
PI/r + MVC	MODERN †	797	DRV + RTV + MVC	Randomised, double-blind, multicentre, non-inferiority study
	A4001078 †	121	ATV + RTV + MVC	Randomised, open-label, multicentre study
	MIDAS	24	MVC + DRV + RTV	Single-arm, open-label, safety/efficacy
INSTI + 3TC	PADDLE	20	DTG + 3TC	Single-arm, open-label, pilot study

RTV, ritonavir; 3TC, lamivudine; ATV, atazanavir; DTG, Dolutegravir; MVC, maraviroc

* ATV was administered 300 mg twice daily

† Comparator arm contained TDF

1. Raffi F, et al. CROI, 2014, Abstract #84LB (NEAT 001); 2. Bedimo RJ, et al. PLoS One 2014;9:e106221 (RADAR); 3. Reynes J, et al. AIDS Res Hum Retroviruses 2013;29:256-65 (PROGRESS); 4. Kozal MJ, et al. HIV Clin Trials 2012;13:119-30 (SPARTAN); 5. Taiwo B, et al. AIDS 2011;25:2113-22 (ACTG5262); 6. Cahn P, et al. Lancet Infect Dis 2014;14:572-80 (GARDEL); 7. Stellbrink HJ, et al. IAC, 2014, Abstract TUAB0101 (MODERN); 8. Mills et al. J Acquir Immune Defic Syndr. 2013 Feb 1;62(2):164-70; 9. Taiwo B, et al. J Acquir Immune Defic Syndr 2013;64:167-73 (MIDAS); 10. Figueroa MI, et al. EACS 2015. Barcelona, Spain. #LBPS4/1 (PADDLE).

NRTI-reducing: naïve virological outcomes

Strategy	Study	N	Reducing regimen	Virological outcomes	
PI/r + INSTI	NEAT 001	805	DRV + RTV + RAL	**Lower efficacy**	Week 96 (TTF); 17.4% vs 13.7% in triple ART arm; diff 3.7% (95% CI: -1.1, 8.6)
	RADAR	85	DRV + RTV + RAL	**Lower efficacy**	Week 48 (ITT): 60.0% vs 83.7% in triple ART arm; diff -23.7% (95% CI: -42.9, -5.0), p=0.016
	PROGRESS	206	LPV/r + RAL	Similar efficacy	Week 96 (ITT): 66.3% vs 68.6% in triple ART arm; diff -1.6% (95% CI: -12.0, 8.8), p=0.767
	SPARTAN	94	ATV + RAL	Similar efficacy	Week 24 (ITT): 74.6% vs 63.3% in triple ART arm
	ACTG5262	112	DRV + RTV + RAL	**Lower efficacy**	Week 24 (VFR): 16% (95% CI: 10, 24). After data review, study was closed at week 24
PI/r + 3TC	GARDEL	217	LPV/r + 3TC	Similar efficacy	Week 48 (ITT): 88.3% vs 83.7% in triple ART arm; diff 4·6% (95% CI: -2.2, 11.8)
PI/r + MVC	MODERN	797	DRV + RTV + MVC	**Lower efficacy**	Week 48 (ITT): 77.3% vs 86.8% in triple ART arm; diff -9.5% (95% CI: -14.8, -4.2)
	A4001078	121	ATV + RTV + MVC	**Lower efficacy**	Week 48: HIV RNA <50 copies/mL 74.6% vs 83.6% in triple ART arm
	MIDAS	24	MVC + DRV + RTV	**Lower efficacy**	Week 48: VFR 12.5% (95% CI: 2.7, 32.4)
INSTI + 3TC	PADDLE	20	DTG + 3TC	90% VL <50 copies/mL at week 48	

TTF, time to failure; ITT, intention to treat; VFR, virologic failure rate

1. Raffi F, et al. CROI, 2014, Abstract #84LB (NEAT 001); 2. Bedimo RJ, et al. PLoS One 2014;9:e106221 (RADAR); 3. Reynes J, et al. AIDS Res Hum Retroviruses 2013;29:256-65 (PROGRESS); 4. Kozal MJ, et al. HIV Clin Trials 2012;13:119-30 (SPARTAN); 5. Taiwo B, et al. AIDS 2011;25:2113-22 (ACTG5262); 6. Cahn P, et al. Lancet Infect Dis 2014;14:572-80 (GARDEL); 7. Stellbrink HJ, et al. IAC, 2014, Abstract TUAB0101 (MODERN); 8. Mills et al. J Acquir Immune Defic Syndr. 2013 Feb 1;62(2) (A4001078):164-70; 9. Taiwo B, et al. J Acquir Immune Defic Syndr 2013;64:167-73 (MIDAS); 10. Cahn P et al. AIDS 2016. Abstract #10270 (PADDLE).

NRTI-reducing: naïve Development of resistance

Strategy	Study	N	Reducing regimen	Development of Resistance
PI/r + INSTI	NEAT 001	805	DRV + RTV + RAL	5 mutations seen in NRTI reducing arm vs 0 in triple ART arm
	RADAR	85	DRV + RTV + RAL	No resistance mutation
	PROGRESS	206	LPV/r + RAL	3 patients with mutations in NRTI reducing arm (1 with N155HH and G163R, 1 with G140S and Q148H, 1 with N155H, T97A, D232N for INSTI and M46I, V32I, I47V for PI/r) vs 1 patient with M184V in triple ART arm
	SPARTAN	94	ATV + RAL	4 participants with mutations in NRTI-reducing arm (1 with Q148R, 1 with Q148Q/R and T97T/A, 2 with N155H)
	ACTG5262	112	DRV + RTV + RAL	5 patients with mutations (2 with N155H/N, 1 with N155H, 1 with Q148Q/R & N155H/N, 1 with Q148K/Q and N155H/N/W. All baseline VL > 100.000 copies /mL)
PI/r + 3TC	GARDEL	217	LPV/r + 3TC	2 participants with M184V in NRTI reducing arm, none in triple ART arm
PI/r + MVC	MODERN	797	DRV + RTV + MVC	No resistance mutation
	A4001078	121	ATV + RTV + MVC	No resistance mutation
	MIDAS	24	MVC + DRV + RTV	No resistance mutation
INSTI + 3TC	PADDLE	20	DTG + 3TC	No resistance mutation

1. Raffi F, et al. CROI, 2014, Abstract #84LB (NEAT 001); 2. Bedimo RJ, et al. PLoS One 2014;9:e106221 (RADAR); 3. Reynes J, et al. AIDS Res Hum Retroviruses 2013;29:256-65 (PROGRESS); 4. Kozal MJ, et al. HIV Clin Trials 2012;13:119-30 (SPARTAN); 5. Taiwo B, et al. AIDS 2011;25:2113-22 (ACTG5262); 6. Cahn P, et al. Lancet Infect Dis 2014;14:572-80 (GARDEL); 7. Stellbrink HJ, et al. IAC, 2014, Abstract TUAB0101 (MODERN); 8. Mills et al. J Acquir Immune Defic Syndr. 2013 Feb 1;62(2) (A4001078); 9. Taiwo B, et al. J Acquir Immune Defic Syndr 2013;64:167-73 (MIDAS); 10. Figueroa MI, et al. EACS 2015. Barcelona, Spain. #LBPS4/1 (PADDLE).

PADDLE: Dolutegravir + Lamivudine for Treatment-Naive Pts

- Open-label, single-arm phase IV exploratory trial

Treatment-naive patients with HIV-1 RNA > 5000-100,000 c/mL, CD4+ cell count ≥ 200 cells/mm^3, HBsAg negative (N = 20)

→ DTG 50 mg QD + 3TC 300 mg QD (N = 20*)

Wk 48†

*10 patients enrolled initially; additional 10 patients enrolled after confirming virologic success of first cohort at Wk 8. †Primary endpoint.

- 18/20 patients achieved HIV-1 RNA < 50 c/mL at Wk 48
  - 1 patient committed suicide (deemed unrelated to study drugs)
  - 1 patient experienced PDVF at Wk 36 (BL HIV-1 RNA > 100,000 c/mL); resuppressed HIV-1 RNA without ART change by discontinuation visit (Wk 52)
  - 3 other patients with BL HIV-1 RNA > 100,000 c/mL suppressed at Wk 48

NRTI-reducing SWITCH studies for suppressed patients

Strategy	Study	N	Reducing regimen	Design
PI + RTV + 3TC	ATLAS-M ^	266	ATV + RTV + 3TC	Randomised, double-arm, multicentre, non-inferiority, open-label study
	SALT ^	286	ATV + RTV + 3TC	Randomised, double-arm, non-inferiority, open-label study
	NA	48	DRV + RTV + 3TC	Single-arm, monocentric, pilot study
PI + RTV + INSTI	HARNESS †	109	ATV + RTV + RAL	Randomised, double-arm, open label study
PI + RTV + MVC	MARCH ^	395	DRV + RTV + MVC	Randomised, triple-arm, multicentre, open-label study
DTG mono	Katlama	28	DTG	Single-arm observational pilot study
	Rojas #	33	DTG	Single-arm, longitudinal, monocentric, pilot study
DTG mono/dual	Gubavu	52	DTG	Monocentric and pilot, retrospective study
NNRTI + INSTI	LATTE-2	309§ 286 º	CAB ∞ + RPV	Randomised, double-arm, multicentre, open-label study

CAB, cabotegravir; DTG, dolutegravir
† Comparator arm contained TDF
^ Comparator arm contained TDF and ABC
# Comparator arm contained ABC
§ 309 enrolled and treated in Induction Period
º 286 enrolled and treated in Maintenance Period
∞ Cabotegravir does not have a marketing authorisation

1. Di Giambenedetto S, et al. EACS 2015;Abstract 867 (ATLAS-M); 2. Perez-Molina JA, et al. Lancet Infect Dis 2015;15:775-84 (SALT); 3. Casado JL, et al. J Antimicrob Chemother 2015;70:630-2 (NA); 4. van Lunzen J, et al. J Acquir Immune Defic Syndr 2016;71:538-43 (HARNESS); 5. Pett SL, et al. Clin Infect Dis 2016;63:122-32 (MARCH); 6. Katlama C, et al. J Antimicrob Chemother 2016;71:2646-50; 7. Rojas J. et al. EACS 2015. Barcelona, Spain. Oral #LBPS4/2; 8. Gubavu C et al. EACS 2015. Barcelona, Spain. #PE8/37; 9. Margolis DA, et al. CROI 2016; Boston, MA. Abstract 31LB (LATTE-2).

NRTI-reducing: experienced virological outcomes

Strategy	Study	N	Reducing regimen	Virological outcomes	
PI + RTV + 3TC	ATLAS-M	266	ATV + RTV + 3TC	Non inferior/superior efficacy	Week 48 (ITT), 89.5% vs 79.7% in triple ART arm, diff 9.8% (95% CI: 1.2, 18.4)
	SALT	286	ATV + RTV + 3TC	Similar efficacy	Week 48, 84% vs 78% in triple ART arm; diff 6% (95% CI: -5, 16)
	NA	48	DRV + RTV + 3TC	98% remained undetectable and VL blip free	
PI + RTV + INSTI	HARNESS	109	ATV + RTV + RAL	**Lower efficacy**	Week 24 (ITT) 80.6% vs 94.6% in triple ART arm. Study stopped after data review
PI + RTV + MVC	MARCH	395	DRV + RTV + MVC	**Lower efficacy**	Week 48 (ITT) 77.7% vs 95.1% in triple ART arm, diff -17.4 (95% CI -24.9, -8.4)
DTG mono	Katlama	28	DTG	89% VL<50 copies/mL at week 24 (95% CI: 72, 98)	
	Rojas	33	DTG	97% VL<37 copies/mL at week 24 (95% CI: 83, 100)	
DTG mono/dual	Gubavu	52	DTG	98% <50 copies/mL (last visit, median follow-up 34 weeks)	
NNRTI + INSTI	LATTE-2	243	CAB ∞ + RPV	IP (ITT-E): 91% achieved VL < 50c/mL at week 20; MP: (ITT-ME) at week 32) CV < 50c/mL: 91% in CAB + RPV /4weeks vs 95% in CAB + RPV /8 weeks vs 91% in CAB + 2 NRTI	

IP, induction period

∞ Cabotegravir does not have a marketing authorisation

1. Di Giambenedetto S, et al. EACS 2015;Abstract 867 (ATLAS-M); 2. Perez-Molina JA, et al. Lancet Infect Dis 2015;15:775-84 (SALT); 3. Casado JL, et al. J Antimicrob Chemother 2015;70:630-2 (NA); 4. van Lunzen J, et al. J Acquir Immune Defic Syndr 2016;71:538-43 (HARNESS); 5. Pett SL, et al. Clin Infect Dis 2016;63:122-32 (MARCH); 6. Katlama C, et al. J Antimicrob Chemother 2016;71:2646-50; 7. Rojas J. et al. EACS 2015. Barcelona, Spain. Oral #LBPS4/2; 8. Gubavu C et al. EACS 2015. Barcelona, Spain. #PE8/37; 9. Margolis DA, et al. CROI 2016; Boston, MA. Abstract 31LB (LATTE-2).

NRTI-reducing: experienced Development of resistance

Strategy	Study	N	Reducing regimen	Development of Resistance
PI + RTV + 3TC	ATLAS-M	266	ATV + RTV + 3TC	1 participant with L10V, G16E, D60E on protease gene, in triple ART arm
	SALT	286	ATV + RTV + 3TC	1 patient in triple ART arm developed resistance mutation (M184V)
	NA	48	DRV + RTV + 3TC	No resistance reported
PI + RTV + INSTI	HARNESS	109	ATV + RTV + RAL	1 participant with Y143C and N155H, 1 participant with F121Y on integrase and several mutations on protease leading to ATV resistance
PI + RTV + MVC	MARCH	395	DRV + RTV + MVC	1/1 participant with PI/r + 2 NRTIs had K103N, 5/6 patients with MVC + 2 NRTIs had mutations on RT gene (RT in footnote = reverse transcriptase) and 7/18 patients with MVC + PI/r had protease and RT mutation, and 3 with a CXCR4 tropism
DTG mono	Katlama	28	DTG	All 3 patients with VF developed mutations on integrase gene : 1 with E138K, G140A and Q148R, 1 with L74I and E92Q, 1 with N155H
	Rojas	33	DTG	1 participant failing, with no INSTI mutation reported in viral RNA but G118R detected in 7% of integrated DNA in PBMC at week 24
DTG mono/dual	Gubavu	52	DTG	Participant (prior RAL failure and harbouring N155H mutation) had additional mutation : V72I, F121Y, S147G plus a CXCR4 tropism
NNRTI + INSTI	LATTE-2	243	CAB ∞ + RPV	No resistance reported

∞ Cabotegravir does not have a marketing authorisation

1. Di Giambenedetto S, et al. EACS 2015;Abstract 867 (ATLAS-M); 2. Perez-Molina JA, et al. Lancet Infect Dis 2015;15:775-84 (SALT); 3. Casado JL, et al. J Antimicrob Chemother 2015;70:630-2 (NA); 4. van Lunzen J, et al. J Acquir Immune Defic Syndr 2016;71:538-43 (HARNESS); 5. Pett SL, et al. Clin Infect Dis 2016;63:122-32 (MARCH); 6. Katlama C, et al. J Antimicrob Chemother 2016;71:2646-50; 7. Rojas J. et al. EACS 2015. Barcelona, Spain. Oral #LBPS4/2; 8. Gubavu C et al. EACS 2015. Barcelona, Spain. #PE8/37; 9. Margolis DA, et al. CROI 2016; Boston, MA. Abstract 31LB (LATTE-2).

Why are they not guideline recommended?

Quality of Evidence

- Most studies involve small numbers (experimental)
- No placebo controlled studies
- Some are single armed studies
- Data on bone, renal and CNS endpoints not in all studies

Switching an 'undetectable' patient

- Dual therapy with a boosted protease inhibitor and Lamivudine can have advantages in terms of toxicity and costs
- OLE[1], SALT[2] and ATLAS-M[3] demonstrated that dual therapy with 3TC and Lopinavir/r or Atazanavir/r is non inferior to triple therapy with 2 NRTI + Lopinavir/r or Atazanavir/r

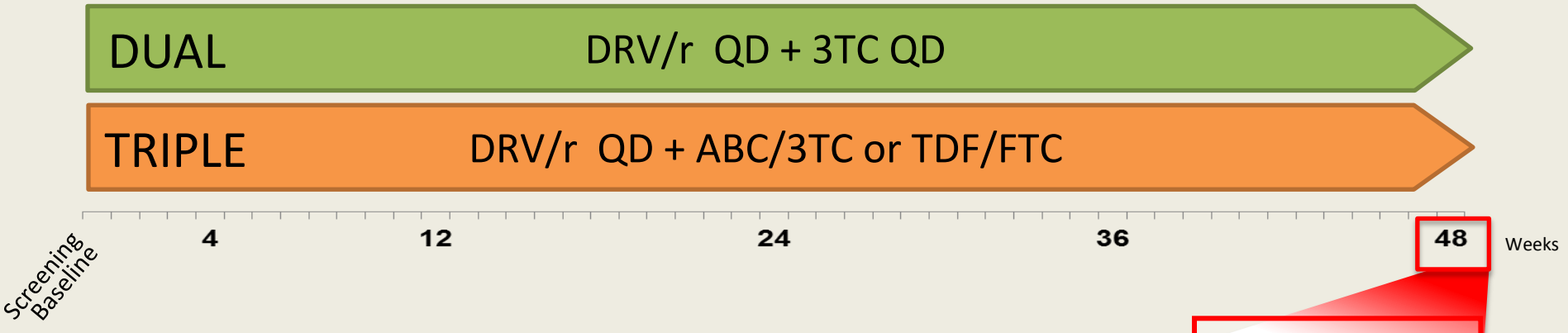
1.Arribas JR *et al. Lancet Infect Dis*. 2015 Jul;15(7):785-92
2.Perez-Molina JA *et al. J Antimicrob Chemother.* 2016 Sep 13. pii: dkw379
3. 5th European AIDS Conference. Barcelona, October 21-24,2015. Abstract BPD1/6

NRTI Sparing strategies at HIV Glasgow

- DUAL
- ATLAS M 96 weeks
- ANRS 12286/MOBIDIP trial
- DOMONO

DUAL Study Design

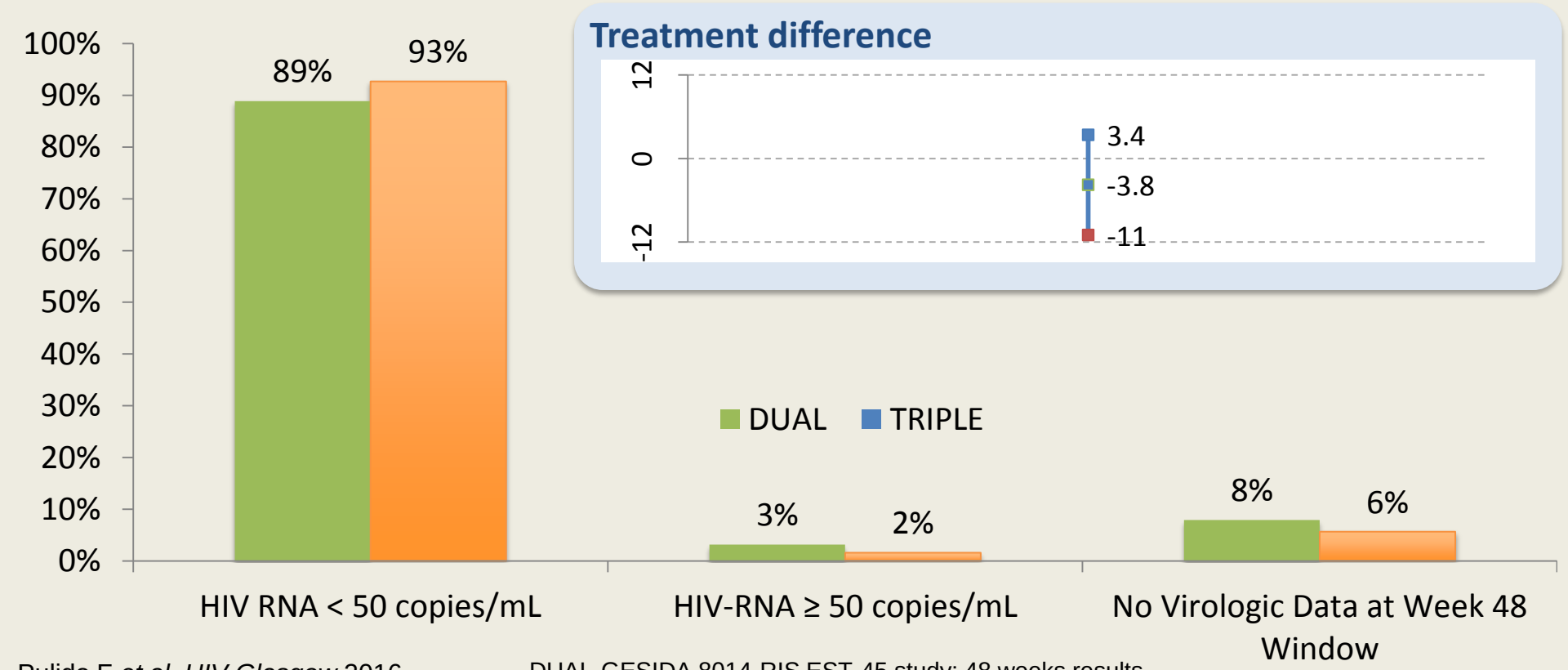
- VL < 50 c/mL > 6 months
- No resistance to DRV/r or 3TC
- On treatment with DRV/r + ABC/3TC or TDF/FTC ≥ 2 months
- HBsAg negative
- Randomized 1:1. Stratified by baseline nucleos(t)ides



DUAL-GESIDA 8014-RIS EST-45 study: 48 weeks results

Pulido F *et al. HIV Glasgow* 2016

Primary Endpoint: Snapshot, ITT-e population



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DUAL-GESIDA 8014-RIS EST-45 study: 48 weeks results

Primary Endpoint: Snapshot, ITT-e population

	DUAL (n=126)		TRIPLE (n=123)	
HIV RNA < 50 copies/mL	**112**	**89%**	**114**	**93%**
HIV-RNA ≥ 50 copies/mL	**4**	**3%**	**2**	**2%**
HIV-RNA ≥ 50 copies/mL in week 48 window	2	2%	2	2%
Discontinued Study Drug Due to Lack of Efficacy	2	2%	0	0%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 c/mL	0	0%	0	0%
No virologic data week 48	**10**	**8%**	**7**	**6%**
Discontinued Study Drug Due to AE/Death	1	1%	2	2%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 c/mL*	6	5%	2	2%
Missing Data During Window but on Study Drug	3	2%	3	2%

* Dual: Consent withdrawal (3), lost to follow up (3). Triple: Consent withdrawal (1). Lost to follow up (1)

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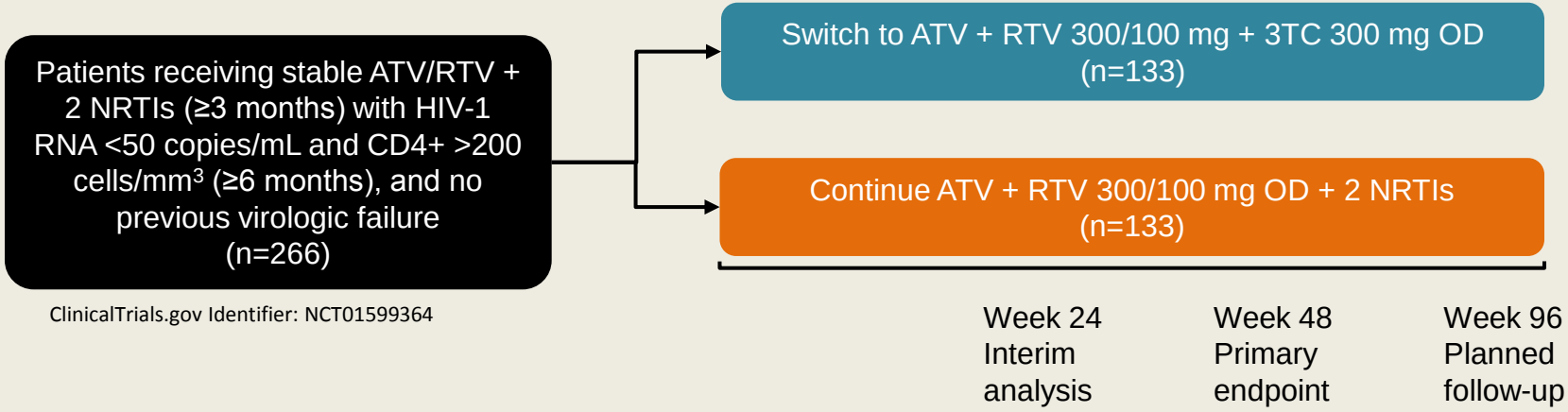
DUAL-GESIDA 8014-RIS EST-45 study: 48 weeks results

ATLAS-M study design: switch from suppressive ATV + RTV + 2 NRTIs to ATV + RTV + 3TC

Randomised, multicentre, open-label Phase IV trial

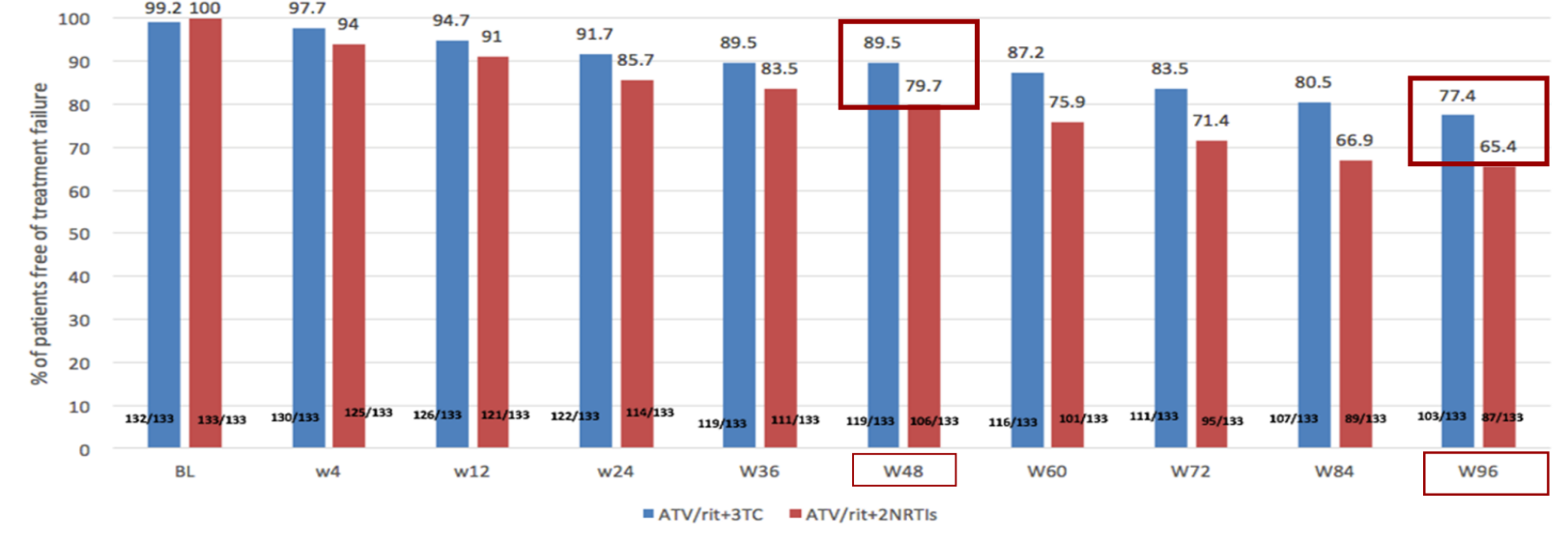


ClinicalTrials.gov Identifier: NCT01599364

- **Study purpose:** To demonstrate promising efficacy and safety of treatment simplification to a dual regimen with ATV + RTV + 3TC in virologically suppressed HIV-positive patients
- **Primary endpoint:** Absence of treatment failure at Week 48, defined as ART modification for any reason and/or virologic failure

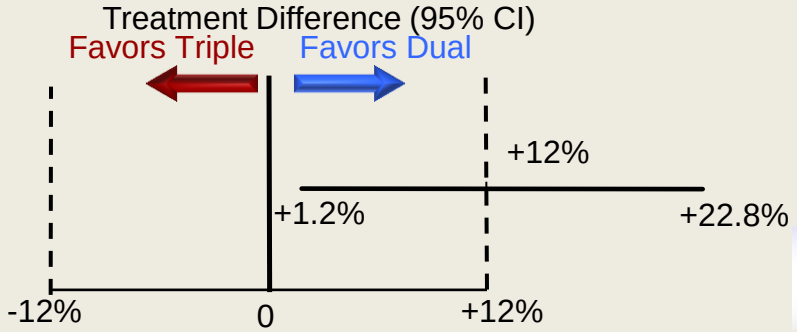
Di Giambenedetto S *et al. EACS* 2015; Abstract 867

Patients free of treatment failure (ITT S=F)



96 weeks free of TF:

- Dual therapy 77.4% (95% CI 70.3-84.5)
- Triple therapy 65.4% (95% CI 57.3-73.5)



Gagliardini R *et al. HIV Glasgow* 2016

ATLAS-M Trial
Causes of treatment failure

	ATV/rit+3TC N=133	ATV/rit+2 NRTIs N=133	p
Any cause	30 (22.6)	46 (34.6)	**0.030**
Virological Failure	2 (1.5)*	9 (6.8)	0.060
Adverse events (potentially treatment-related)[i]	7 (5.3)	11 (8.3)	0.329
Adverse events (not treatment related)[ii]	3 (2.3)	5 (3.8)	0.722
Withdrawal of consent	6 (4.5)	9 (6.8)	0.425
Loss to follow up	10 (7.5)	7 (5.3)	0.452
Other	2 (1.5)	5 (3.8)	0.447

Values are expressed as n (%)
* One VF at baseline, before treatment simplification.

Notes:

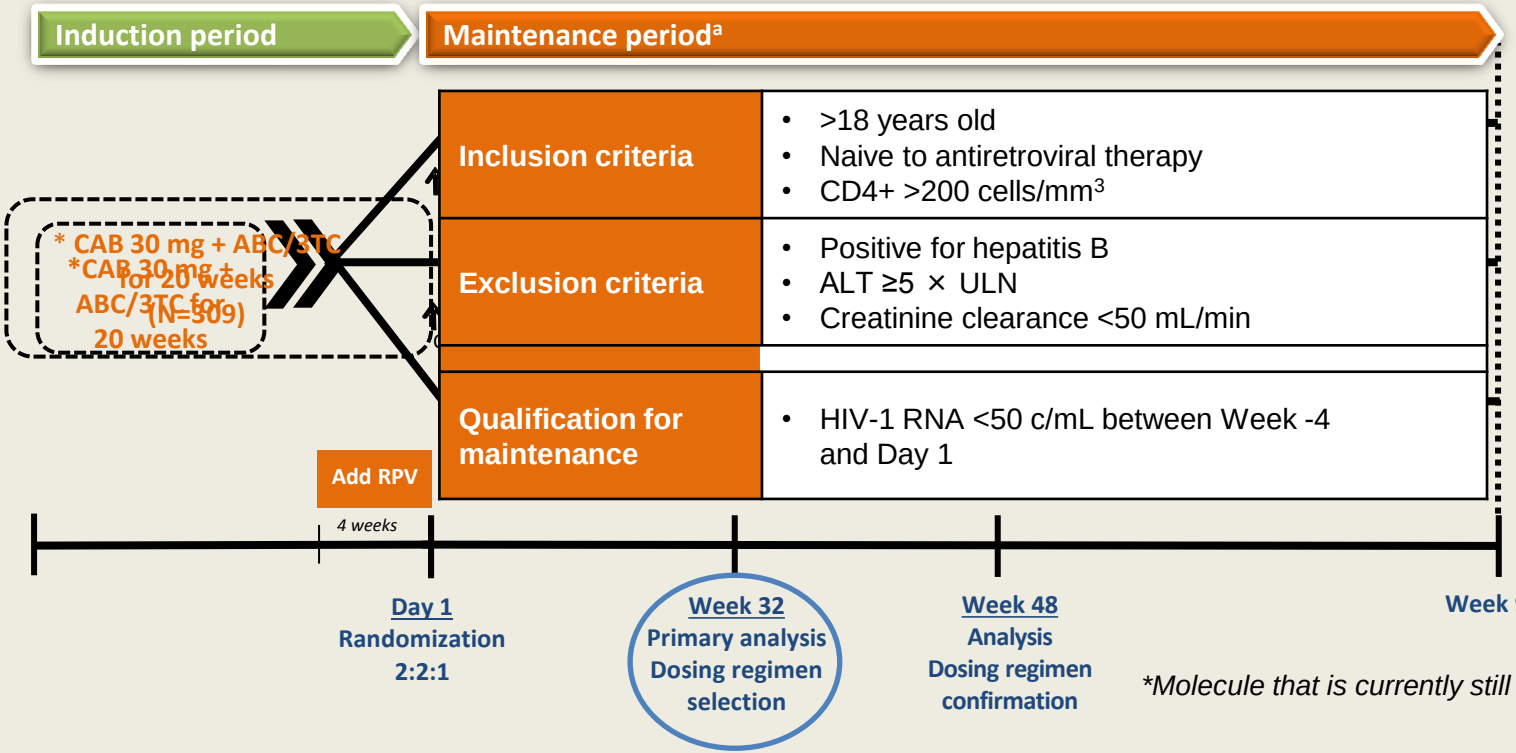
i. DT: skin rash (w4), renal colic (w26 and w49), biliary colic (w60), pancreatitis (w62), hypertriglyceridemia (w72), creatinine increase (w75); TT: creatinine increase (w3 and w7), osteopenia (w16), renal colic (w24, w60, w63, w77, w80), drug nephropathy (w43), proteinuria (w84), hyperbilirubinemia (w84).

ii. DT: sudden death (w10 and w78, suspect cardiac events), thyroid carcinoma (w24); TT: spinal disc herniation (w3), pneumonia (w12), abdominal cancer (w48), creatinine increase (w60), lung cancer (w72).

ATLAS M

Gagliardini R *et al. HIV Glasgow* 2016

Cabotegravir* + rilpivirine* as long-acting maintenance therapy: LATTE-2 Week 32 results



*Molecule that is currently still under development

ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; ULN, upper limit of normal. [a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter LA Extension Phase beyond Week 96. Margolis, et al. CROI 2016; Boston, MA. Abstract 31LB.

Protocol-defined virologic failure (PDVF): Genotype

Maintenance period	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Subjects with PDVF[a]	1[b] (1%)	0	1 (2%)
INI-r mutations	0	0	0
NRTI-r mutations	0	0	0
NNRTI-r mutations	0	0	0

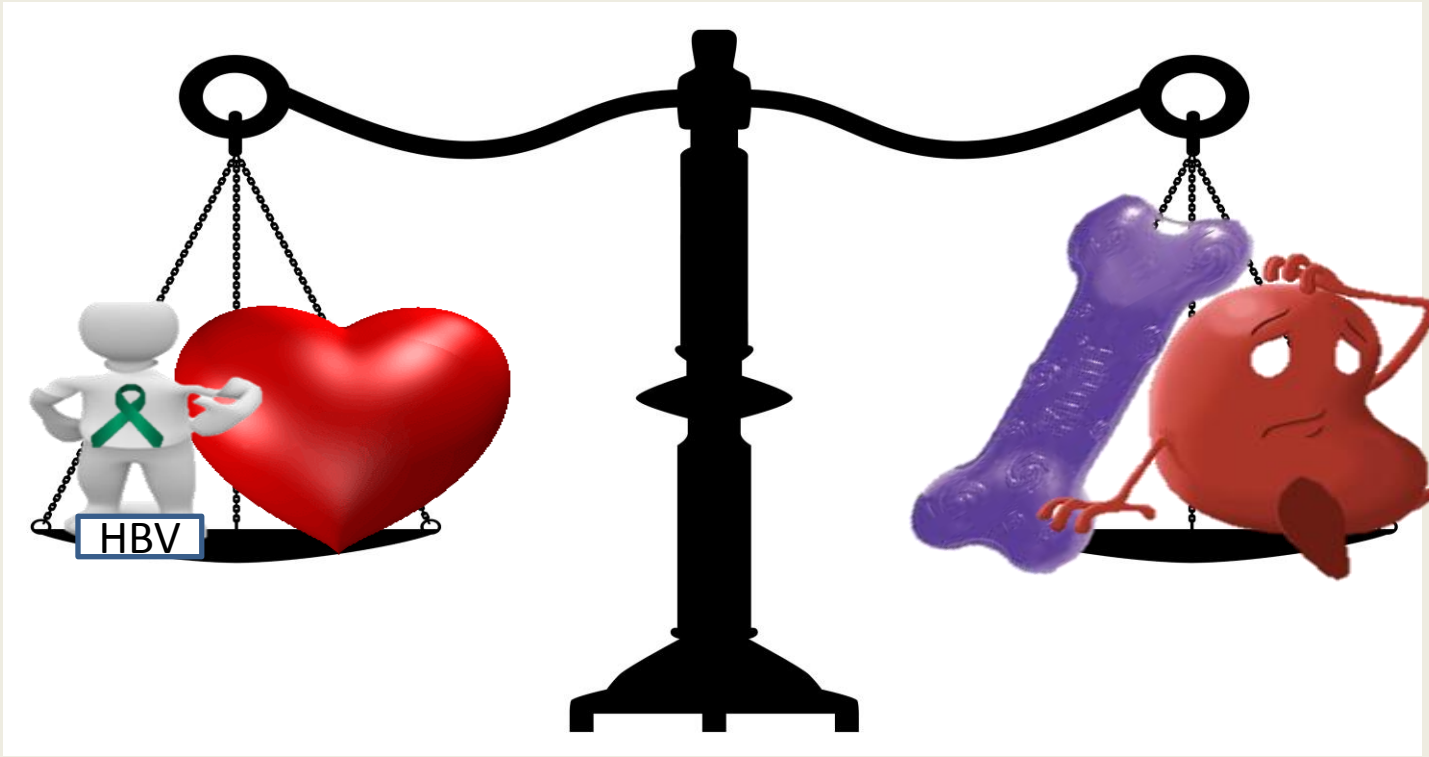
- No INI, NNRTI, or NRTI mutations were detected through Induction or Maintenance

[a]One additional PDVF occurred during oral Induction Period due to oral medication non-adherence.
[b]PDVF at Week 4; no detectable RPV at Week 4 and Week 8, suggesting maladministration.

Margolis *et al. CROI* 2016; Boston, MA. Abstract 31LB

Efficacy: Summary

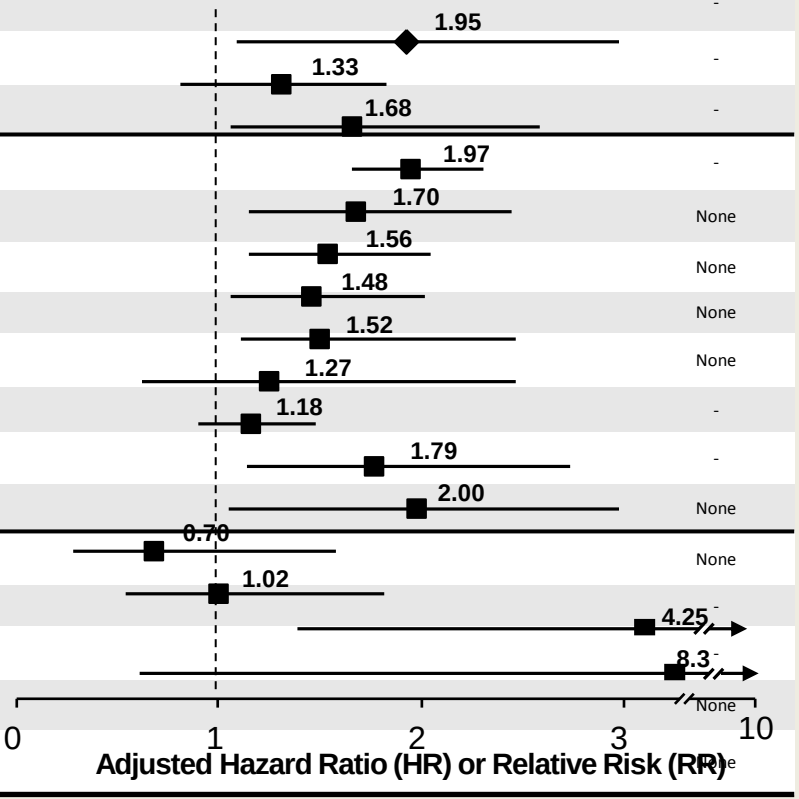
Tolerability and Safety



Association of ABC with Risk of CV Events

(separate trials – not a direct head-to-head comparison)

	Study	(Pt-Yr of follow-up)	Event, n	ABC Association, Risk[d] of MI (95%CI)	TDF Association
NA ACCORD	Restricted Population	(20,998)[1,2]	MI (93)	1.95[1] (1.11-3.44)[2]	-
	Full Population	(64,607)[1,2]	MI (301)	1.33[1] (0.95-1.85)[2]	-
	D:A:D Replication	(>64,607)[1,2]	MI (>301)	1.68[2] (1.08-2.61)[2]	-
Studies >100 MI	D:A:D 2014	(367,559)[3]	MI (941)	1.97 (1.68-2.33)	-
	D:A:D	(178,835)[4]	MI (580)	1.70 (1.17-2.47)	None
	MAGNIFICENT	(NA)[5]	CVD Event[e] (571)	1.56 (1.17-2.07)	None
	VA - Choi	(59,578)[6]	CVD Event[c] (501)	1.48 (1.08-2.04)	None
	Swiss	(NA)[7]	CVD Event[e] (350)	1.52 (1.13-2.04)	None
	French HD	(298,156)[8]	MI (289)	1.27[e] (0.64-2.49)	-
	VA - Bedimo	(76,376)[9]	MI (278)	1.18 (0.92-1.50)	-
	QPHID	(35,851)[10]	MI (125)	1.79 (1.16-2.76)	None
Studies < 100 MI	Danish	(19,124)[11]	MI (67)	2.00 (1.07-3.76)	None
	ALLRT/ACTG	(17,404)[12]	MI (36)	0.70 (0.3 -1.6)	-
	FDA	(range: 42 to 1257)[13]	MI (24)	1.02 (0.56-1.84)	-
	SMART	(NA)[14]	MI (19)	4.25 (1.39-13.0)	None
	START	(NA)[15]	MI (3)	8.3 (1.02-50.0)	None



QPHID = Quebec's public health insurance database; French HD – French Hospital Database

[a]All or majority of patients were treatment-experienced at ABC initiation; [b]All or majority of pts were treatment-naïve at ABC inclusion; [c]MI, unstable angina, CVA, CHF, PVD; [d]Risk reported is the adjusted risk as presented by each study; [e] MI, unstable angina, PCI, CABG, fatal CAD

D:A:D Observational Cohort

Exposure to ARVs and Development of Chronic Kidney Disease Among Persons with an Initial Normal Renal Function

- Overall <1% (201/23,350) of patients developed CKD after a median of 6.3 years who had an initial median eGFR 102 mL/min

Cumulative Risk of CKD*

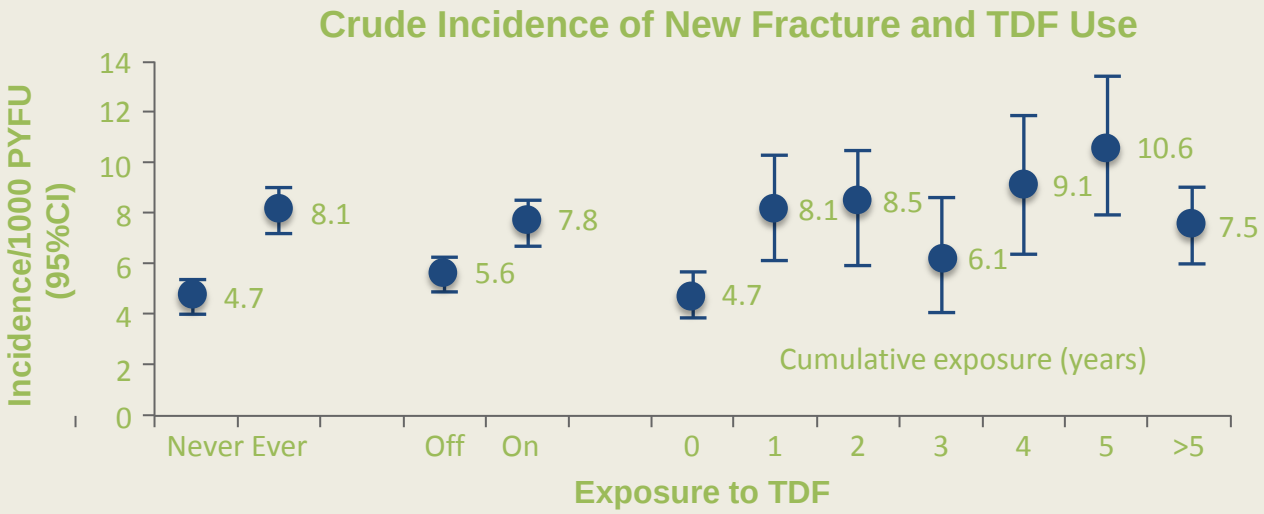
	TDF	ATV + RTV	LPV/r
1 year	1.12	1.27	1.16
2 years	1.25	1.61	1.35
5 years	1.74	3.27	2.11

* Adjusted for fixed variables at baseline (gender, race, HIV exposure, study, prior CVD, age, baseline date, baseline eGFR and CD4 nadir) and time-updated covariates (HBV and HCV status, smoking status, BMI, family history of CVD, HIV RNA, CD4 count, anemia, diabetes,hypertension, starting ART, and an AIDS diagnosis within previous 12 months)

Mocroft A *et al. CROI* 2015. Seattle, WA. Oral #142

Antiretrovirals and Fractures in the EuroSIDA Cohort

- 86,118 person-years of follow up
- Sum: Current or past exposure of TDF but no other antiretrovirals, was independently associated with higher incidence of any fracture



Borges A *et al. CROI* 2016, Boston, 2016, Oral #46

NRTI-reducing: naïve

Renal outcomes

Strategy	Study	N	Reducing regimen	Renal outcomes	
PI/r + INSTI	NEAT 001	805	DRV + RTV + RAL	**eGFR improvement**	eGFR change: +0.9 vs -3.8 mL/min (p=0.02) in triple ART arm
	RADAR	85	DRV + RTV + RAL	Comparable	eGFR change: −4.4 vs −7.9 mL/min (p=0.44) in triple ART arm
	PROGRESS	206	LPV/r + RAL	**eGFR improvement**	eGFR change: -1.43 vs -7.33 mL/min (p=0.035) in triple ART arm
	SPARTAN	94	ATV + RAL	No data reported	
	ACTG5262	112	DRV + RTV + RAL	No data reported	
PI/r + 3TC	GARDEL	217	LPV/r + 3TC	No data reported	No discontinuation for creatinine increase in both arms
PI/r + MVC	MODERN	797	DRV + RTV + MVC	**eGFR improvement**	eGFR change: 3.4 vs -9.3mL/min in triple arm (p=0.0001). 3 vs 7 participants in triple ART arm discontinued due to renal AEs
	A4001078	121	ATV + RTV + MVC	**eGFR improvement**	Mean change from baseline to week 48 in eGFR estimated at 0 vs -13 mL/min in triple ART arm
	MIDAS	24	MVC + DRV + RTV	No data reported	
INSTI + 3TC	PADDLE	20	DTG + 3TC	No data reported	

CrCl, creatinine clearance rate
AEs, adverse events

1. Raffi F, et al. CROI, 2014, Abstract #84LB (NEAT 001); 2. Bedimo RJ, et al. PLoS One 2014;9:e106221 (RADAR); 3. Reynes J, et al. AIDS Res Hum Retroviruses 2013;29:256-65 (PROGRESS); 4. Kozal MJ, et al. HIV Clin Trials 2012;13:119-30 (SPARTAN); 5. Taiwo B, et al. AIDS 2011;25:2113-22 (ACTG5262); 6. Cahn P, et al. Lancet Infect Dis 2014;14:572-80 (GARDEL); 7. Stellbrink HJ, et al. IAC, 2014, Abstract TUAB0101 (MODERN); 8 Mills A et al. IAC 2012 Abstract TUAB0102 (A4001078) 9. Taiwo B, et al. J Acquir Immune Defic Syndr 2013;64:167-73 (MIDAS); 10. Figueroa MI, et al. EACS 2015. Barcelona, Spain. #LBPS4/1 (PADDLE).

NRTI-reducing: naïve
Bone outcomes

Strategy	Study	N	Reducing regimen	Bone outcomes	
PI/r + INSTI	NEAT 001	146 (sub study)	DRV + RTV + RAL	**BMD improvement**	Mean % loss in BMD: in lumbar spine -0.43 vs -2.8, diff -2.37 (95% CI -4.0, -0.74) in triple arm (p=0.0054); in total hip -1.57 vs -3.86, diff -2.29 (95% CI -3.78, -0.80) in triple arm (p=0.0032)
	RADAR	85	DRV + RTV + RAL	**BMD improvement**	Subtotal BMD change: +9.2 vs −7.0 g/cm^3 in triple ART arm (p=0.002)
	PROGRESS	206	LPV/r + RAL	**BMD improvement**	BMD change (%): -2.48 vs +0.68 in triple ART arm (p<0.001)
	SPARTAN	94	ATV + RAL	No data reported	
	ACTG5262	112	DRV + RTV + RAL	No data reported	
PI/r + 3TC	GARDEL	217	LPV/r + 3TC	No data reported	
PI/r + MVC	MODERN	797	DRV + RTV + MVC	**BMD improvement (hip only)**	Mean change in BMD: hip -1.4 vs -2.6 in triple ART arm (p=0.0052); lumbar spine -2.5 vs -3.0 in triple ART arm (p=0.5441)
	A4001078	121	ATV + RTV + MVC	No data reported	
	MIDAS	24	MVC + DRV + RTV	No data reported	
INSTI + 3TC	PADDLE	20	DTG + 3TC	No data reported	

1. Bernardino JI, et al. Lancet HIV 2015;2(11):e464–73 (NEAT 001); 2. Bedimo RJ, et al. PLoS One 2014;9:e106221 (RADAR); 3. Reynes J, et al. AIDS Res Hum Retroviruses 2013;29:256-65 (PROGRESS); 4. Kozal MJ, et al. HIV Clin Trials 2012;13:119-30 (SPARTAN); 5. Taiwo B, et al. AIDS 2011;25:2113-22 (ACTG5262); 6. Cahn P, et al. Lancet Infect Dis 2014;14:572-80 (GARDEL); 7. Stellbrink HJ, et al. IAC, 2014, Abstract TUAB0101 (MODERN); 8. Mills et al. J Acquir Immune Defic Syndr. 2013 Feb 1;62(2) (A4001078); 9. Taiwo B, et al. J Acquir Immune Defic Syndr 2013;64:167-73 (MIDAS); 10. Figueroa MI, et al. EACS 2015. Barcelona, Spain. #LBPS4/1 (PADDLE).

BMD, bone mineral density in g/cm^3

NRTI-reducing: experienced
Renal outcomes

Strategy	Study	N	Reducing regimen	Renal outcomes	
PI + RTV + 3TC	ATLAS-M	266	ATV + RTV + 3TC	**eGFR improvement**	eGFR change: +2 vs -4 mL/min (p=<0.001) in triple ART arm. 4 patients presented urolithiasis when TDF discontinued
	SALT	286	ATV + RTV + 3TC	No change in eGFR	eGFR: -1.1 (-8.3 to 5.8) vs -0.5 (-6.6 to 4.4) mL/min in triple ART arm (p=0.78)
	NA	48	DRV + RTV + 3TC	**eGFR improvement**	eGFR change from +10.1 (overall) vs +16.2 mL/min when TDF is removed from regimen (p=0.03)
PI + RTV + INSTI	HARNESS	109	ATV + RTV + RAL	**Fewer patients with renal/urinary disorders**	1 vs 6 participants with renal and urinary disorders (all grades) in triple ART arm
PI + RTV + MVC	MARCH	395	DRV + RTV + MVC	No significant change	Mean eGFR changes (mL/min): -1.96 in PI/r + 2 NRTI vs -9.54 in MVC + 2NRTI vs -0.69 in MVC + PI/r
DTG mono	Katlama	28	DTG	No data reported	
	Rojas	33	DTG	Decreased eGFR	Decreased from 97 to 89 mL/min (p=<0.0001)
DTG mono/dual	Gubavu	52	DTG	No change in eGFR	eGFR changes: -4.5 vs 0 mL/min in DTG + ARV and DTG
NNRTI + INSTI	LATTE-2	243	CAB ∞ + RPV	No data reported	

CKD EPI, Chronic Kidney Disease Epidemiology Collaboration

- Cabotegravir does not have a marketing authorisation

1. Di Giambenedetto S, et al. EACS 2015;Abstract 867 (ATLAS-M); 2, Fabbiani M et al. J Infect 2011 Apr; 62(4):319-21 (ATLAS-M). 3. Perez-Molina JA, et al. Lancet Infect Dis 2015;15:775-84 (SALT); 4. Casado JL, et al. J Antimicrob Chemother 2015;70:630-2 (NA); 5. van Lunzen J, et al. J Acquir Immune Defic Syndr 2016;71:538-43 (HARNESS); 6. Pett SL, et al. Clin Infect Dis 2016;63:122-32 (MARCH); 7. Katlama C, et al. J Antimicrob Chemother 2016;71:2646-50; 8. Rojas J. et al. EACS 2015. Barcelona, Spain. Oral #LBPS4/2; 9. Gubavu C et al. EACS 2015. Barcelona, Spain. #PE8/37; 10. Margolis DA, et al. CROI 2016; Boston, MA. Abstract 31LB (LATTE-2).

NRTI-reducing: experienced
Bone outcomes

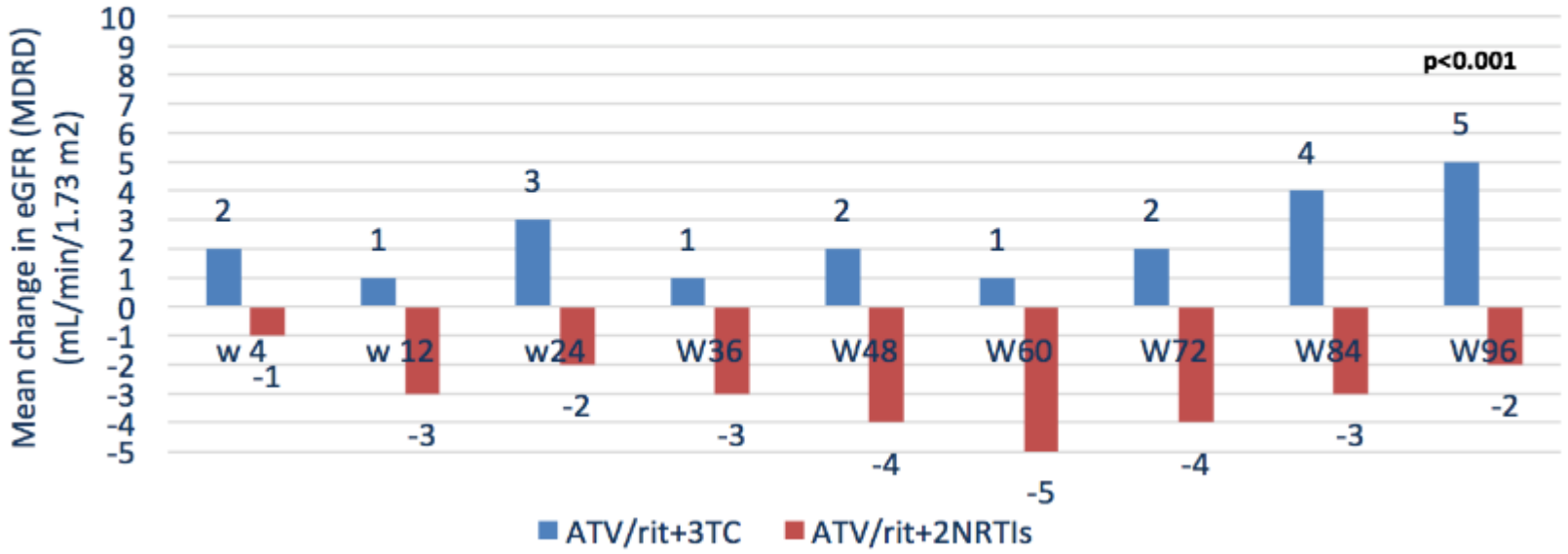
Strategy	Study	N	Reducing regimen	Bone outcomes	
PI + RTV + 3TC	ATLAS-M	266	ATV + RTV + 3TC	**Significant improvement in lumbar spine**	Mean BMD change in total hip: -2.24% (p=0.076) and in lumbar spine: +1.13% (p=0.289) in NRTI reducing arm at week 144. Significant improvement in Z-score and T-score for lumbar spine only
	SALT	286	ATV + RTV + 3TC	No significant difference	Lumbar BMD (% T-score): -6.7% vs -9.4% in triple ART arm (p=0.53); femoral neck BMD (% T-score): 0.0% vs 0.0% in triple ART arm (p=0.93)
	NA	48	DRV + RTV + 3TC	No data reported	
PI + RTV + INSTI	HARNESS	109	ATV + RTV + RAL	No data reported	
PI + RTV + MVC	MARCH	395	DRV + RTV + MVC	No data reported	
DTG mono	Katlama	28	DTG	No data reported	
	Rojas	33	DTG	No data reported	
DTG mono/dual	Gubavu	52	DTG	No data reported	
NNRTI + INSTI	LATTE-2	243	CAB ∞ + RPV	No data reported	

∞ Cabotegravir does not have a marketing authorisation

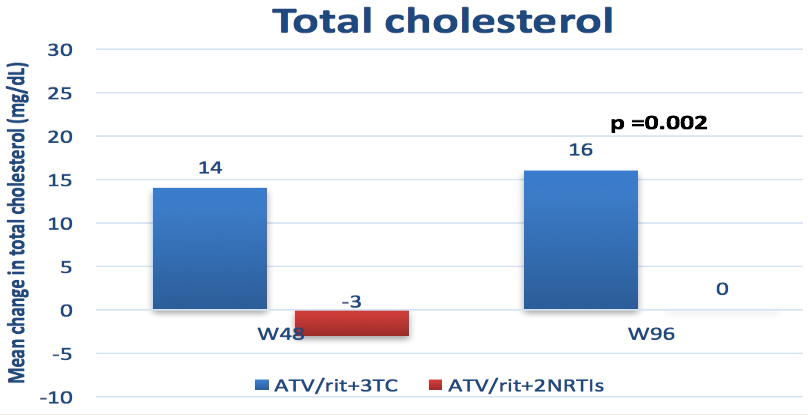
1. Mondi A et al J Antimicrob Chemother doi:10.1093/jac/dkv037 (ATLAS-M); 2. Perez-Molina JA, et al. Lancet Infect Dis 2015;15:775-84 (SALT); 3. Casado JL, et al. J Antimicrob Chemother 2015;70:630-2 (NA); 4. van Lunzen J, et al. J Acquir Immune Defic Syndr 2016;71:538-43 (HARNESS); 5. Pett SL, et al. Clin Infect Dis 2016;63:122-32 (MARCH); 6. Katlama C, et al. J Antimicrob Chemother 2016;71:2646-50; 7. Rojas J. et al. EACS 2015. Barcelona, Spain. Oral #LBPS4/2; 8. Gubavu C et al. EACS 2015. Barcelona, Spain. #PE8/37; 9. Margolis DA, et al. CROI 2016; Boston, MA. Abstract 31LB (LATTE-2).

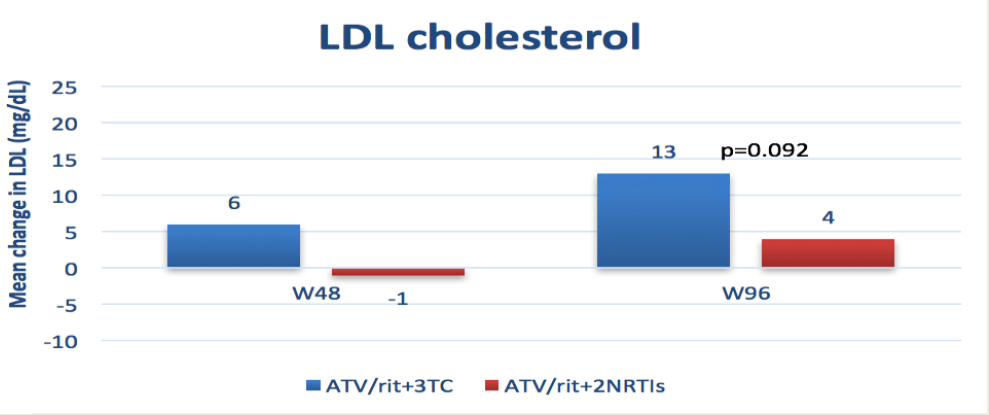
ATLAS M- W96
Evolution of renal function

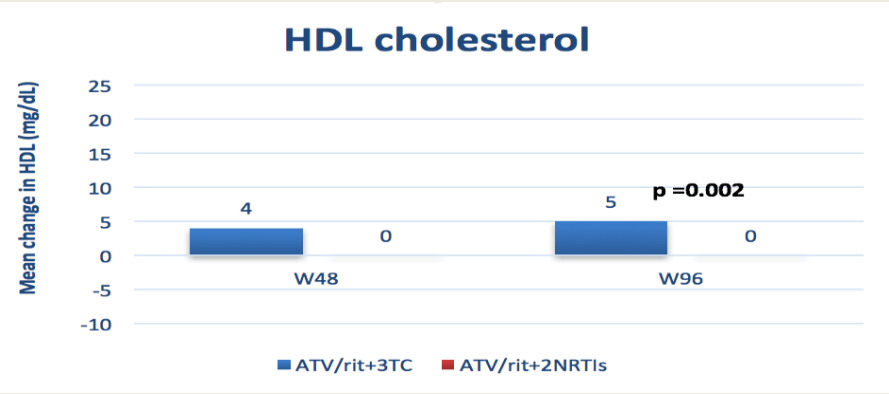
Renal function (eGFR MDRD)

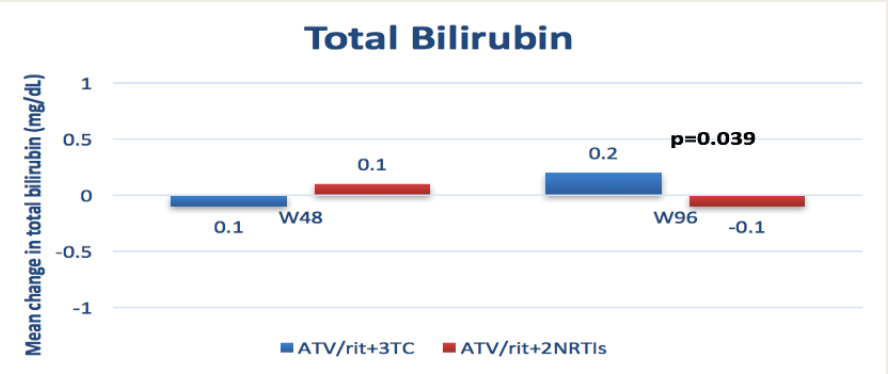


ATLAS M W48: Evolution of lipid profile and bilirubin

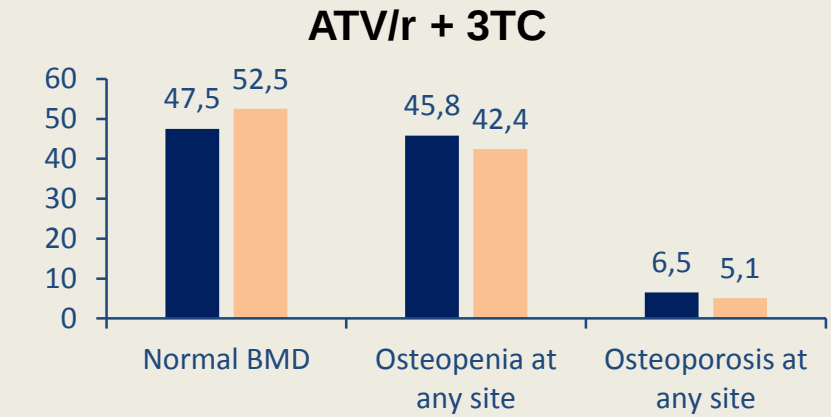


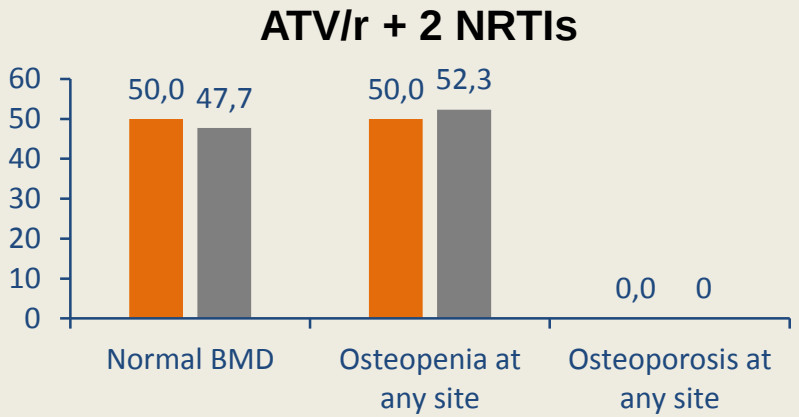


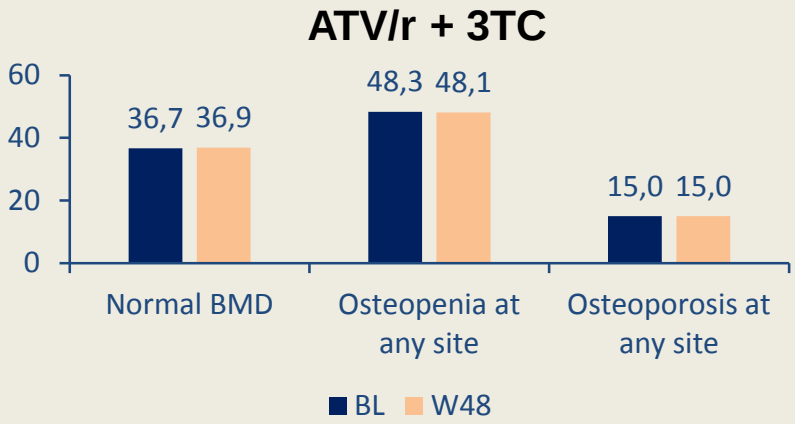


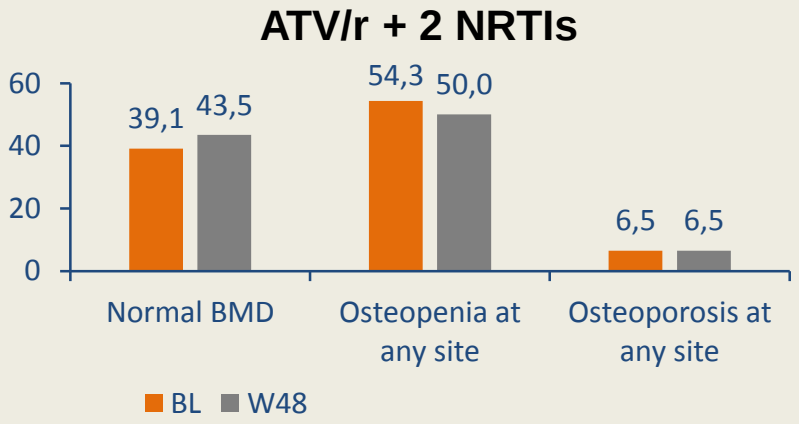


ATLAS M WK 48: Bone density outcomes









Adapted from D'Avino *et al. CROI* 2016

Guidelines??

UK NHS Prescribing

- Our first line treatment is Atripla®
- Our first line PIs are Rezolsta® and Evotaz®

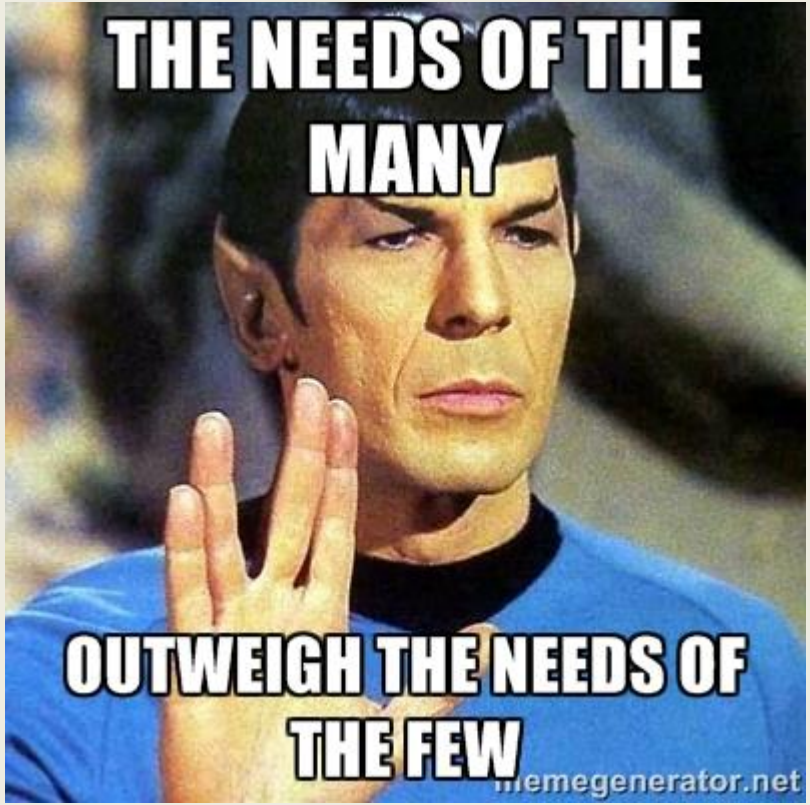
→ I would like you to please find these drugs on the next slide

Where are they?

Guidelines	NRTI	INSTI	PI/r	NNRTI
	TDF/FTC TAF/FTC ABC/3TC (only with DTG)	DTG,RAL,EVG/c	DRV/r or DRV/c	RPV
	TDF/FTC or TAF/FTC	DTG,RAL,EVG/c	DRV/r ATV/r	RPV
	TDF/FTC TAF/FTC (with EVG) ABC/3TC(with DTG)	DTG,RAL,EVG/c	DRV/r (DRV/c alternative)	
IAS USA 2016			No PI	

DHHS Accessed at: http://aidsinfo.nih.gov/guidelines on 27th June 2016
EACS: Accessed at http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html 19th April 2015
BHIVA Guidelines 2015

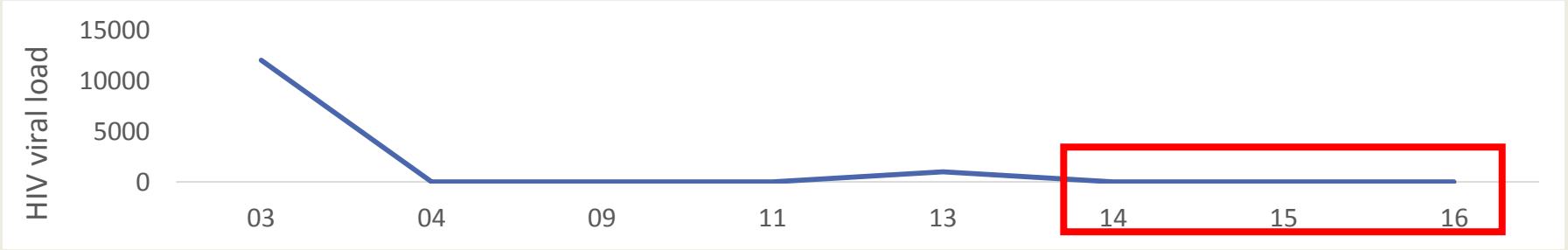
Summation Ethics of Health = Generics or lower prices



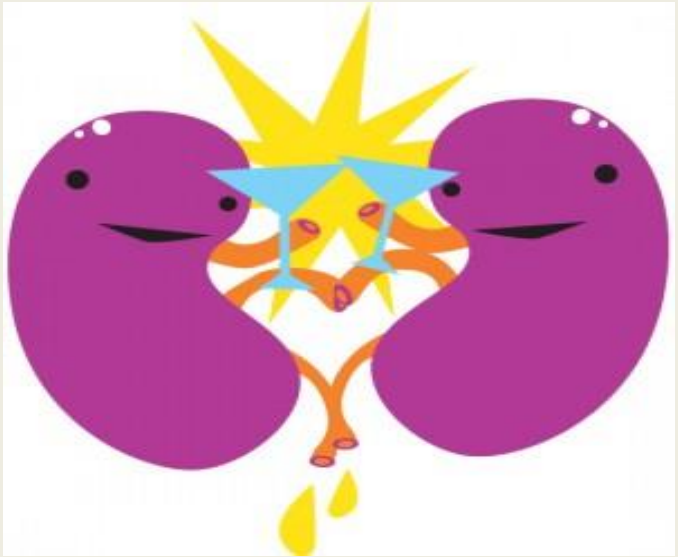
Why does this have to sound negative or bad?

ARV History

2004	2009	2010	2011	2013	2014
KIV/EFV	Atripla	TRV/DRV/R	DRV/R	TRV/DRV/R	DRV/R/RAL



NRTI-Sparing therapy



Summation = Upcycling

Recycling old things to make new things = ingenuity

Thank you

?

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@drchloe_orkin

Back-up

New treatment strategies: Novelties in ART & strategy

Moderator: Josep Maria Llibre, Spain

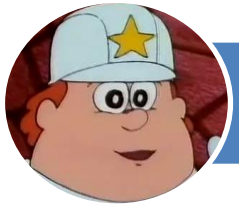
Pawel Jakubowski, Poland
Chloé Orkin, UK

New treatment strategies: Novelties in ART & strategy

Pawel Jakubowski M.D.

Pomeranian Center of Infectious Diseases and Tuberculosis, POLAND

New strategies already in use (guidelines)

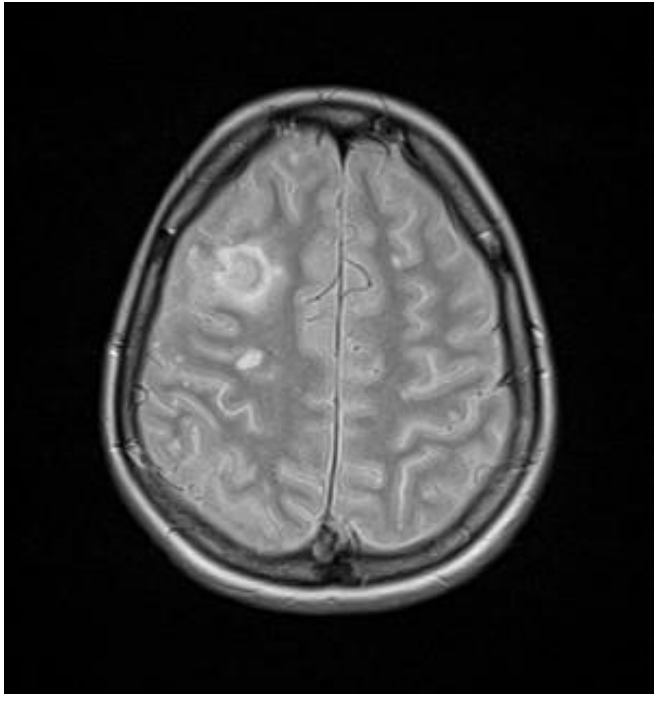


Agents under studying

Antibodies in HIV therapy

Clinical case

- 34, woman
- Epileptic seizure
- HIV-1 WB pos. Nov 2015
- VL $2{,}2 \times 10^6$ c/ml
- CD4 16/ul
- no drug resistance detected
- TDF/FTC/EVG/c
- Sulfasalazine+Pirymethamine +folinic acid



Clinical case

	Dec 15	Jan 16	Apr 16	Aug 16
HIV RNA	$2x10^6$	115	228	$9x10^4$
CD_4	16 (5%)	96 (7%)	148 (13%)	81 (7%)

Resistance to:

FTC, 3TC, ABC, TDF, RAL, EVG, ATV, LPV

DTG + ... ?

NNRTI + ... ?

M41L, K65R, M184V, L10V, L33V, T69S, L10I, I47A, V32I, E92Q, E157Q, ...

New strategies in guidelines

- IAS July 2016
- DHHS
- EACS October 2016

- July 2016
- Recommendations for first-line regimens
  - Modern & simple
  - Focused on INSTI
  - Resistance?
  - Unexpected side effects?
  - Are new agents perfect?

Regimen	DHHS[1]	IAS-USA[2]
DTG/ABC/3TC	Preferred/recommended	Preferred/recommended
DTG + TAF/FTC	Preferred/recommended	Preferred/recommended
DTG + TDF/FTC	Preferred/recommended	Alternative
EVG/COBI/TAF/FTC	Preferred/recommended	Preferred/recommended
EVG/COBI/TDF/FTC	Preferred/recommended	Alternative
RAL + TAF/FTC	Preferred/recommended	Preferred/recommended
RAL + TDF/FTC	Preferred/recommended	Alternative
DRV + RTV + TAF/FTC	Preferred/recommended	Alternative
DRV + RTV + TDF/FTC	Preferred/recommended	Alternative

1. DHHS Guidelines. July 2016.
2. Günthard HF *et al. JAMA*. 2016;316:191-210.

Table 4. Advantages and Disadvantages of Currently Available Integrase Strand Transfer Inhibitors

	Dolutegravir	Elvitegravir	Raltegravir
Year of US Food and Drug Administration approval	2013	2012	2007
Advantages	Superior to efavirenz and ritonavir-boosted darunavir in comparative clinical trials[36,37] Once-daily dosing Coformulated with abacavir/lamivudine as part of a complete initial regimen Dolutegravir (not coformulated) pill size is small Lowest risk of resistance with virologic failure[36,37,40,43] Relatively few drug interactions Can be taken with or without food Superior to raltegravir in treatment-experienced patients	Superior to ritonavir-boosted atazanavir in comparative clinical trial in HIV-infected women[38] Once-daily dosing Coformulated with tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine as a complete regimen	Superior to ritonavir-boosted atazanavir and ritonavir-boosted darunavir in comparative clinical trial[39] Longest safety record Fewest drug interactions Can be taken with or without food
Disadvantages	Only available coformulation is with abacavir/lamivudine Raises serum creatinine owing to inhibition of tubular secretion of creatinine Higher rates of insomnia and headache than comparators in some studies[36,37] Largest tablet among coformulated single-pill regimens	Requires pharmacokinetic boosting with cobicistat or ritonavir for once-daily dosing Most drug interactions Cobicistat raises serum creatinine owing to inhibition of tubular secretion of creatinine Should be taken with food	Currently must be taken twice daily (formulation consisting of 2 pills given once daily in development) Not coformulated as part of a complete regimen

Günthard HF *et al. JAMA*. 2016;316:191-210.

EACS 2016

Initial Combination Regimen for ART-naïve Adult HIV-positive Persons

A) Recommended regimens (one of the following to be selected)[*,**]

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC/DTG[I, II]	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	None	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before). DTG 50 mg bid with rifampicin.
TAF/FTC[III] or TDF/FTC[IV, V] + DTG	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	None	
TAF/FTC/EVG/c[III] or TDF/FTC/EVG/c[IV, V]	TAF/FTC/EVG/c 10/200/150/150 mg, 1 tablet qd or TDF/FTC/EVG/c 300/200/150/150 mg, 1 tablet qd	With food	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before).
TAF/FTC[III] or TDF/FTC[IV, V] + RAL	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Co-administration of antacids containing Al or Mg not recommended. RAL 400 or 800 mg bid with rifampicin.
2 NRTIs + NNRTI			
TAF/FTC/RPV[III] or TDF/FTC/RPV[IV]	TAF/FTC/RPV 25/200/25 mg, 1 tablet qd or TDF/FTC/RPV 300/200/25 mg, 1 tablet qd	With food (min 390 Kcal required)	Only if CD4 count > 200 cells/µL and HIV-VL < 100,000 copies/mL. PPI contra-indicated; H2 antagonists to be taken 12h before or 4h after RPV.
2 NRTIs + PI/r or PI/c			
TAF/FTC[III] or TDF/FTC[IV, V] + DRV/c or + DRV/r	TAF/FTC 10/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Monitor in persons with a known sulfonamide allergy.

EACS 2016

B) Alternative regimens (to be used when none of the preferred regimens are feasible or available, whatever the reason)

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC[i, ii] + RAL	ABC/3TC 600/300 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Co-administration of antacids containing Al or Mg not recommended. RAL 400 or 800 mg bid with rifampicin.
2 NRTIs + NNRTI			
ABC/3TC[i, ii] + EFV[vii]	ABC/3TC 600/300 mg, 1 tablet qd + EFV 600 mg, 1 tablet qd	At bed time or 2 hours before dinner	Only if HIV-VL < 100,000 copies/mL
TDF/FTC/EFV[iv, vii]	TDF/FTC/EFV 300/200/600 mg, 1 tablet qd		
2 NRTIs + PI/r or PI/c			
ABC/3TC[i, ii] + ATV/c or + ATV/r[viii]	ABC/3TC 600/300 mg, 1 tablet qd + ATV/c 300/150 mg, 1 tablet qd or + ATV 300 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Only if HIV-VL < 100,000 copies/mL
TAF/FTC[iii] or TDF/FTC[iv, v] + ATV/c or ATV/r[viii]	TAF/FTC 10/200 mg 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + ATV/c 300/150 mg 1 tablet qd or + ATV 300 mg, 1 tablet qd + RTV 1 tablet 100 mg qd		
ABC/3TC[i, ii] + DRV/c or + DRV/r	ABC/3TC 600/300 mg, 1 tablet qd + DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 1 tablet 100 mg qd	With food	Monitor in persons with a known sulfonamide allergy.
TAF/FTC[iii] or TDF/FTC[iv, v] + LPV/r	TAF/FTC 10/200 mg 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + LPV 200 mg + RTV 50 mg, 2 tablets bid	With food	Use with caution in persons with high cardiovascular risk
Other combinations			
3TC[iii] + LPV/r	3TC 300 mg, 1 tablet qd + LPV 200 mg, 2 tablets bid + RTV 50 mg, 2 tablets bid	With food	
RAL[iii] + DRV/c or + DRV/r	RAL 400 mg, 1 tablet bid + DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Only if CD4 count > 200 cells/µL and HIV-VL < 100,000 copies/mL. Co-administration of antacids containing Al or Mg not recommended.

Dolutegravir Discontinuation and Neuropsychiatric AEs in German Patients

- Retrospective assessment of therapy discontinuation
- 1704 HIV-positive patients from 2 German clinics
  - Initiating INSTI-based regimen January 2007 - April 2016
  - Excluded clinical trial participants

Discontinuation Reason	Drug (Exposures)		
	Dolutegravir (n = 985)	Elvitegravir (n = 287)	Raltegravir (n = 678)
Any AE, n (%)	67 (6.8)	27 (9.4)	28 (4.1)
Neuropsychiatric AE,* n (%)			
▪ Insomnia/sleep	49 (5.0)	3 (1.0)	14 (2.1)
disturbances	36 (3.7)	2 (0.7)	4 (0.6)
▪ Poor concentration/slow	8 (0.8)	0 (0)	0 (0)
thinking	13 (1.3)	1 (0.3)	3 (0.4)
▪ Dizziness	16 (1.6)	1 (0.3)	6 (0.9)
▪ Headache/paresthesia	7 (0.7)	0 (0)	1 (0.1)
▪ Depression			

Sabranski M *et al. HIV* Glasgow 2016. Abstract O214

Neuropsychiatric AEs-Associated Dolutegravir Discontinuation

- Discontinuation of DTG resulted in resolution of neuropsychiatric symptoms
- Risk factors associated with neuropsychiatric symptoms and DTG discontinuation
  - Female *vs* male sex: 2.64 (95% CI: 1.23-5.65; P = .0122)
  - Age > 60 *vs* < 60 yrs: 2.86 (95% CI: 1.42-5.77; P = .0033)
  - DTG initiation in 2016 *vs* 2014-15: 11.36 (95% CI: 4.31-9.41; P < .0001)

Sabranski M *et al. HIV* Glasgow 2016. Abstract O214

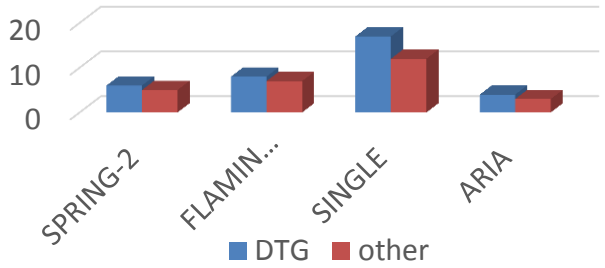
Psychiatric AEs in trials containing DTG

- Analysis of treatment-naive pts (n=2634) in phase III/IIb trials comparing dolutegravir (n=1315) *vs* other INSTI/NNRTI/PIs
- AEs reported at study visits coded with Medical Dictionary for Regulatory Activities into 5 categories
  - Anxiety
  - Insomnia
  - Depression
  - Suicidality
  - Nightmares/abnormal dreams

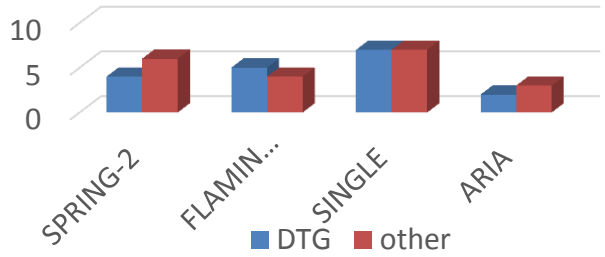
Quercia R *et al. HIV* Glasgow 2016. Abstract P210

DTG-associated AEs in trials

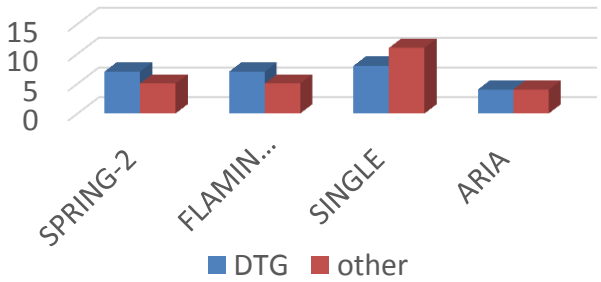
Insomnia



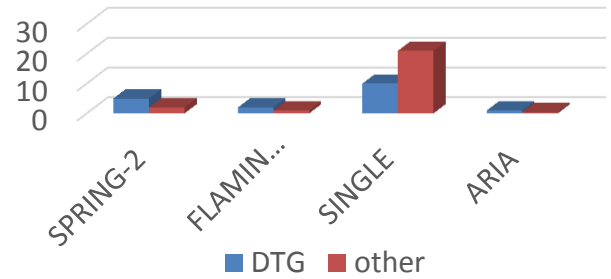
Anxiety



Depression



Nightmares



SPRING-2 DTG vs RAL
SINGLE DTG vs EFV
FLAMINGO DTG vs DRV/r
ARIA DTG vs ATV/r

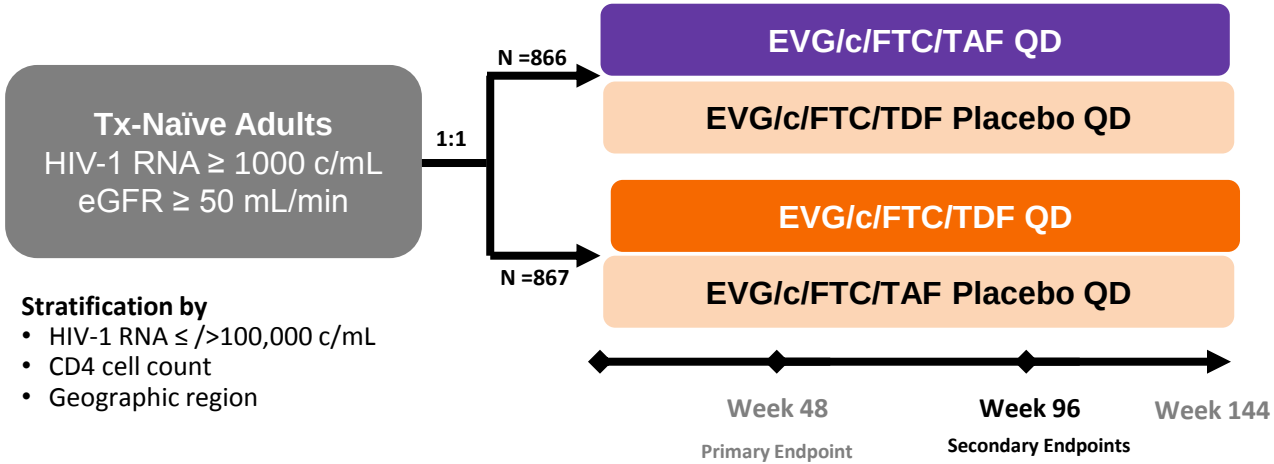
Quercia R *et al. HIV* Glasgow 2016. Abstract P210

TAF

- Lower concentration of unbinded TFV in plasma
- TAF molecule more stable than TDF
- t_{50} higher for TAF

Studies 104 and 111: ART-Naïve Adults

Phase 3, International, randomized, double-blind, active-controlled studies



Primary Endpoint

Non-inferiority (12% margin) of E/C/F/TAF to Stribild based on HIV-1 RNA <50 copies/mL* at Week 48

Secondary Endpoints

Efficacy, safety and tolerability observed through Week 96, Week 144

ClinicalTrials.gov Identifier: NCT01780506 and NCT01797445
Sax P *et al. Lancet* 2015;385(9987):2606-15
Wohl D *et al. EACS* 2015. Barcelona, Spain. #LBBPD1/1

Studies 104 and 111

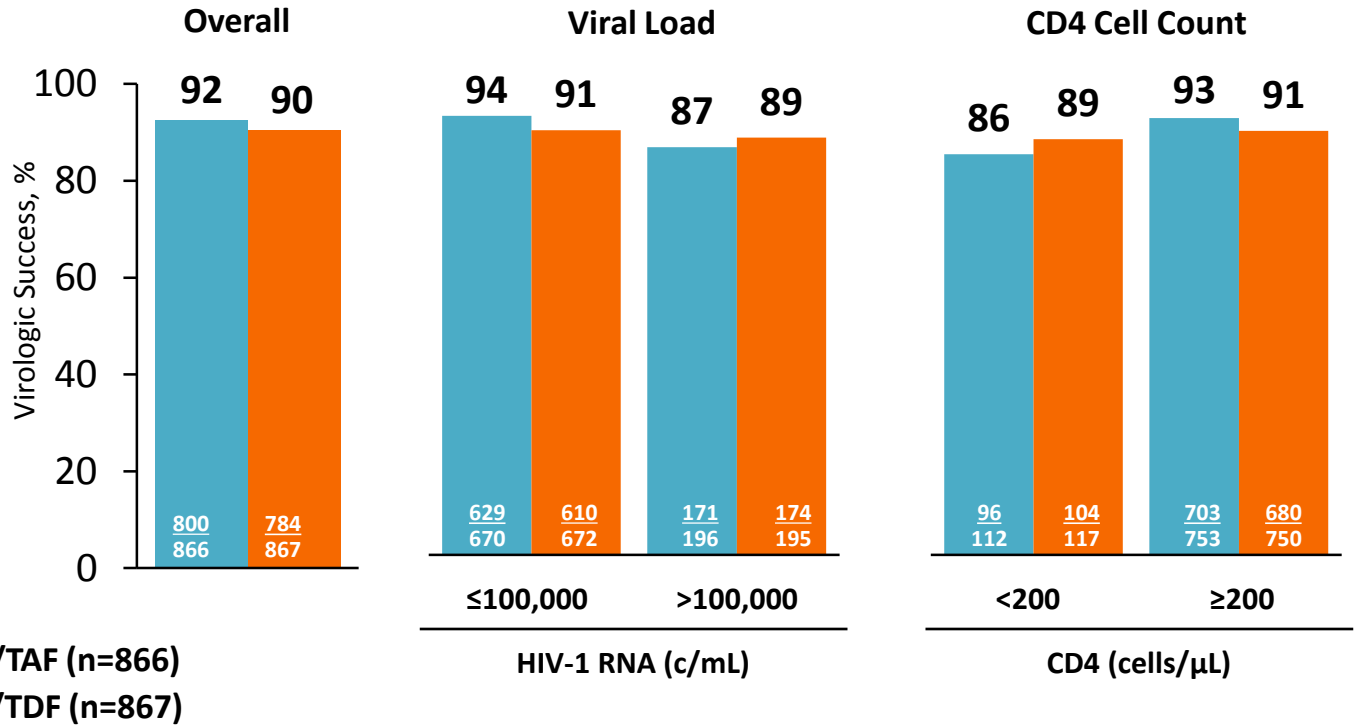
Baseline Characteristics

	EVG/c/FTC/TAF n=866	EVG/c/FTC/TDF n=867
Age, median years	33	35
Female, %	15	15
Black or African descent, %	26	25
Median HIV-1 RNA, log_{10} c/mL	4.58	4.58
HIV-1 RNA >100,000 c/mL, %[2,3]	23	22
Median CD4 count, cells/μL	404	406
CD4 count <200, %[2,3]	13	14
Median estimated GFR_{CG}, mL/min	117	114
Dipstick proteinuria (any grade), %[2,3]	10	10
Comorbidities, %		
HTN	14	17
DM	3	5

1.Wohl D *et al. EACS* 2015. Barcelona, Spain. #LBBPD1/1; 2. Wohl D *et al. CROI* 2015. Seattle, WA. Oral #113LB
3. Sax P *et al. CROI* 2015. Seattle, WA. Oral #143LB

Studies 104 and 111

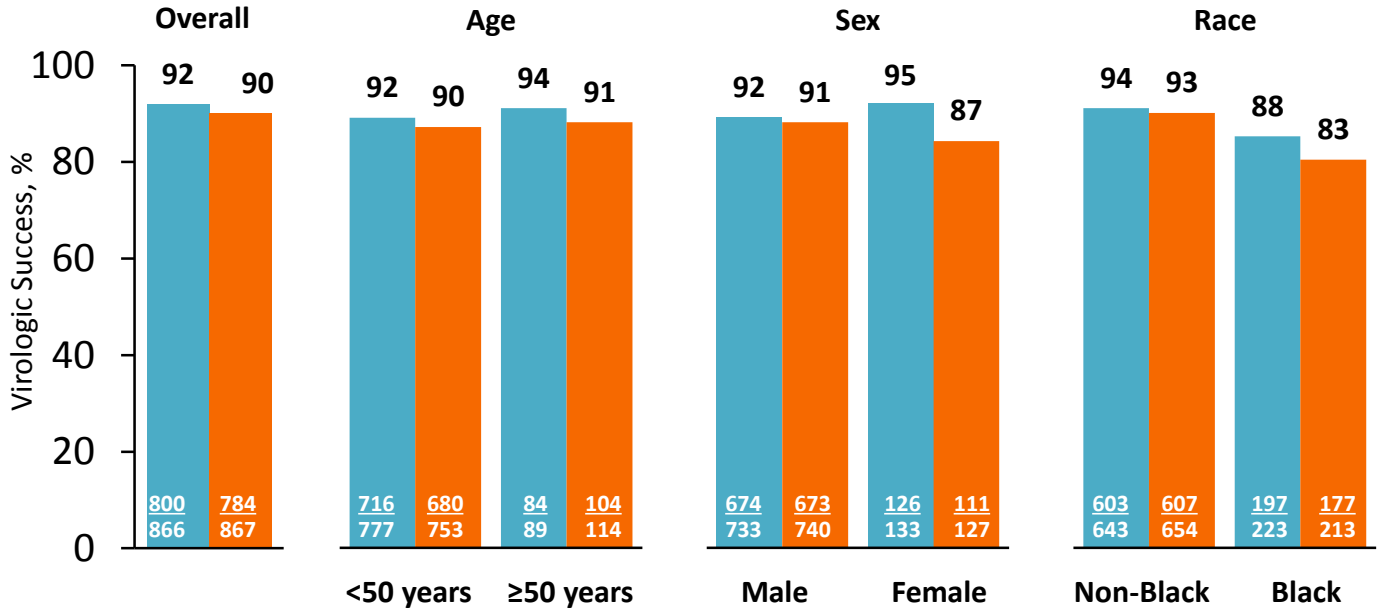
Efficacy by Baseline HIV-1 RNA and CD4 Cell Count



Wohl D *et al. CROI* 2015. Seattle, WA. Oral #113LB

Studies 104 and 111

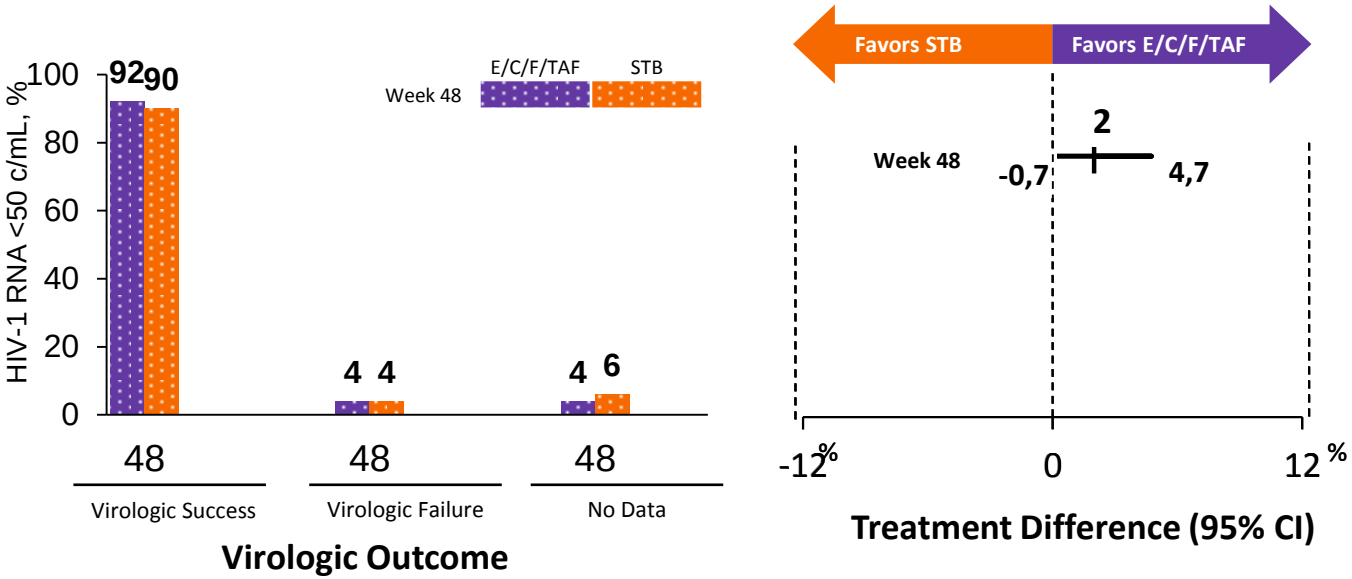
Efficacy by Age, Sex, and Race Subgroups



EVG/c/FTC/TAF (n=866)
EVG/c/FTC/TDF (n=867)

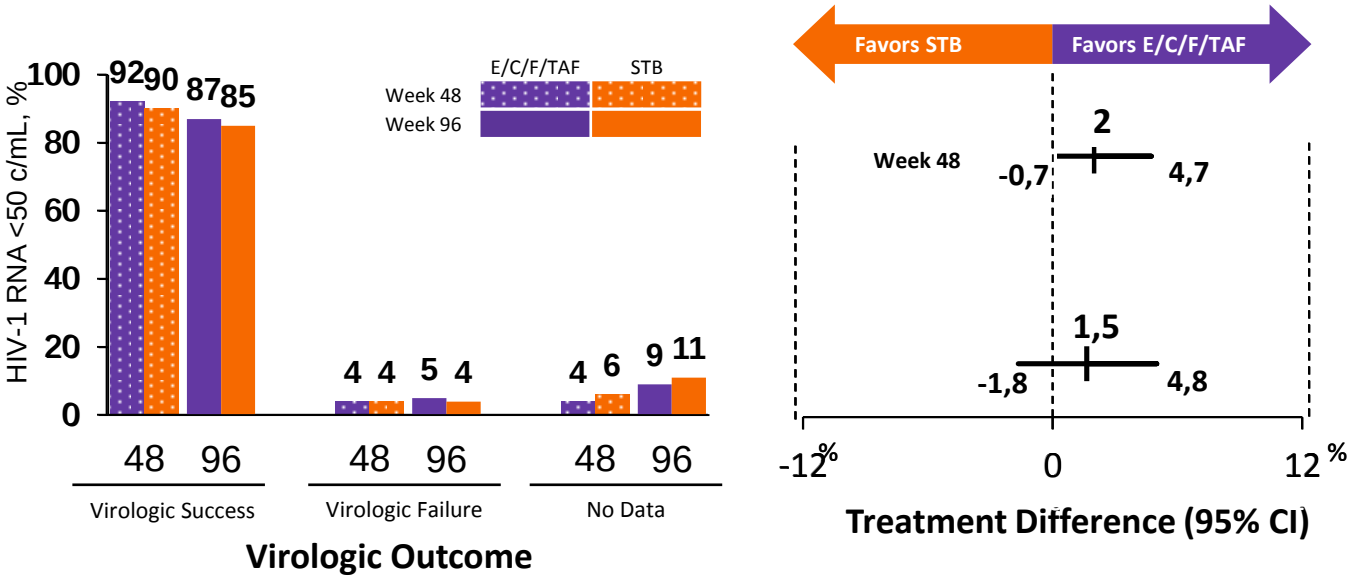
Wohl D *et al. CROI* 2015. Seattle, WA. Oral #113LB

Virologic Outcomes at Week 48



Wohl D *et al. EACS* 2015. Barcelona, Spain. #LBBPD1/1

Virologic Outcomes at Week 48 and 96



VF with resistance through week 96: 1% (10 of 866) on TAF *vs*. 1% (8 of 867) on TDF

- NRTI-R: M184V/I (9 TAF *vs* 6 TDF); K65R/N (2 TAF *vs* 3 TDF)
- INSTI-R: 8 TAF *vs*. 5 TDF, all genotypically susceptible to DTG

Wohl D *et al. EACS* 2015. Barcelona, Spain. #LBBPD1/1

Studies 104 and 111

Safety

	E/C/F/TAF n=866			STB n=867		
	Week 48	Week 96	Total	Week 48	Week 96	Total
Grade 3 or 4 AE, %	8	+4	**12**	9	+3	**12**
Serious AE, %	8	+3	**11**	7	+3	**10**
Discontinuations due to AEs, % (n)	0.9% (8)	+0.3% (2)	**1.2 % (10)**	1.5% (13)	+0.8% (7)	**2.3% (20)**
Renal AE discontinuation, % (n)	0	0	**0**	0.5% (4)	+0.2% (2)	**0.7% (6)**
Deaths, n	2**	0	**2**	3‡	0	**3**

E/C/F/TAF was well-tolerated through Week 96

- Most discontinuations due to AEs occur in the first 48 weeks
- 10 (1%) discontinuation due to AEs on TAF *vs*. 20 (2%) on TDF
- 0 discontinuation due to renal AEs in the TAF *vs* 6 in the TDF arm (p=0.03)

1. Wohl D *et al. EACS* 2015. Barcelona, Spain. #LBBPD1/1
2. Sax P *et al. CROI* 2015. Seattle, WA. Oral #143LB
3. Data on File. Gilead Sciences, Inc.

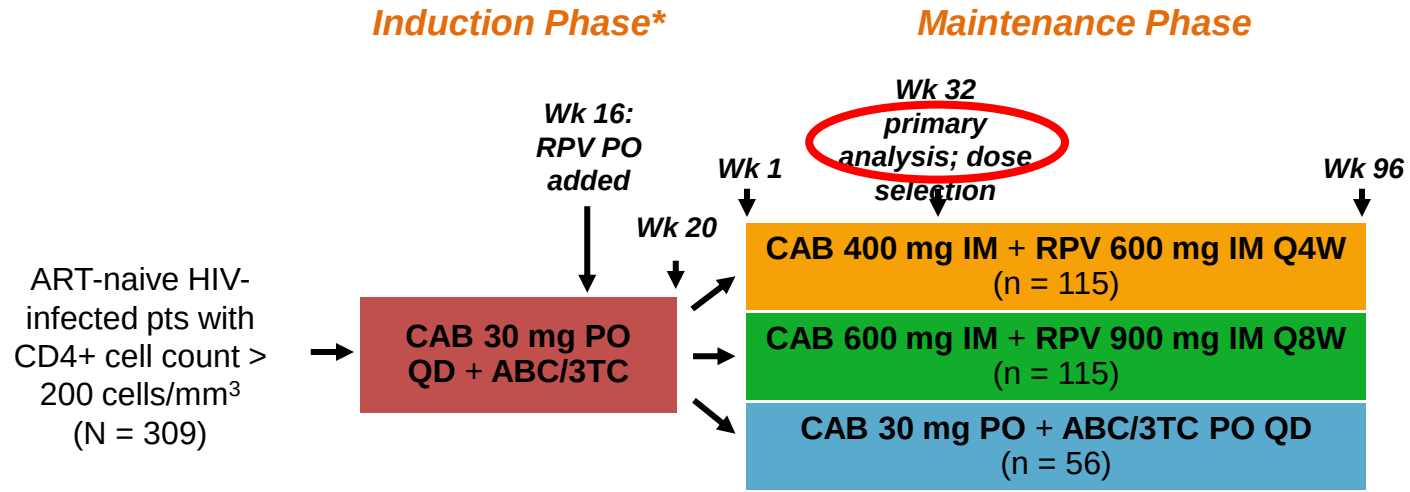
RAL qd ONCEMRK

- ONCEMRK: RAL 1200 mg QD Non inferior to 400 mg BID at Wk 48
- ONCEMRK: randomized, phase III trial in ART-naive, HIV-infected pts (N = 802)
  - Wk 48: non inferior efficacy (HIV-1 RNA < 40 c/mL) of RAL 1200 mg QD + FTC/TDF vs RAL 400 mg BID + FTC/TDF
- Similar to RAL 400 mg BID, RAL 1200 mg QD well-tolerated and with expected safety profile

NEW AGENTS IN TRIALS

Long-Acting Maintenance ART

- LATTE-2: Cabotegravir IM + Rilpivirine IM
- Multicenter, open-label phase IIb study
  - Primary endpoints: HIV-1 RNA < 50 c/mL by FDA snapshot, PDVF, and safety at maintenance Wk 32

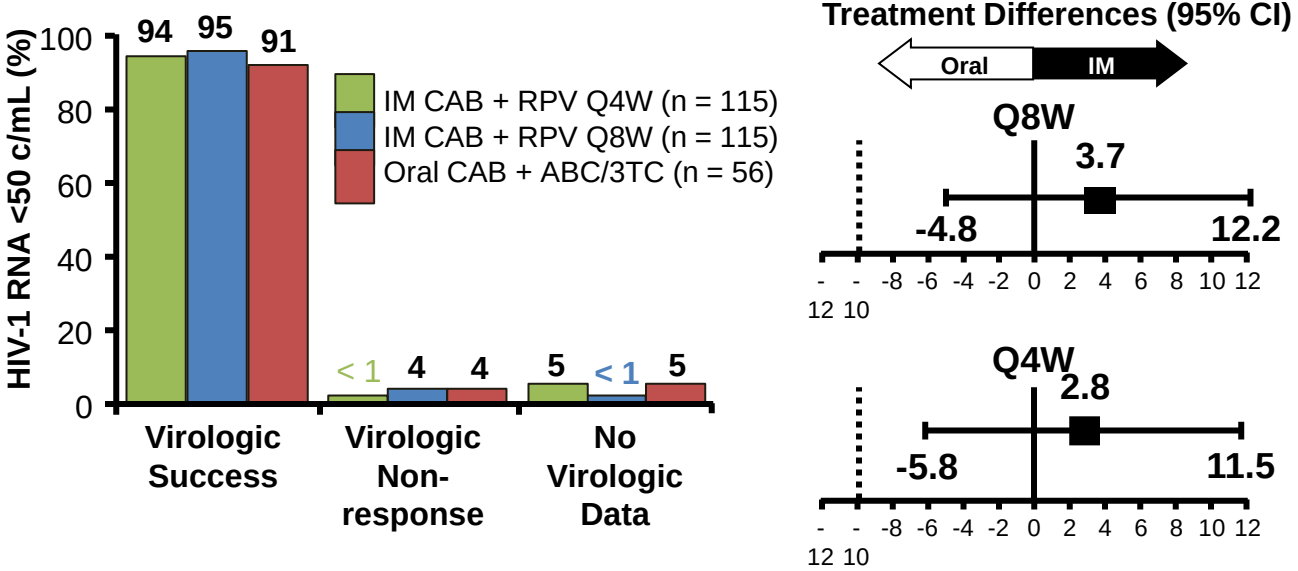


*Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. 6 pts discontinued for AEs or death in induction analysis.

Margolis DA *et al. CROI* 2016. Abstract 31LB

LATTE-2: Maintenance Wk 32 Virologic Efficacy

- Virologic efficacy of Q4W and Q8W IM regimens similar to oral regimen
- No INSTI, NNRTI, or NRTI resistance mutations detected



Margolis DA *et al. CROI* 2016. Abstract 31LB.
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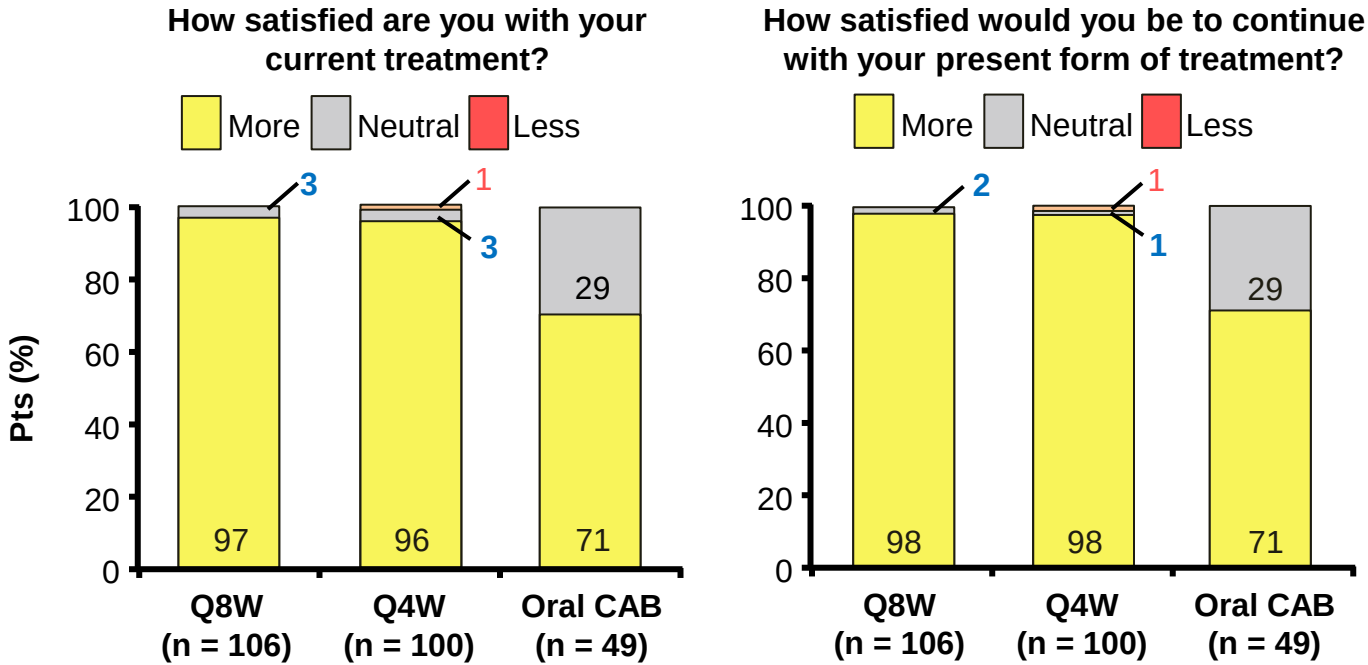
LATTE-2: Safety Through Maintenance Wk 32

- Most frequent ISRs were pain (67%), swelling (7%), and nodules (6%)
  - ISR events/injection: 0.53
  - 99% of ISRs grade 1/2; none grade 4
  - Proportion of pts reporting ISRs decreased with time from 86% on Day 1 to 33% at Wk 32; 1% of pts withdrew for ISRs

AEs, %	Pooled CAB + RPV IM Arms (n = 230)	Oral CAB + ABC/3TC (n = 56)
Drug-related grade 3/4 AEs (excluding ISRs)	3	0
Serious AEs	6	5
AEs leading to withdrawal	3	2

Margolis DA *et al. CROI* 2016. Abstract 31LB

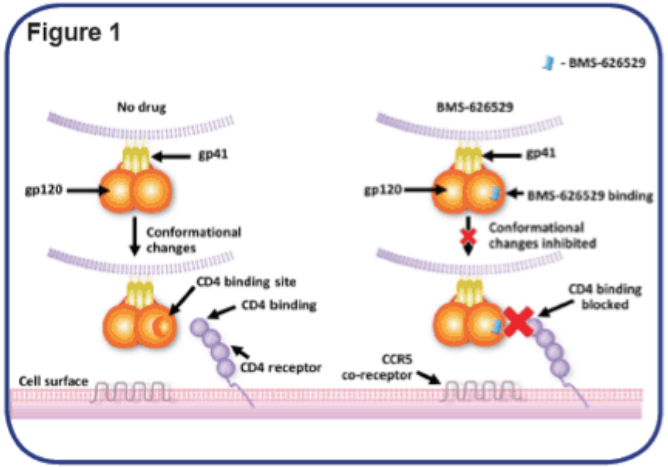
LATTE-2: Wk 32 Patient Satisfaction



Margolis DA *et al. CROI* 2016. Abstract 31LB

Attachment inhibitor GSK3684934

- AI438011: randomized, controlled phase IIb study, blinded to dose
- Subgroup analysis of efficacy, safety of attachment inhibitor GSK3684934 (formerly known as BMS-663068) at Wk 96
- 5 study groups containing OBR (RAL+TDF) (N=200)
  - 4 GSK3684934 groups (400mg BID, 800mg BID, 600mg QD, 1200mg QD)
  - ATV/RTV 300/100mg QD
  - HIV-1 RNA ≥ 1000 c/mL; CD4+ ≥ 50 cells/mm^3; virus susceptible to RAL, TDF, ATV, and GSK-2616713 IC_{50} <100 nM
  - Not powered for differences between subgroups



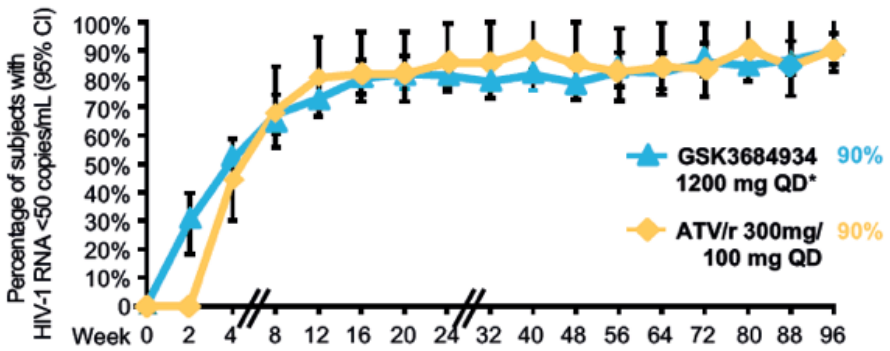
I.Savant Landry, CROI 2015

- At w48 1200mg group with most similar to ATV/r efficacy
- W48 to W96 continued on 1200mg dose in all studied groups

Granados-Reyes ER *et al. HIV* Glasgow 2016. Abstract O335A
Llamoso C *et al. HIV* Glasgow 2016. Abstract O335B

GSK3684934 + RAL + TDF: Virologic Efficacy Across Subgroups at Wk 96

Figure 1. Proportion of subjects achieving HIV-1 RNA <50 c/mL at Week 96 in study AI438011 (observed analysis)[10]



* GSK3684934 1200 mg QD was selected as the open-label continuation dose after Week 48.
GSK3684934 was formerly BMS-663068.
ATV/r, ritonavir-boosted atazanavir; CI, confidence interval. QD, once daily.

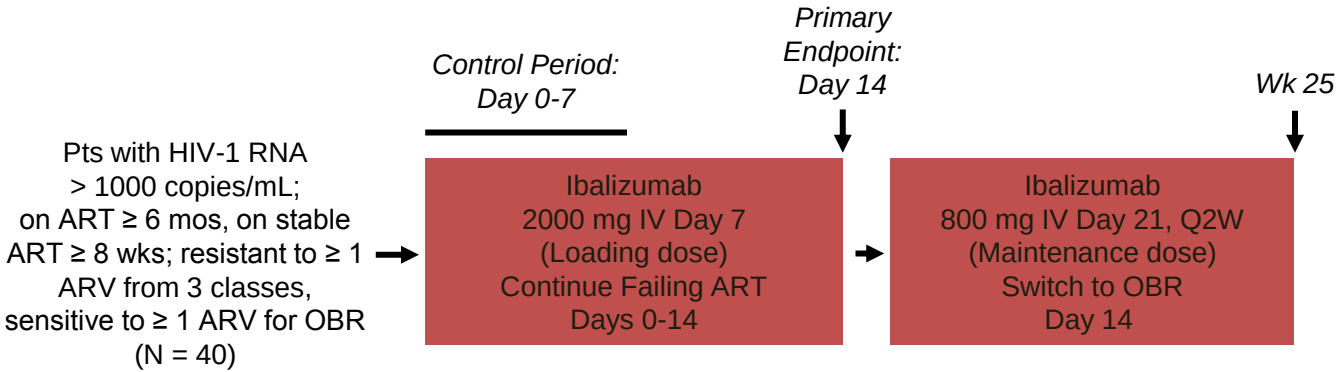
HIV-1 RNA < 50 c/mL, %	GSK-934 (n = 200)	ATV/RTV (n = 51)
Baseline HIV-1 RNA		
▪ < 100,000 c/mL	86.9	95.0
▪ ≥ 100,000 c/mL	94.2	80.0
Baseline CD4+ count		
▪ < 200 cells/mm^3	88.1	92.3
▪ ≥ 200 cells/mm^3	91.4	88.2
Sex		
▪ Male	88.5	94.1
▪ Female	91.4	84.6
Age		
▪ < 40 yrs	92.3	85.7
▪ ≥ 40 yrs	87.3	93.8

GSK-934 generally well tolerated, with no new safety signals arising in this analysis
Phase III trial of GSK3684934 in heavily treatment-experienced pts under way

Granados-Reyes ER *et al. HIV* Glasgow 2016. Abstract O335A

TMB-301: Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Ibalizumab: humanized mAb to CD4 receptor that blocks post-attachment HIV entry into CD4+ T-cells
- Single-arm, open-label phase III trial
  - Primary endpoint: ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14



Lalezari J *et al. IDWeek* 2016. Abstract LB-6

TMB-301: Efficacy, Safety of Ibalizumab

- Primary efficacy endpoint: HIV-1 RNA reduction at Day 14 after Day 7 ibalizumab loading dose
  - 83% of pts achieved ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14 vs 3% at end of control period
  - 60% of pts achieved ≥ 1.0 $\log_{10}$ HIV-1 RNA decrease at Day 14 vs none at end of control period
- Safety/tolerability
  - No discontinuations for AEs
  - No treatment-related serious AEs

Lalezari J *et al. IDWeek* 2016. Abstract LB-6

Clinical case

	Dec 15	Jan 16	Apr 16	Aug 16
HIV RNA	$2x10^6$	115	228	$9x10^4$
CD4	16 (5%)	96 (7%)	148 (13%)	81 (7%)

M41L, K65R, M184V, L10V, L33V, T69S, L10I, I47A, V32I, E92Q, E157Q, ...

Resistance to:

FTC, 3TC, ABC, TDF, RAL, EVG, ATV, LPV

DTG + ... ?

NNRTI + ... ?

Thank you