ARV Guidelines – Optimising Care
Optimising Salvage Therapy

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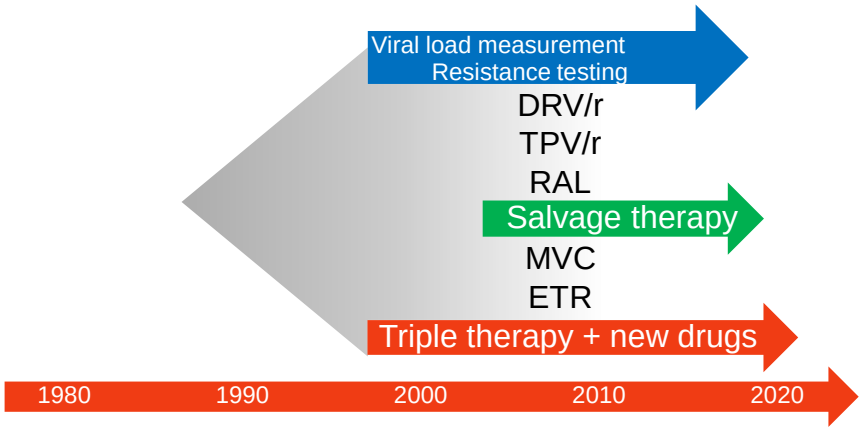
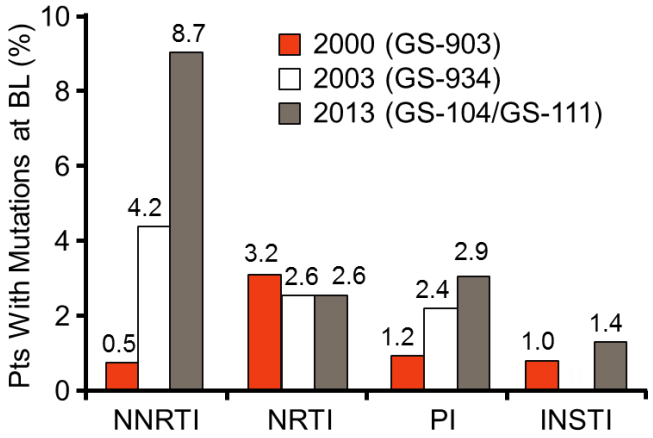
Successful prevention and treatment of resistance development in HIV therapy



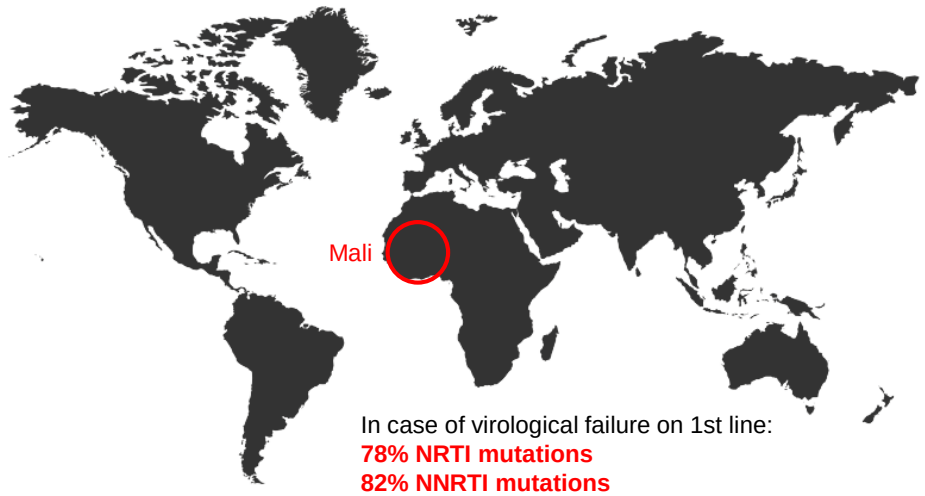
Prevalence of drug resistance mutations in treatment-naive patients, 2000-2013

Baseline plasma samples from 4 phase III trials (GS 903, 934, 104, 111; N = 2531)



Margot NA, et al. CROI 2014. Abstract 578.

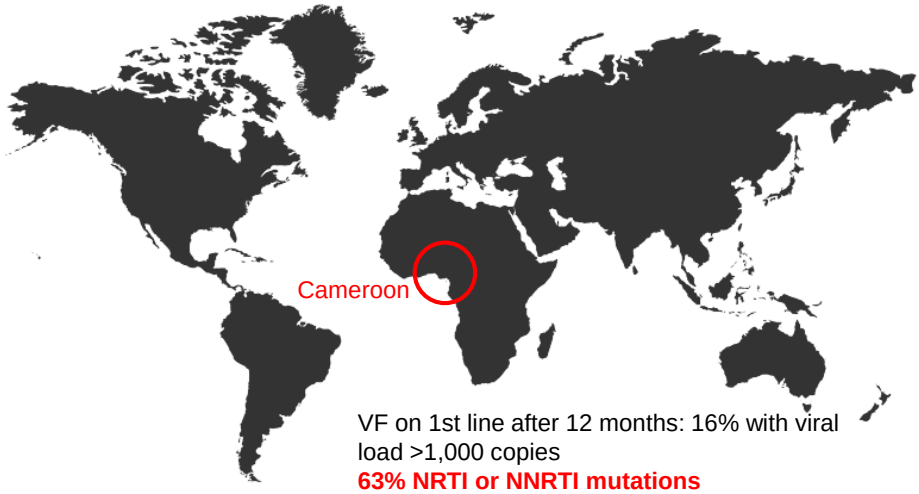
Real life resistance mutations after 1st line virological failure



In case of virological failure on 1st line:
78% NRTI mutations
82% NNRTI mutations

Fofana DB et al. J Antimicrob Chemother 2014; 69:2531-35

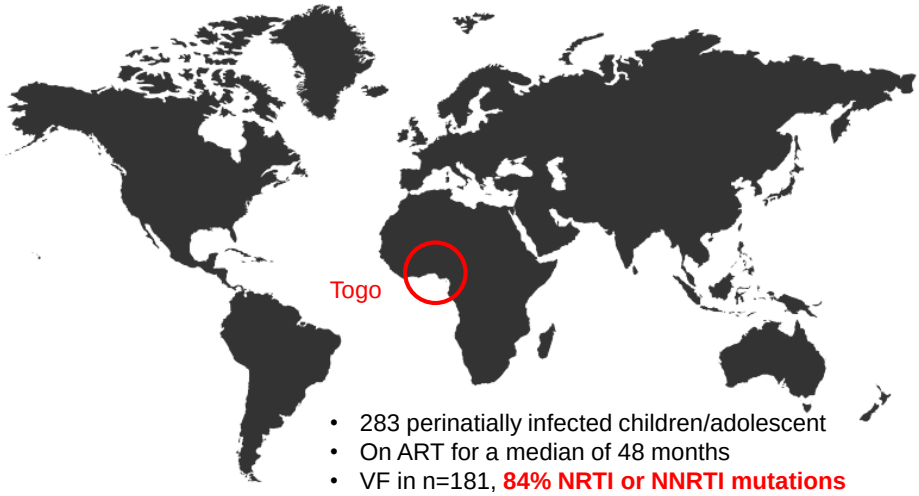
Real life resistance mutations after 1st line virological failure



VF on 1st line after 12 months: 16% with viral load >1,000 copies
63% NRTI or NNRTI mutations

Fofana DB et al. J Antimicrob Chemother 2014; 69:2531-35

Real life resistance mutations after 1st line virological failure



- 283 perinatially infected children/adolescent
- On ART for a median of 48 months
- VF in n=181, **84% NRTI or NNRTI mutations**

Eg; 69:2531-35

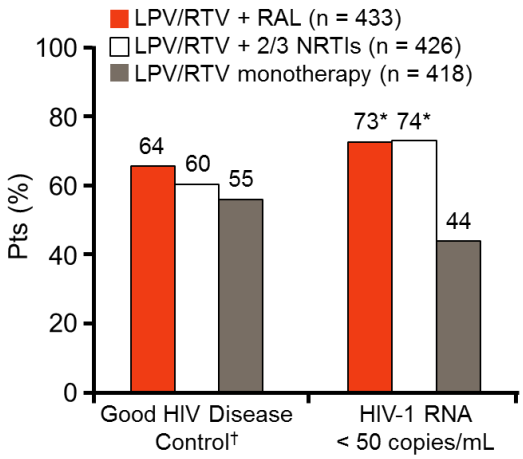
SECOND-LINE: Treament options after failure of NNRTI + 2 NRTI

- 541 patients failing initial therapy randomized to:
  - LPV/r + 2-3 NRTIs selected by genotype
  - LPV/r + RAL

	LPV/r + NRTs (N=271)	LPVr + RAL (N=270)	P
VL <200	219 (81%)	223 (83%)	0.59
VL <50	191 (70%)	192 (71%)	0.56
CD4 increase	114	150	0.01

Boyd M et al. CROI 2013, 180 LB

EARNEST, first-line NNRTI failure: Boosted PI + NRTIs non-inferior to boosted PI + RAL



*P < .0001 vs LPV/RTV monotherapy. †Alive with no new stage 4 events, CD4+ count > 250 cells/mm^3, and HIV-1 RNA < 10,000 c/mL or no PI mutations.

Paton NI, et al. N Engl J Med. 2014;371:234-247

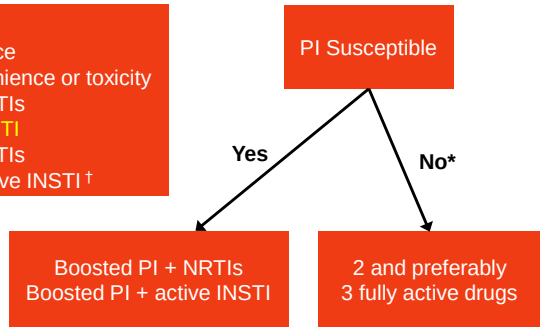
Managing first-line INSTI and second-line and beyond failures

First-line therapy

Failing regimen (+ NRTI)

▪ Boosted PI	Enforce adherence Modify for convenience or toxicity
▪ NNRTI	Boosted PI + NRTIs Boosted PI + INSTI
▪ INSTI	Boosted PI + NRTIs Boosted PI + active INSTI †

Second line and beyond



*Rare in pts never exposed to nonboosted PI. †If RAL or EVG resistance detected, DTG + boosted PI can be used if DTG susceptible.

DHHS Guidelines. April 2015.

Case Report

History

- 18 year-old female
- 60 kg
- 166 cm
- HIV-infected since birth

Other conditions:

- Atopic dermatitis
- Herpes zoster 09/2002
- Lipodystrophy syndrome
- Thrombocytopenia

Case Report

History

- Transition from pediatric into adult care
- Report states:

  „*During the previous three years viral loads in between <50 to 1,600 copies/ml […] CD4 cell counts in between 300 and 430/µl (21-27%). ART is well tolerated and clinically it appears to be a immunologically stable situation.*“

Case Report

History

First visit

- Last three years on:
  - TDF/FTC 1x1
  - Nelfinavir 2 x 5
- Patient just finished school and wants to go to university

Case Report

History

First visit

- Lab values:
  - CD4 cell counts: 326/µl
  - Viral load: 750 copies/ml

Case Report

History

First visit

- Lab:
  - Resistence-associated mutations:
    - Reverse Transcriptase: **M41L**, **D67N**, V118I, M184V, **L210W**, **T215Y**, **K219N**
    - Protease:
      V11I, K20T, M46I, A71I, T74S, L90M
    - Viral load 750 copies/ml

Genotype interpretation with HIV-Grade.de

NRTIs

M41L, **D67N**, V118I, M184V, **L210W**, **T215Y**, **K219N**

NRTI	GRADE_12/2008				ANRS_07/2008			HIVDB_5.1.2			Rega v8.0.1			Final Rating
	Mutation List	Algorithm Result	ADS	SIR	Mutation List	Algorithm Result	SIR	Mutation List	Algorithm Result	SIR	Mutation List	Algorithm Result	SIR	
3TC	M184V	Resistance	0	R	M184V	Resistance	R	M41L, V118I, M184V, L210W, T215Y	High-level resistance	R	M184V	Resistant GSS 0	R	
ABC	M41L, D67N, M184V, L210W, T215Y	Resistance	0	R	M41L, D67N, M184V, L210W, T215Y	Resistance	R	M41L, D67N, V118I, M184V, L210W, T215Y	High-level resistance	R	M41L, D67N, M184V, L210W, T215Y, K219N	Resistant GSS 0	R	
AZT	M41L, D67N, L210W, T215Y	Resistance	0	R	D67N, T215Y, M41L, L210W	Resistance	R	M41L, D67N, V118I, M184V, L210W, T215Y, K219N	High-level resistance	R	M41L, D67N, L210W, T215Y, K219N	Resistant GSS 0	R	
AZT_SP	M41L, L210W, T215Y	Resistance	0	R										
D4T	M41L, D67N, L210W, T215Y	Resistance	0	R	D67N, T215Y, M41L, L210W	Resistance	R	M41L, D67N, V118I, M184V, L210W, T215Y, K219N	High-level resistance	R	D67N, K219N, T215Y, M41L, L210W	Resistant GSS 0	R	
D4T_SP	M41L, L210W, T215Y	Resistance	0	R										
DDI	M41L, D67N, M184V, L210W, T215Y	Resistance	0	R		Susceptible	S	M41L, D67N, V118I, M184V, L210W, T215Y	Intermediate resistance	I	M41L, D67N, L210W, T215Y, K219N	Resistant GSS 0	R	
FTC	M184V	Resistance	0	R	M184V	Resistance	R	M41L, V118I, M184V, L210W, T215Y	High-level resistance	R	M184V	Resistant GSS 0	R	
TDF	D67N, T215Y, M41L, L210W	Resistance	0	R	M41L, D67N, L210W, T215Y	Possible resistance	I	M41L, D67N, V118I, M184V, L210W, T215Y	Intermediate resistance	I	M41L, D67N, L210W, T215Y, K219N	Resistant GSS 0	R	
TDF_SP	M41L, L210W, T215Y	Resistance	0	R										

Genotype interpretation with HIV-Grade.de

NNRTIs

M41L, **D67N**, V118I, M184V, **L210W**, **T215Y**, **K219N**

NNRTI	GRADE_12/2008				ANRS_07/2008			HIVDB_5.1.2			Rega v8.0.1			Final Rating
	Mutation List	Algorithm Result	ADS	SIR	Mutation List	Algorithm Result	SIR	Mutation List	Algorithm Result	SIR	Mutation List	Algorithm Result	SIR	
DLV									Susceptible	S		Susceptible GSS 1	S	
EFV		Susceptible	1	S		Susceptible	S		Susceptible	S		Susceptible GSS 1	S	
ETR		Susceptible	1	S		Susceptible	S		Susceptible	S		Susceptible GSS 1	S	
NVP		Susceptible	1	S		Susceptible	S		Susceptible	S		Susceptible GSS 1	S	

Resistance mutations in plasma RNA and proviral DNA following treatment interruption

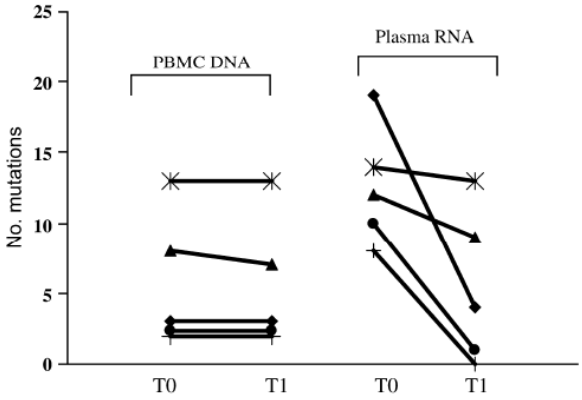


FIGURE 4. Number of drug-resistant mutations in plasma RNA and in PBMC DNA before (T0) and after treatment interruption (T1).

Turriziani et al. AIDS 2007

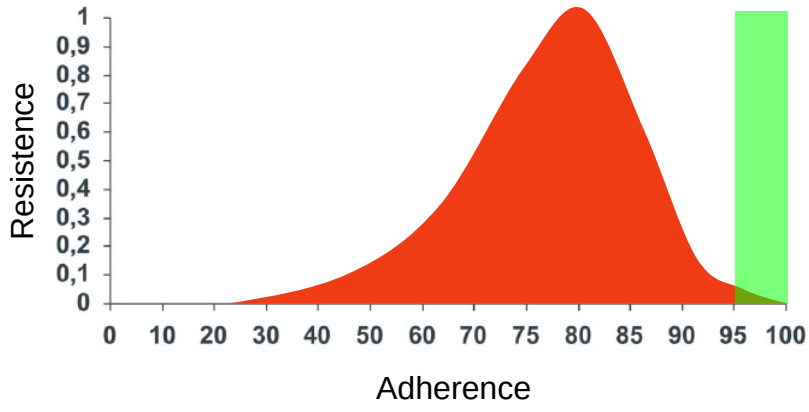
Genotype interpretation with HIV-Grade.de

PIs

V11I, K20T, M46I, A71I, T74S, L90M

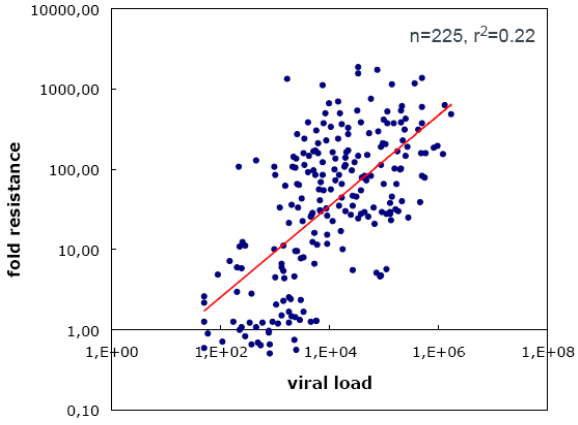
PI	GRADE_07/2010			ANRS_07/2009			HIVDB_6.0.9			Rega v8.0.2			Final Rating
	Mutation List	Algorithm Result	SIR	Mutation List	Algorithm Result	SIR	Mutation List	Algorithm Result	SIR	Mutation List	Algorithm Result	SIR	
APV/FPV	M46I	Intermediate	I							L90M, K43R, K20T, M46I	Susceptible GSS 1	S	
APV/FPV_RTV	M46I, L90M	Intermediate	I		Susceptible	S	V11I, M46I, A71I, L90M	Intermediate resistance	I	L90M, K43R, K20T, M46I	Susceptible GSS 1.5	S	
ATV	L90M	Intermediate	I							K20T, M46I, A71I, T74S, L90M	Intermediate Resistant GSS 0.5	I	
ATV_RTV	L90M	limited susceptibility			Susceptible	S	M46I, A71I, L90M	Intermediate resistance	I	K20T, M46I, A71I, T74S, L90M	Intermediate Resistant GSS 0.75	I	
ATV_SP	L90M	limited susceptibility											
DRV	V11I	Susceptible	S		Susceptible	S	V11I	Susceptible	S	M46I, V11I	Susceptible GSS 1.5	S	
IDV	M46I	Resistance	R	M46I	Resistance	R							
IDV_RTV	M46I, L90M	Resistance	R				M46I, A71I, L90M	Intermediate resistance	I	K20T, K43R, M46I, A71I, T74S, L90M	Resistant GSS 0	R	
LPV	M46I	limited susceptibility			Susceptible	S	M46I, A71I, L90M	Low-level resistance	I	K20T, K43R, M46I, A71I, L90M	Intermediate Resistant GSS 0.75	I	
NFV	L90M	Resistance	R	L90M	Resistance	R	M46I, A71I, T74S, L90M	High-level resistance	R	K20T, K43R, M46I, A71I, T74S, L90M	Resistant GSS 0	R	
SQV	L90M	Intermediate	I										
SQV_RTV	L90M	limited susceptibility			Susceptible	S	M46I, A71I, L90M	Intermediate resistance	I	V11I, K20T, M46I, A71I, T74S, L90M	Resistant GSS 0	R	
SQV_SP	L90M	limited susceptibility											
TPV		Susceptible	S		Susceptible	S	L90M, M46I	Susceptible	S	L90M	Susceptible GSS 1.5	S	

Resistence and Aderence



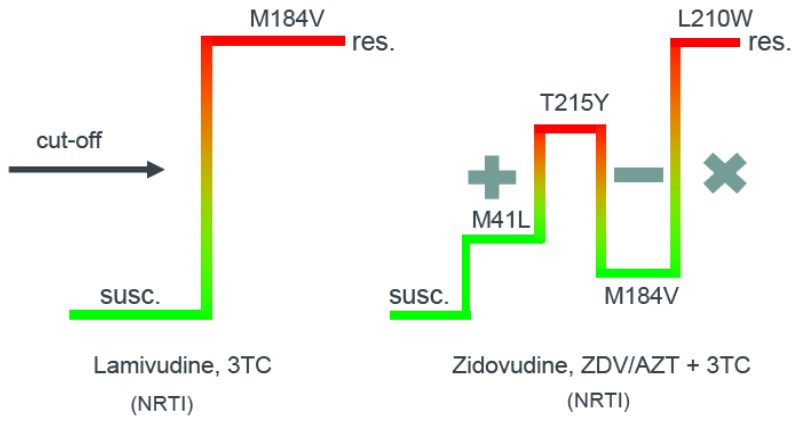
Don‘t wait until it get‘s worse

Correlation of AZT resistance and viral load



Däumer et al. Eur J Med Res 2006

Resistance patterns: addition, subtraction, multiplication



Some possible options (at that time)

- **DRV/r + ETR** + TDF/FTC
- **DRV/r** + **RAL** + 3TC
- **DRV/r** + **RAL**
- **DRV/r** + **ETR**
- **RAL** + **ETR**+ 3TC

Major salvage therapy trials for HIV therapy

	POWER	RESIST	MOTIVATE	BENCHMRK	DUET
Study drug	DRV	TPV	MVC	RAL	ETV
Patients included n=	245	1.509	1.049	701	612
Baseline characteristics					
Median VIL, lg RNA/mL	4,5–4,6	4,7	4,9	4,5–4,7	4,8
Median CD4/µL	153–163	195–196	187–195	102–140	99–109
0-1 active drugs, %	49–55	43–45	38–44	48–51	54
Background therapy					
With *de novo* T-20, %	29–33	18–23	40–44	20	25
With Darunavir, %	100	0	0	25–50	100
With Tipranavir	0	100	14–16	19–23	0
Response					
Total	45 vs. 10	23 vs. 10	44 vs. 17	64 vs. 34	61 vs. 40
With *de novo* T-20, %	58 vs. 11	28 vs. 14	61 vs. 27	84 vs. 62	71 vs. 59
0-1 active drugs, %	37 vs. 1	n.a.	37 vs. 6***	48 vs. 12	57 vs. 24

Case Report

New therapy

- TDF/FTC 1-0-0
- Darunavir 600 mg 1-0-1
- Ritonavir 100 mg 1-0-1
- Etravirine 100 mg 2-0-2

Case Report

Current therapy

Two weeks later

- TDF/FTC 1-0-0
- Darunavir 600 mg 1-0-1
- Ritonavir 100 mg 1-0-1
- Etravirine 100 mg 2-0-2

- Patient reports an itchy generalised exanthema

Case Report

- TDF/FTC 1-0-0
- Darunavir 600 mg 1-0-1
- Ritonavir 100 mg 1-0-1
- Raltegravir 200 mg 1-0-1

New therapy

Case Report

- TDF/FTC 1-0-0
- Darunavir 600 mg 1-0-1
- Ritonavir 100 mg 1-0-1
- Raltegravir 200 mg 1-0-1

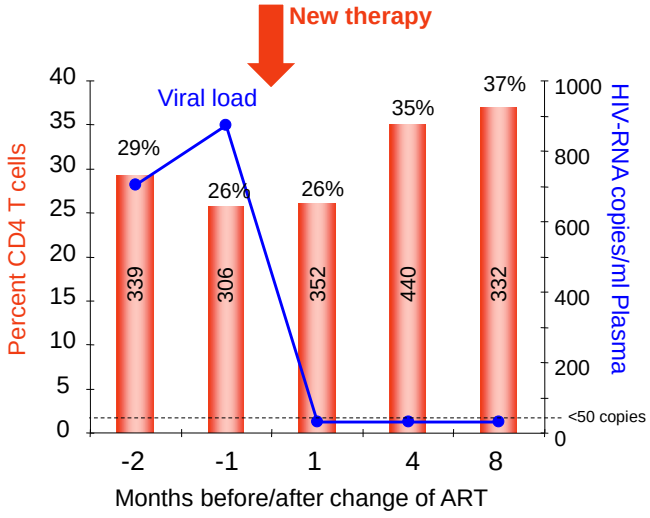
Current therapy

Four weeks later

- Lab values:
  - CD4 cell count: 351/µl (26%)
  - Viral load <50 copies/ml

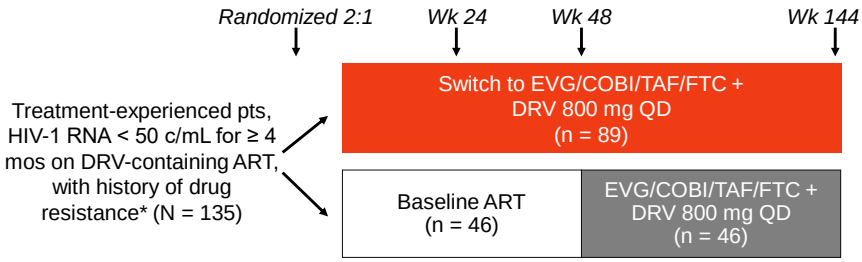
Case Report

Follow up



Study 119: Switch to EVG/COBI/TAF/FTC + DRV in Treatment-Experienced Pts

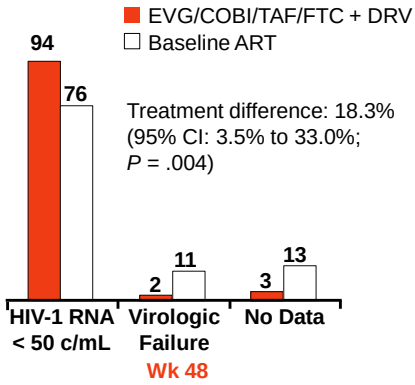
- Multicenter, open-label randomized trial



*Resistance to ≥ 2 ARV classes, including ≤ 3 thymidine analogue mutations and K65R, but not integrase inhibitors, unless currently receiving raltegravir, and no DRV resistance.

Huhn GD, et al. IDWeek 2015. Abstract 726.

Study 119: Virologic Suppression After Switch to EVG/COBI/TAF/FTC + DRV

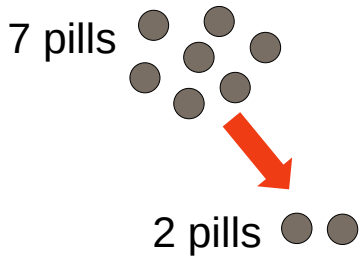


Huhn GD, et al. IDWeek 2015. Abstract 726.

Case Report „Life long“

Current therapy:

- TDF/FTC 1-0-0
- Darunavir 1-0-1
- Ritonavir 1-0-1
- Raltegravir 1-0-1



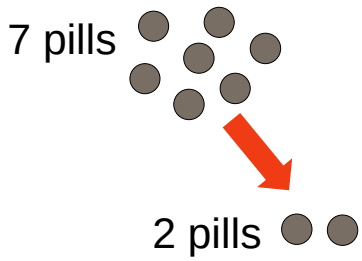
New therapy 2016

- TAF/FTC/EVG/C 1-0-0
- Darunavir 800 mg 1-0-0

Case Report „Life long“

Current therapy:

- TDF/FTC 1-0-0
- Darunavir 1-0-1
- Ritonavir 1-0-1
- Raltegravir 1-0-1



Nuke free option

- Dolutegravir 50 mg 1-0-0
- Darunavir/c 800 mg 1-0-0

ACTG OPTIONS: Are NRTIs necessary in treatment experienced patients?

- 360 pts failing ART w/ NRTI, NNRTI, and PI resistance or experience
- Regimen chosen based on review of ART history, resistance, and tropism
  - PSS >2 required
- Randomized to omit or include NRTIs

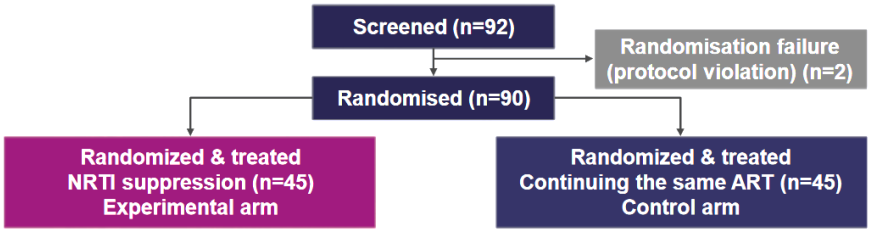
	Omit NRTIs N=179	Include NRTIs N=181
Regimen failure through wk 48	53 (30%)	48 (26%)
VL <50 at wk 48	64%	68%
Severe signs/Sx or lab abnormality	67 (38%)	65 (35%)

(Mostly ETR, RAL, DRV/r ± TDF/FTC)

Tashima K et al. CROI 2013, 153 LB

Withdrawing inactive NRTIs in subjects with suppressed viremia

NRTIs + 2 active drugs, one of them PI/r



NRTIs Removed in the Experimental Arm (n=45)

Removed 1 NRTI (32/45, 71,1%)		Removed 2 NRTIs (13/45, 28,9%)	
Tenofovir	12	Tenofovir + Emtricitabine	9
Emtricitabine	9	Abacavir + Lamivudine	3
Lamivudine	8	Abacavir + Tenofovir	1
Abacavir	2		
Didanosine	1		

Llibre J, et al. 22nd CROI 2015, Seattle

Withdrawing inactive NRTIs in subjects with suppressed viremia, week 48 outcomes

	Experimental (n=45)	Control (n=45)
Virologic Success at Week 48		
HIV-1 RNA <50 copies	41 (91.1%)	44 (97.8%)
Virologic Failure (VF) at Week 48		
HIV-1 RNA ≥50 copies/mL	1 (2.2%)	0
Discontinued due to lack of efficacy	2 (4.4%)	0
No Virologic Data in Week 48 Window		
Discontinued study drug due to AE	1 (2.2%)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA <50 copies/mL	0	1 (2.2%)

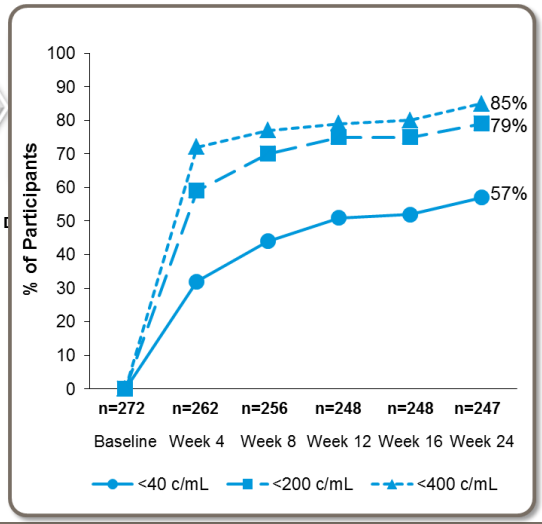
Llibre J, et al. 22nd CROI 2015, Seattle

Fostemsavir in heavily treatment-experienced HIV-1-infected participants

BRIGHTE is an ongoing Phase 3 randomised, placebo-controlled, double blind trial

Randomised Cohort §:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:
- 1 or 2 ARV classes remaining & ≥1 fully active & available agent per class
- Unable to construct viable regimen from remaining agents

Randomised 3:1



Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

Optimising Salvage Therapy