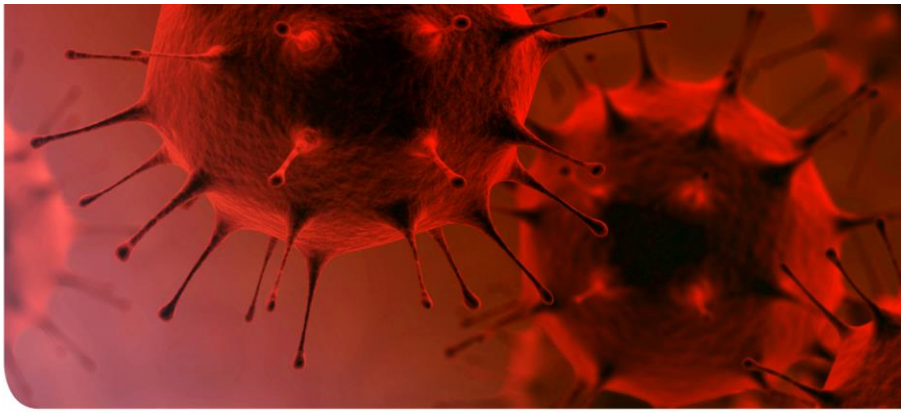


Workshop
Update in ART: Should I stay or should I go?

Don Smith *The Albion Centre, Sydney*
Frederick Lee *Royal Prince Alfred Hospital, Sydney*

12 May 2018

Learning Objectives

- Have an increased understanding of currently used ART regimens in treatment-experienced patients
- Understand the principles of simplifying salvage regimens in suppressed patients with known resistance
- Feel more confident in modifying regimens to minimise toxicity
- Explore factors which must be considered when switching suppressed patients with unclear treatment histories and in the absence of resistance genotypes
- Feel confident to initiate conversations about switch/simplification in treatment-experienced patients

Why Switch?

- In setting of virological control
  - Regimen simplification
  - Improve tolerability & decrease long-term toxicity
  - Lessen chance of drug-drug interactions
  - Pregnancy

- In setting of virological failure & resistant mutants
  - maintain virological suppression
  - Improve tolerability & decrease long-term toxicity
  - Lessen chance of drug-drug interactions

CASE STUDY: TOXICITY

Background

- 65-year-old male
- Diagnosed with HIV-1 infection in 1985
  - Risk factors: MSM only
- Treatment history (incomplete)
  - ZDV monotherapy
  - d4T-ddI + hydroxyurea
  - ZDV-3TC + **IDV** (**nephrolithiasis**)
  - ABC + **TDF** + RAL (**profound asthenia**)
  - ABC-3TC-DTG
- Immunovirological parameters (March 2018)
  - VL<20 copies/mL plasma
  - CD4+ 1.00x10^9 cells/L (27% of lymphocytes)
  - No documented virological failure (wild-type genotype 2008)

Background

- Other history
  - Diabetes mellitus (diagnosed at initial visit, 2017)
  - Prostate cancer & radical resection
  - Obesity
  - Osteoporosis (& lower back pain)
  - Depressed mood
- Concomitant medications
  - Paroxetine
  - Perindopril
  - Rosuvastatin
  - Denosumab
  - Tramadol
  - Esomeprazole
  - Metformin (commenced at initial visit)

Examination

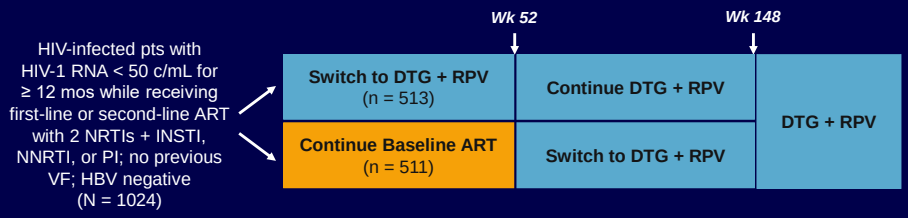
- Blood pressure 140/75 mmHg
- Weight 89.3 kg; BMI 32 kg/m^2
- Adipose tissue
  - Marked subcutaneous lipoatrophy on face & limbs
  - Central abdominal obesity
- Cardio-respiratory examination & urinalysis normal

Management priorities?

- Newly diagnosed diabetes mellitus
  - & other attendant cardiovascular risk
- HIV-1 infection
  - Very treatment experienced
- Prostate cancer
- Other?

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

DOLULAM study: Introduction and methods

- DTG is an INI with potent antiviral activity and a high genetic barrier to resistance
- However, during DTG monotherapy maintenance therapy, viral rebounds with emergence of integrase resistance mutations were observed
- **M184I/V** mutations against 3TC could prevent the emergence of resistance mutations against DTG[1]

Pilot, monocentre cohort study[2]

- **Objective:** To explore the efficacy, safety and tolerability of switching to DTG + 3TC in HIV-1-infected patients who are virologically suppressed

- On a stable ARV regimen with HIV-1 RNA <50 copies/mL for >12 months
- Tolerability issues on current regimen
- No INI-associated resistance mutations*
- Informed consent
- N=27

Switch → DTG 50 mg + 3TC 300 mg QD

Visits and laboratory tests:

- Plasma HIV-1 RNA levels† were scheduled at baseline, W6, W12, W24, W36, W48, then every 12–24 weeks

This study was conducted at the Infectious Diseases Department, Montpellier University Hospital
*Historical RNA Sanger genotypes and DNA Sanger genotypes;
†Roche Cobas Ampliprep/Cobas Taqman HIV-1 v2.0, limit of detection 20 copies/mL

1. Oliveira M *et al* AIDS 2016; 2. Reynes J *et al* IAS 2017 MOPEB0322

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DOLULAM study: Baseline (switch) characteristics

Switch to DTG + 3TC (N=27)		
Age (years): Median (range)	59	41–77
Male: n (%)	20	74%
CD4+ cell counts (cells/mm³)		
Baseline: Median (range)	601	196–153
Nadir: Median (range)	167	8–450
Nadir <200 cells/mm³: n (%)	17	63
Highest HIV-RNA pre-HAART: n (%)		
>300,000 copies/mL	8	30%
100,000–300,000 copies/mL	7	26%
<100,000 copies/mL	11	41%
Not available	1	3%
M184I/V mutations prior to switch		
M184V in historical RNA resistance genotypes	**8**	**30%**
M184V in historical RNA and/or DNA resistance genotypes*	**10**	**37%**
M184I/V combining all available genotype data†	**17**	**63%**
Duration of ARV therapy (months): Median (range)	215	22–329
Duration of last HAART (months): Median (range)	51	13–108
Regimen at switching: n (%)		
TDF-containing regimen	13	48%
PI/r-containing regimen	22	81%
RAL-containing regimen	7	26%

*Sanger technology; †Historical RNA genotypes + DNA Sanger genotypes + baseline DNA UDS genotype

Reynes J *et al* IAS 2017 MOPEB0322

DOLULAM study: Disposition after 2 years

Disposition after 2 years (median follow-up 104 weeks, range 99–117)		
Virologic failure (defined as confirmed viral load >50 copies/mL)	0	
Discontinuations of DTG/3TC combination	3	
Due to adverse event	2*	Stop W16: fatigue, intestinal discomfort Stop W24: fatigue
Patient decision	1†	Intensification at Q18 after blip (W12, 52 copies/mL)
Lost in follow-up	0	
Severe biological adverse event	0	

*The 2 patient returned to last treatment; †W18 (before intensification) viral load <20 copies/mL.
NB: the patient experienced blips before enrolment and after intensification

Reynes J *et al* IAS 2017 MOPEB0322

DOLULAM study: Virological data

Values of plasma HIV-1 RNA	Day 0 Switch n=27	Week 12 n=27	Week 24 n=25	Week 48 n=24	Week 104 n=24
<20 copies/mL, no signal	17 (63%)	21 (78%)	18 (72%)	16 (67%)	20 (83%)
<20 copies/mL, PCR signal	8	5	6	8	4
≥20 copies/mL	2 (21 and 22 copies/mL)	1 (blip: 52 copies/mL)	1 (31 copies/mL)	0	0

- Evolution of CD4 and CD4/CD8 ratio (median increase from baseline to W104): + 23 cells/mm^3, + 0.07
- Evolution of $eGFR_{CKD-EPI}$ median change (range) from baseline:
  - Baseline to W6: –9 mL/min/1.73m^2
  - Baseline to W104: –6 mL/min/1.73m^2

Reynes J *et al* IAS 2017 MOPEB0322

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DOLULAM study: Discussion

- Over 2 years, **all patients remained free from virological failure**, only one patient experienced a blip and two subjects wanted to stop dual therapy for fatigue[1]
- The majority of these heavily treatment-experienced patients, with a previous history of virological failures and adverse events, expressed satisfaction for **simplification** (2 small pills QD) and **absence of symptoms**[1]
- We enrolled patients with excellent adherence and rigorous follow-up. However, many of our patients had potential factors of virological failure (low nadir CD4, high pre-therapeutic viral load, high HIV DNA)[1]
- Prior to switching, an **M184I/V** mutation was detected at least once in RNA/DNA genotypes in 63% of the patients **without detrimental impact** on the efficacy of DTG + 3TC dual therapy[1]
- It is noteworthy that the **M184I** mutation was exclusively present in **defective** viral genomes of the cellular reservoir whereas the **M184V** mutation was mainly detected at the time of previous virological failure in **historical RNA genotypes**[2]

Despite the small sample size, the impressive results of this first pilot study support the concept of a maintenance regimen combining DTG and 3TC in this heavily experienced population[1]

1. Reynes J *et al* IAS 2017 MOPEB0322 ; 2. Charpentier *et al* IAS 2017 MOPEB0315

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CASE STUDY: TREATMENT FAILURE

Case background

- Joseph, 35 year old heterosexual male,
- Living in Iran, Christian, fled persecution,
- Arrested in Turkey, imprisoned and tortured,
- Escaped to Greece and met Australian Iranian GF,
- Applied for asylum and moved to Australia,
- Both found to be HIV+ on immigration screening for PR
- PTSD

- Baseline CD4 430, VL 73,000, WT genotype,
- Smoker, unemployed,
- No social contacts, poor English
- HLA B5701-, normal other bloods,
- Commenced Atripla in 2008,
- Poor attendance and intermittent compliance,
- 2010 VL 5,300 copies.

Genotyping test

GuideLines™ Rules 15.0
RESISTANCE REPORT

Sample ID: 10-4859185
Patient ID: DAC-2848
Patient Name: ASC, 029215
Date Drawn: 04-11-10
Physician: SMITH

St Vincent's Hospital, Sydney
NSW State Reference
Laboratory for HIV/AIDS
Tel: 61 2 8382 9178
Fax: 61 2 8382 2760

Report Date: November 19, 2010 12:19PM

Resistance associated RT Mutations: A62V, K65R*, K101P/Q, K103N, M184V*, K219E, P225H

Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
abacavir (ABC)	Resistance
didanosine (ddI)	Resistance
lamivudine (3TC)/emtricitabine (FTC)	Resistance
stavudine (d4T)	*Possible Resistance*
tenofovir (TDF)	Resistance
zidovudine (AZT)	No Evidence of Resistance

NonNucleoside RT Inhibitors	Resistance Interpretation
efavirenz (EFV)	Resistance
etravirine (ETR)	*Possible Resistance*
nevirapine (NVP)	Resistance

Resistance associated PR Mutations: No relevant mutations detected.

Protease Inhibitors	Resistance Interpretation
atazanavir (ATV)	No Evidence of Resistance
ATV/r **	No Evidence of Resistance
darunavir + ritonavir (DRV/r)	No Evidence of Resistance
fosamprenavir (FPV)	No Evidence of Resistance
FPV/r **	No Evidence of Resistance
indinavir (IDV)	No Evidence of Resistance
IDV/r **	No Evidence of Resistance
lopinavir + ritonavir (LPV/r)	No Evidence of Resistance
nelfinavir (NFV)	No Evidence of Resistance
saquinavir + ritonavir (SQV/r)	No Evidence of Resistance
tipranavir + ritonavir (TPV/r)	No Evidence of Resistance

** Protease Inhibitors administered with low-dose ritonavir for pharmacological boosting.

SUMMARY REPORT

	DRUGS		FOLD[1] CHANGE	CUT-OFF[2]		RESISTANCE ANALYSIS[3]	CLINICAL NOTES (see p2 for details)
	NRTI / NtRTI mutations[4]: 62wt/V, 65wt/R, 184V, 219wt/E						
NRTI/NtRTI	Retrovir®	Zidovudine	0.8	1.5	11.4	MAXIMAL RESPONSE	
NRTI/NtRTI	Epivir®	Lamivudine	46.6	2.1	4.6	MINIMAL RESPONSE	
NRTI/NtRTI	Videx®	Didanosine	3.2	0.9	2.6	MINIMAL RESPONSE	
NRTI/NtRTI	Zerit®	Stavudine	1.0	1.0	2.3	MAXIMAL RESPONSE	
NRTI/NtRTI	Ziagen®	Abacavir	4.0	0.9	3.5	MINIMAL RESPONSE	
NRTI/NtRTI	Emtriva®	Emtricitabine	41.1	3.1		RESISTANT	
NRTI/NtRTI	Viread®	Tenofovir DF	1.7	1.0	2.3	REDUCED RESPONSE	
	NNRTI mutations[4]: 101P/Q, 103N, 225wt/H						
NNRTI	Viramune®	Nevirapine	72.1	6.0		RESISTANT	
NNRTI	Sustiva® , Stocrin®	Efavirenz	>999.9	3.3		RESISTANT	
NNRTI	intelence™	Etravirine	190.4	3.2	27.6	MINIMAL RESPONSE	Note 2
	PI mutations[4]: 15V, 72V						
PI	Crixivan ®; boosted	Indinavir/r	0.6	2.3	27.2	MAXIMAL RESPONSE	
PI	Viracept®	Nelfinavir	0.7	2.2	9.4	SUSCEPTIBLE	Note 1
PI	Invirase®; boosted	Saquinavir/r	0.6	3.1	22.6	MAXIMAL RESPONSE	
PI	Lexiva®,Telzir®; boosted	Fosamprenavir/r	0.5	1.5	19.5	MAXIMAL RESPONSE	
PI	Kaletra®	Lopinavir/r	0.7	6.1	51.2	MAXIMAL RESPONSE	
PI	Reyataz®; boosted	Atazanavir/r	0.5	2.5	32.5	MAXIMAL RESPONSE	
PI	Aptivus®; boosted	Tipranavir/r	0.8	1.5	7.0	MAXIMAL RESPONSE	Note 2
PI	Prezista™; boosted	Darunavir/r	0.6	10.0	106.9	MAXIMAL RESPONSE	

Case study, resistance from poor adherence

- Switched to dolutegravir +darunavir/r
- Variable adherence,
- 2017 dolutegravir + darunavir/c

- Now VL <20 -<50,
- Improved English
- Working as Uber driver
- Still smoking, now 45

- Any better ARV options?

Advising remote colleagues

- Teleconf with patient and Dr K.
- Currently ARV of Kivexa, Kaletra, VL <20 but keen for once daily option as does shift work and heard better options around.
- Also hypercholesterolaemia, smoker, overweight.
- Past ARVs:
- AZT/3TC/saquinavir *but viral failure*,
- d4T/ddI, nevirapine *also viral failure*
- tenofovir/kivexa/kaletra, *suppressed but creatinine creep*.
- kivexa/kaletra.

- Treated for HCV last year, now SVR12.