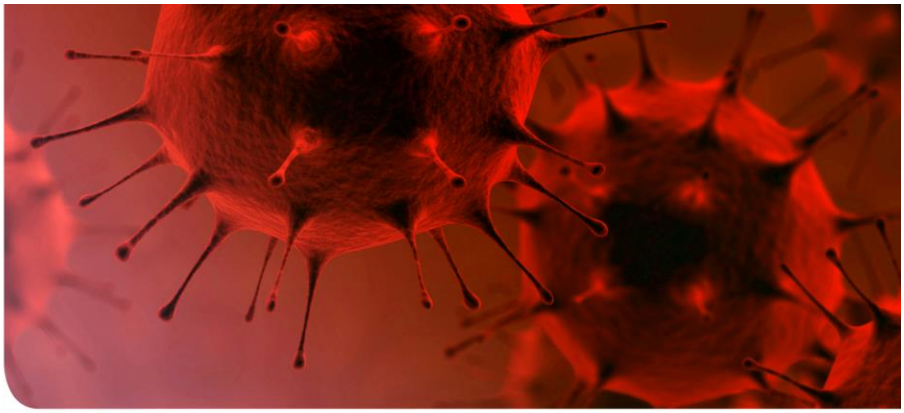

Should I stay or should I go now?

Dr Don Smith, FAChSHM, FRCP
Conjoint Professor, SPH&CM UNSW

Senior Staff Specialist,

Albion Centre,

Disclosures

Just check Medicines Australia or the Telegraph

Research funding from: GSK, Viiv; MSD, Gilead Science, Kirby Institute, UNSW, Commonwealth of Australia

Travel/educational support from: Gilead Science,

Consultancy services to: Viiv; MSD, Gilead Science,

When to let go of the past?

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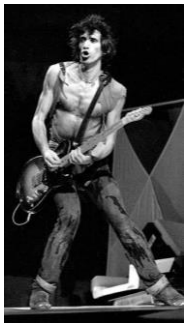
Where are we at now with ARVs?



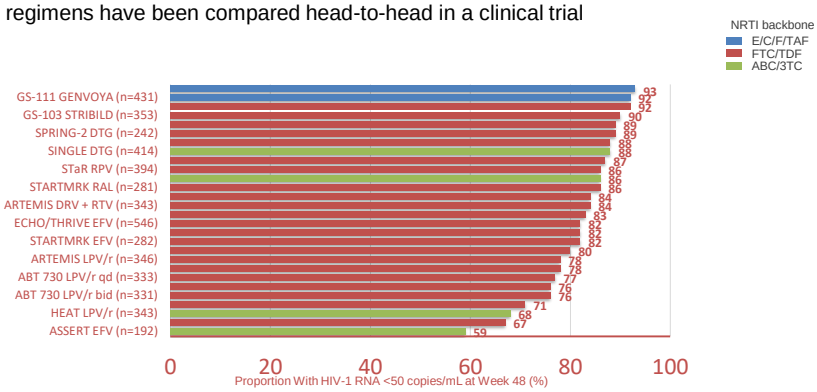
Step 1; control the virus
Step 2: avoid ARV toxicity

Step 3; sort out the other shit:

- hypertension
- smoking
- lipids
- metabolic (NASH, T2D, BMD)
- mental health
- Drugs and alcohol

Virological suppression rates over time

Data from multiple studies published from 2004–2015
Not all regimens have been compared head-to-head in a clinical trial



Registrational Treatment-Naïve Clinical Trials: Historical Data

DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART

Class	DHHS[1]	IAS-USA*[2]
INSTI	▪ **BIC/TAF/FTC** ▪ **DTG/ABC/3TC** ▪ DTG + (TAF or TDF)/FTC ▪ **EVG/COBI/(TAF or TDF)/FTC** ▪ RAL + (TAF or TDF)/FTC	▪ **DTG/ABC/3TC** ▪ DTG + TAF/FTC ▪ **EVG/COBI/TAF/FTC** ▪ RAL + TAF/FTC

Bold text identifies single-tablet regimens. *IAS-USA guidelines not updated since the approval of BIC/TAF/FTC.

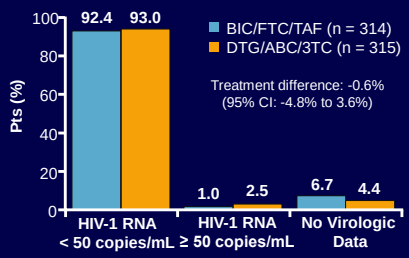
- Recommendations may differ based on BL HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, and osteoporosis status
- With FDA approval of 1200-mg RAL,[3] all options now available QD (except in pregnancy)

1. DHHS guidelines. March 2018. 2. Günthard HF, et al. JAMA. 2016;316:191-210. 3. Raltegravir [package insert]. 2018.

Slide credit: clinicaloptions.com

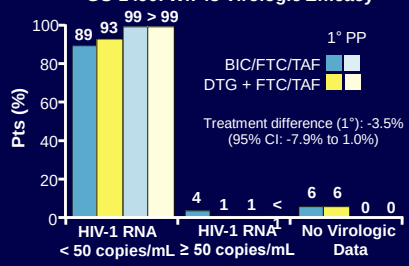
BIC/FTC/TAF vs DTG-Containing Regimens: Key Efficacy Findings

GS-1489: Wk 48 Virologic Efficacy[1]



- BIC/FTC/TAF noninferior to DTG/ABC/3TC for HIV-1 RNA < 50 copies/mL
- No resistance for any regimen components detected for either group

GS-1490: Wk 48 Virologic Efficacy[2]

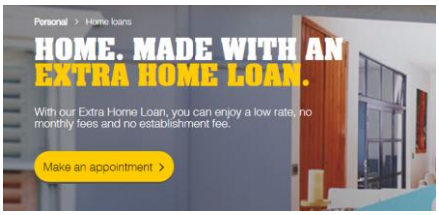


- BIC/FTC/TAF noninferior to DTG + FTC/TAF for HIV-1 RNA < 50 copies/mL
- No resistance for any regimen components detected for either group

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. 2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB.

Slide credit: clinicaloptions.com

Why do the new clients get the best offers?



Or check out our new limited time offer:

Any TV pack free~ for 2 months

+ $75 off iQ3 box fee~
+ Save up to $349~ (with Platinum HD)
+ Short 6 month plan

GET FOXTEL

~Min cost ranges from $254 (Entertainment pack) to $698.03 (Platinum HD) on direct debit (incl. $50 iQ3 equipment fee & $100 std install). New residential subscribers and standard install only. Cancel fee applies. Offer ends 26-05-2018.

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Federal Govt will happily pay $25,000 pp/pa to get you to a happier place.

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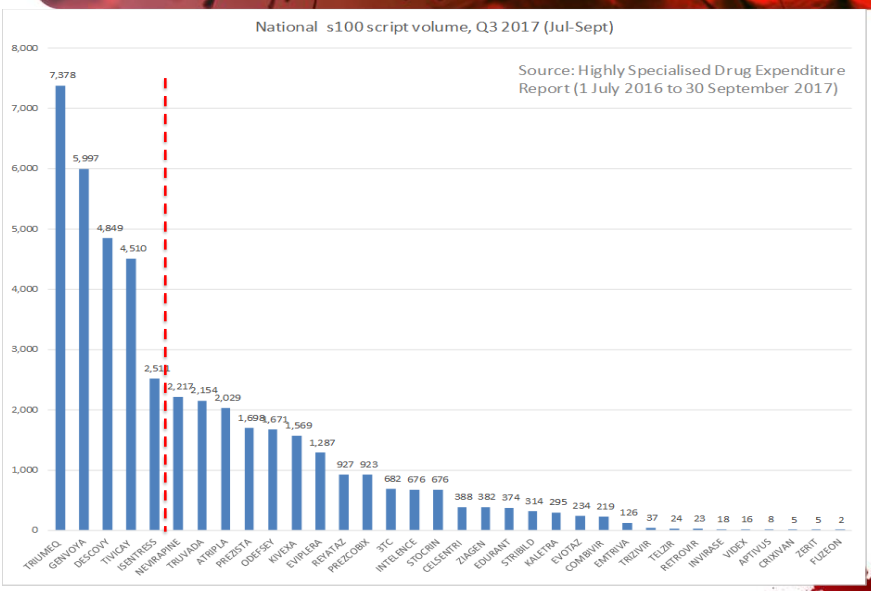

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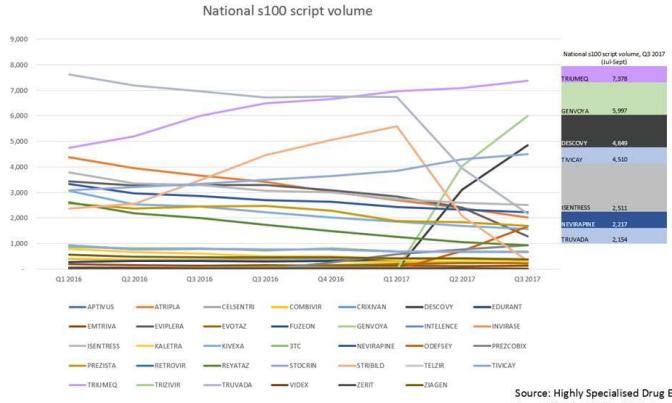
Should I switch stable patients off old regimens?



Source: Highly Specialised Drug Expenditure Report (1 July 2016 to 30 September 2017)

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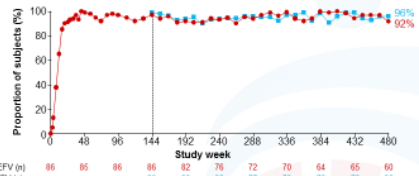
Most patients have been suppressed for years

Study 903E

Efficacy of TDF + EFV + 3TC over 10 years

OLE of subjects[*] who continued with, or were switched to a TDF + 3TC + EFV QD regimen for 10 years, following a 144-week, phase 3, randomised, double-blinded study in ART-naive PLWHIV, comparing the efficacy and safety of d4T + 3TC + EFV and TDF + 3TC + EFV[1,2]

Proportion with HIV RNA <50 copies/mL (missing=excluded analysis) by visit over 10 years[1]



TDF/TDF + 3TC + EFV (n)	86	86	86	86	82	76	72	70	64	65	60
d4T/TDF + 3TC + EFV (n)				86	83	82	77	73	73	72	56

- **Once-daily TDF-containing ART for up to 10 years demonstrated:**[2]
  - **Sustained virologic and immunologic benefit**
  - **No evidence of lipoatrophy or clinically relevant bone effects**

[*] From select sites in Argentina, Brazil and the Dominican Republic

3TC, lamivudine; ART, antiretroviral therapy; d4T, stavudine; EFV, efavirenz; OLE, open-label extension; PLWHIV, people living with HIV; QD, once daily; TDF, tenofovir disoproxil fumarate

1. Madruga JV *et al.* International Congress on Drug Therapy in HIV Infection 2010. Glasgow, UK. #P086.
2. Cassetti I *et al.* J Int AIDS Soc 2010;13:P86

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Where to next with ARVs?
Not so simples

Avoiding TDF	-renal/bone toxicity
Avoiding ABV	–CVD risk
Reducing role of PIs	-GI intolerance MI risk
Reducing role of nnRTIs	–lower potency, CNS intolerance

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nnRTI weaknesses

- Efavirenz: Sleep disturbance, CNS issues, suicide risk, “Brain fog”
- Nevirapine: Hepatotoxicity/rash at initiation, chronic GGT elevation and hepatic impairment.
- Rilpivirine; PPI interactions, food requirements, less efficacious with high viral loads

I. Low genetic barrier to resistance; Must be used with high barrier partners.

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Switch Studies With Evidence of Sustained Efficacy

Within Class

- EFV ➟ RPV
- RAL ➟ EVG or DTG
- DTG ➟ BIC
- Boosted DRV, boosted ATV, or LPV/RTV ➟ DRV/C/FTC/TAF
- TDF or ABC ➟ TAF

Between Class

- Boosted PI ➟ RPV
- Boosted PI ➟ EVG, DTG, or BIC
- NNRTI ➟ EVG or DTG

References in slidenotes

Slide credit: clinicaloptions.com

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Nucleoside waste

Incorporated by DNA polymerase into mtDNA,
Impairment of mitochondrial replication,
Reduction in ATP production,
Lactic acid production,

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Where are they now?

Thymidine analogues:

- AZT — myleosuppression
- d4T — neuropathy, lipodystrophy

Adenosine analogues:

- ddI — neuropathy, lipodystrophy
- Adefovir — lactic acidosis
- TDF — proximal tubularopathy
- TAF

Cytidine analogues:

- ddC — neuropathy, lipodystrophy
- 3TC
- FTC

Guanosine analogues:

- ABV — platelet/endothelial reactivity

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ARV usage: Albion dispensing: Dumping TDF

		TAC			
		2015		2017	
TDF	ATRIPLA	46	6%	4	0.7%
	EVIPLERA	140	18%	6	1.0%
	STRIBILD	73	9%	0	0.0%
	TRUVADA	221	28%	5	0.8%
TAF	VIREAD	21	3%	2	0.3%
	GENVOYA (approved Apr 2016)	n/a	0%	184	31%
	DESCOVY 10+25 (approved Dec 2016)	n/a	0%	129	22%
	ODEFSEY (approved May 2017)	n/a	0%	79	13%

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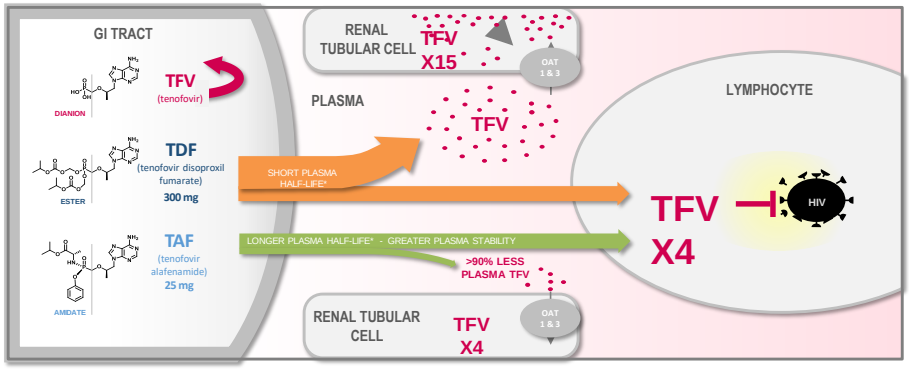
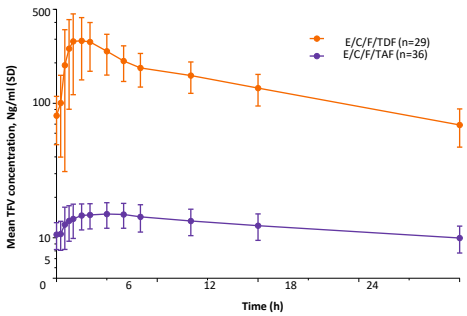
What's the diff? TAF: not an anion, so not concentrated in renal cells



Animation for illustrative purposes only. Components not to scale; *T½ based on in vitro plasma data. TDF=0.4 minutes, TAF=90 minutes[2]
TFV, tenofovir
1. Gupta SK. et al. IAS2015 #TVAB0103; 2. Ray AS, et al. Antivir Res 2016;125:63–70

Plasma TFV concentrations

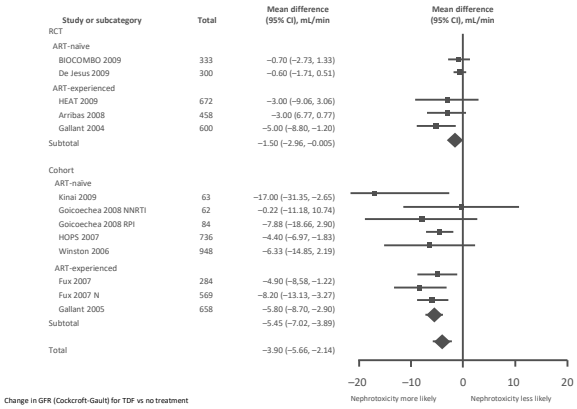
Studies 104 & 111: E/C/F/TAF in ART-naïve adults



- **91% reduction in TFV plasma exposures with E/C/F/TAF compared with E/C/F/TDF**

ART, antiretroviral therapy; C, cobicistat; E, elvitegravir; F, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; SD, standard deviation
Sax P et al. Lancet 2015;385:2606–2615 (appendix)

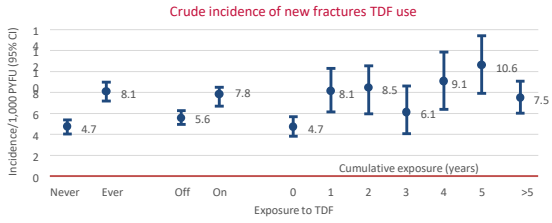
TDF has been associated with a decline in GFR[1]



1. Cooper RD *et al. Clin Infect Dis* 2010;51:496–505.

Antiretrovirals and fractures in a large European HIV cohort

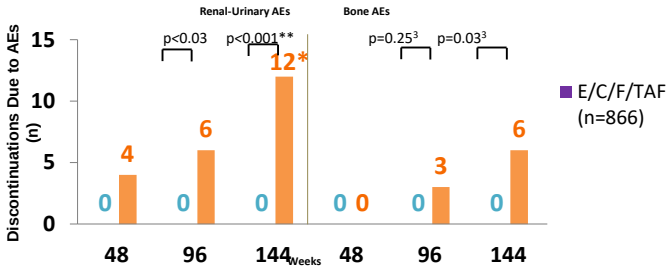
- 86,118 person-years of follow-up (PYFU) from patients in the EuroSIDA cohort, >16 years, with prospective follow-up after January 1, 2004 and baseline data on CD4 and viral load
- Current or past exposure of TDF but no other antiretrovirals, was independently associated with higher incidence of any fracture



PYFU, person-years of follow-up
Borges A et al., CROI 2016, Boston, 2016, Oral #46

Studies 104 and 111: ART-Naïve Adults, Week 144 Combined Analysis

Renal and Bone Events Leading to Discontinuation through Week 144[1,2]



- **Through Week 144, E/C/F/TAF had**
  - **No discontinuations for renal AEs (0 vs. 11; p<0.001)**
  - **No cases of renal tubulopathy (including Fanconi Syndrome)** **vs 4 on E/C/F/TDF (1 case of Fanconi Syndrome)**
  - **No discontinuations due to bone AEs (0 vs. 6; p=0.03)**

* 1.4% (12/867) rate of discontinuations due to renal-urinary AEs is consistent with TDF trials
** Discontinuations due to renal-urinary AEs includes 1 case of bladder spasm
1. Wohl D, et al. JAIDS 2016;72:S8-64, supplemental materials; 2. Arribas J, et al. CROI 2017. Seattle, WA. Poster #453; 3. Data on File, Gilead Sciences Inc.

25

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E/C/F/TAF versus E/C/F/TDF, Studies 104/111, Week 144

Baseline Characteristics of Renal Related Discontinuations on TDF

Subject	Gender	$eGFR_{CG}$, mL/min	Age, yrs	Race	Renal Adverse Event on TDF
1*	Male	116	45	White	Renal Tubular Disorder
2*	Male	104	51	White	Fanconi Syndrome, Glycosuria
3	Male	98	27	Am Indian/Alaska Native	Proteinuria
4	Male	94	50	White	Blood Creatinine Increased, BMD decreased
5	Male	92	50	White	GFR decreased
6*	Male	88	33	White	Renal Tubular Disorder
7	Male	83	36	White	Blood Creatinine Increased, GFR decreased
8	Male	83	41	Black	Renal failure
9*	Male	82	53	White	Renal Tubular Disorder
10	Female	73	53	Other	Renal failure
11	Male	66	37	Black	Nephropathy
12	Male	63	59	White	Bladder Spasm

- **Four of 12 were under age 40; 11/12 were male, and racial backgrounds were mixed**
- **Of the 4 cases with development of PRT and/or Fanconi syndrome:**
  - **2/4 had normal renal function at baseline, 2/4 had mild renal impairment**
  - **0/4 had medical history of renal disease noted at enrollment**

Gilead Sciences, data on file

26

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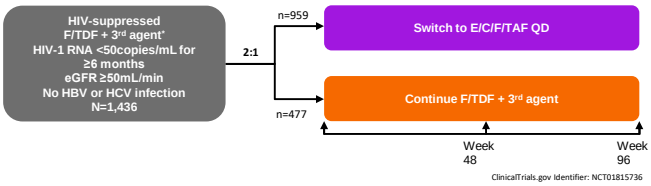
Study design

Study 109: ART-suppressed adults switched to E/C/F/TAF

Phase 3, 96-week, multicentre, randomised, open-label, active-controlled study[1–3]



- Primary endpoint: Non-inferiority (12% margin) of switch to E/C/F/TAF vs continuation of baseline regimen by FDA Snapshot analysis (HIV-1 RNA <50copies/mL at Week 48)[3]
- Secondary endpoints: Efficacy through Week 96, safety and tolerability through Weeks 48 and 96[2]

* E/C/F/TDF=459 (32%), EFV/F/TDF=376 (26%), or COBI-boosted ATV+F/TDF=601 (42%)

1. DeJesus E et al. ASM 2016. Boston, MA. #087LB; 2. Overton T et al. ASM 2016 Boston, MA. #3537; 3. Huhn G et al. ASM 2016. Boston, MA. Oral

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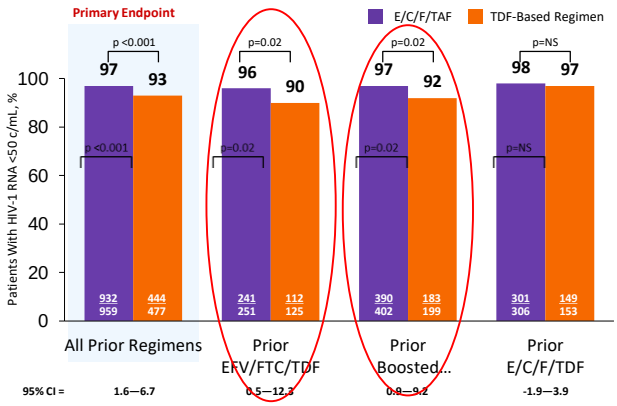
GS-US-292-0109

Virologic Outcome, Prior Treatment Regimens



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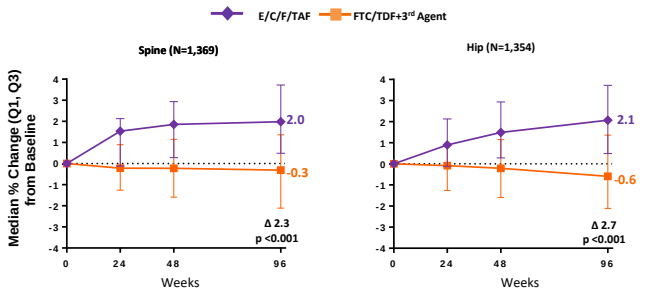
Study 109: Suppressed Adults Switched from a TDF-containing regimen to E/C/F/TAF

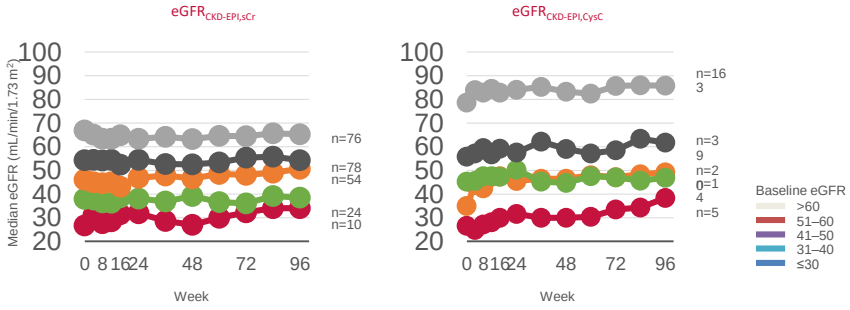
Changes in Spine and Hip BMD through Week 96



Switching to E/C/F/TAF from a regimen containing FTC/TDF + 3rd agent resulted in progressive increase in spine and hip BMD over 96 weeks

DeJesus E, et al. ASM 2016. Boston MA. #087LB

Switch Study 112: suppressed with GFR 30-70mL/min
Changes in eGFR by baseline eGFR strata

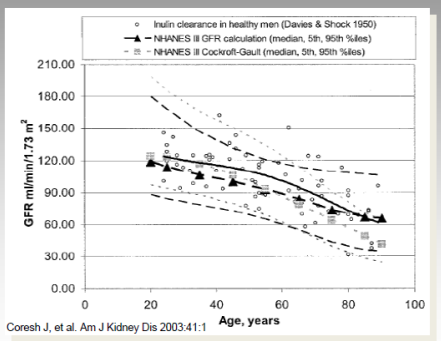


One patient was excluded due to missing cysC data at baseline.
cysC, cystatin C; sCr, serum creatinine
Post F, et al. CROI 2016. Boston, MA. Poster #680.

Just how bad does it have to get?

Kidney function and age

Glomerular filtration rate and kidney size decline with age and people over 60 years have 20-30% lower GFR than those under 50 years



Coresh J, et al. Am J Kidney Dis 2003:41:1

Percentiles of GFR and Cockcroft-Gault CCr by age plotted on the same graph as data on inulin clearance in healthy men

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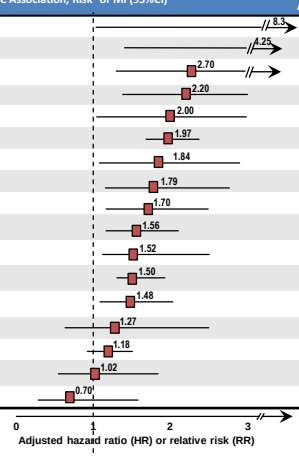
Avoiding CVD. Which ARVs worsen CVD?

Background: Association of ABC and TDF Exposure with Risk of CV Events

(NOT A CROSS STUDY COMPARISON – EACH LINE REPRESENTS A SEPARATE STUDY)

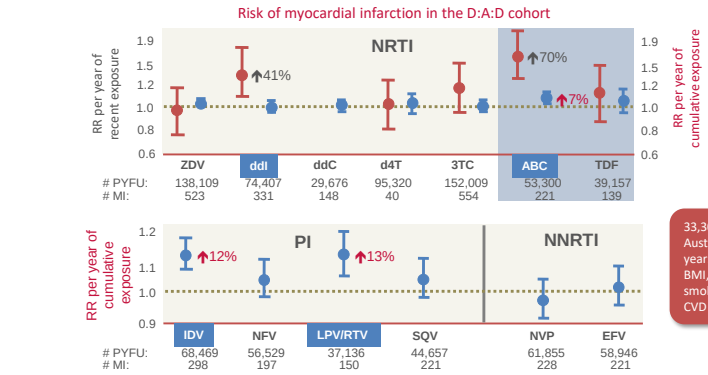
Study	(Pt-Yr of Follow-up)	Event, n	ABC Association, Risk[d] of MI (95%CI)	TDF Association
STEAL	(NR)[14]	CVD Event (8)[f]	8.3 (1.02–50.0)	-
SMART	(NR)[13]	MI (19)	4.25 (1.39–13.0)	None
North Carolina Medicaid	(6399)[17]	MI (38)	2.70 (1.24-5.91)[h]	-
Kaiser	(31,211)[15]	CVD (178)	2.20 (1.4–3.5)	-
Danish	(19,124)[10]	MI (67)	2.00 (1.07–3.76)	-
D:A:D 2014	(367,559)[2]	MI (941)	1.97 (1.43–2.72)[i]	-
NA-ACCORD Overall	(29,077)[1]	MI (123)	1.84 (1.17–2.91)	-
QPHID	(35,851)[9]	MI (125)	1.79 (1.16–2.76)	None
D:A:D	(178,835)[3]	MI (580)	1.70 (1.17–2.47)	None
MAGNIFICENT	(NA)[4]	CVD Event[e] (571)	1.56 (1.17–2.07)	-
Swiss	(NA)[6]	CVD Event[e] (350)	1.52 (1.13–2.04)	-
VA - Desai	(164,059)[16]	CVD Event[g] (934)	1.50 (1.26–1.79)	None
VA - Choi	(59,578)[5]	CVD Event[c] (501)	1.48 (1.08–2.04)	None
French HD	(298,156)[7]	MI (289)	1.27[e] (0.64–2.49)	None
VA - Bedimo	(76,376)[8]	MI (278)	1.18 (0.92–1.50)	None
Ding meta-analysis	(range: 42 to 1,257)[12]	MI (24)	1.02 (0.56–1.84)	-
ALLRT/ACTG	(17,404)[11]	MI (36)	0.70 (0.3–1.6)	-



French HD, French Hospital Database; NNA-Acc, NA-ACCORD;NR, not reported; QPHD, Quebec's public health insurance database. [a] All or majority of patients were treatment-experienced at ABC initiation; [b] All or majority of pts were treatment-naive 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; [f] MI, coronary artery surgery, PVD, ischemic stroke, deep vein thrombosis, [g] MI, stroke, percutaneous coronary intervention, and coronary artery bypass surgery; [h] association compared with TDF (unadjusted); [i] Post-2008 association when patients with moderate/high CVD risk were more likely to receive ABC.

[1] Elion R, et al. JAIDS 2018 [epub ahead of print]; [2] Sabin C, et al. BMC Medicine 2016; [3] Worm SW, et al. JID 2010; [4] Rotger M et al, CID 2013; [5] Choi AI, et al. AIDS 2011; [6] Young J, et al. IAS 2013. MOPED070; [7] Lang S, et al. Arch Intern Med 2010; [8] Bedimo RJ, et al. CID 2011; [9] Durand M, et al. JAIDS 2011; [10] Obel N, et al. HIV Medicine 2010; [11] Ribaudo HJ, et al. CID 2011; [12] Ding X, et al. JAIDS 2012; [13] SMART/INSIGHT Study Group. AIDS 2008; [14] Martin A, et al. CID 2009; [15] Marcus, JL, et al, JAIDS 2016; [16] Desai M, et al. CID 2015; [17] Brouwer, E. et al. Epidemiology 2014

CVD and HIV: Role of ART in MI risk;



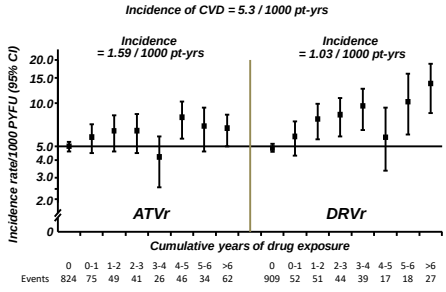
33,308 patients in Europe, USA and Australia; 580 MI (3.2/1,000 patient years); all RR adjusted for age, gender, BMI, race, family history of CAD, smoking, transmission mode, and prior CVD

Recent exposure = current of within the last 6 months
Worm SW et al. J Infect Dis 2010;201:318–30

D:A:D Study

Association Between Cardiovascular Disease (CVD) and Boosted Darunavir

Evaluation of association between CVD (myocardial infarction, stroke, sudden cardiac death, invasive cardiovascular procedures) and PIs from 2009 to 2016 (N=35,711)

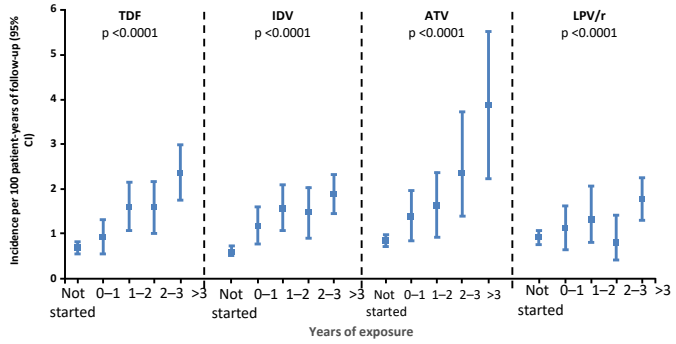


Cumulative DRVr independently associated with a CVD risk of 59% per 5 yrs use

Ryom L, et al. CROI 2017.
Seattle, WA. Oral #128LB

But atazanavir's still OK, isn't it?

Incidence of CKD according to ARV exposure[1]

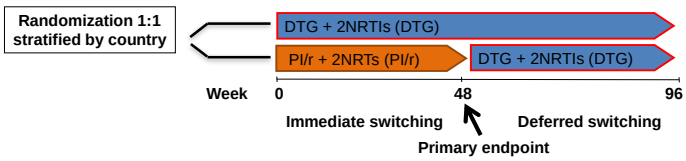


CI: confidence interval

1. Morcroft A *et al. AIDS* 2010;24:1667–78.

NEAT 022: Methods and Study Design

- 96-weeks European (6 countries), multicenter (32 sites), prospective, randomized, open-label, non-inferiority trial (~10%)
- Eligibility criteria
  - HIV-infected patients with plasma HIV-1 RNA < 50 copies/ml for ≥ 6 months on triple therapy PI/r + 2NRTIs
  - Age >50 years and/or Framingham risk score >10% at 10 years
  - No documented resistance mutations and no previous episodes of confirmed virological failure whilst receiving ART unless documented lack of resistance mutations



Gatell et al. AIDS 2017, 31:2503–2514

Baseline Characteristics : N(%) Or Median (IQR)

	DTG (n=205)	PI/r (n=210)	Total (n=415)
Age > 50 years	179(87.3)	184(87.6)	363(87.5)
Framingham score > 10% at 10 years	155(75.6)	151(71.9)	306(73.7)
Male gender	181(88.3)	189(90.0)	370(89.2)
White race	173(84.4)	180(85.7)	353(85.1)
Mode of HIV transmission			
Male homosexual sexual intercourse	130(63.4)	131(62.4)	261(62.9)
Heterosexual sexual intercourse	43(23.9)	48(22.9)	97(23.4)
Other	26(12.7)	31(14.8)	57(13.7)
CD4 count; cells per µL	635(495-819)	585(471-830)	617(477-820)
HIV RNA >50 copies/ml	7(3.4)	1(0.5)	8(2)
Hepatitis C IgG antibodies	27(13.4)	24(11.6)	51(12.5)
Time since undetectable viral load (<50 copies per ml); years	4.9(2.5-9.1)	5.3(2.3-8.5)	5(2.4-8.8)
Current Smokers	78(38)	79(37.8)	157(37.9)
Diabetes	11(5.5)	13(6.3)	24(5.9)
Family history of cardiovascular disease	87(43.3)	89(43.4)	176(43.3)
Receiving lipid lowering agents	63(30.7)	60(28.6)	123(29.6)
Daily exercise	64(32.5)	59(28.9)	123(30.5)
Fasting plasma lipids			
Total cholesterol; mmol/L	5.2(4.5-5.8)	5.1(4.5-5.6)	5.1(4.5-5.7)
Triglycerides; mmol/L	1.6(1.2-2.3)	1.6(1.2-2.2)	1.6(1.2-2.2)

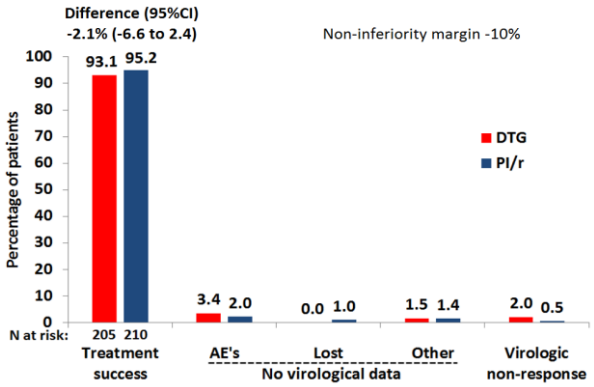
Gatell et al. AIDS 2017, 31:2503–2514

Baseline Characteristics (II): n (%)

	DTG (n=205)	PI/r (n=210)	Total (n=415)
Backbone nucleos(t)ides			
TDF / FTC	134 (65.4)	135 (64.3)	269 (64.8)
Abacavir/ 3TC	63 (30.7)	67 (31.9)	130 (31.3)
Other	8 (3.9)	8 (3.8)	16 (3.9)
PI/r at baseline			
Darunavir/r	105 (51.5)	107 (51.0)	212 (51.2)
Atazanavir/r	77 (37.7)	74 (35.2)	151 (36.5)
Other	22(10.7)	29(13.8)	51(12.3)

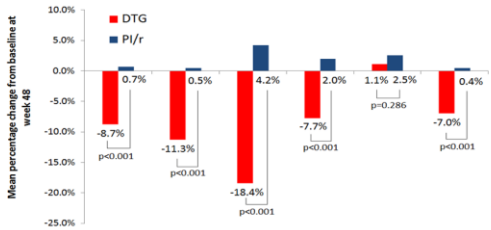
Gatell et al. AIDS 2017, 31:2503–2514

Co-Primary Efficacy Endpoint (ITT Population)



Gatell et al. AIDS 2017, 31:2503–2514

Co-Primary Lipids Endpoint

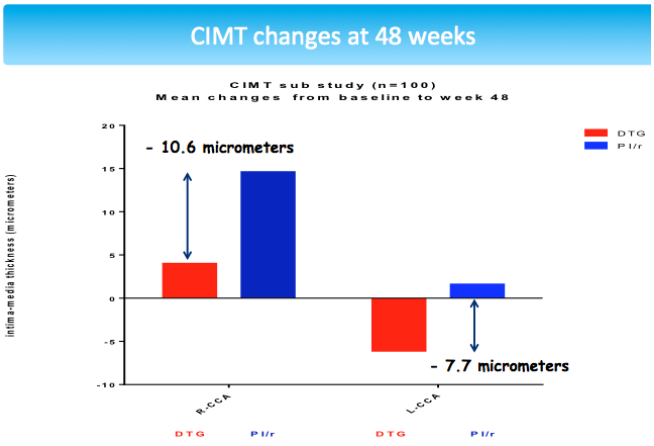


	Total cholesterol	Non-HDL cholesterol	Triglycerides	LDL cholesterol	HDL cholesterol	TC/HDL ratio
Mean concentration (SD) at baseline (mmol/L)						
DTG	5.20 (1.04)	3.93 (1.03)	1.87 (1.15)	3.13 (0.88)	1.27 (0.43)	4.45 (1.41)
PI/r	5.08 (0.95)	3.81 (0.91)	1.87 (1.02)	3.03 (0.80)	1.26 (0.39)	4.29 (1.22)
Mean concentration (SD) at week 48 (mmol/L)						
DTG	4.69 (0.91)	3.42 (0.87)	1.38 (0.86)	2.83 (0.83)	1.27 (0.44)	4.05 (1.43)
PI/r	5.07 (1.02)	3.78 (0.99)	1.81 (0.98)	3.04 (0.90)	1.29 (0.42)	4.26 (1.39)

No changes in the utilization of lipid lowering agents.
Around 30% in each arm and both at baseline and week 48.

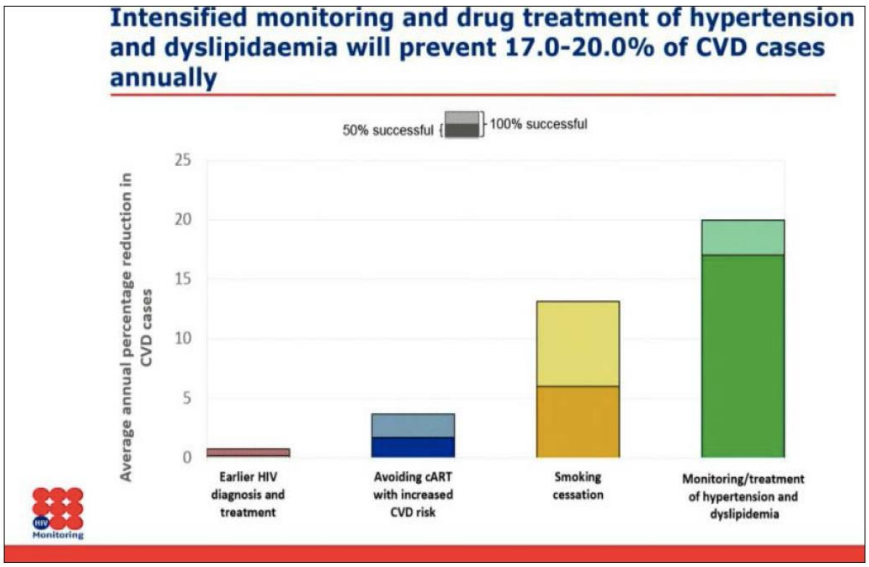
Gatell et al. AIDS 2017, 31:2503–2514

Carotid Intima-Medial Thickness: sub study



Martinez et al. EACS 2017; Milan, Italy. Abstract2/6

What to do about CVD risk?



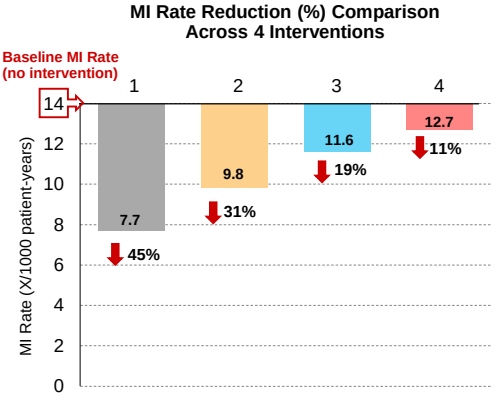
van Zoest R, CROI, Abstract 129

HEOR

‡

Comparing Strategies for Reducing Myocardial Infarction Rates in HIV Patients

Intervention Type	
HIV+ Patient Base Case Profile: 50 years old, Male, on ABC, smoker, w/ hypertension, w/ hyperlipidemia	
1	ABC substitution with an alternative antiviral without association to higher MI rate
2	Prescribing anti-hyperlipidemia medication
3	Prescribing anti-hypertensive medication
4	Counseling including standard treatment for smoking cessation such as nicotine patch and varenicline

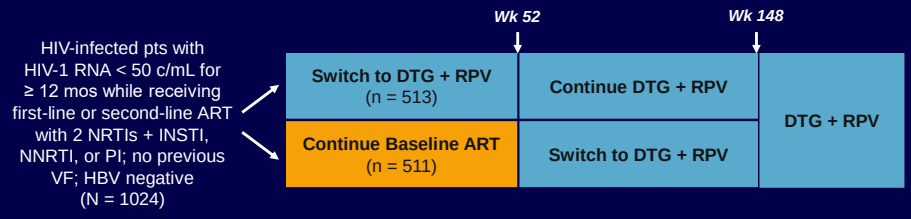


Replacing ABC has a greater impact on MI risk than interventions solely based on attempting to modifying each of three traditional risk factors

Hsue P, et al. CROI 2018. Boston, MA. Poster 692

SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV Dual Therapy

- Randomized, open-label, multicenter phase III trials
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-E snapshot)



- 70% to 73% of pts receiving TDF at baseline

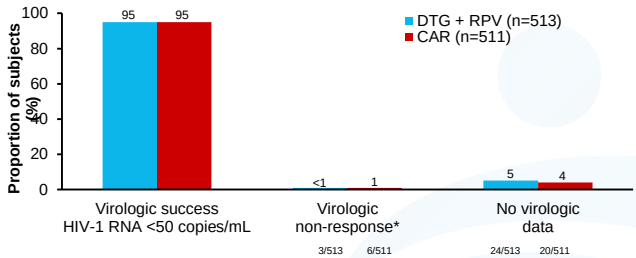
Llibre JM, et al. CROI 2017. Abstract 44LB.

Slide credit: clinicaloptions.com

SWORD 1 and 2: Switch from CAR to DTG + RPV

Pooled efficacy results

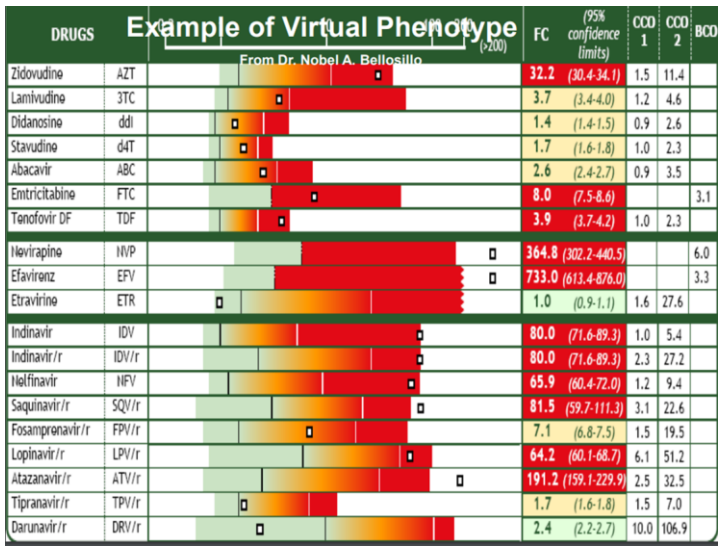
Virologic outcomes at Week 48 (ITT-E) pooled analysis



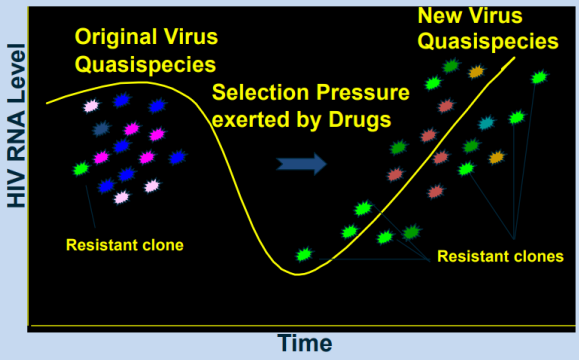
- **DTG + RPV was non-inferior† to CAR with respect to snapshot in the ITT-E population[1]**
- **Emergence of NNRTI RAM (K101K/E) in DTG + RPV arm (n=1) [1]**

* Virologic non-response = data in window not <50 copies/mL, discontinued for lack of efficacy, discontinued while VL not <50 copies/mL, or change in ART; † –8% non-inferiority margin for pooled analysis
ART, antiretroviral therapy; CAR, current antiretroviral regimen; DTG, dolutegravir; ITT-E, intent-to-treat exposed; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine; VL, viral load
Llibre JM et al. CROI 2017. Seattle, WA. #44LB

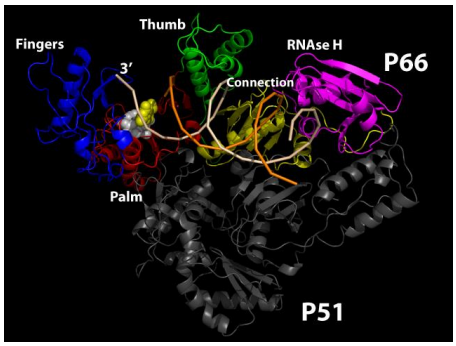
But what if there was resistance is the past ?

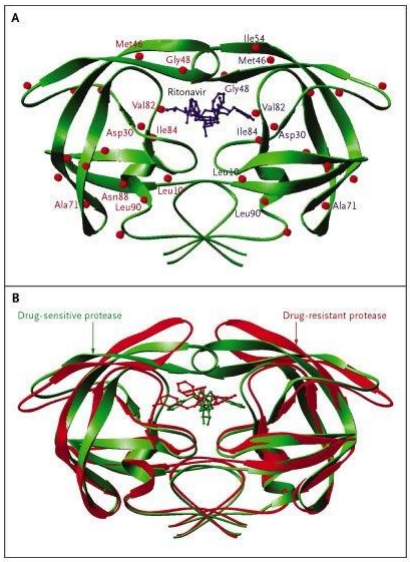


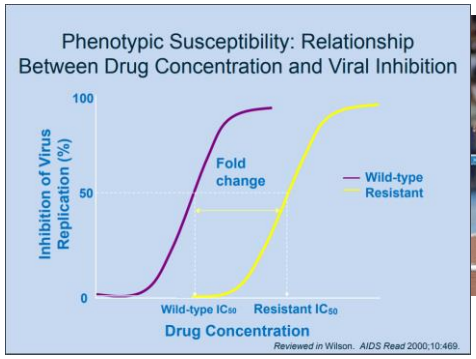
Viral Resistance is the Outcome of Viral Replication, Mutations & Selection Pressure



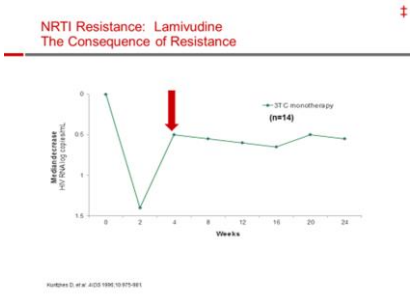
Hirsch. *JAMA* 1998;279:1984.







Overcoming the drug hurdles comes at a fitness cost



SWITCHMRK -1 and -2: Switch From Stable LPV/RTV- to RAL-Based HAART

Stratified by duration of previous lopinavir/ritonavir therapy (≤ vs > 1 yr)

Mean change in lipids at Wk 12

HIV-1 RNA < 50 c/mL at Wk 24

HIV-infected patients with undetectable HIV-1 RNA for ≥ 3 mos on LPV/RTV-based regimen

(Protocol 032: N = 348; Protocol 033: N = 354)

Switch to RAL + LPV/RTV placebo*
(Protocol 032: n = 174;
Protocol 033: n = 176)

Continue LPV/RTV + RAL placebo*
(Protocol 032: n = 174;
Protocol 033: n = 178)

*All patients continued treatment with background regimen including at least 2 NRTIs. No exclusion for number of previous regimens or history of previous virologic failure

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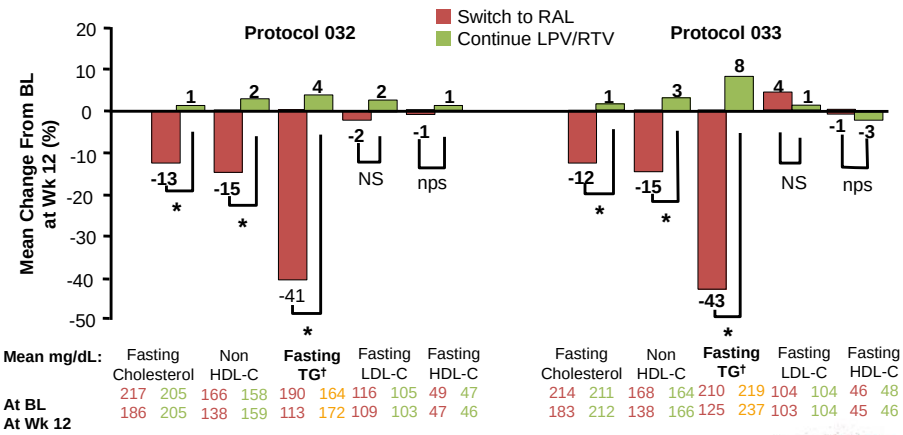
SWITCHMRK -1 and -2: Patient Characteristics at Baseline

Characteristic	Protocol 032		Protocol 033	
	RAL (n = 174)	LPV/RTV (n = 174)	RAL (n = 176)	LPV/RTV (n = 178)
Mean age, yrs	44.4	43.6	42.0	41.9
Female, %	16.1	25.9	22.2	22.5
Nonwhite, %	16.1	19.0	51.7	54.5
HIV-1 RNA ≤ 50 copies/mL, %	94.3	92.5	96.0	95.5
Mean CD4+ cell count, cells/mm^3	478	508	471	482
LPV/RTV use ≤ 1 yr, %	16.7	17.8	17.6	18.5
Median duration of previous ART, yrs (range)	3.3 (0.3-22.3)	3.6 (0.5-20.2)	3.7 (0.5-19.2)	4.6 (0.6-16.3)
Median previous antiretroviral drugs, n (range)	5.0 (4.0-16.0)	5.0 (2.0-15.0)	5.5 (3.0-13.0)	6.0 (4.0-14.0)

Eron J, et al. CROI 2009. Abstract 70aLB

SWITCHMRK -1 and -2: Significant Decrease in Lipids With Switch to RAL



P <. 001. †Median change from BL at Wk 12, %.

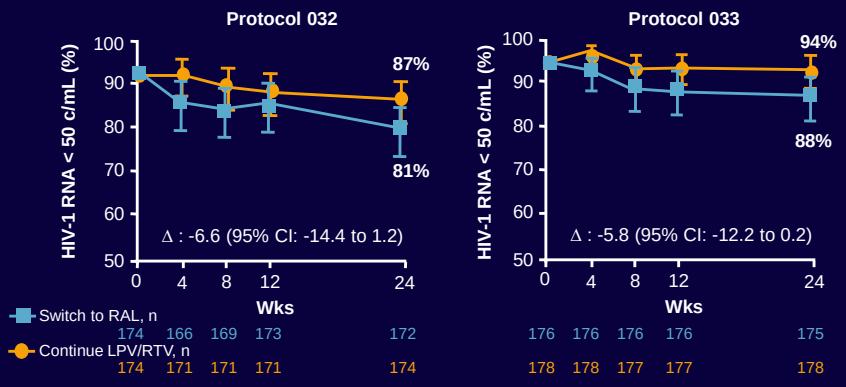
Eron J, et al. CROI 2009. Abstract 70aLB.

Class in Session: Defining the Role of the Newest Class of Antiretrovirals
clinicaloptions.com/hiv

CLINICAL CARE OPTIONS® HIV

SWITCHMRK -1 and -2: Virologic Outcomes at Wk 24, NC = F

- Predefined criteria for noninferiority: lower limit of the 95% CI for treatment difference > -12%



Eron J, et al. CROI 2009. Abstract 70aLB. Adapted with permission of Merck & Co., Inc., Whitehouse Station, New Jersey, USA. Copyright © 2009 Merck & Co., Inc., Whitehouse Station, NJ, USA. All rights reserved.

SWITCHMRK -1 and -2: Virologic Failure and Resistance Analysis

Patients, n	Protocol 032		Protocol 033	
	RAL (n = 174)	LPV/RTV (n = 174)	RAL (n = 176)	LPV/RTV (n = 178)
VF* with HIV-1 RNA > 400 c/mL	3	2†	9†	2
Known RAL resistance	1	0	7	0
PI resistance	0	1	0	2
RTI resistance	3	0	4	1

*Repeat values of > 400 c/mL > 1 wk apart.
†Genotyping not performed on 1 patient.

Eron J, et al. CROI 2009. Abstract 70aLB.liste

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Potential Reasons for Higher VF Rate With Switch to RAL in SWITCHMRK

- In 84% (27/32) of patients with VF in RAL switch arm, LPV/RTV was not first antiretroviral regimen
  - 67% (18/27) experienced previous treatment failure
  - Raises possibility of NRTI-associated resistance at study entry decreasing potency of NRTI backbone
- Study enrolled only patients already tolerating a virologically suppressive LPV/RTV-based regimen
  - Potential that any new adverse effects may have resulted in selective nonadherence to raltegravir component

Eron J, et al. CROI 2009. Abstract 70aLB.

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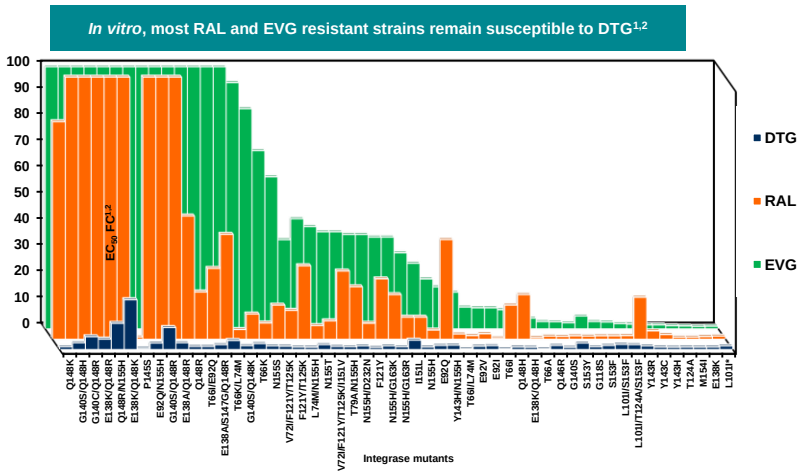
Fold change in EC_{50} against molecular clones with INI substitution "the Wall of Death"

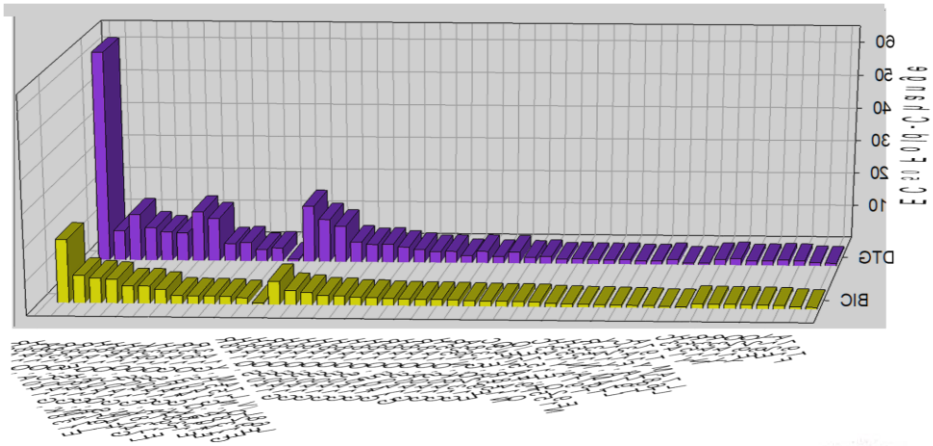
ViiV Healthcare



*Not tested for EVG

1. Adapted from Seki T, et al. CROI 2010. Poster J-122;
2. Adapted from Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21

Bictegravir (BIC) has an Improved Resistance Profile Relative to DTG Against 47 HIV-1 Patient-derived Isolates with INSTI Resistance Mutations



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6

High genetic barriers stop almost everything

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In vitro, most RAL- and EVG-resistant single mutants were susceptible to DTG

Viruses	Mean FC IC_{50} DTG	RAL	EVG
WT[1,2]	1	1	1
T66A[1,2]	0.26	0.61	4.1
T66I[1,2]	0.26	0.51	8.0
T66K[1,2]	2.3	9.6	84
E92I[1,2]	1.5	2.1	8.0
E92Q[1,2]	1.6	3.5	19
E92V[1,2]	1.3	1.4	8.3
G118S[1,2]	1.1	1.2	4.9
F121Y[1,2]	0.81	6.1	36
T124A[1,2]	0.95	0.82	1.2
E138K[1,2]	0.97	1	0.93
G140S[1,2]	0.86	1.1	2.7
Y143C[1,2]	0.95	3.2	1.5
Y143H[1,2]	0.89	1.8	1.5

Viruses	Mean FC IC_{50} DTG	RAL	EVG
Y143R[1,2]	1.4	16	1.8
P145S[1,2]	0.49	0.87	>350
Q146R[1,2]	1.6	1.2	2.8
Q148H[1,2]	0.97	13	7.3
Q148K[1,2]	1.1	83	>1700
Q148R[1,2]	1.2	47	240
I151L[1,2]	3.6	8.4	29
S153F[1,2]	1.6	1.3	2.8
S153Y[1,2]	2.5	1.3	2.3
M154I[1,2]	0.93	0.82	1.1
N155H[1,2]	0.99	8.4	25
N155S[1,2]	1.4	6.2	68
N155T[1,2]	1.9	5.2	39
G193E[2]	1.3	1.3	1.3

3 ≤ FC IC_{50} < 5 | 5 ≤ FC IC_{50} < 10 | 10 ≤ FC IC_{50}

RAL and EVG-related single mutation SDMs

1. Adapted from Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21;
2. Adapted from Seki T, et al. CROI 2010. Abstract 555

Bictegravir (BIC) has an Improved Resistance Profile Relative to DTG Against 47 HIV-1 Patient-derived Isolates with INSTI Resistance Mutations

INSTI Resistance Mutations[a]	Susceptibility (Fold-change vs. WT)[b] BIC	DTG	EVG	RAL
L74M,T97A	0.50	0.64	16	8.48
L68V,Y143C	0.54	0.54	1.9	4.06
L68L/V,L74M,Y143R	0.59	0.74	26	>143
T97A	0.66	0.88	10	1.78
T97A,F121Y	0.80	1.63	>150	112
T97A,Y143R	0.83	1.11	20	>143
F121Y	0.84	1.05	38	12
L74M,N155H	0.90	1.08	103	89
T97A,N155H	0.99	1.51	95	53
T97A,Y143C	1.02	1.35	29	>143
E92Q,E157E/Q	1.16	1.41	51	4.8
E92Q	1.19	1.58	60	18
N155H,E157E/Q	1.23	1.66	28	19
E92Q	1.30	1.73	61	6.7
Y143R	1.39	1.50	2.26	22
Y143R	1.39	1.40	2.19	16
N155H	1.42	2.07	>150	107
Y143C	1.49	1.76	4.24	14
T97A,Y143C	1.60	1.47	42	>143
Q148R,E138A	1.69	2.17	>150	43
N155H,G163R	1.70	1.95	31	15
E92Q,N155H	1.72	3.49	>150	>143
E138K,Q148R	1.80	2.05	>150	54
G140S,Q148H	1.99	3.60	>150	>143

INSTI Resistance Mutations[a]	Susceptibility (Fold-change vs. WT)[b] BIC	DTG	EVG	RAL
E92Q,N155H,G163R	2.02	4.12	>150	>143
G140A,Q148R	2.03	2.22	>150	88
G140S,Q148H	2.03	3.52	>150	>143
G140S,Q148H	2.12	3.44	>150	>143
G140S, Q148H	2.17	4.00	>150	>143
E138K,G140S,Q148H	2.42	3.59	>150	>143
G140S,Q148H	2.46	4.73	>150	>143
G140S,Q148H, G163K	2.48	5.68	>150	>143
G140S,Q148H	2.49	5.56	>150	>143
E138K,G140S,Q148H	2.52	5.34	>150	>143
E138K G140S Q148H	2.62	13	>141	>114
G140S,Q148H	2.92	5.46	>150	>143
G140S,Q148R	3.01	6.15	>150	>143
G140S,Q148H	3.81	11	>150	>143
G140S,Q148H	4.37	13	>150	>143
T97A,G140S,Q148H	4.39	15	>150	>143
E138K,G140C,Q148R	5.32	8.58	>150	>143
L74L/M,G140A,Q148R	5.38	8.81	>150	>143
G140S,Q148R	7.05	17	>150	>143
G140S,Q148H,E138A	7.23	10	>150	>143
T97A,G140S,Q148H	7.62	14	>150	>143
L74M,G140C,Q148R	8.36	9.06	>150	>143
E138K,G140A,Q148K	19	63	>150	>143

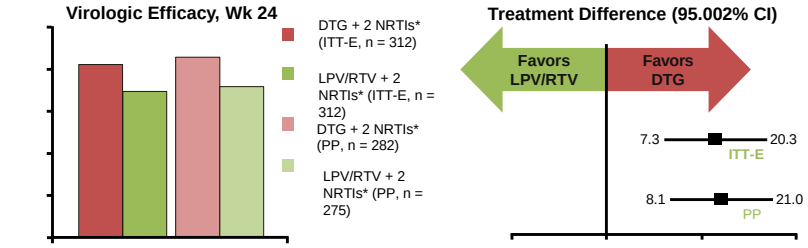
FC ≤ 2.5
FC > 2.5 & ≤ 5
FC > 5 & ≤ 10
FC > 10

[a] Primary and other integrase strand transfer inhibitor resistance (INSTI-R) mutations are listed. Primary INSTI-R mutations are T66I/A/K, E92Q/G, T97A, Y143C/H/R, S147G, Q148H/K/R, N155H, and other INSTI-R mutations are H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q148I/K/L/R, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K in IN.

[b] Susceptibility was determined as the fold-change in EC_{50} vs. NL4-3 wild-type vector by Monogram Biosciences, Inc. The biological or lower clinical cut-offs for reduced susceptibility in this assay are 4.0 for DTG, 1.5 for RAL, and 2.5 for EVG. No cut-off has been determined for BIC.

DAWNING: Second-line DTG vs LPV/RTV + 2 NRTIs in Patients With Virologic Failure

- Interim results of an international, randomized, open-label phase IIIb study of patients with virologic failure after first-line NNRTI + 2 NRTIs in resource-limited settings (N = 627)



*Including at least 1 active NRTI.

Aboud M, et al. IAS 2017. Abstract TUAB0105LB.

Slide credit: clinicaloptions.com

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SAILING: Dolutegravir vs Raltegravir in ART-Exp'd, Integrase Inhibitor–Naive Pts

- Randomized, double-blind, noninferiority, phase III study

Stratified by number of fully active background agents, use of DRV, screening HIV-1 RNA (≤ vs > 50,000 copies/mL)

Wk 48

Treatment-experienced, integrase inhibitor–naive patients with HIV-1 RNA > 400 copies/mL and ≥ 2 class resistance (N = 715)

Dolutegravir 50 mg QD + **Raltegravir placebo** + OBR* (n = 354)

Raltegravir 400 mg BID + **Dolutegravir placebo** + OBR* (n = 361)

*OBR comprising at least 1 and no more than 2 active agents.

Cahn P, et al. Lancet. 2013;382:700-708.

Baseline Characteristics

	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)
Age, median (y)	42	43
Gender, female	30%	34%
Race, white	50%	49%
African American/African heritage	41%	44%
HIV-1 RNA, median (log_{10} c/mL)	4.17	4.21
>50,000 c/mL	30%	29%
CD4+ count, median (cells/mm^3)	205	193
<200 cells/mm^3	49%	51%
HBV/HCV coinfection	14% 81% no infection	18% 75% no infection
Duration prior ART, median (y)	6.7	6.0
≥3 Class resistance	47%	51%
DRV/r in background regimen		
DRV/r use without primary PI mutations	72 (20%)	77 (21%)
No DRV/r use or DRV/r use with primary PI mutations	282 (80%)	284 (79%)

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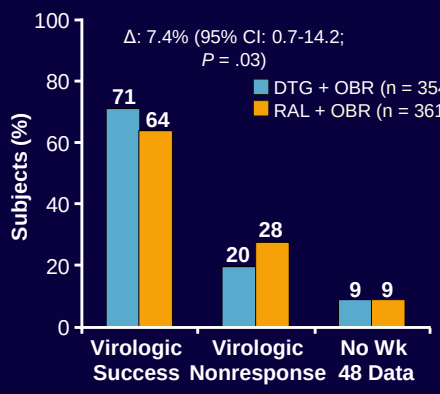
SAILING: Superior Rate of Virologic Suppression With DTG vs RAL at Wk 48



- Lower incidence of resistance at VF with DTG vs RAL
  - Integrase resistance: 1% (4/354) vs 5% (17/361); *P* = .003
  - OBR resistance: 1% (4/354) vs 3% (12/361)
- Both regimens well tolerated with similar AE profiles
  - Grades 2-4: 8% vs 9%
  - Discontinuations: 3% vs 4%
- No difference in outcome between study arms when combined with fully active DRV/RTV

Cahn P, et al. Lancet. 2013;382:700-708.

Insights

- It is possible to successfully switch patients with archived resistance if:
- At least 1 new ARV has a high genetic barrier:
  - Dolutegravir
  - Bictegravir
  - Darunavir- boosted
  - Lopinavir/r

  - At least 1 nRTI is used.

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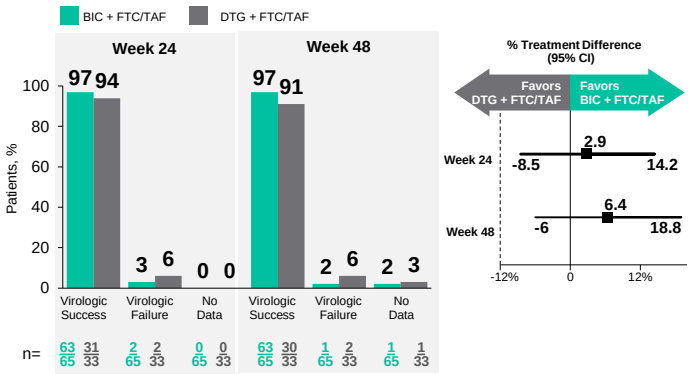
Weeks 24 and 48
Virologic Outcomes (HIV-1 RNA <50 copies/mL)

Study 1475 (Treatment-Naïve Adults): BIC + FTC/TAF Week 48 ‡

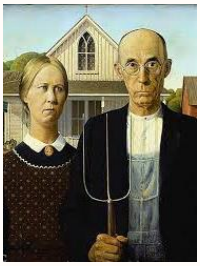


No resistance to study medications was detected in either arm

1. Sax P, et al. CROI 2017. Seattle, WA. Oral #41. 2. Sax P, et al. Lancet HIV 2017. E-Pub Feb. 14, 2017.

69

Learning to let go



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