Treatment Failure Workshop

Dr John Evans-Jones
Countess of Chester Hospital
Dr Iain Reeves
Homerton Hospital

Outline

- Introduction: the role of the Multidisciplinary Team (MDT) in antiretroviral prescribing
- 3 x Case Presentations (JEJ) , each followed by voting (BHIVA audience), and then by commentary (IR)
- Mock MDT format

Multidisciplinary Teams

(BHIVA Standards of for people living with HIV in 2013)

Standard 3 -Provision of outpatient treatment and care for HIV, and access to care for complex comorbidity

"Evidence of a care pathway to demonstrate that all patients who have detectable HIV viraemia and two-class or greater and/or HIV multi-drug resistance have their case reviewed directly or remotely (by virtual clinic) by a multidisciplinary team consisting of at least one consultant virologist, two HIV consultants and a specialist HIV pharmacist. Evidence should be available to demonstrate that patients are reviewed via this clinic"

Infection Pharmacology Group

HIV Network

Guidelines & Policies

Virtual Clinic - Resources

Referrals to Royal Liverpool University Hospital

Expanded Access Drugs

Living Wills

Mersey Network

Merseyside , Cheshire and North Wales HIV Managed Care Network

Central site or 'hub' at Royal Liverpool University Hospital

Peripheral or 'spoke' site

Meeting Layouts Pods Audio Help

e case presentation Dec 2014.ppt Draw Stop Sharing

19th Dec 2014

27y man from Angola
2004 arrived in UK
2006 HIV diagnosed: baseline CD4 550
2009-2013 DNA
April 2013 started Atripla

Nadir CD4	136
Current CD4	345 (9%)
Co-infections	Previous Hepatitis B
OIs	None
CVS risk	
eGFR	>90

Sync

Attendees (1)
Active Speakers
Hosts (1)
Mas Chaponda
Presenters (0)
Participants (0)

Video
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Sharing
Discussion
Collabo...

Size
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Chat 3 (Everyone)
Everyone

Case 1 -March 2014

- 47 year old MSM
- Diagnosed 1995
- Recruited to UK HIV seroconverters study (negative test 1994)
- Kaposi`s Sarcoma (cutaneous) – 2000 (RTx)
- Eczema
- Non-HIV medications – Tadalafil, Dermovate Cream, Betamethasone scalp, Emollients

Case 1- March 2014

- Current CD4 462
- Current HIV Viral Load 338
- ART regimen at MDT referral: Kivexa / Atazanavir/Ritonavir
- No concerns about adherence
- Tropism R5
- HLAB5701: negative
- Hep B/C - negative

Case 1- March 2014

- Past ARV History

Previous HIV Medication	Start	Stop	Reason for discontinuation
Kivexa / Atazanavir / Ritonavir	Feb 2014	Mar 2014	NRTI resistance mutations identified
Kivexa / Darunavir / Ritonavir	Feb 2014	Feb 2014 (16 days)	Insomnia / paraesthesia
Kivexa / Nevirapine	May 2010	Feb 2014	Low level viraemia (also changed from 400mg od to 200mg bd Jan 2013 for same reason)
Truvada / Nevirapine	Dec 2009	May 2010	Diabetes insipidus secondary to Tenofovir
Trizivir	Oct 2009	Dec 2009	Risk of lipodystrophy
Atripla	Dec 2008	Oct 2009	Sleep disturbance
Trizivir	Mar 2001	Dec 2008	Risk of lipodystrophy

Case 1- March 2014

HIV PARAMETERS				
Date	CD4 (abs)	CD4 (%)	Viral Load (copies/ml)	
25.03.14	-	-	101	
25.02.14	462	27	338	**Retrospective resistance test**
26.11.13	289	29	354	
15.08.13	-	-	281	
21.02.13	573	32	50	**Nevirapine to bd**
30.10.12	579	35	90	
26.07.12	**548**	**27**	**<400**	

Stanford - Protease

HIVdb: Genotypic Resistance Interpretation Algorithm

Report: BHIVA Date: Nov 2015

Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	None
PI Minor Resistance Mutations:	**A71AT**
Other Mutations:	E35D, N37D, K43R, Q61E, L63P, V77I, V82IV, I93L

Protease Inhibitors

atazanavir/r (ATV/r)	Susceptible
darunavir/r (DRV/r)	Susceptible
fosamprenavir/r (FPV/r)	Susceptible
indinavir/r (IDV/r)	Susceptible
lopinavir/r (LPV/r)	Susceptible
nelfinavir (NFV)	Susceptible
saquinavir/r (SQV/r)	Susceptible
tipranavir/r (TPV/r)	Susceptible

Stanford – Reverse Transcriptase

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**M41L, D67DG, M184V, L210W, T215Y, K219EK**
NNRTI Resistance Mutations:	**V90I, K103N**
Other Mutations:	M16LM, K20R, V21I, E28EG, V35M, T39A, V60I, S68G, D123N, I135T, I178L, E203K, Q207A, R211K, K238R, A272P, K311R, S322AT, I329IL, G333EG, Q334HQ

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	High-level resistance	efavirenz (EFV)	High-level resistance
abacavir (ABC)	High-level resistance	etravirine (ETR)	Susceptible
zidovudine (AZT)	High-level resistance	nevirapine (NVP)	High-level resistance
stavudine (D4T)	High-level resistance	rilpivirine (RPV)	Susceptible
didanosine (DDI)	High-level resistance		
emtricitabine (FTC)	High-level resistance		
tenofovir (TDF)	High-level resistance		

Question 1: It is March 2014, what should the MDT recommend ?

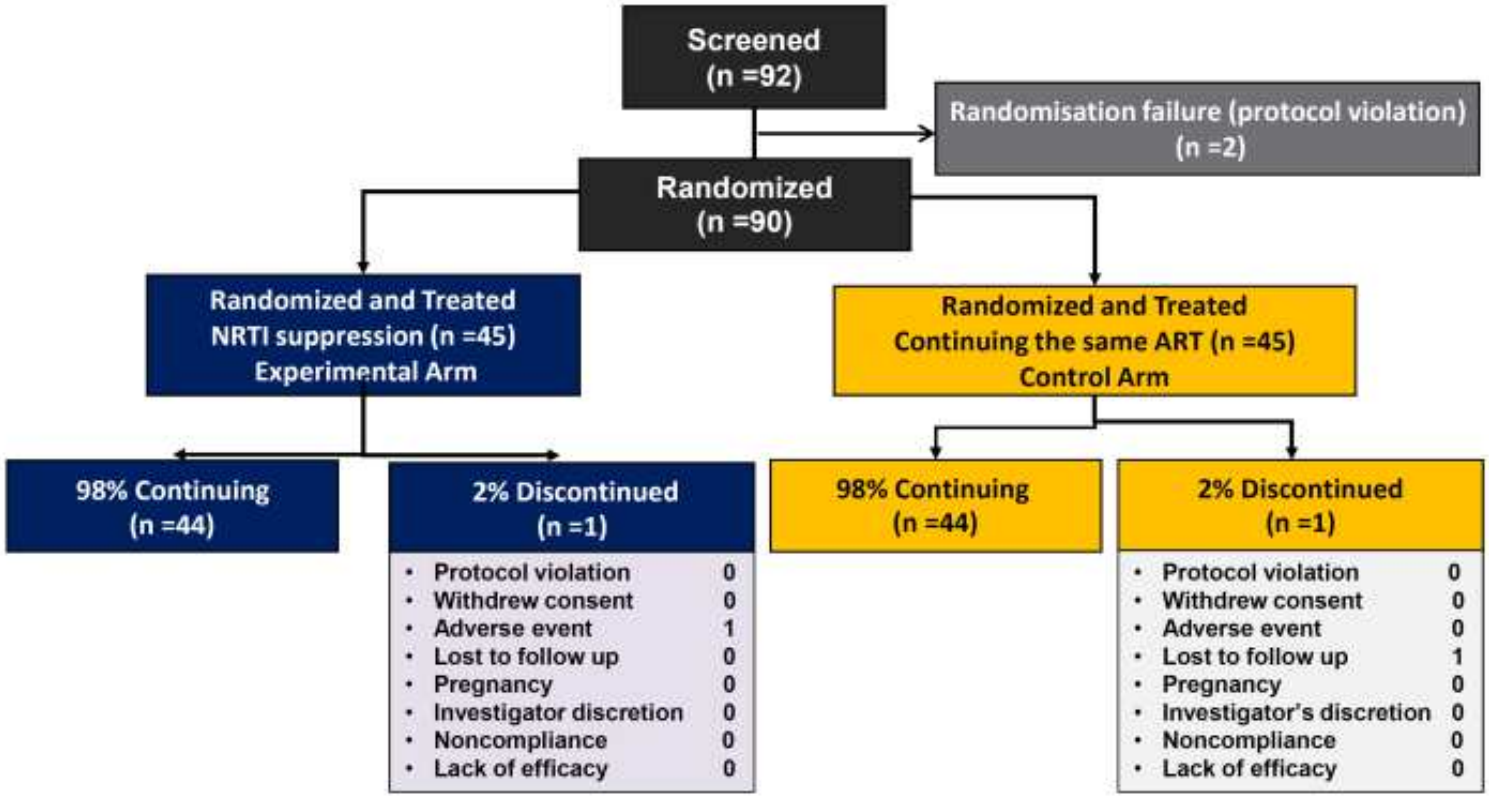
1. Kivexa/Atazanavir/Ritonavir/Raltegravir
2. Kivexa/Atazanavir/Ritonavir/Maraviroc
3. Etravirine/Atazanavir/Ritonavir/Raltegravir
4. Atazanavir/Ritonavir/Raltegravir
5. Atazanavir /Ritonavir/ Raltegravir/ Maraviroc
6. Something else ? (you will be asked to specify !)

ACTG (A5241) OPTIONS study

- N = 360 on failing PI based regimen with past experience or resistance to NRTI and NNRTI
- New regimen constructed after resistance and tropism testing
- Patient / clinician selection of NRTI but open label randomisation to inclusion or not of this backbone
- Non-inferiority met, BUT:
  - Median phenotypic sensitivity score of new regimen = 3

Tashima et al, Abs 153LB CROI 2013

Keep the NRTIs in or not?



- Subjects with VL <50 for 6 months, on ≥ 2 active drugs, including PI/r
- Randomised to stop vs continue inactive NRTI in regimen

Llibre et al, P553, CROI 2015

Llibre et al: mutations

	Control	NRTI withdrawal
Patients with previous DRMs to NRTIs (n, %)		
M184V/I	77.8%	86.6%
L74I/V	8 (18)	8 (18)
K65R	-	4 (9)
K65R	0	9%
T69D/S/N	4 (8.9)	13 (28.9)
V75A/I	5 (11.1)	4 (9)
Q151M	2 (4)	2 (4)
Y115F	2 (4)	1 (2)
Thymidine-associated mutations		
M41L	38%	57.8%
L210W	36%	48.9%
T215F/Y	46.7%	56.7%
K219E/N/Q/R/T/W	13 (28.9)	16 (35.6)

Results: Llibre et al 2015

- Non-inferiority met:
  - Wk 48 VL <50 = **97.8% vs 91.1%** (Control vs Withdrawal)
- Virological failure for 6.6% on NRTI withdrawal arm
  - 1 patient developed new integrase resistance
- No difference in AEs reported

ATTN: DR JOHN EVANS-JONES.

Chester case

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25 MAR 2014

MERSEY, CHESHIRE & NORTH WALES HIV NETWORK

HIV CASE DISCUSSION MEETING OUTCOME REPORT

21ST MARCH 2014

Patient: 46 Diagnosed in 1995

Antiretroviral mutations identified	Other issues
- Drug Hx Trivizir → Atripla → Trizivir → Truvada/NVP → Kivexa/Nevirapine → Kivexa/DRV/r → Kivexa/ATZ/r. - No baseline resistance test. - Recent test: NRTI - M41L/D67DG/M184V/L210W/T215Y/K219EK. NNRTI - V90I/K103N	- Cutaneous Kaposi in 2000. - Current CD4 520. - Low level viraemia
Outcome - currently on "PI monotherapy" (given resistance test result) for 3/52 Suggestion: - Atazanavir/ritonavir/Etravirine/Raltegravir as BD regime. - wait for tropism test result - maraviroc as reserve.	

Signed: SpR Dr N. Hude. M. Fadzilah. GUM SpR.

Outcome - currently on "PI monotherapy" (given resistance test result) for 3/52

Suggestion:

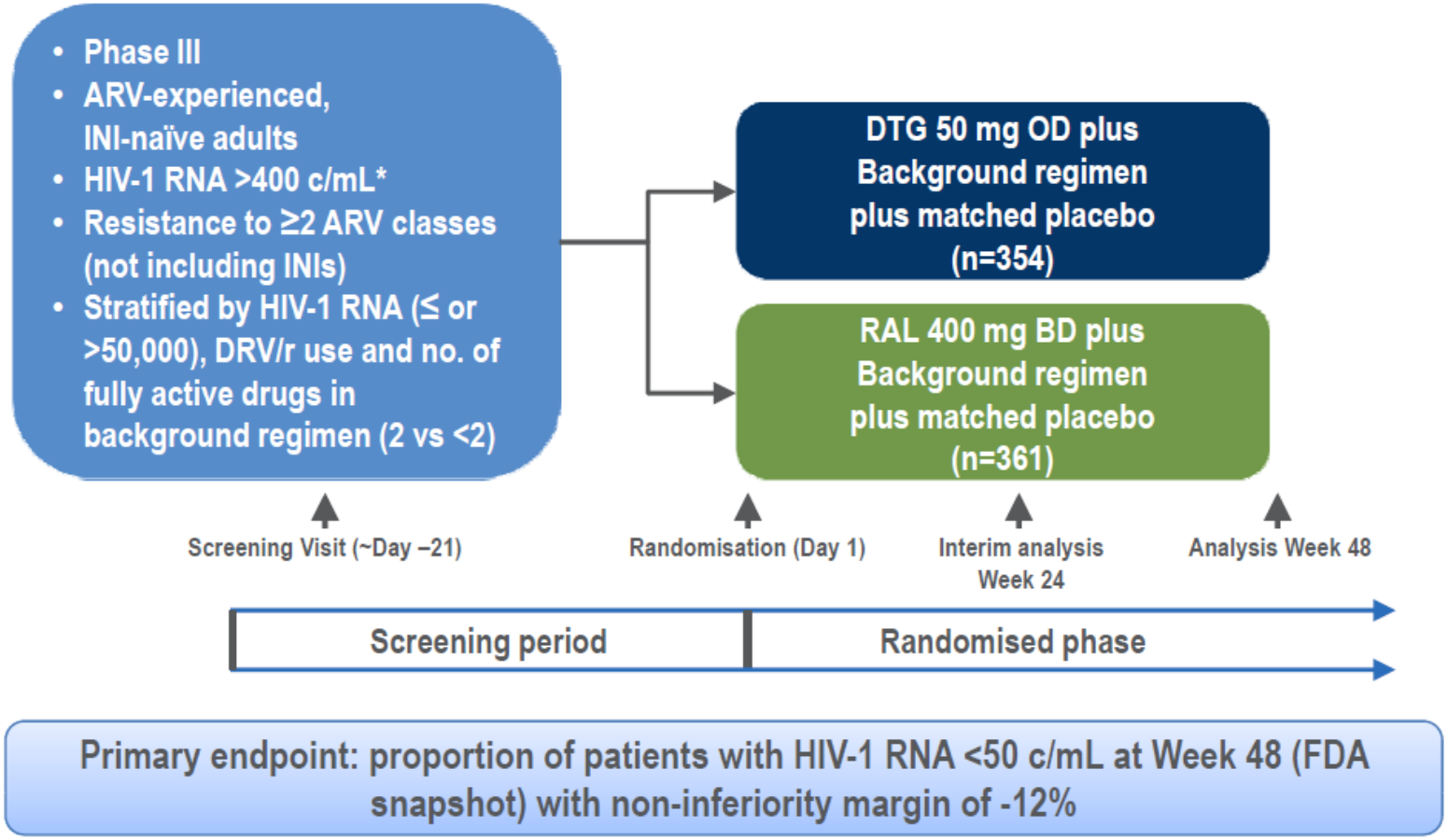
- Atazanavir / ritonavir / Etravirine / Raltegravir as BD regime.
- wait for tropism test result - maraviroc as reserve.

Question 2: It is now November 2015, what should the MDT recommend ?

1. Atazanavir/Ritonavir/Etravirine/Raltegravir
2. Atazanavir/Ritonavir/Etravirine/Dolutegravir
3. Atazanavir/Ritonavir/Dolutegravir
4. Atazanavir/Ritonavir/Dolutegravir/Maraviroc
5. Atazanavir / Ritonavir/ Triumeq (Abacavir/Lamivudine/Dolutegravir)
6. Something else ? (you will be asked to specify once again !)

Which integrase inhibitor?

SAILING: Study design



Primary endpoint: proportion of patients with HIV-1 RNA <50 c/mL at Week 48 (FDA snapshot) with non-inferiority margin of -12%

*With 2 consecutive HIV-1 RNA ≥400 c/mL, unless screening HIV-1 RNA >1,000 c/mL

Adapted from Cahn P et al. *Lancet* 2013;382(9893):700-708

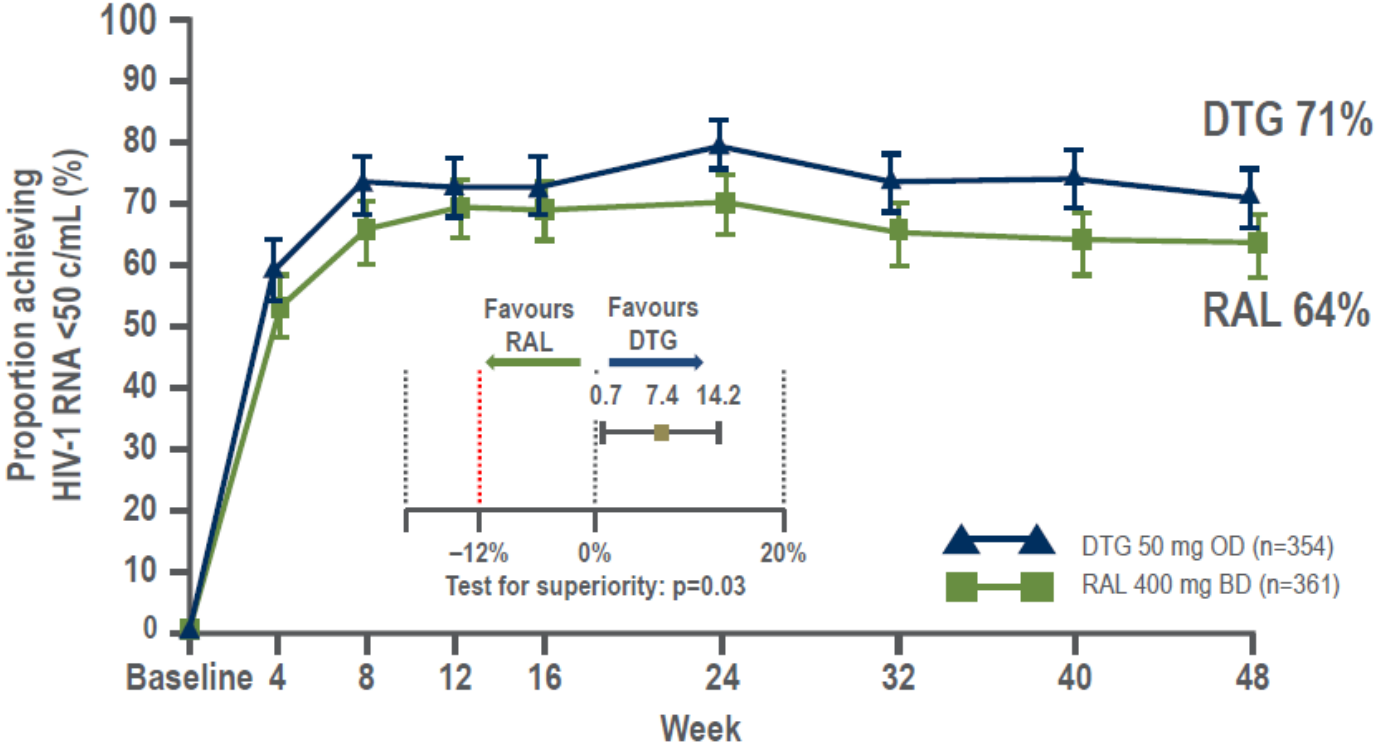
SAILING

SAILING: Baseline Characteristics

	DTG 50 mg OD (n=354)	RAL 400 mg BD (n=361)
≥3 class resistance (%)	47	51
Phenotypic susceptibility score		
PSS ≤2	352 (99)	361 (100)
PSS >2	2 (1)	0
Most common background regimens, n (%)		
DRV/r, TDF	62 (18)	73 (20)
LPV/r, TDF	40 (11)	40 (11)
DRV/r, ETR	33 (9)	40 (11)
LPV/r	36 (10)	35 (10)
ATV/r, TDF	37 (10)	33 (9)
DRV/r, MVC	23 (6)	19 (5)

Adapted from Cahn P et al. *Lancet* 2013;382(9893):700-708

SAILING: Proportion of subjects with HIV-1 RNA <50 c/mL

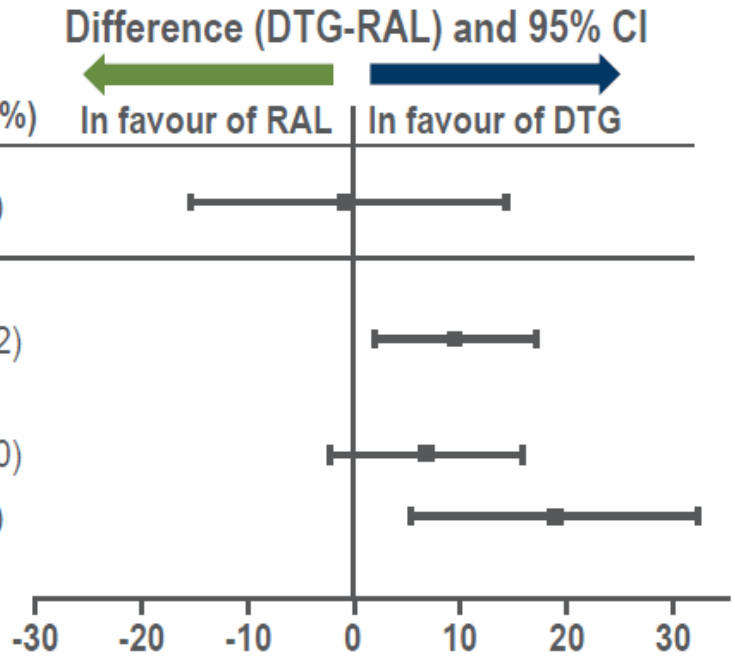


DTG 50 mg OD was statistically superior to RAL 400 mg BD based on a pre-specified snapshot analysis (HIV-1 RNA <50 copies / mL) at Week 48 (p =0.03)

Adapted from Cahn P et al. *Lancet* 2013;382(9893):700-708

SAILING: Percentage of Subjects With HIV-1 RNA <50 c/mL by Background Regimen Use of Darunavir

Subgroup	Response rates DTG No. with response/total no. (%)	Response rates RAL No. with response/total no. (%)
DRV/r use without primary PI mutations	50/72 (69)	54/77 (70)
No DRV/r use or DRV/r use with primary PI mutations	201/282 (71)	176/284 (62)
No DRV/r use	143/214 (67)	126/209 (60)
DRV/r use with primary PI mutations[a]	58/68 (85)	50/75 (67)



[a] The proportion of individuals who used fully active DRV/r (e.g. without phenotypic resistance) was also balanced across treatment groups: DTG 58/65 (89%), RAL 68/74 (92%)

Adapted from Hagins D, et al. ICAAC 2013. Abstract H-1460

Case 2 – Feb 2015

- 55 year old MSM
- HIV Diagnosis 2005
- Epilepsy / Non-epileptic seizures
- Gout
- Osteomyelitis
- Peripheral Neuropathy (small fibre)
- Alcohol excess
- Childhood sexual abuse

Case 2- Feb 2015

- PMH Head Injury
- Psychotic Episode 2005
- Worked as a chef but now on Disability Living Allowance
- Poor memory – MMSE 19/30, MRI Brain: atrophy (awaiting neuropsychological testing)
- Poor adherence to antiretroviral therapy, partner also HIV+ve, helps with medication.

Case 2- Feb 2015

- Current antiretroviral regimen:

Kivexa (Abacavir/Lamivudine)/ Darunavir 800mg od/Ritonavir 100mg od - since Aug 2009

Previously Kivexa /Atazanavir/Ritonavir – March –Aug 2009, switched due to nausea

Other medication: Levetiracetam, Thiamine, Allopurinol

Case 2 – Feb 2015

HIV PARAMETERS			
Date	CD4 (abs)	CD4 (%)	Viral Load (copies/ml)
10.02.15	545	29	25,646
20.11.14	441	29	404
08.07.14	577	30	<40

Stanford - Protease

HIVdb: Genotypic Resistance Interpretation Algorithm

Report: BHIVA Date: 03-Sep-2015 13:20:33 UTC

Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	None
PI Minor Resistance Mutations:	None
Other Mutations:	D60E, L63P

Protease Inhibitors

atazanavir/r (ATV/r)	Susceptible
darunavir/r (DRV/r)	Susceptible
fosamprenavir/r (FPV/r)	Susceptible
indinavir/r (IDV/r)	Susceptible
lopinavir/r (LPV/r)	Susceptible
nelfinavir (NFV)	Susceptible
saquinavir/r (SQV/r)	Susceptible
tipranavir/r (TPV/r)	Susceptible

PR Comments

Stanford – Reverse Transcriptase

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	None
Other Mutations:	R211K

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Susceptible	efavirenz (EFV)	Susceptible
abacavir (ABC)	Susceptible	etravirine (ETR)	Susceptible
zidovudine (AZT)	Susceptible	nevirapine (NVP)	Susceptible
stavudine (D4T)	Susceptible	rilpivirine (RPV)	Susceptible
didanosine (DDI)	Susceptible		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		

RT Comments

Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
Total:	0	0	0	0	0	0	0	0

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
Total:	0	0	0	0	0	0	0	0	0	0	0

Question 3: Feb 2015 – What should the MDT recommend ?

1. Continue Kivexa/ Darunavir/Ritonavir
2. Darunavir/Ritonavir (bd) only
3. Stribild(Tenofovir/Emtricitabine/Elvitegravir/ Cobisistat)
4. Triumeq(Abacavir/Lamivudine/Dolutegravir)
5. Eviplera(Tenofovir/Emtricitabine/ Rilpiverine)
6. Something else ?

Case 3 - Feb 2012

- 36 year old MSM
- HIV Diagnosis 2008
- Eosinophilic Cystitis – presumed ketamine related
- Recurrent Klebsiella UTIs
- Hand and facial warts
- Seborrhoeic Dermatitis

Case 3 – Feb 2012

- No baseline resistance
- HLAB5701 negative
- Truvada (Tenofovir/Emtricitabine) / Efavirenz initiated July 2009 (CD4 17, HIV Viral Load 66,540 copies/mil)
- Viral Load undetectable at 3 months – remained so for 2 years

Case 3 – Feb 2012

- Loss to follow-up for 14 months due to illness of father, stopped medication
- Returned to clinic Feb 2012 – CD4 17, HIV Viral Load 148,040
- Hep B/C negative
- Resistance Testing -

Stanford – Protease

HIVdb: Genotypic Resistance Interpretation Algorithm

Report: BHIVA Date: Feb 2012

Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	None
PI Minor Resistance Mutations:	None
Other Mutations:	I15V, N37S, R41K, I62IV

Protease Inhibitors

atazanavir/r (ATV/r)	Susceptible
darunavir/r (DRV/r)	Susceptible
fosamprenavir/r (FPV/r)	Susceptible
indinavir/r (IDV/r)	Susceptible
lopinavir/r (LPV/r)	Susceptible
nelfinavir (NFV)	Susceptible
saquinavir/r (SQV/r)	Susceptible
tipranavir/r (TPV/r)	Susceptible

PR Comments

Stanford – Reverse Transcriptase

Drug Resistance Interpretation: RT

NRTI Resistance Mutations: None
NNRTI Resistance Mutations: **K103N**
Other Mutations: E6D, K82R, I142M, S162C, G196E, L210F

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Susceptible	**efavirenz (EFV)**	High-level resistance
abacavir (ABC)	Susceptible	**etravirine (ETR)**	Susceptible
zidovudine (AZT)	Susceptible	**nevirapine (NVP)**	High-level resistance
stavudine (D4T)	Susceptible	**rilpivirine (RPV)**	Susceptible
didanosine (DDI)	Susceptible		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		

RT Comments

NNRTI

- K103N is a nonpolymorphic mutation that causes high-level resistance to NVP (~50-fold reduced susceptibility) and EFV (~20-fold reduced susceptibility).

Other

- L210F/S are rare mutations not associated with NRTI-resistance.

Question 4: What should the MDT recommend ?

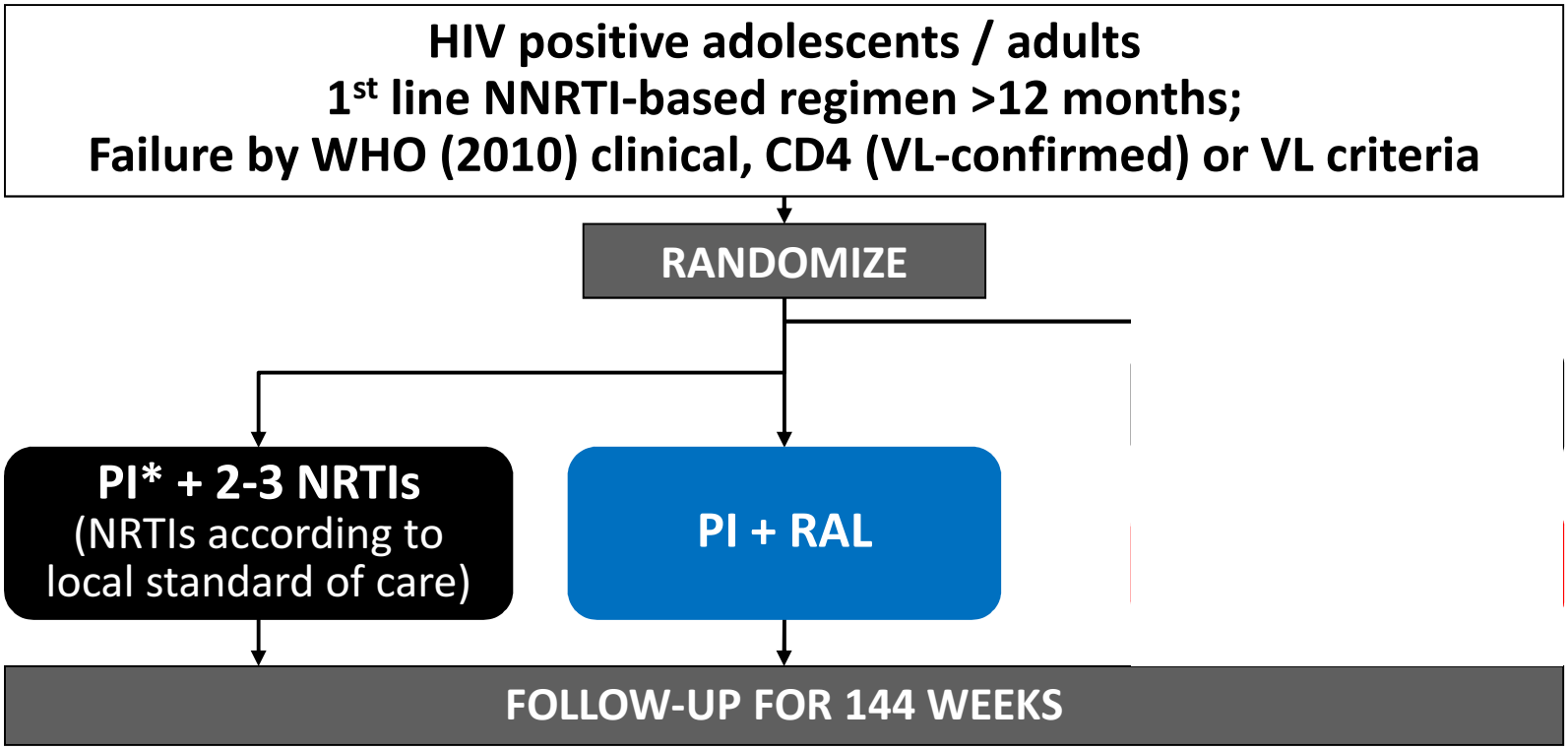
1. Truvada (Tenofovir/Emtricitabine)/ Efavirenz
2. Truvada (Tenofovir/Emtricitabine) + Boosted Protease Inhibitor
3. Raltegravir + Boosted Protease Inhibitor
4. Protease Inhibitor Monotherapy – after 12 weeks Raltegravir induction
5. Boosted Protease Inhibitor + Dolutegravir
6. Something else ?

Impact of NRTI Cross-Resistance on Second-line PI + NRTI Therapy Outcomes in Africa

N. Paton[1,7], C.Kityo[2], L. Bagenda[2], A. Kambugu[3], J. van Oosterhout[4,5], J. Hakim[6], J.Thompson[7], A. Hoppe[7], S. Walker[7], for the EARNEST Trial Team

[1]Dept. Of Medicine, National University of Singapore, Singapore
[2]Joint Clinical Research Centre, Kampala, Uganda
[3]Infectious Diseases Institute, Kampala, Uganda
[4]Coll. of Med., Univ. Malawi, Blantyre, Malawi
[5]Dignitas International, Zomba, Malawi
[6]University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe
[7]MRC Clinical Trials Unit at UCL, London, UK

Methods (1): EARNEST Trial design



Visits: 1-2 monthly, mainly nurse-led
Adherence: assessed at all visits by structured questions; intensive counselling
Monitoring: Clinical + CD4 count every 12–16 weeks (open)
VL annually in batch – results seen only by Data Monitoring Committee

*PI standardized to LPV/r all arms
NRTIs physician-selected without resistance testing

Paton et al, NEJM 2014; 371: 234-47

Methods (2): VL and resistance analysis

- **Viral load**
  - Batch tested on stored samples
  - In PI/NRTI & PI/RAL group to week 144, PI-mono to week 96
  - Central lab at JCRC Kampala, Uganda using Abbott m2000rt assay

- **Resistance**
  - Batch tested on stored samples
  - All PI/NRTI group at baseline
  - WHO-accredited reference lab at JCRC Kampala, Uganda using WHO-approved PCR assay
  - Mutations classified using Stanford algorithm
  - Calculated predicted activity of NRTIs in prescribed 2nd line PI/NRTI regimen:

    1) Number of "active" NRTIs (without int/high resistance) in prescribed regimen

    2) GSS of NRTIs in prescribed regimen:
    - Score activity of individual NRTI drugs used
      - High-level resistance 0
      - Intermediate level resistance 0.25
      - Low-level resistance 0.5
      - Potential low-level resistance 0.75
      - Susceptible 1
    - Added scores & categorised total as: 0, 0.25-0.75, 1-1.75, ≥2

Results: trial population

Baseline characteristics

- 58% female, median age 37, median 4 years on 1st line
- Median CD4 71 cells/mm^3 (pre-ART 62 cells/mm^3)
- 42% with VL > 100,000 at baseline

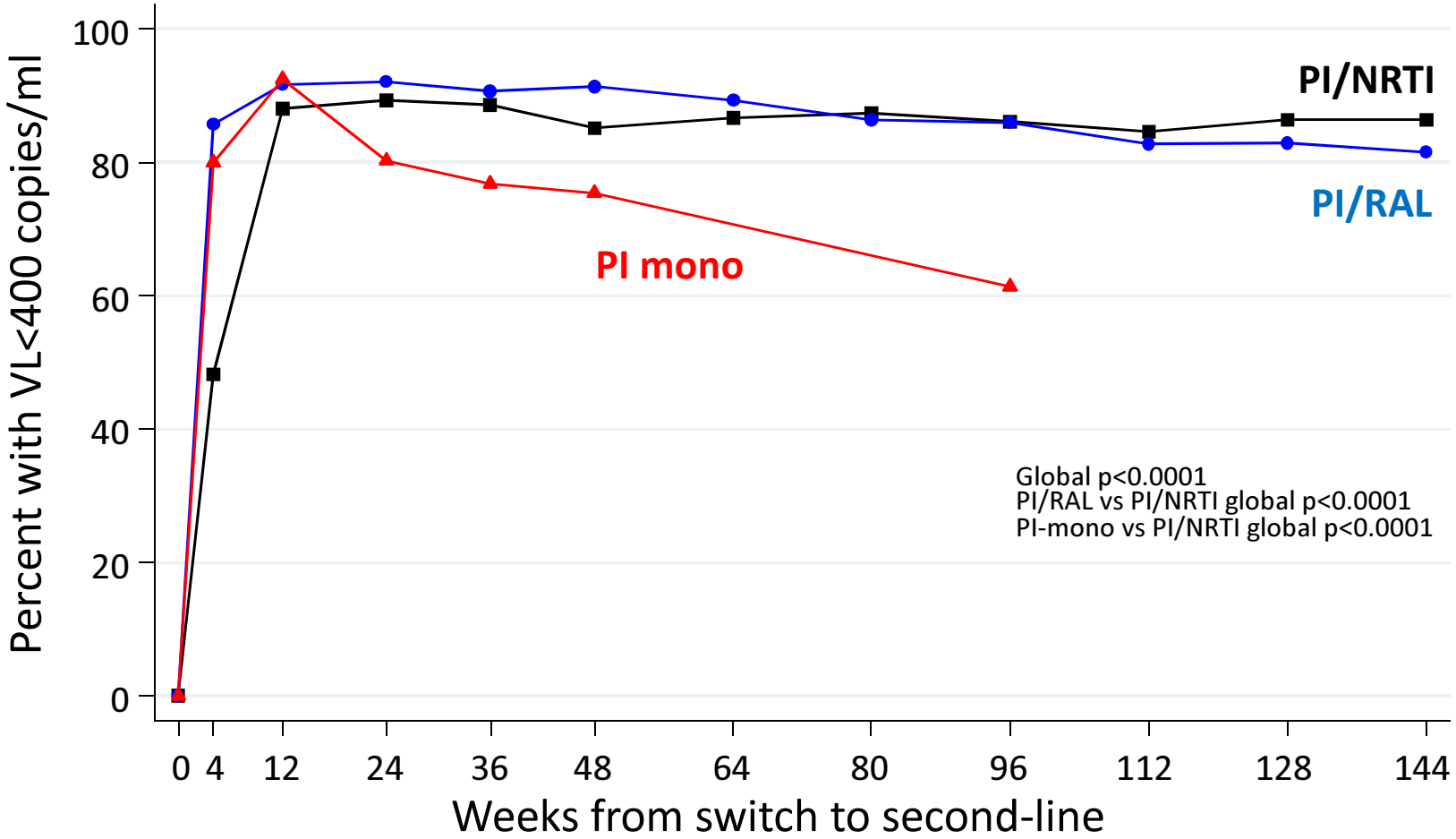
Trial follow-up

- Died: 8% by week 144
- LTFU/withdrawn: 2.3% by week 144
- Visits attended: 99% to week 144
- Visits with reported complete ART adherence: 88% to week 144

NRTIs prescribed in PI/NRTI arm

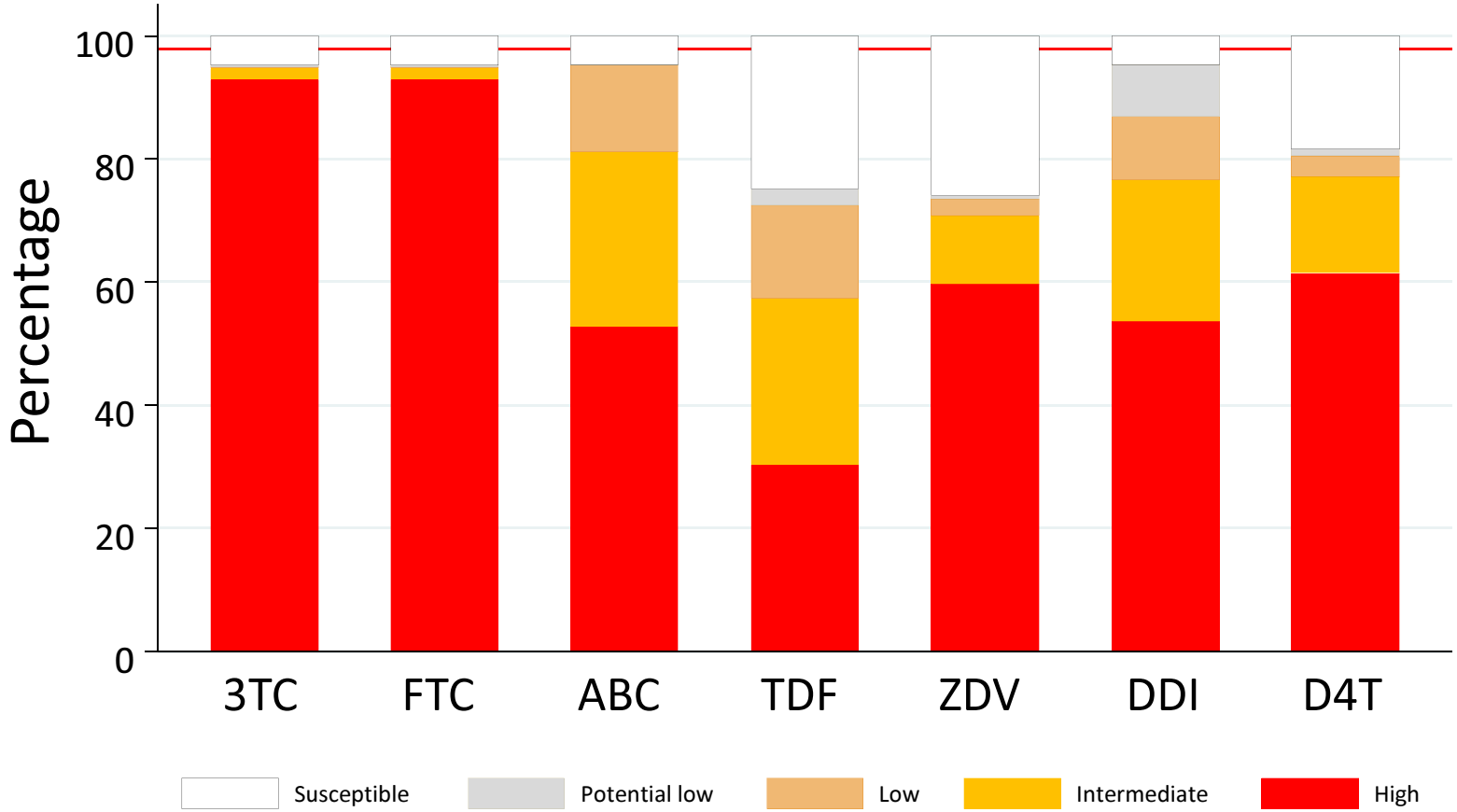
- TDF + 3TC/FTC ± ZDV in 79%
- ABC + DDI or 3TC in 16%
- ZDV + DDI or 3TC in 5%
- Other: < 1%

VL responses by randomized arm



Week 96 outcomes: Paton, NEJM 2014; 371; 234-47; Week 144 outcomes: Hakim, Poster 552, CROI 2015

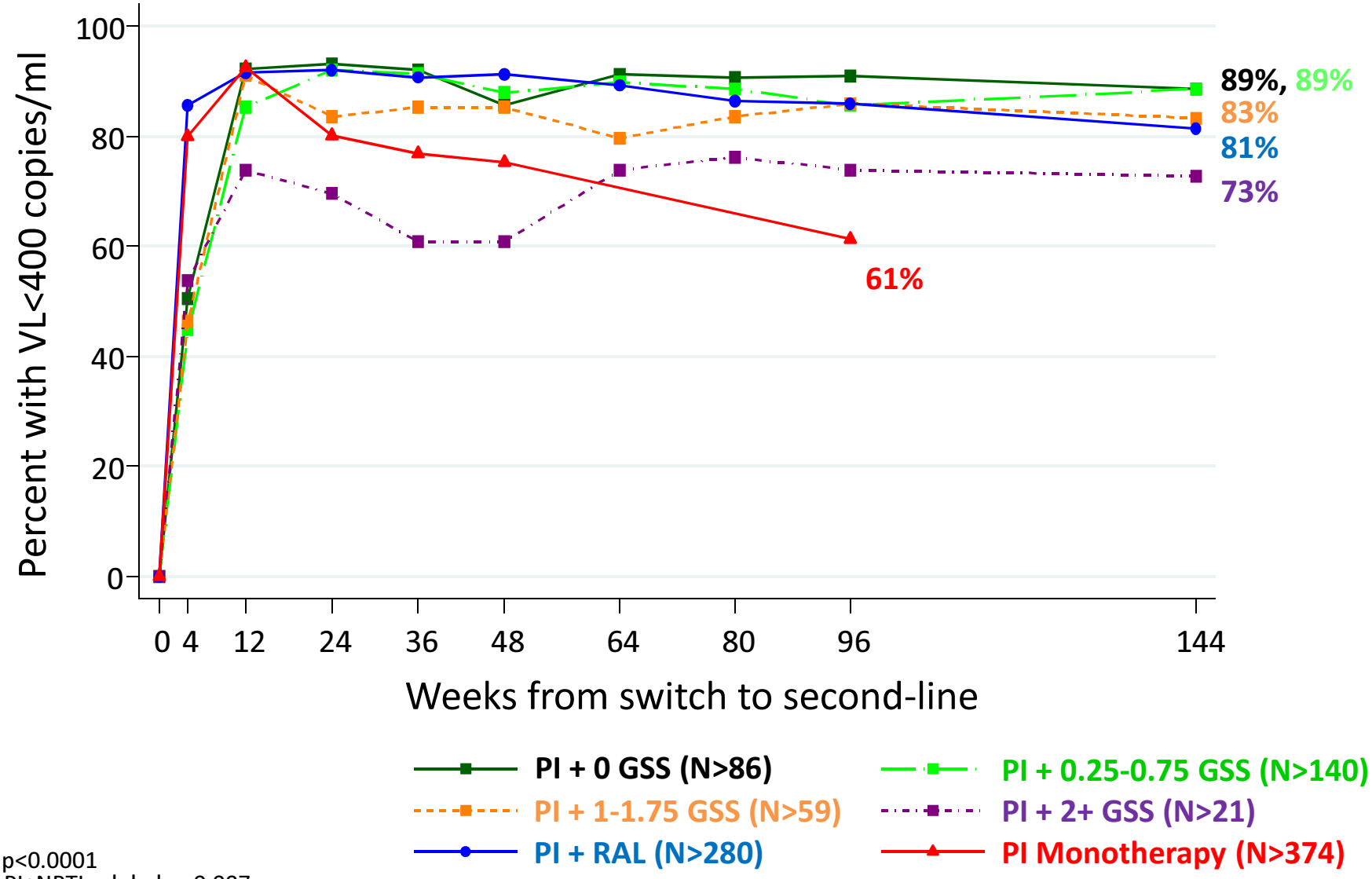
NRTI resistance at baseline



Baseline sequences obtained in 92% of those randomized to PI/NRTI arm
Figure shows resistance data from 792 randomized patients

Kityo et al, Poster 595, CROI 2015

VL response by GSS of NRTIs in the regimen



Global p<0.0001
Within PI+NRTIs global p=0.007

Factors Associated with VL < 400c/ml in PI/NRTI

	Unadjusted Odds ratio (95% CI)	p value	Adjusted Odds ratio (95% CI)	P value
GSS of second line regimen				
0	1	0.19	1	0.12
0.25-0.75	0.59 (0.26, 1.33)	(trend	0.46 (0.19, 1.09)	(trend
1-1.75	0.60 (0.23, 1.61)	0.08)	0.39 (0.13, 1.19)	0.03)
2-3	0.28 (0.09, 0.89)		0.23 (0.06, 0.88)	
Viral load at baseline (per doubling)	0.70 (0.60, 0.83)	<0.001	0.66 (0.55, 0.80)	<0.001
Proportion non-adherent visits (per 5% higher)*	0.89 (0.82, 0.96)	0.003	0.89 (0.81, 0.98)	0.01
Unemployed at baseline	0.51 (0.28, 0.94)	0.03	0.48 (0.24, 0.98)	0.04
Age (per 10 years older)	1.45 (1.10,1.92)	0.008	1.60 (1.15,2.22)	0.005

Note: Multivariable regression modelling for VL suppression at week 96. N=346, excluding those with missing week 96 VL, baseline genotype or baseline employment status. Factors with p>0.1 sex, centre, baseline CD4, diabetes, cardiovascular disease, prior tuberculosis, smoking, alcohol consumption, hours worked per week, household income, food availability, presence of M184V in the baseline genotype, years on first-line, eGFR, haemoglobin, and glucose, previous CNS disease; viral subtype

*Non-adherent visit defined as missed, more than 7 days late, or reported any missing ART in the last month.

Learning Points

- EARNEST: Management of first line failure
- SAILING: Dolutegravir vs Raltegravir in more treatment-experienced
- NRTIs and their role in more treatment experienced?
- Determinants of Adherence
- Use of MDTs