Regimen switching

in the setting of suppressed virus

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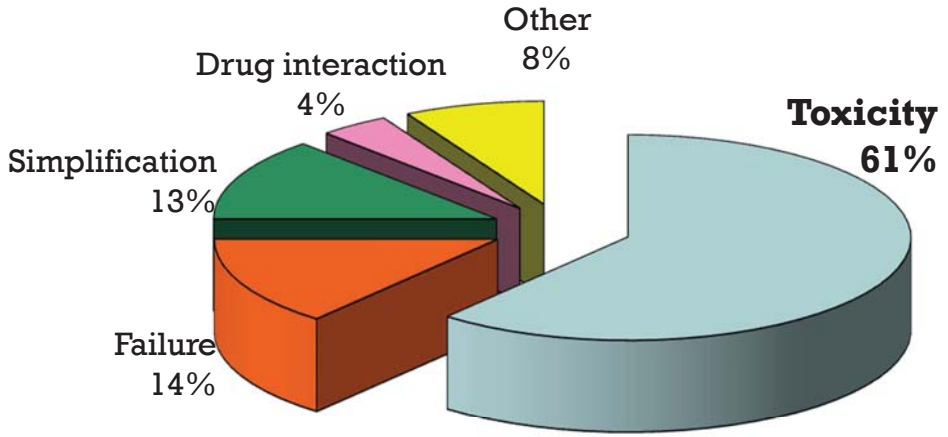
สาเหตุของการเปลี่ยนสูตรยาต้านไวรัส



Davidson I. 13th Annual Conference of British HIV Association with British Infection Society, Edinburgh 2007, #25.

Simplification of ARV regimen

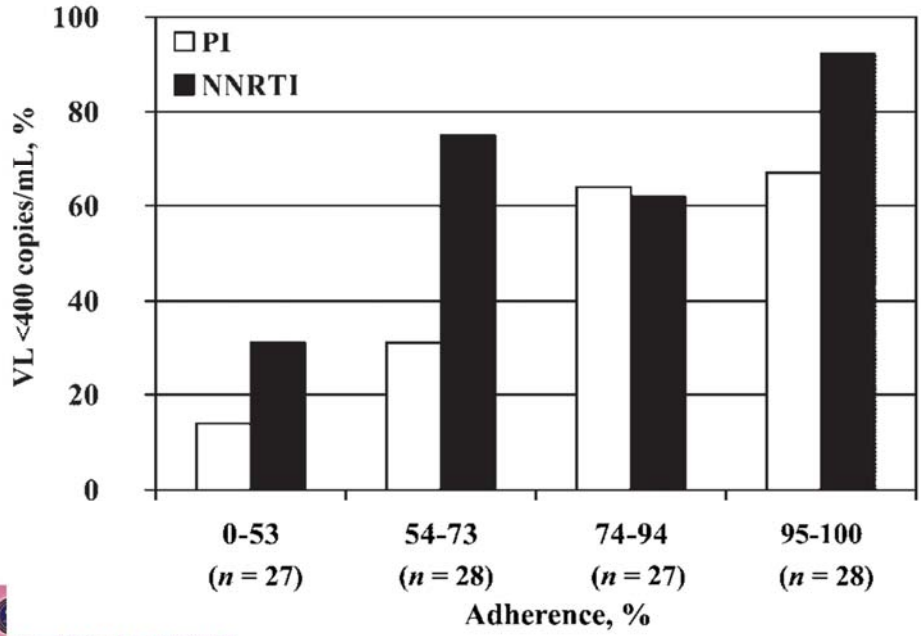
Contents

- Background
- Factors to be considered
- Options
- Conclusion

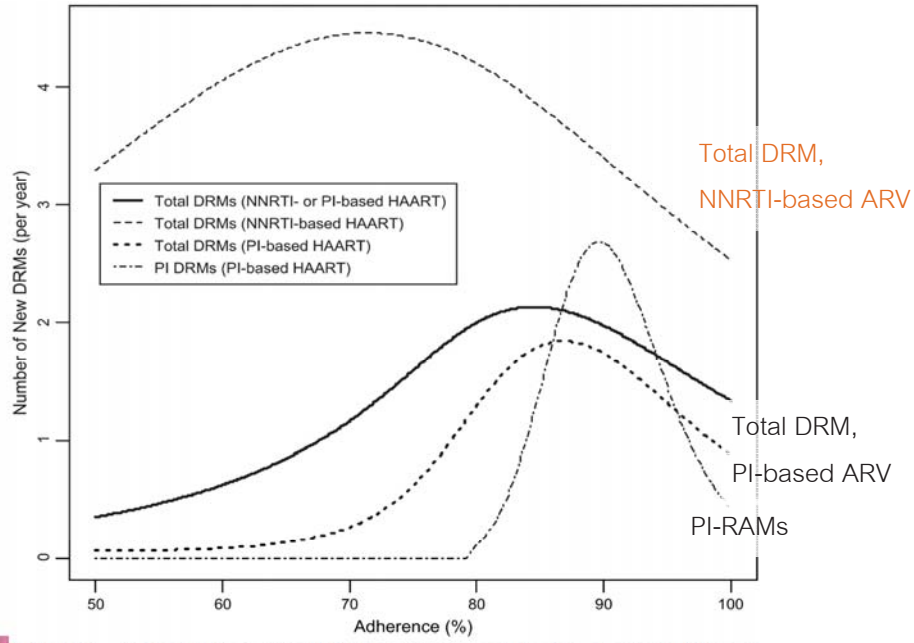
Background of ART simplification

- ART efficacy depended on adherence
- Adherence inversely related to number of doses / day

The proportion of patients with an HIV load < 400 copies/mL, as indicated by unannounced pill count adherence



Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis.* Oct 1 2006;43(7):939-941



Total DRM, NNRTI-based ARV

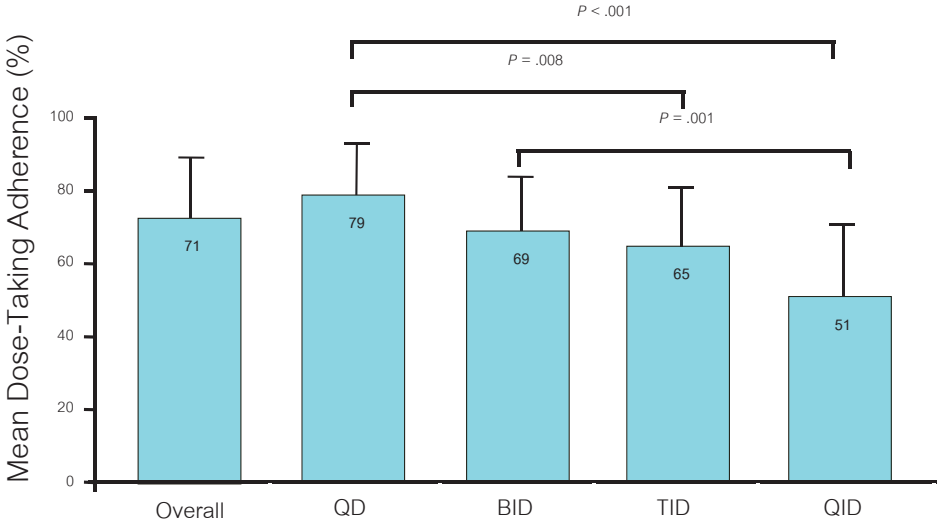
Total DRM, PI-based ARV

PI-RAMs

FIGURE 1. Relationship between HAART adherence and the rate of accumulation of drug resistance mutations (DRMs).

Raffa JD, et al. Intermediate highly active antiretroviral therapy adherence thresholds and empirical models for the development of drug resistance mutations. *J Acquir Immune Defic Syndr.* Mar 1 2008;47(3):397-399

Adherence inversely related to number of doses per day



Studies of Electronic Monitoring of Adherence

Claxton AJ, et al. Clin Ther. 2001;23:1296-1310.

Simplification of ARV regimen

A change in established effective therapy to reduce pill burden and dosing frequency, to enhance tolerability, or to decrease specific food and fluid requirment

DHHS guideline

Contents

- Background
- Factors to be considered
- Options
- Conclusion

Factors to be considered

- Previous ARV resistance
- Previous ARV adverse experiences
- HBV co-infection
- Co-morbidities
- Drug-drug interaction

Contents

- Background
- Factors to be considered
- Options
- Conclusion

Options

- Monotherapy
- Single Tablet Regimen, STR
- Switch to other classes
- Dual therapy

Options

- Monotherapy → PI, INSTI, 3TC
- Single Tablet Regimen, STR
- Switch to other classes
- Dual therapy

PI monotherapy for long-term management of HIV infection

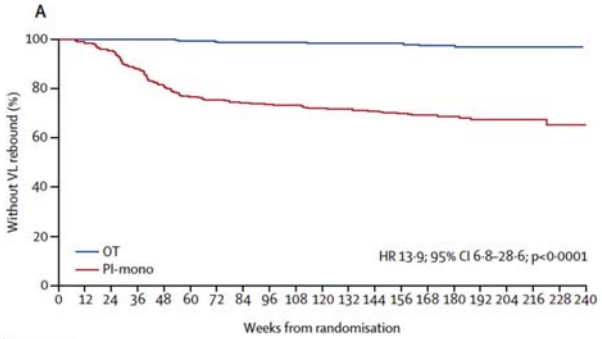
Articles

a randomised, controlled, open-label, non-inferiority trial

587 pts, undetectable VL≥ 24 wks, unchanged ART 12 wks, CD4 ≥100

→ Ongoing Triple therapy

→ PI mono



Paton N. Lancet HIV 2015

PI monotherapy for long-term management of HIV infection

Articles

a randomised, controlled, open-label, non-inferiority trial

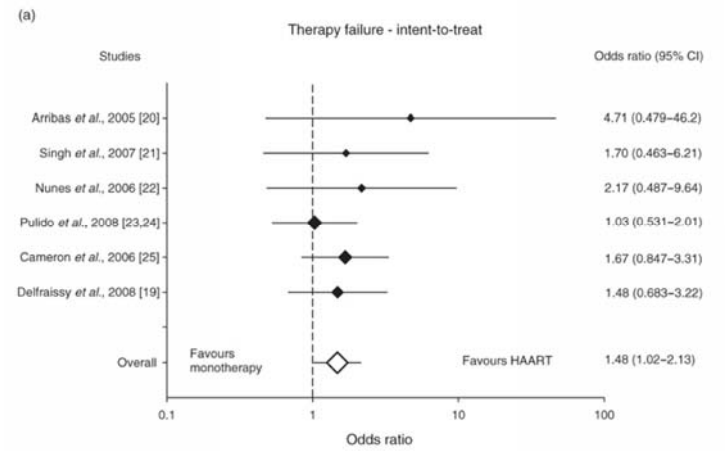
	Drugs received during trial	Reverse transcriptase mutations	Protease mutations	Lost drug options
OT				
1*	ABC, 3TC, ATV	Val118Ile, Val179Asp, Met184Val	Ile84Val	3TC, FTC, ATV, SQV, FPV, TPV
2	TDF, FTC, RPV, DRV	Leu100Ile, Lys103Asn, Met184Val	Ala71Val	3TC, FTC, NVP, EFV, ETV, RPV
3	TDF, FTC, ETV, NVP, EFV, DRV	Lys65Arg, Glu138Ala, Tyr181Cys, Met184Val/Ile, His221Tyr, Met230Leu	..	3TC, FTC, ABC, TDF, NVP, EFV, ETV, RPV
4*	TDF, FTC, DRV	Val106Ala	..	NVP,‡ EFV‡
PI-mono				
5*	ATV	..	Lys20Thr, Ile50Leu/Ile, Ala71Thr	ATV
6*	DRV	..	Leu90Met	SQV†
7*	DRV	..	Ala71Thr, Leu90Met	SQV†
8*	DRV	Lys103Asn	..	NVP,‡ EFV‡
9*	DRV	Lys103Asn	..	NVP,‡ EFV‡
10*	DRV	Met41Leu, Thr215Asp	..	ZDV‡

Individual patients with loss of future drug options by end of trial

Paton N. Lancet HIV 2015

HIV monotherapy with ritonavir-boosted PIs

a systematic review



The overall efficacy of ritonavir-boosted PI monotherapy is inferior to HAART.

The efficacy improves in patients started on monotherapy after suppressed HIV-RNA for at least 6 months.

Ten percent of patients have viral rebound with HIV-RNA levels between 50 - 500 copies/ml

Bierman FWF. AIDS 2009

HIV monotherapy with ritonavir-boosted PIs

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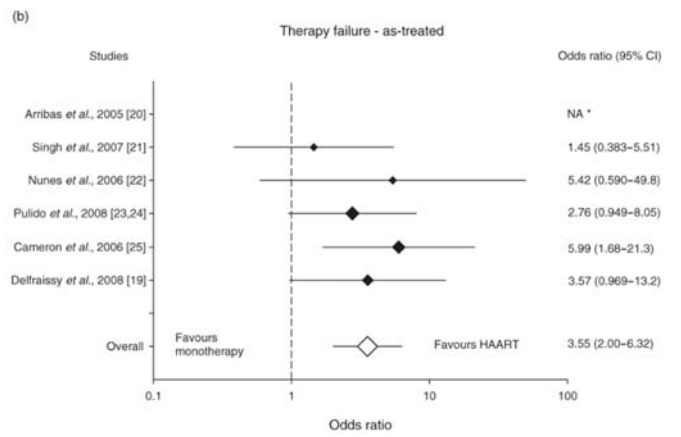

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Bierman FWF. AIDS 2009

Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial

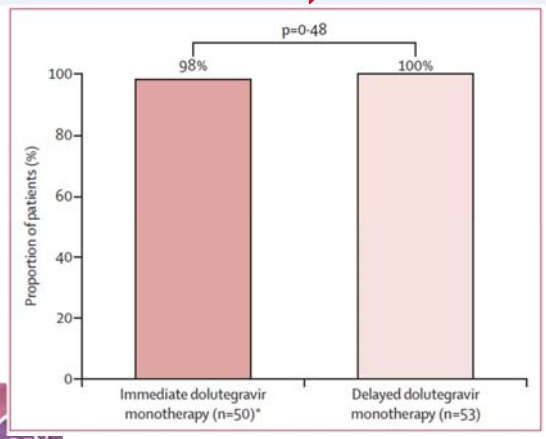
Articles

104 pts, undetectable VL≥ 6 mo,

no Hx of virologic failure

→ switch to DTG mono n=51

→ Cont. cART 24 wks, then DTG n=53

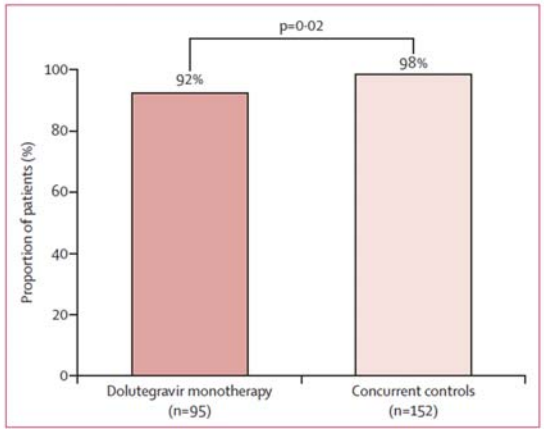


Proportion of patients with virological suppression (VL < 200) at week 24

Wijting I. Lancet HIV 2017

Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial

Articles



F/U at least 48 wks

VF=8; imm sw=6, delayed sw=2

	Duration of monotherapy at time of failure (weeks)	Plasma dolutegravir at failure (mg/mL)†	Self-reported adherence	Integrase sequence at failure
1	4	1·29 (14 h)	>95%	No RAMs
2	12	2·00 (19 h)	>95%	Not successful
3	30	2·59 (16 h)	>95%	No RAMs
4	30	2·96 (22 h)	>95%	Ser230Arg
5	36	1·00 (24 h)	>95%	Not successful
6	48	1·44 (24 h)	>95%	No RAMs
7	60	0·70 (13 h)	>95%‡	Arg263Lys
8	72	2·15 (9 h)	>95%	Asn155His

Proportion of patients with virological suppression in the entire on-tx population on DTG monotherapy compared with concurrent controls

Wijting I. Lancet HIV 2017

Options

- Monotherapy
- Single Tablet Regimen, STR → GPOvir S, Z
  TDF/FTC/EFV
  TDF/FTD/EVG/C
  TAF/FTC/EVG/Cobi + DRV
- Switch to other classes
- Dual therapy

IDAT Week 2018

A randomized, open-label trial to evaluate switching to EVG/Cobi/FTC/TAF+DRV in treatment-experienced pts

135 pts, undetectable VL≥ 4 mo, DRV-based ART, ≥ 2-class ARV-R

- switch to E/C/F/TAF+DRV n=89
- Cont. baseline ART n=46

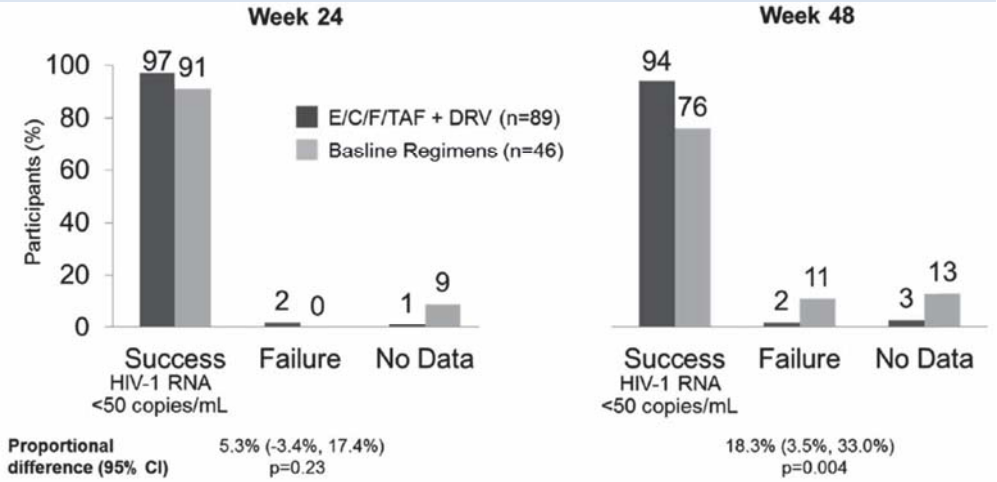
IDAT Week 2018

Huhn GD. JAIDS 2017

TABLE 1. Baseline Demographic and Antiretroviral Regimen Characteristics

	E/C/F/TAF + DRV (n = 89)	Baseline Regimens (n = 46)
Baseline characteristics		
Age, median (range), yrs	49 (29–70)	47 (23–64)
Male, n (%)	73 (82)	28 (61)
Black (or African descent), n (%)	35 (39)	26 (57)
CD4 count, median (range), cells/μL	519	518
Resistance history		
2-class resistance, n (%)	62 (70)	34 (74)
3-class resistance, n (%)	23 (26)	9 (20)
M184V/I, n (%)	76 (85)	36 (78)
K65R, n (%)	18 (20)	14 (30)
NNRTI-R, n (%)	79 (89)	40 (87)
PI-R, n (%)	34 (38)	13 (28)

A randomized, open-label trial to evaluate switching to EVG/Cobi/FTC/TAF+DRV in treatment-experienced pts



Virologic outcome at week 24 and 48.

IDAT Week 2018

Huhn GD. JAIDS 2017

Options

- Monotherapy
- Single Tablet Regimen, STR
- Switch to other classes → PI to NNRTI; PI to INSTI
- Dual therapy

Options

- Monotherapy
- Single Tablet Regimen, STR
- Switch to other classes
- Dual therapy

Options

- Monotherapy
- Single Tablet Regimen, STR
- Switch to other classes
- Dual therapy → PIs + 3TC; PIs + INSTI; INSTI + 3TC; INSTI + NNRTI

Novel TDF- and ABC-Sparing ART Strategies

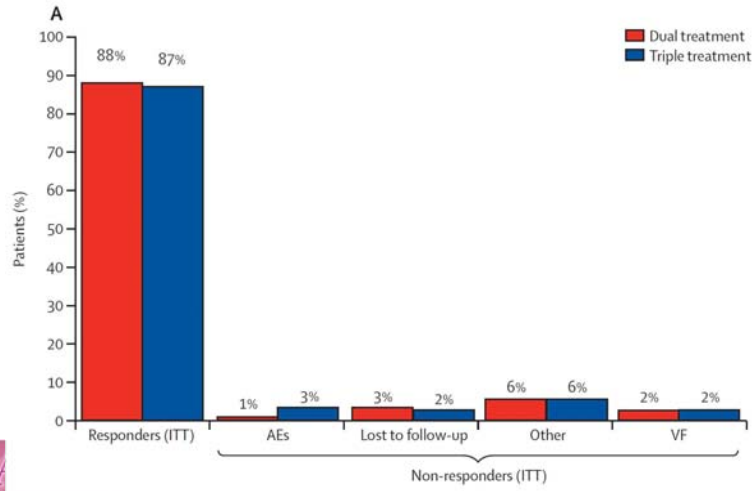
Study	Initial or Switch from suppr. ART	N	Regimen	Results
GARDEL[1]	Initial	426	LPV/RTV + 3TC	Similar efficacy as LPV/RTV + 2 NRTIs
PADDLE[2]	Initial	20	DTG + 3TC	Small study; encouraging efficacy
NEAT001/ ANRS143[3]	Initial	805	DRV/RTV + RAL	Similar efficacy as DRV/RTV + TDF/FTC
SALT[4]	Switch	286	ATV/RTV + 3TC	Similar efficacy as ATV/RTV + 2 NRTIs
ATLAS-M[5]	Switch	266	ATV/RTV + 3TC	Similar (improved in post hoc analysis) efficacy vs ATV/RTV + 2 NRTIs
OLE[6]	Switch	250	LPV/RTV + 3TC	Similar efficacy as cont. standard ART
NA[7]	Switch	48	DRV/RTV + 3TC	Small study; encouraging efficacy
LATTE[8]	Switch	243	CAB + RPV	Similar efficacy as cont. standard ART
LATTE-2[9]	Induction-Maintenance	309	Induct: CAB + ABC/3TC PO; Maint: LA CAB + LA RPV IM	Similar efficacy as cont. oral CAB + ABC/3TC; high pt satisfaction

1. Cahn P, et al. EACS 2015. Abstract 961. 2. Raffi F, et al. Lancet. 2014;384:1942-1951. 3. Figueroa MI, et al. EACS 2015. Abstract 1066. 4. Perez-Molina JA, et al. Lancet Infect Dis. 2015;15:775-784. 5. Di Giambenedetto S, et al. EACS 2015. Abstract 867. 6. Arribas JR, et al. Lancet Infect Dis. 2015;15:785-792. 7. Casado JL, et al. J Antimicrob Chemother. 2015;70:630-632. 8. Margolis DA, et al. Lancet Infect Dis. 2015;15:1145-1155. 9. Margolis DA, et al. CROI 2016. Abstract 31LB.

Slide credit: clinicaloptions.com

Dual treatment with LPV/r + 3TC vs triple treatment with LPV/r + 3TC or FTC + a second NRTI for maintenance (OLE)

a randomised, open-label, non-inferiority trial



Arribas JR. Lancet Infect Dis 2015

3TC + DRV/r as simplification dual regimen

Prospective cohort, n=48, on suppressive HAART

They had received a mean of 3 regimens before (2-20).
In 8 cases, a previous resistance test showed 2-7 secondary mutations in the protease gene, without resistance to DRV/r.

During 104.3 patients-year of follow-up (median 912 days), only 2 patients (4%) failed at 27 and 505 days, due to nonadherence and lost to follow up, respectively.

Luis Casado J, et al.

Switch to DTG + RPV in Suppressed Pts With Multiple Previous Treatment Failures

- Open-label cohort study based in clinical practice setting (N = 38)
  - DTG 50 mg/day + RPV 25 mg/day for pts with long-term virologic suppression but virologic failure on > 1 previous ART regimens

Baseline Characteristic , %	Switch to DTG + RPV (N = 38)	
Regimen at time of switch	NRTI + NNRTI + PI	85
	NRTI + NNRTI + PI + INSTI	53
Reasons for switch to DTG + RPV	Drug–drug interaction	38
	Toxicity	33
	Simplification	25
Pre-existing resistance mutations	NRTI: 65; NNRTI: 37; PI: 32; INSTI: NA	

Slide credit: clinicaloptions.com

Diaz A, et al. AIDS 2016. Abstract TUPDB0106.

Switch to DTG + RPV in Suppressed Pts With Multiple Previous Treatment Failures

Efficacy at 24 weeks

- 88.4% (intention to treat)
- 96.8% (per protocol).

Diaz A, et al. AIDS 2016. Abstract TUPDB0106.

DTG Plus RPV as a Switch Option in cART-Experienced Patients: 96-Week Data

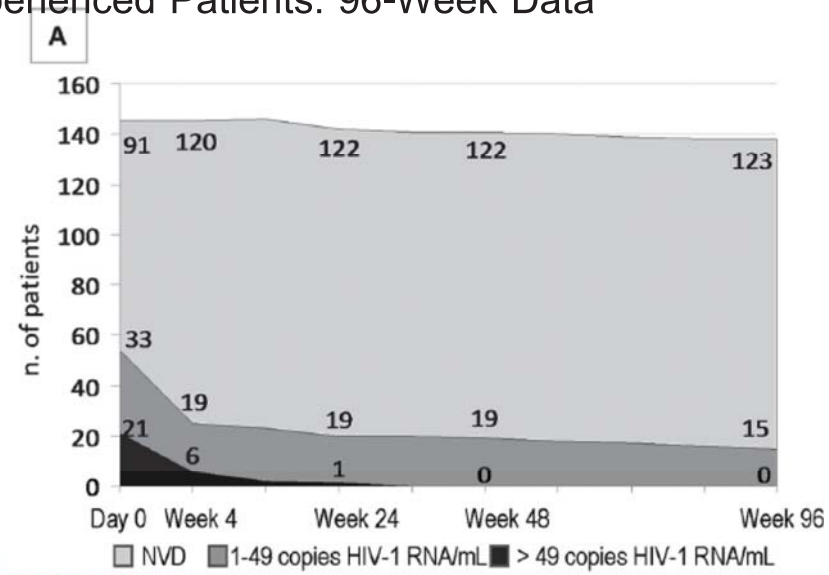
F/U 145 pts who had switched to DTG+RPV

Table 1. Baseline Characteristics of the Study Population.

Demographic parameters	
Age, median [IQR]	52 [44-61]
Virological parameters	
Zenith HIV RNA, $\log_{10}$ copies/mL, median [IQR]	5.11 [4.89-5.43]
Patients with baseline HIV RNA ≥50 copies/mL, n (%)	21 (14.5)
No. of drug classes affected by resistance, n (%): 1:2:3	20 (13.8):32 (22.1):19 (13.1)
Overall resistance to NRTI, n (%)	67 (46.2)
NRTI alone, n (%); NNRTI alone, n (%)	52 (35.9); 1 (0.7)
NRTI + NNRTI, n (%); NRTI + RPV, n (%)	15 (10.3); 6 (4.1)
PI	75 (51.7)
INSTI	1 (0.7)[a]

Capetti AF. Annals of Pharmacotherapy 2018

DTG Plus RPV as a Switch Option in cART-Experienced Patients: 96-Week Data



Capetti AF. Annals of Pharmacotherapy 2018

Conclusion

- Simplify ARV regimen to achieve long-term adherence for the durable maximal viral suppression
- Options of effective simplified ART are available
- The less viral resistances, the more ART options

จะเปลี่ยนสูตรยามั้ยครับ ?

- ให้ข้อมูลข้อดีและข้อเสียของสูตรยาที่ใช้อยู่
- ให้ผู้ป่วยตัดสินใจ
- เรา หรือ เขา ที่ทนสูตรยาปัจจุบันไม่ได้