Management of ART Failure

EACS Advanced HIV Course 2015

Dr Nicky Mackie

Outline

- Defining treatment success
- Defining treatment failure
- Reasons for ART failure
- Management of ART failure
- Choice of second line therapy

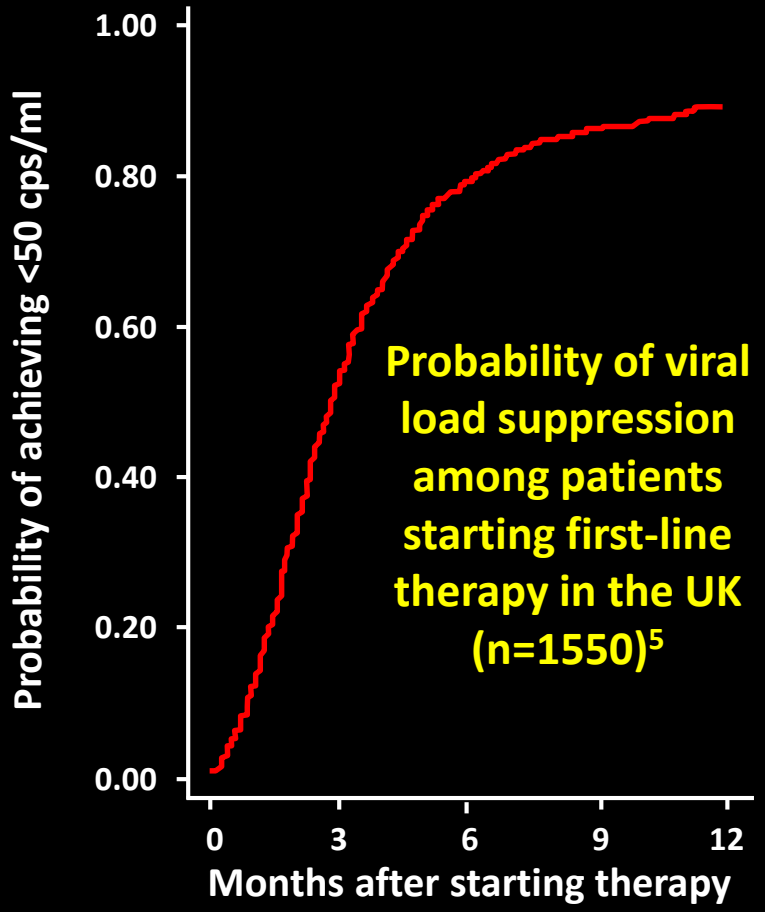
Defining treatment success

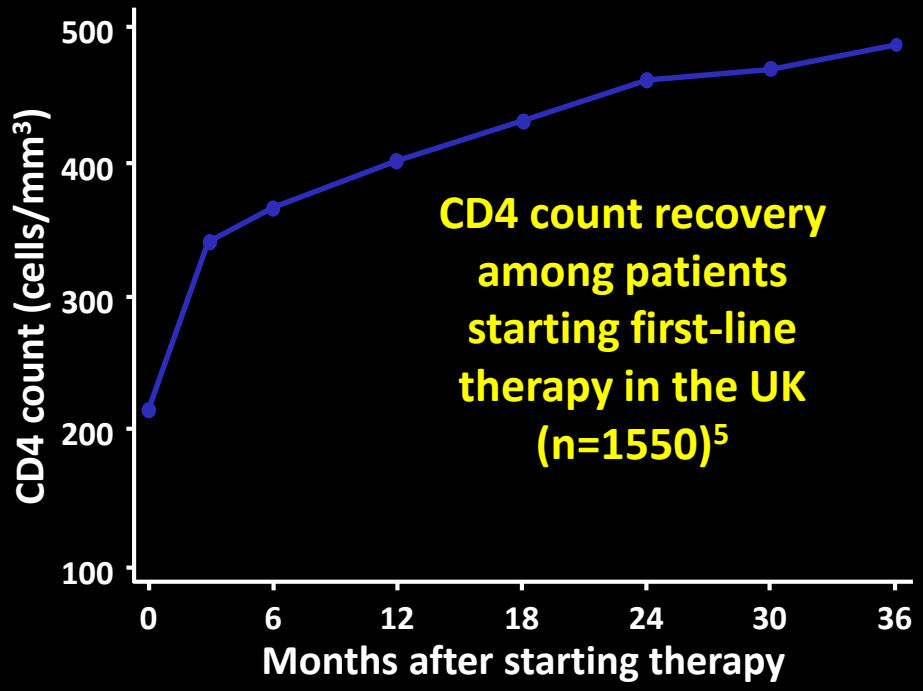
- Reduce HIV-associated morbidity and prolong the duration and quality of survival
- Restore and preserve immune function
- Prevent HIV transmission
- Maximally and durably suppress plasma HIV viral load*

*Includes treatment-experienced patients with ART failure +/- drug resistance

The goal of antiretroviral therapy

- ***Treatment guidelines:*** **The goal of therapy is to achieve & maintain viral load suppression below detection limits[1-4]**





1. BHIVA 2013; 2. DHHS 2015; 3. EACS 2014; 4. IAS-US A 2013; 5.Geretti et al. Clin Infect Dis 2009

Which of the following correctly defines virological failure?

1. Any confirmed HIV RNA detection
2. Confirmed viral load >50 cps
3. Confirmed viral load >200 cps
4. Confirmed viral load >400 cps
5. Confirmed viral load >1000 cps

Definitions of virological failure vary

EACS 2014: Confirmed >50 cps ≥6 months after ART initiation or modification

DHHS 2014: Inability to achieve or maintain <200 cps

IAS-USA 2014: HIV-1 RNA level >200 cps should prompt evaluation of factors leading to failure and consideration of switching ART

BHIVA 2015 (draft): Incomplete virological response after commencing treatment or evidence of confirmed virologica rebound to >200 copies/ml

WHO 2014: Confirmed >1000 cps after ≥6 months of ART

Treatment Failure

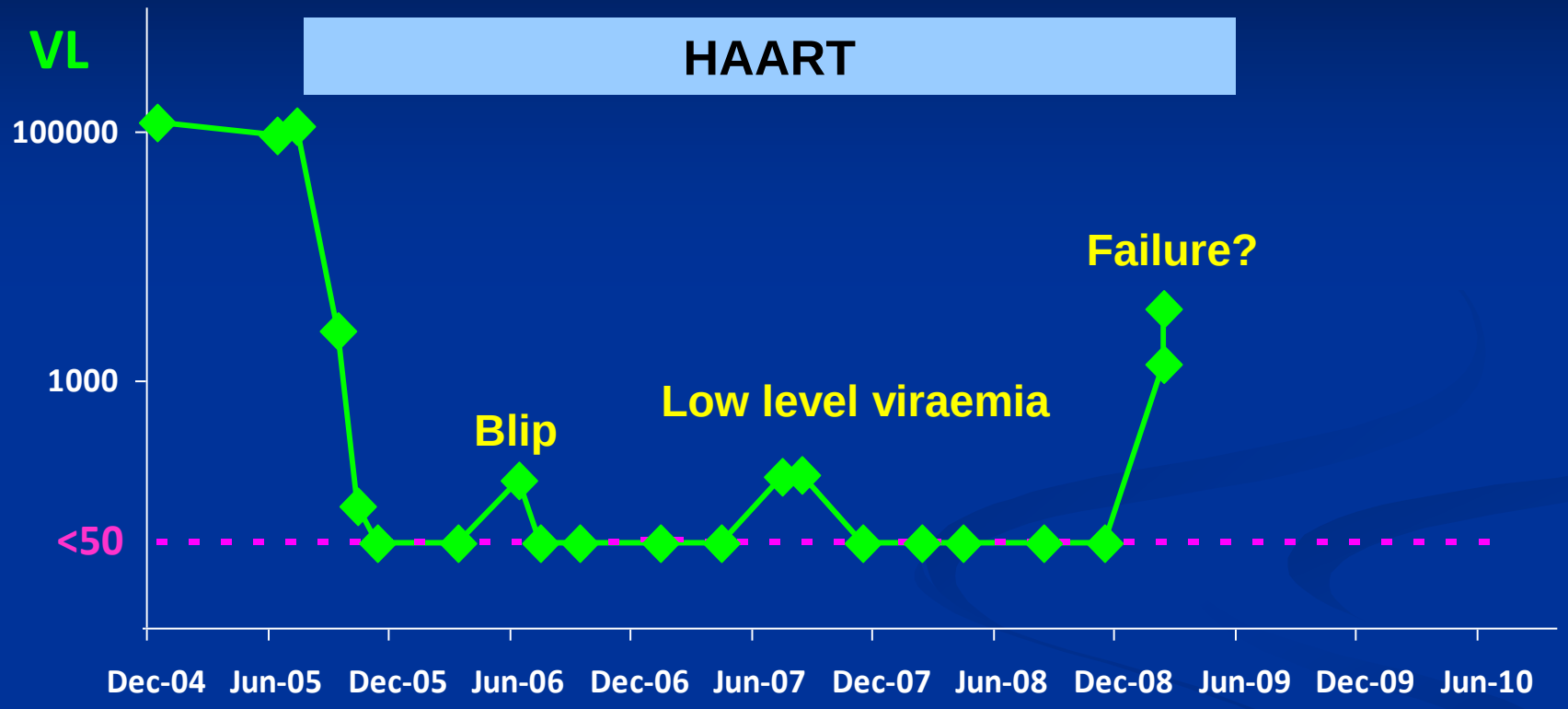
Immunological treatment failure

- This includes a fall in CD4 count towards pre-treatment levels or a blunted or 'discordant' CD4 response despite suppressed viral load

Clinical Treatment Failure

- For example a new AIDS-defining illness

Viral load rebound during therapy

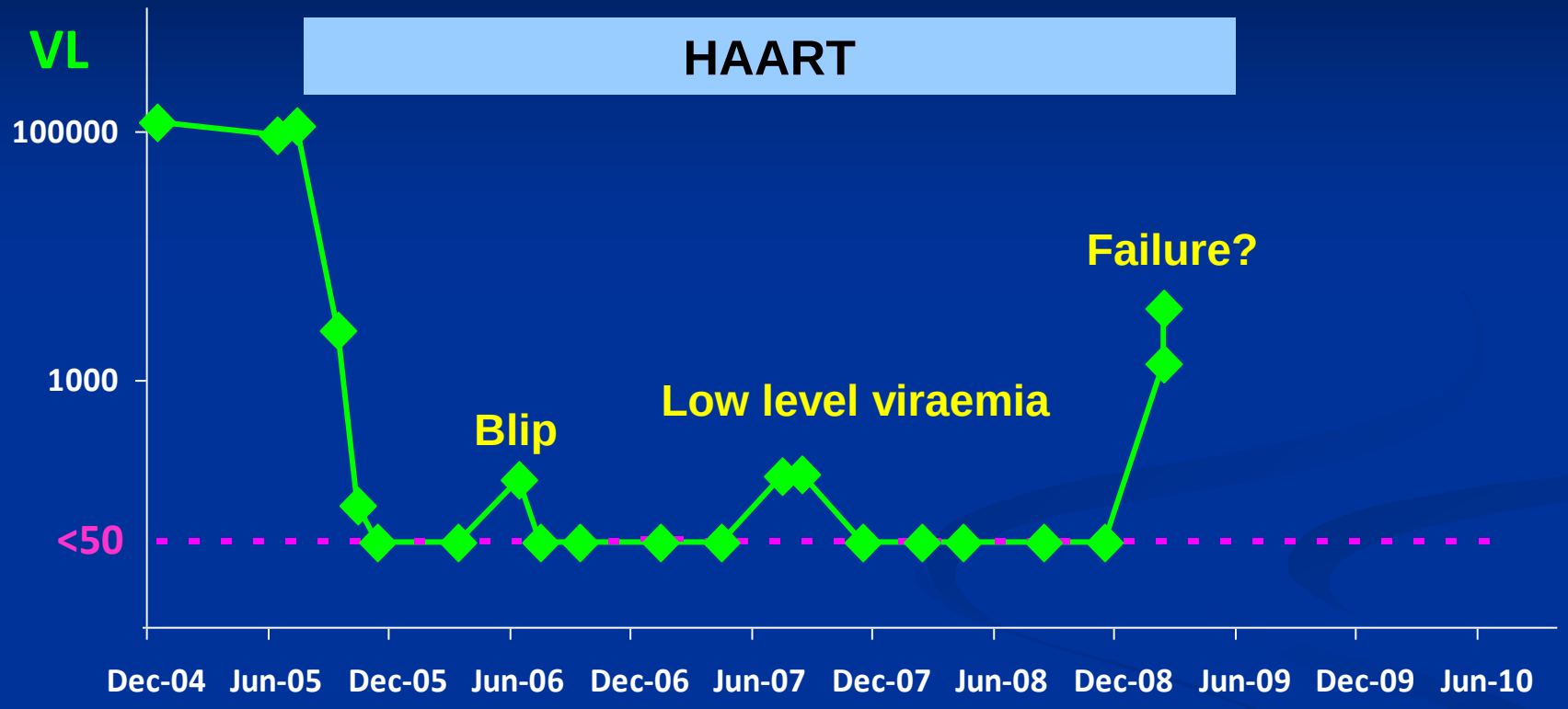


A virological blip is defined as a single measurement of detectable viraemia which is preceded and followed by an undetectable result without any change in therapy

Viral Load Blips

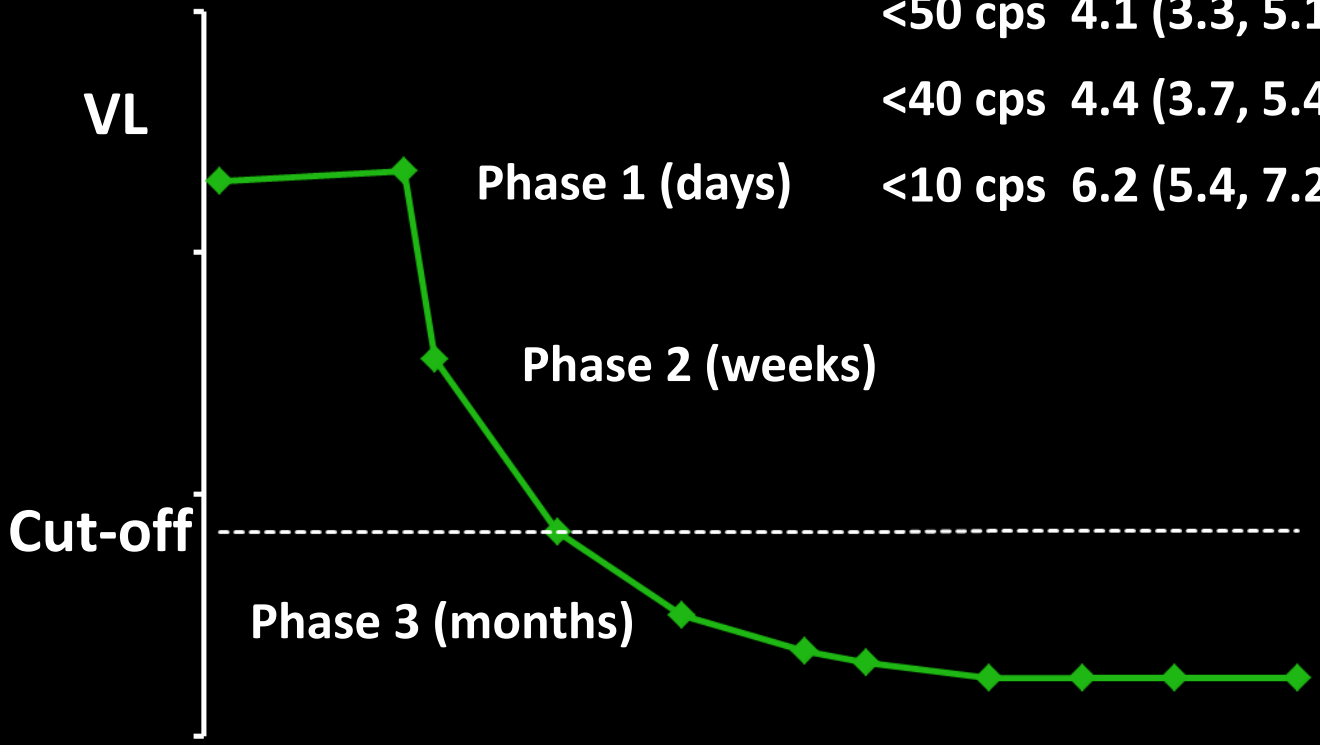
- Confirm with a repeat sample within 4-6 weeks
- A single detectable viral load, preceded and followed by an undetectable viral load, is usually not a cause for clinical concern
- Resistance testing should be considered for those with ‘large’ or repeated blips

Viral load rebound during therapy



Low level viraemia is defined as persistent detectable low level viraemia over a sustained period of time

HIV-1 RNA kinetics after starting ART

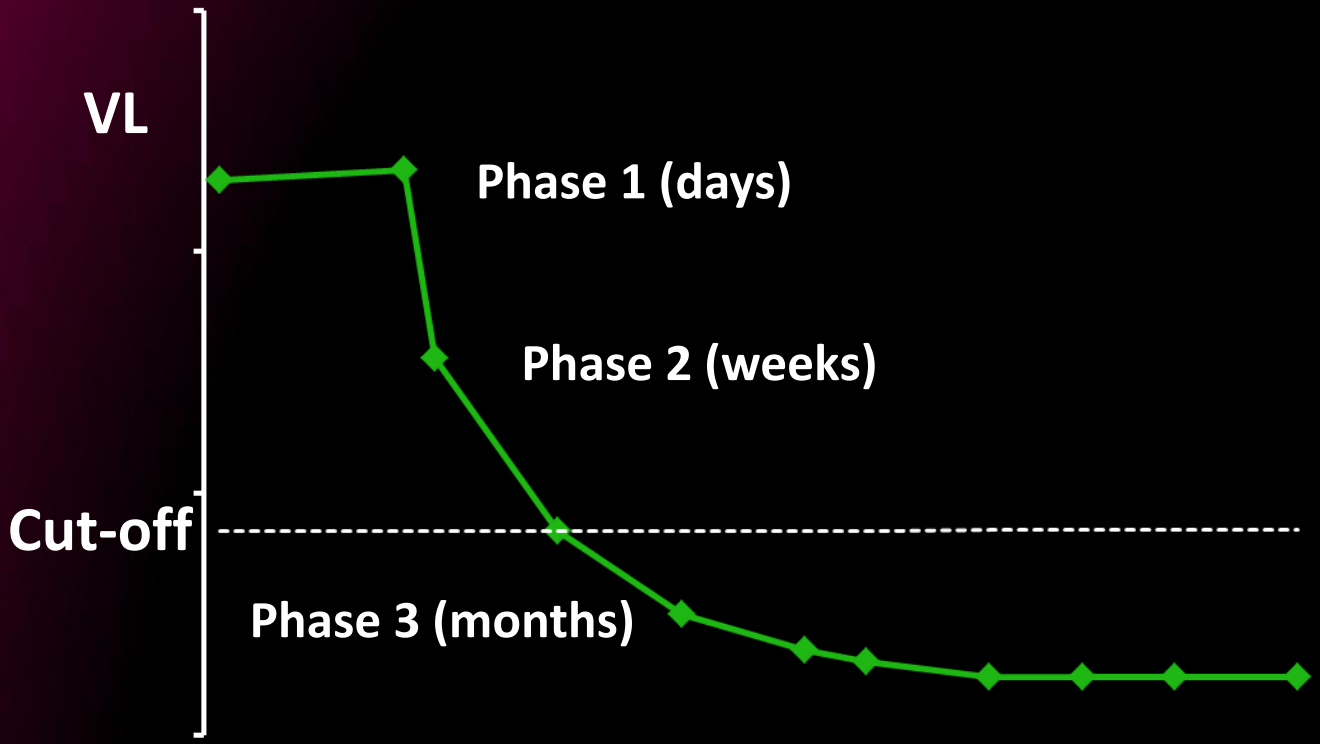


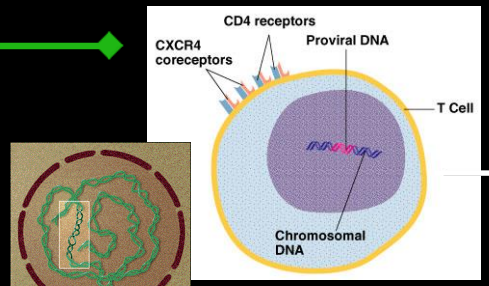
Median months to cut-off (95%CI)[1]

<50 cps	4.1 (3.3, 5.1)
<40 cps	4.4 (3.7, 5.4)
<10 cps	6.2 (5.4, 7.2)

1. Doyle et al. Clin Inf Dis 2012

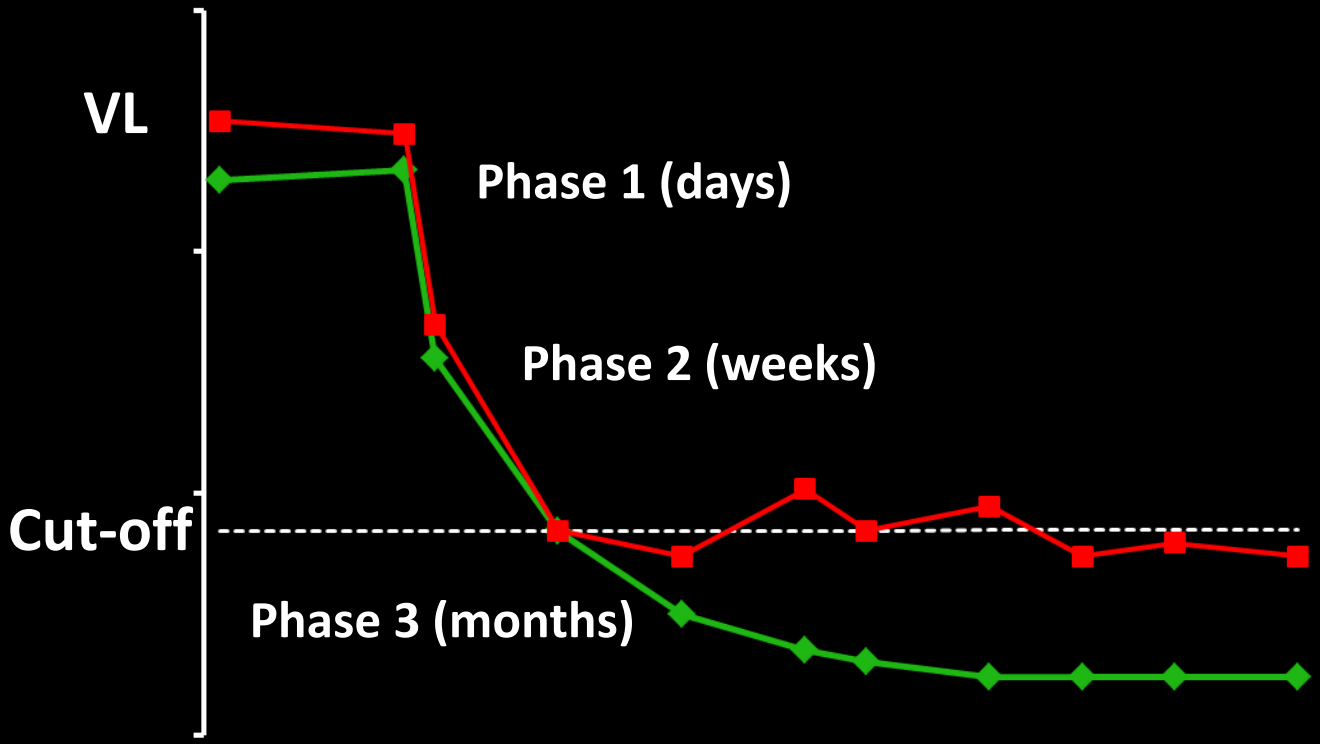
HIV-1 RNA kinetics after starting ART

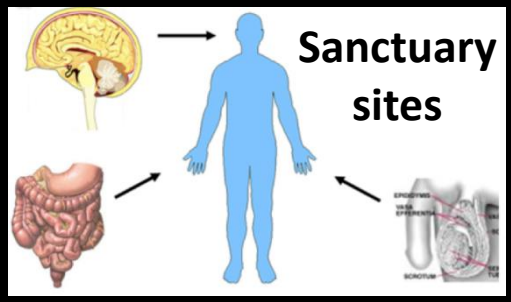


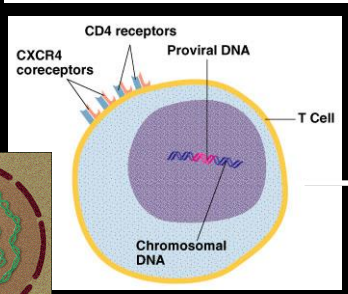


Latently infected cell

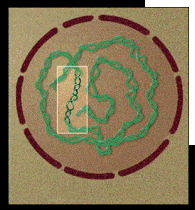
HIV-1 RNA kinetics after starting ART







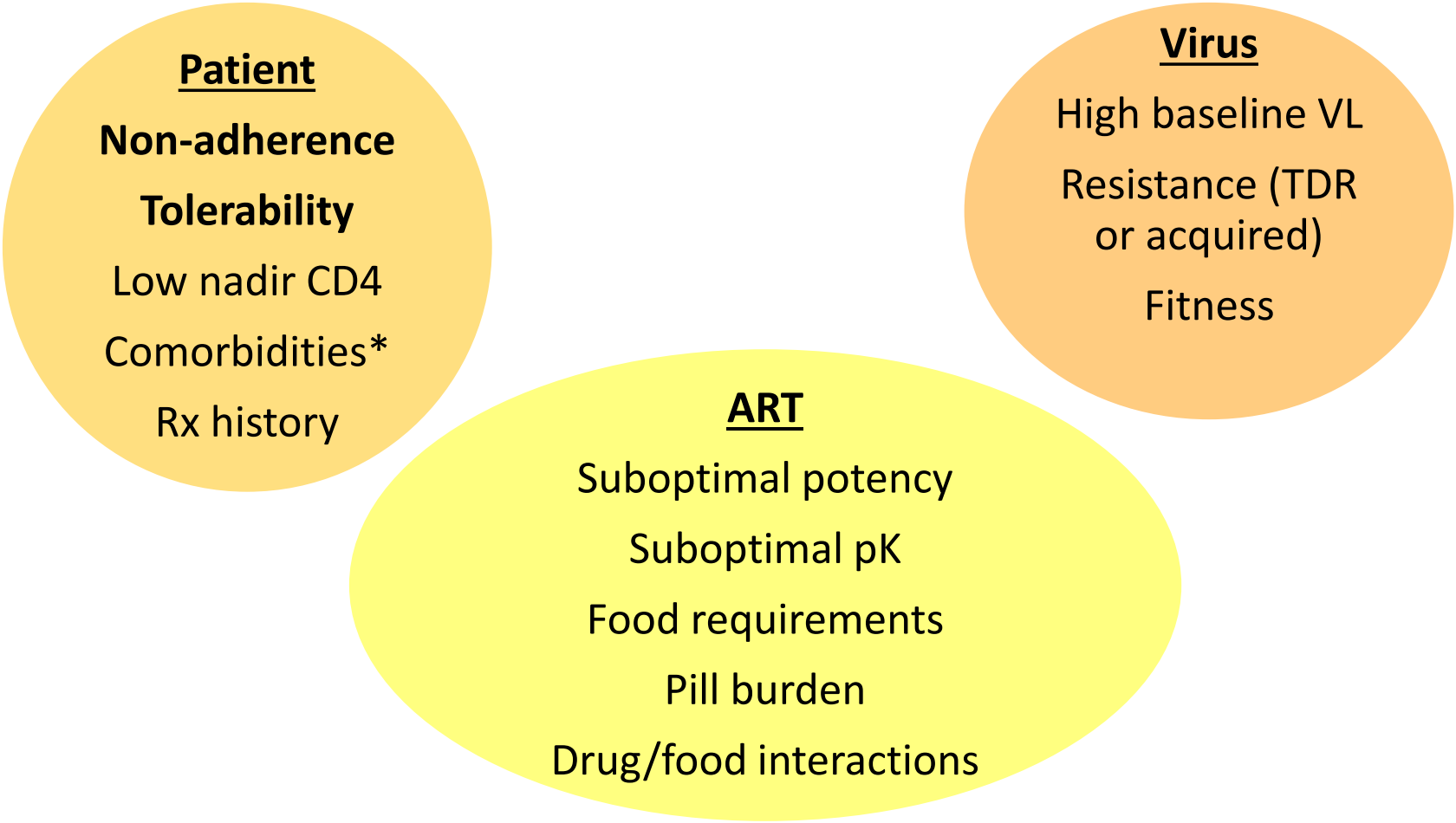
Latently infected cell →



Consequences of LLV

- If reflects on-going viral replication
  - May predict VL rebound (may be dependent on level of VL)
  - Potential for viral genetic evolution and emergence of drug resistance
  - Immune activation/inflammation
  - May signal suboptimal control in certain compartments

Reasons for ART Failure



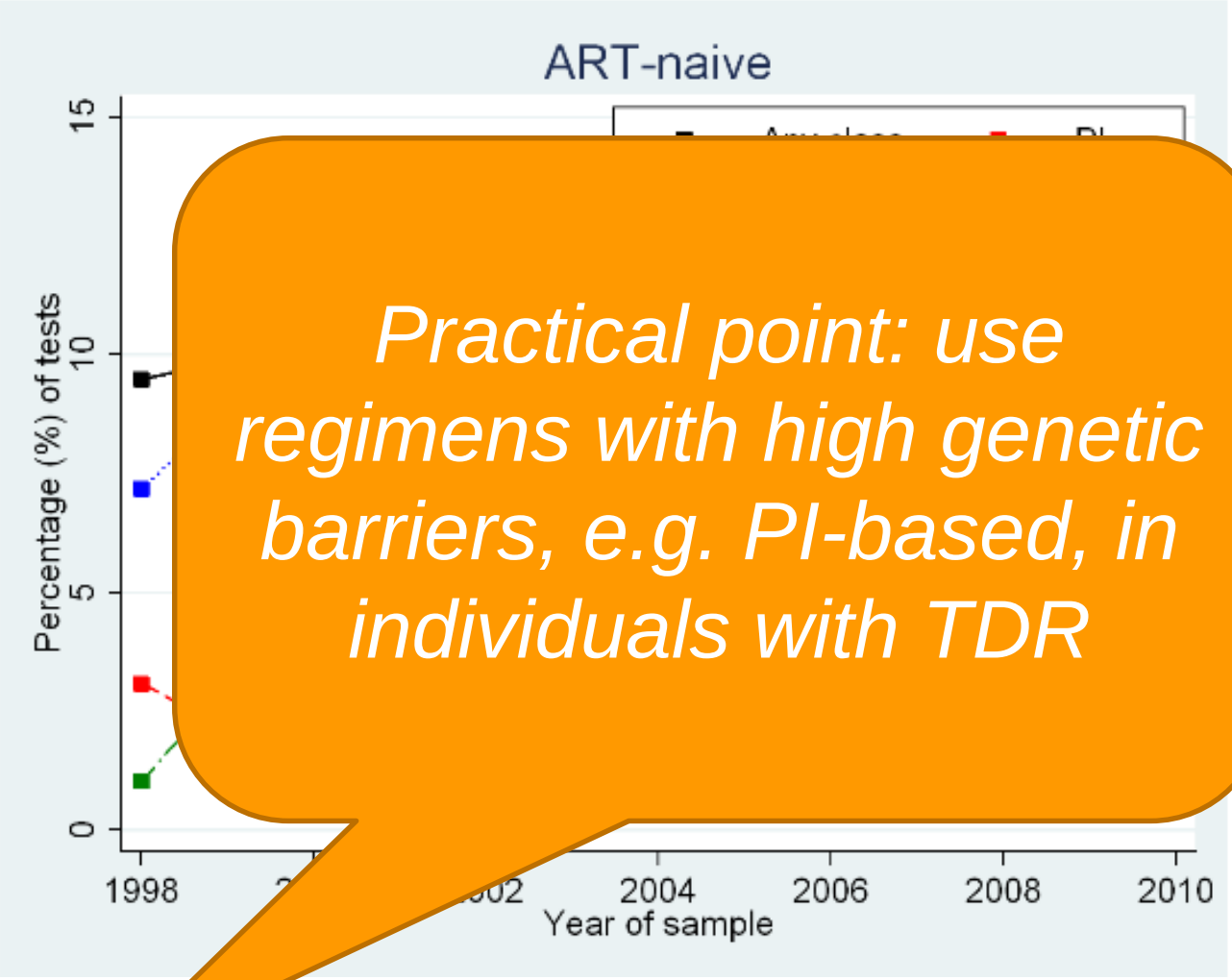
*Includes active substance abuse, psychiatric disease, neurocognitive defects

Types of resistance

- **Acquired drug resistance:** resistance of HIV to drugs in individuals on treatment

- **Primary drug resistance (*transmitted drug resistance, TDR*):** resistance of HIV to drugs in individuals who have never received treatment

Prevalence of TDR in UK



- Transmitted resistant species persist prior to initiating treatment, and represent a risk for onward transmission and sub-optimal response to treatment
- Current levels 7-8% in UK

Management of ART failure (1)

- Review the patient
- Assess:
  - Adherence
  - Drug tolerability/toxicity
  - Lifestyle, health beliefs
  - Drug-drug or drug-food interactions
  - Co-morbidities including renal/liver disease and mental health/drug dependency problems
  - ARV potency

Management of ART failure (2)

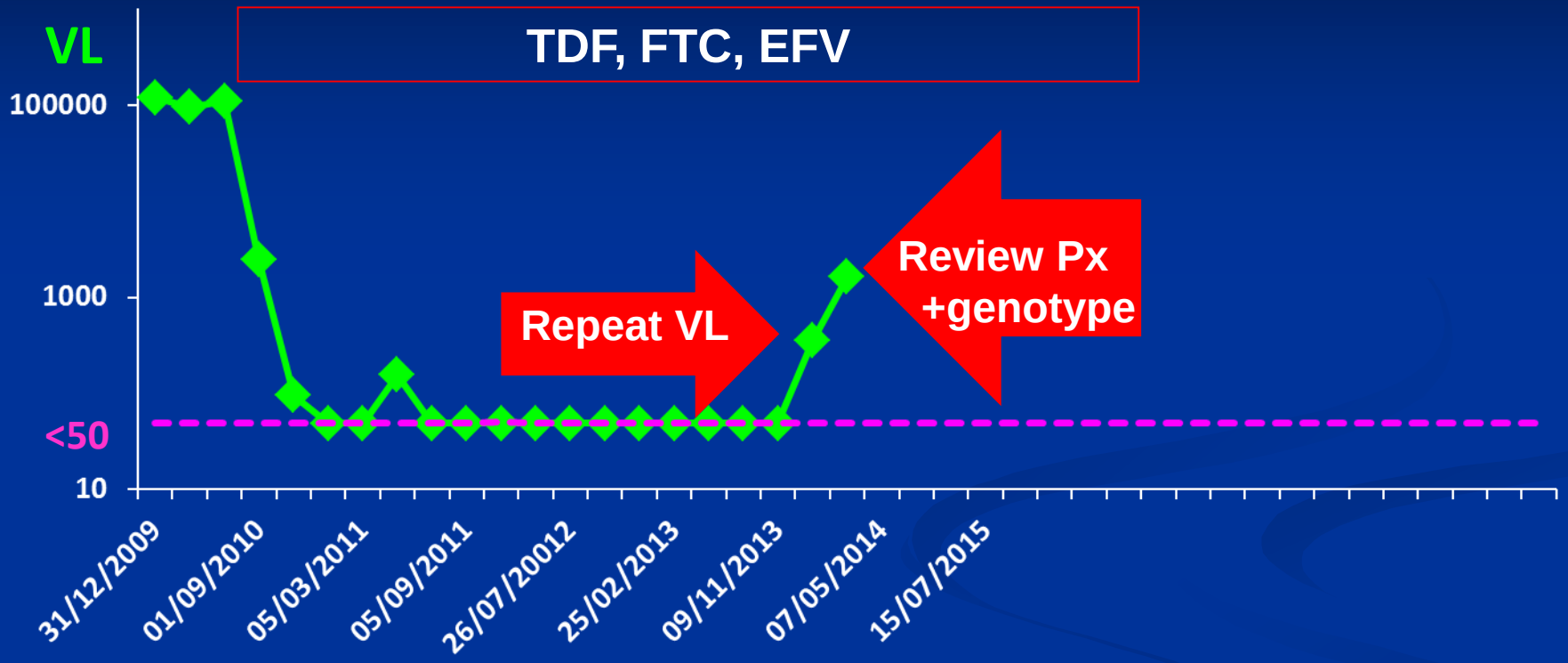
- Assess:
  - Treatment history
  - Prior and current drug resistance test results
  - HIV VL/CD4 over time
- Tests
  - Repeat VL
  - Perform resistance test (ideally whilst patient on treatment or within 2-4 weeks of discontinuation)
  - Tropism testing
  - ?consider TDM
- Change regimen as required

Genetic barrier and cross-resistance

Class	ARVs	Genetic barrier	Cross Resistance
NRTIs	ZDV/3TC, d4T/3TC	+/++	+++
	ABC/3TC, TDF/3TC	+	+++
			+++
NNRTIs			+++
			+++
PIs			++/+++
		+++/++++	+/++
Fusion inhibitors	T20	+	NA
CCR5 antagonists	MVC	+/++	NA
Integrase inhibitors	RAL, EVG	+	+++
	DTG	++/+++	++

LLV on a low genetic barrier regimen may warrant prompt regimen change

First ART failure: NNRTIs



Mr CM starts Atripla™ in September 2010
Baseline RT: wild-type; suppresses within 3 months

First ART failure: NNRTIs

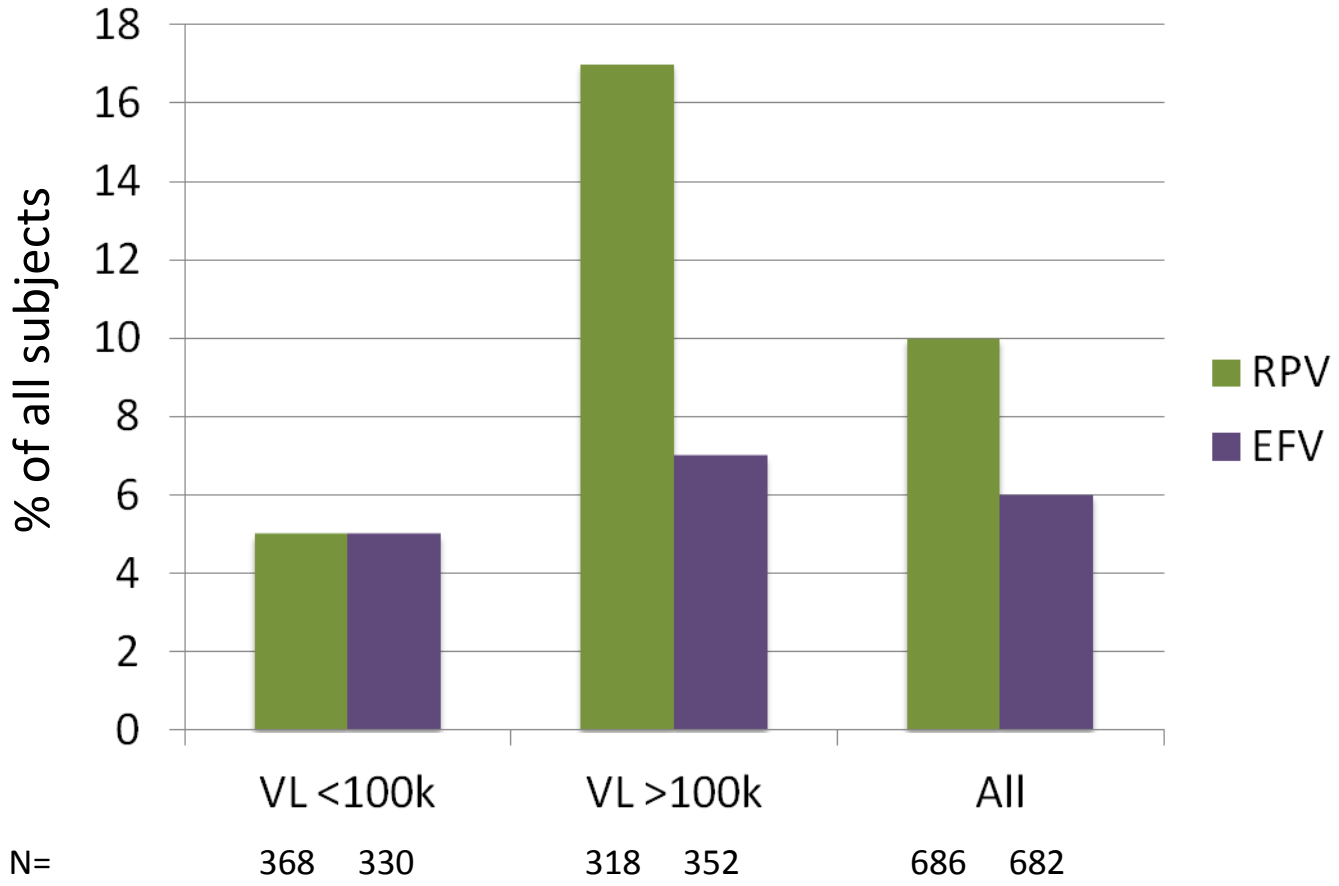
- Resistance patterns
  - No resistance (WT virus).
  - 3TC/FTC resistance (M184V/I) following any first-line therapy, including TDF/FTC or ABC/3TC.
  - NNRTI resistance (e.g. K103N, Y181C/I/V, or E138K) and/or 3TC/FTC resistance
  - Extended RT resistance (e.g. K65R/L74V or thymidine analogue mutations)

Genotypic and Phenotypic Characterization of HIV-1 Isolates Obtained From Patients on Rilpivirine Therapy Experiencing Virologic Failure in the Phase 3 ECHO and THRIVE Studies: 48-Week Analysis

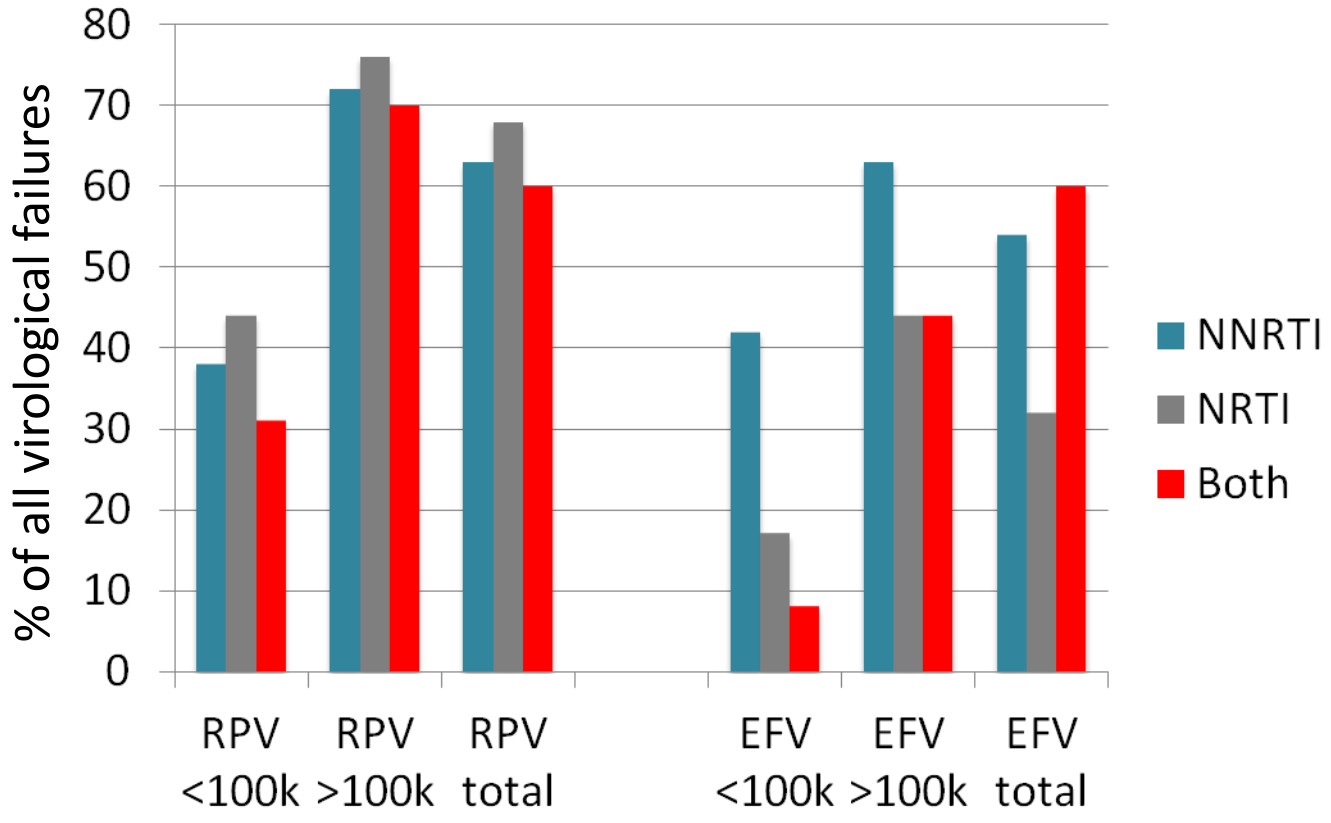
Laurence Rimsky, PhD, Johan Vingerhoets, PhD,* Veerle Van Eygen, MSc,* Joseph Eron, MD,† Bonaventura Clotet, MD,‡ Annemie Hoogstoel, MSc,* Katia Boven, MD,§ and Gaston Picchio, PhD§*

J Acquir Immune Defic Syndr 2012;59:39–46

% experiencing VF by week 48



% of VF developing resistance



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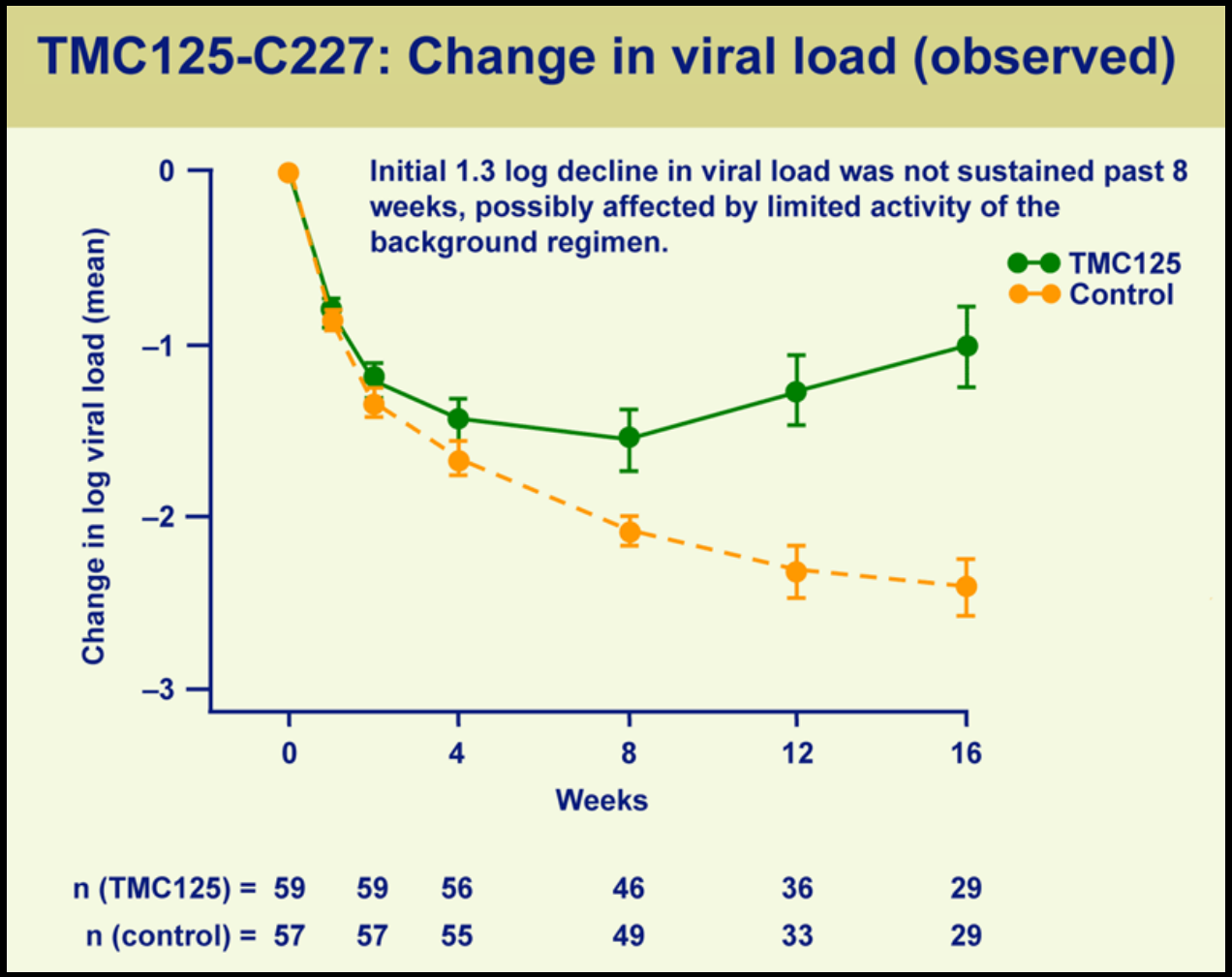
  - Extended RT resistance (e.g. K65R/L74V or thymidine analogue mutations)
- Options:
  - Review adherence, ?TDM
  - **Switch to a bPI-based regimen is optimal**
  - **To include NRTIs or another ARV(s)??**

Activity of ETV with a weak backbone
Study TMC125-C227: 2 NRTIs + ETV or PI

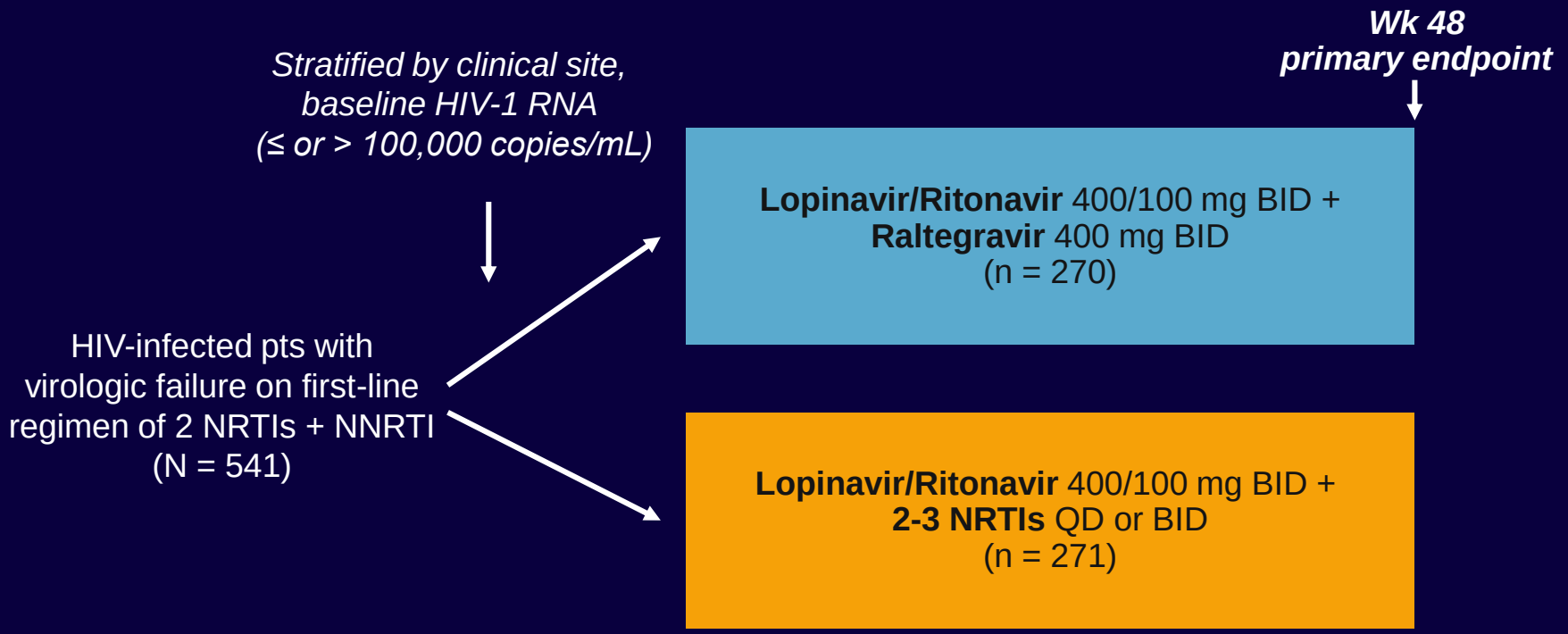


ART-experienced, PI-naive patients with documented NNRTI resistance

Ruxrungtham, HIV Med 2008

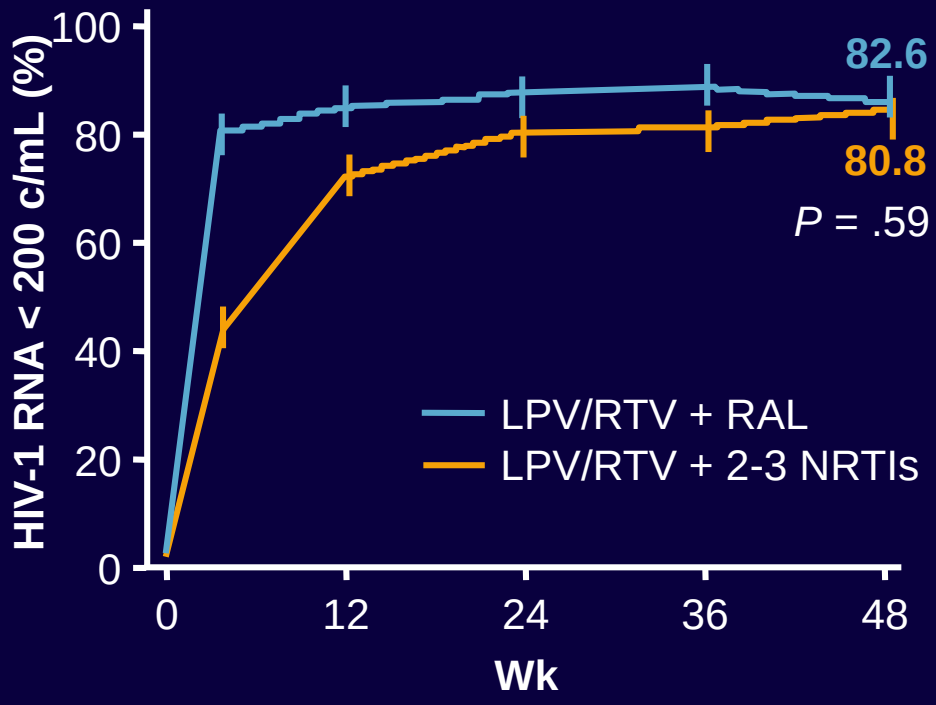
SECOND-LINE: LPV/RTV + RAL vs LPV/RTV + NRTIs After First-line VF

- Randomized, open-label, international, multicenter trial



SECOND-LINE: Noninferiority of LPV/RTV + RAL vs LPV/RTV + NRTIs

- Similar high levels of virologic suppression with each strategy in primary mITT analysis[1]



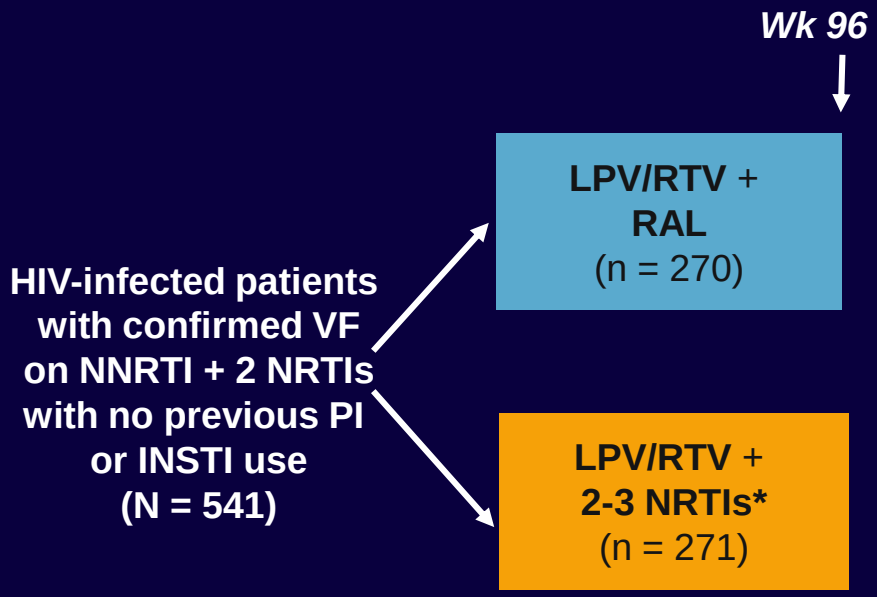
- LPV/r once daily or twice daily
- Non-inferiority demonstrated
- No effect of baseline VL
- 83% vs. 81% <200 cps at wk 48
- No major safety issues
- RAL arm significantly larger CD4 gains: + 167 vs. + 132
  (NB: ZDV use in 45% of control patients)
- RAL arm significantly higher total cholesterol, HDL, LDL

- Non-inferiority also confirmed at week 96
- 80% vs 76% <200 cps

1. SECOND-LINE study group Lancet 2013; 2. Amin *et al*. PLOS one 2015

SECOND-LINE Subanalysis: Resistance to NRTIs and Risk of Virologic Failure

- Resistance analysis of randomized, open-label, multicenter trial



*NRTIs selected by genotypic resistance test or by algorithm.

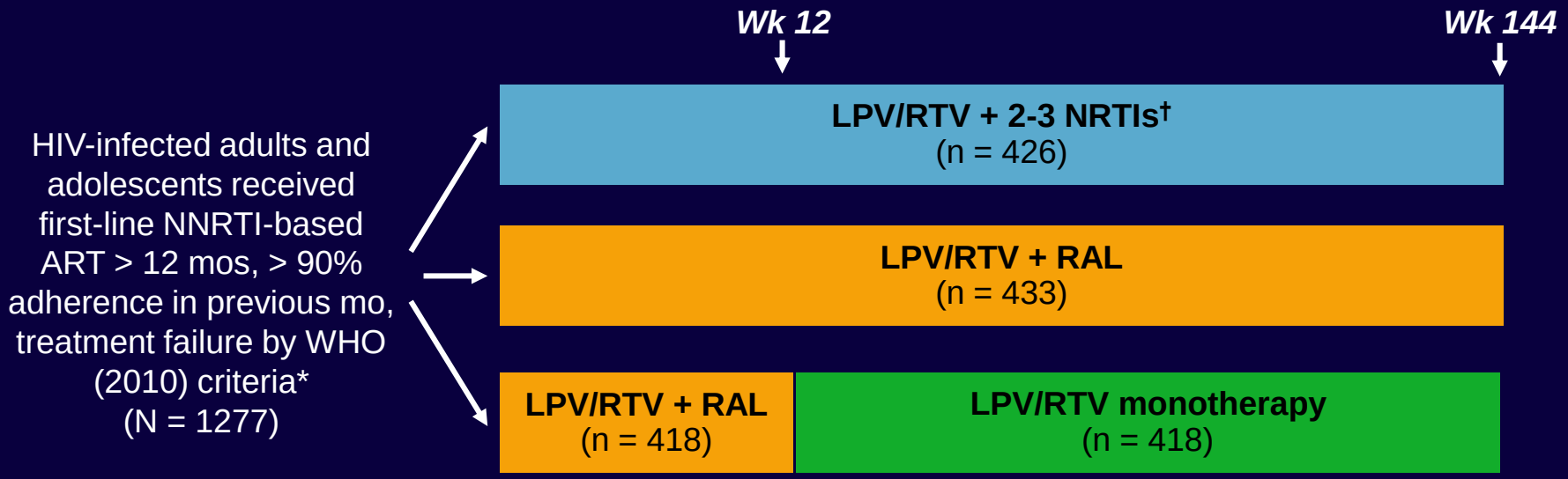
- Primary analysis: LPV/RTV + RAL noninferior to LPV/RTV + 2-3 NRTIs after VF of initial NNRTI regimen
- 46% with high-level NRTI resistance at baseline by global genotypic sensitivity score
- Risk of VF at Wk 96 in both treatment arms higher among pts with *lower* levels of NRTI resistance by gGSS

VF at Wk 96 by BL Resistance Level, %	LPV/RTV + 2-3 NRTIs	LPV/RTV + RAL
High	9	14
Moderate	13	12
Low	43	38

Boyd M, et al. AIDS 2014. Abstract TUAB0105LB. Graphic used with permission.

EARNEST: Second-line LPV/RTV-Based ART After Initial NNRTI Failure

- Randomized, controlled, open-label, phase III trial

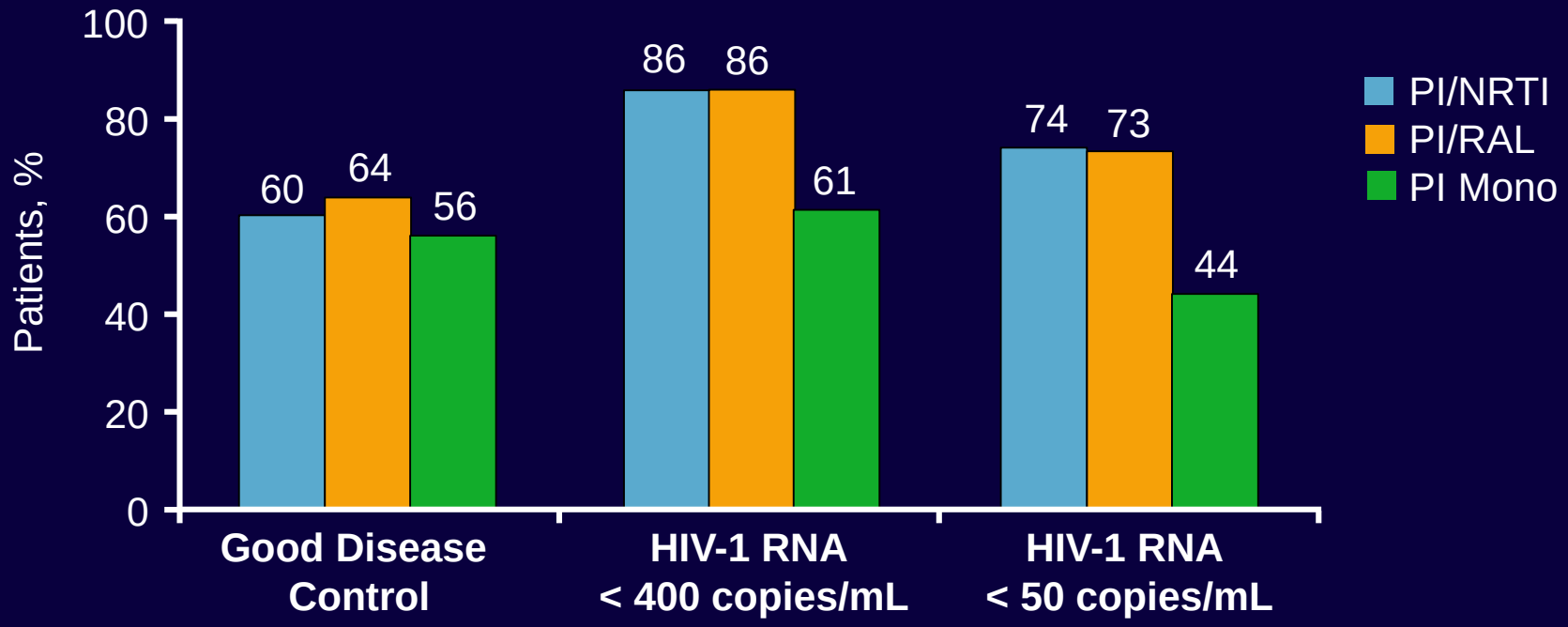


- Baseline demographics (medians): HIV-1 RNA 69,782 copies/mL; CD4+ 71 cells/mm^3; time on ART 4 yrs

*Including clinical, CD4+ cell count (HIV-1 RNA confirmed), or virologic criteria.
†Selected by physician according to local standard of care.

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

EARNEST: Clinical Outcomes at Wk 96



- "Good disease control" at Wk 96 defined as pt alive, no new WHO 4 events from Wks 0-96, *and* CD4+ cell count > 250 cells/mm^3, *and* HIV-1 RNA < 10,000 copies/mL *or* > 10,000 copies/mL without PI resistance mutations

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

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: 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

Predicted activity of NRTIs in regimens

- **Number of predicted "active" NRTIs in prescribed second-line Rx*:**

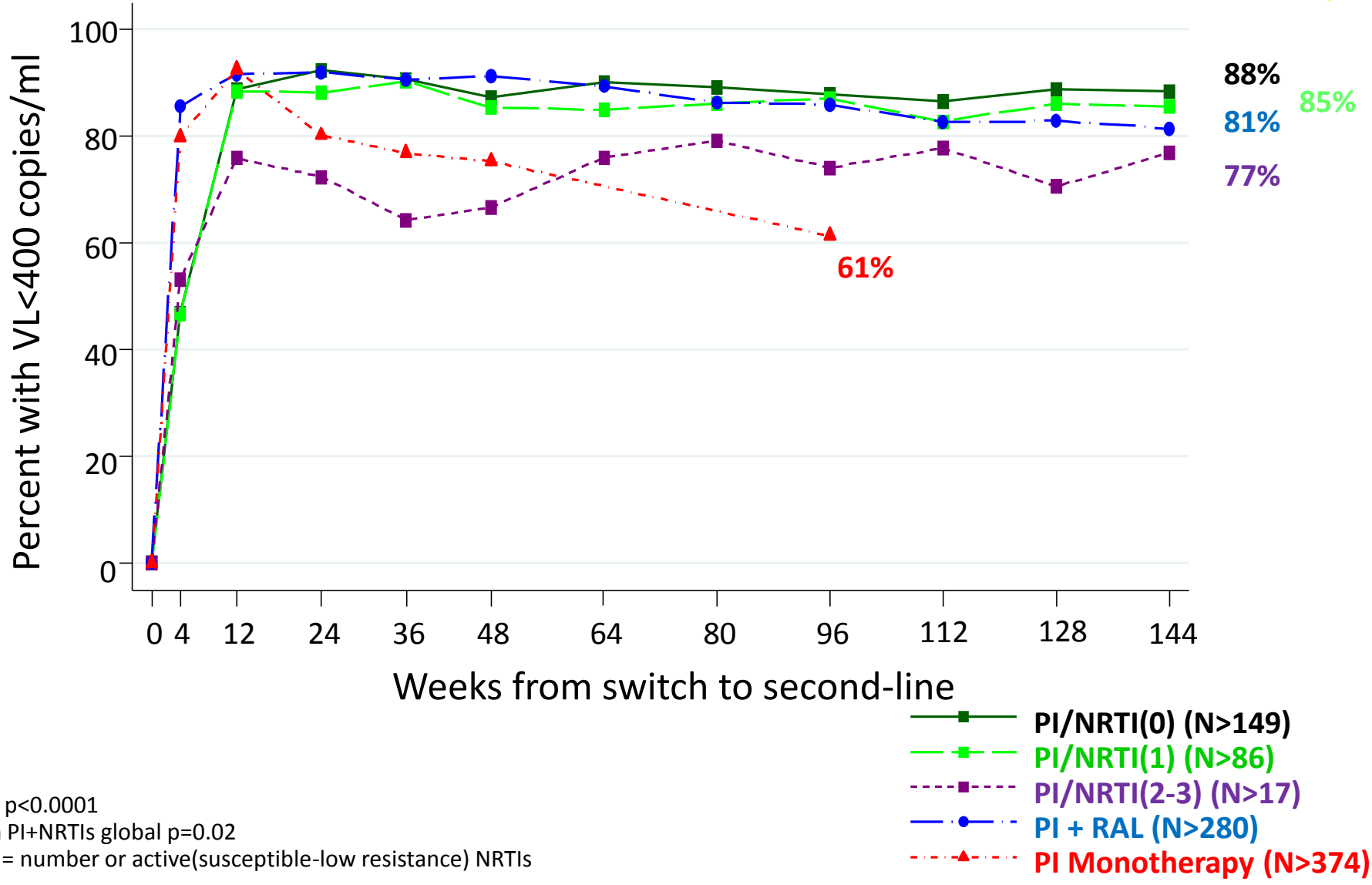
0	230 (59%)
1	128 (33%)
≥2	33 (8%)

*NRTI predicted "active" if no int./high level resistance by Stanford

- **GSS for NRTIs in prescribed second-line Rx:**

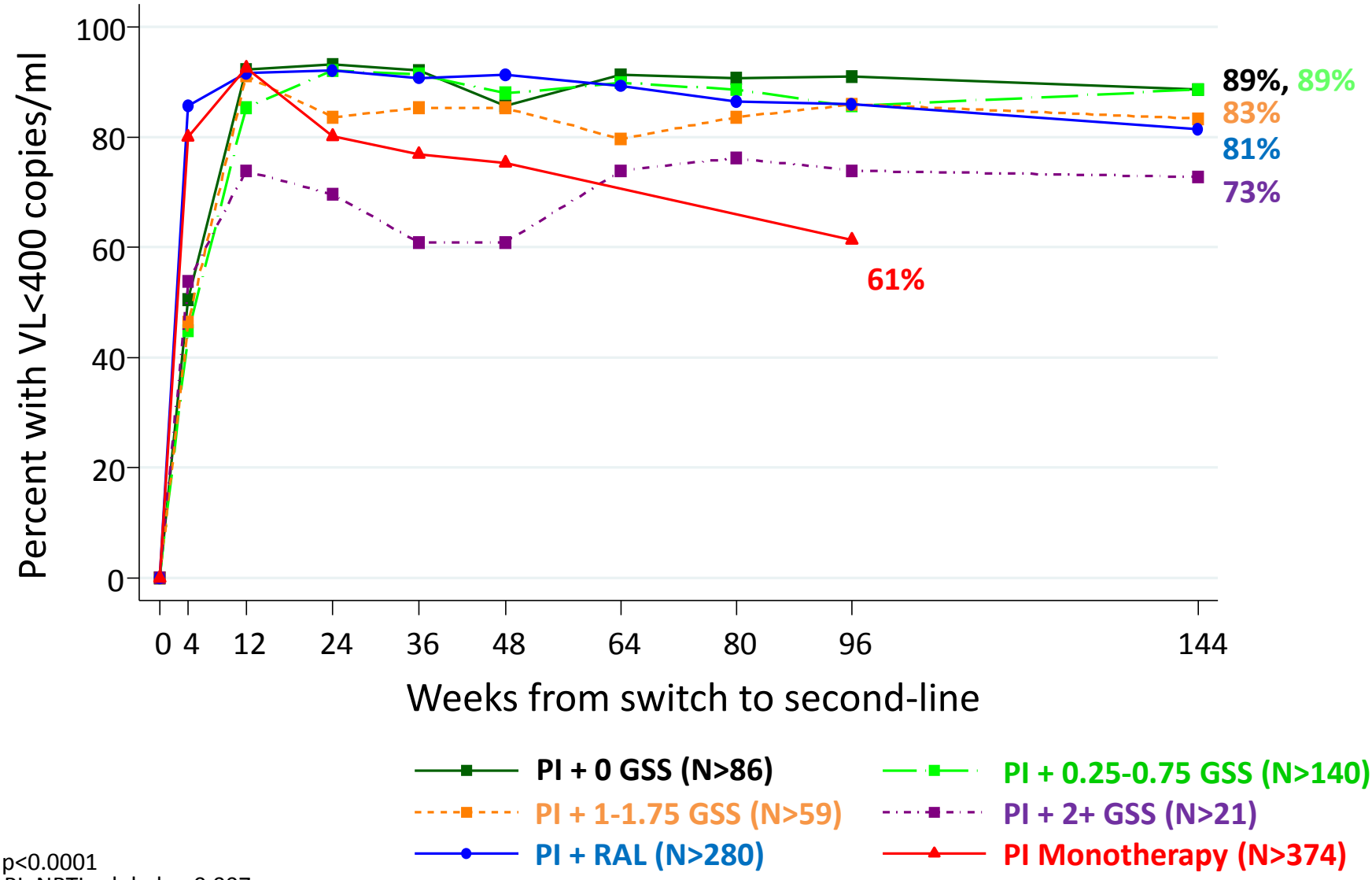
0	114 (29%)
0.25-0.75	177 (45%)
1-1.75	73 (19%)
≥2	27 (7%)

VL response by number of active NRTIs in the regimen



Global p<0.0001
Within PI+NRTIs global p=0.02
NRTI() = number or active(susceptible-low resistance) NRTIs

VL response by GSS of NRTIs in the regimen



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

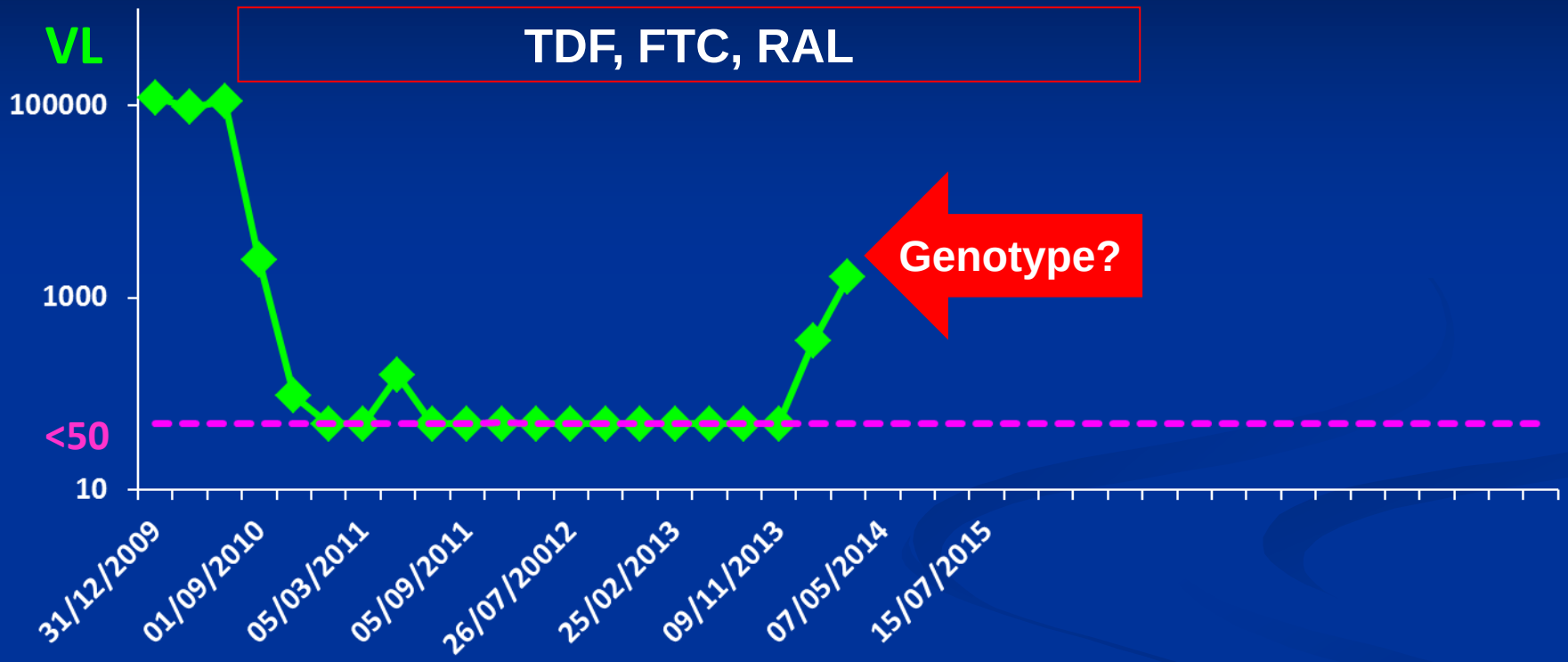
Conclusions

- **Even when no predicted activity due to resistance, NRTIs have major beneficial effect in PI (LPV/r)/NRTI 2nd-line therapy**
  - with clear added activity over a PI alone
  - equivalent to adding a new drug class
  - NRTI contribution may not be direct drug effect (fitness?)

- **Paradoxical relationship between resistance and VL suppression**
  - Confounding by adherence (although persists after adjustment)
  - Also consistent with fitness effect

- **Algorithmic NRTI drug selection + attention to adherence can achieve excellent outcomes from 2nd-line therapy in public health approach**
  - Resistance testing to select NRTIs is of little added value.

First ART failure: Integrase Inhibitors



Mr CM starts Truvada + Raltegravir in September 2010
Baseline RT: wild-type; suppresses within 3 months

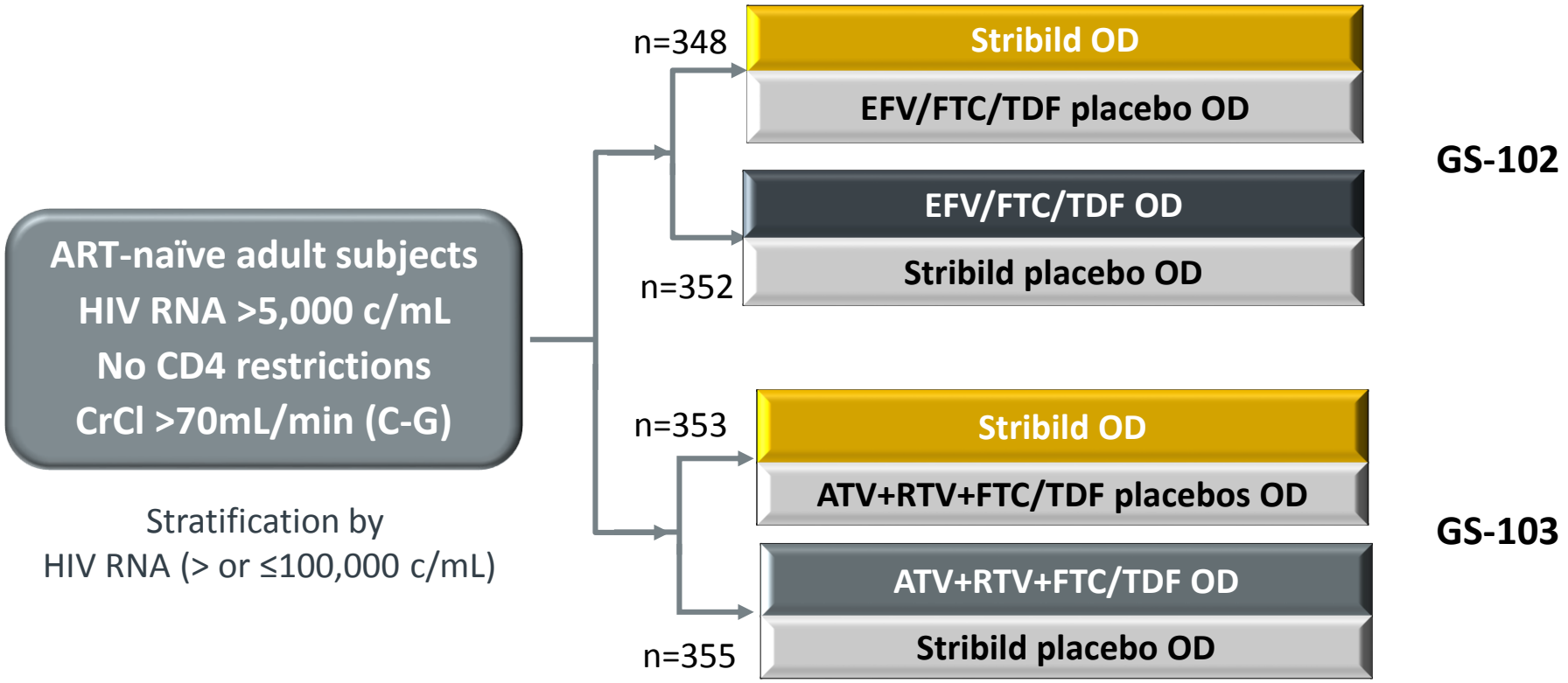
First ART failure: IIs

- Resistance patterns
  - No resistance (WT virus).
  - 3TC/FTC resistance (M184V/I) following any first-line therapy, including TDF/FTC or ABC/3TC.
  - INI resistance (e.g. K143C/R, Q148R/H, or N155H) and/or 3TC/FTC resistance (following first-line therapy with RAL or ELV-based regimen, including TDF/FTC or ABC/3TC)

Study Design

Stribild Phase 3 Studies

- **Multicentre, randomised, Phase 3, blinded, 192-week studies**



Primary endpoint: HIV-1 RNA <50 c/mL at Week 48;
FDA Snapshot analysis with non-inferiority margin of 12%

STRIBILD™
elvitegravir 150mg/ cobicistat 150mg/ emtricitabine 200mg/ tenofovir disoproxil 245mg tablets

Sax P et al. Lancet 2012; 379: 2439–48
DeJesus E et al. Lancet 2012; 379: 2429–38

C-G: Cockcroft-Gault

Primary Endpoint

FDA Snapshot

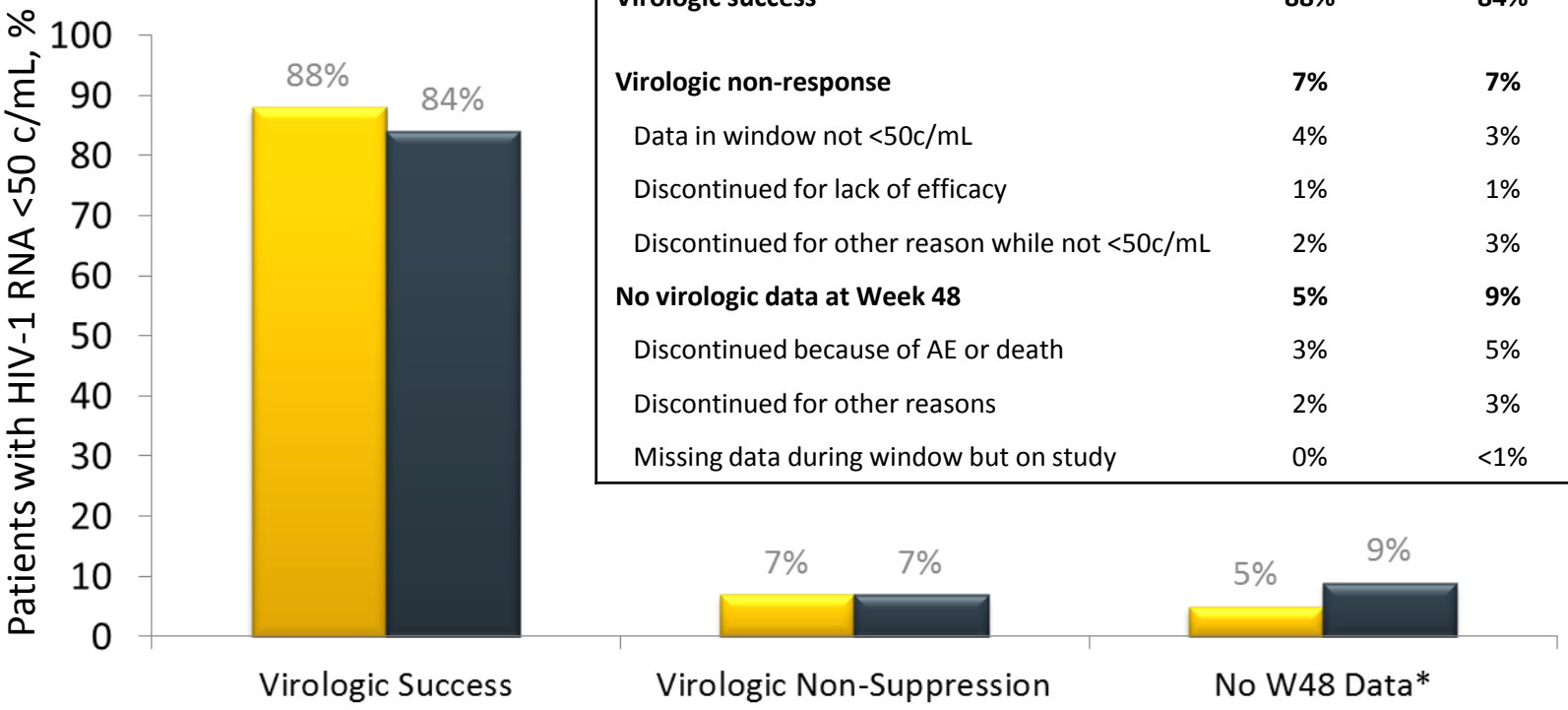
Study GS-102 – 48-week Virologic Efficacy

Stribild was non-inferior to EFV/FTC/TDF at Week 48

STB (n=348)

EFV/FTC/TDF (n=352)

Outcome (snapshot) at Week 48	STB (n=348)	EFV/FTC/TDF (n=352)	Prop Diff (95% CI)
Virologic success	**88%**	**84%**	**3.6% (–1.6%, 8.8%)**
Virologic non-response	**7%**	**7%**	
Data in window not <50c/mL	4%	3%	
Discontinued for lack of efficacy	1%	1%	
Discontinued for other reason while not <50c/mL	2%	3%	
No virologic data at Week 48	**5%**	**9%**	
Discontinued because of AE or death	3%	5%	
Discontinued for other reasons	2%	3%	
Missing data during window but on study	0%	<1%	



*Includes patients who had ≥50 copies/mL in the Week 48 window, patients who discontinued early due to lack or loss of efficacy, patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL

Sax P et al. Lancet 2012; 379: 2439–48

Data on file (STBUK1303)

STRIBILD™ 150 150 200

elvitegravir 150mg/ cobicistat 150mg/ emtricitabine 200mg/ tenofovir disoproxil 245mg tablets

Emergent Resistance Through Week 96

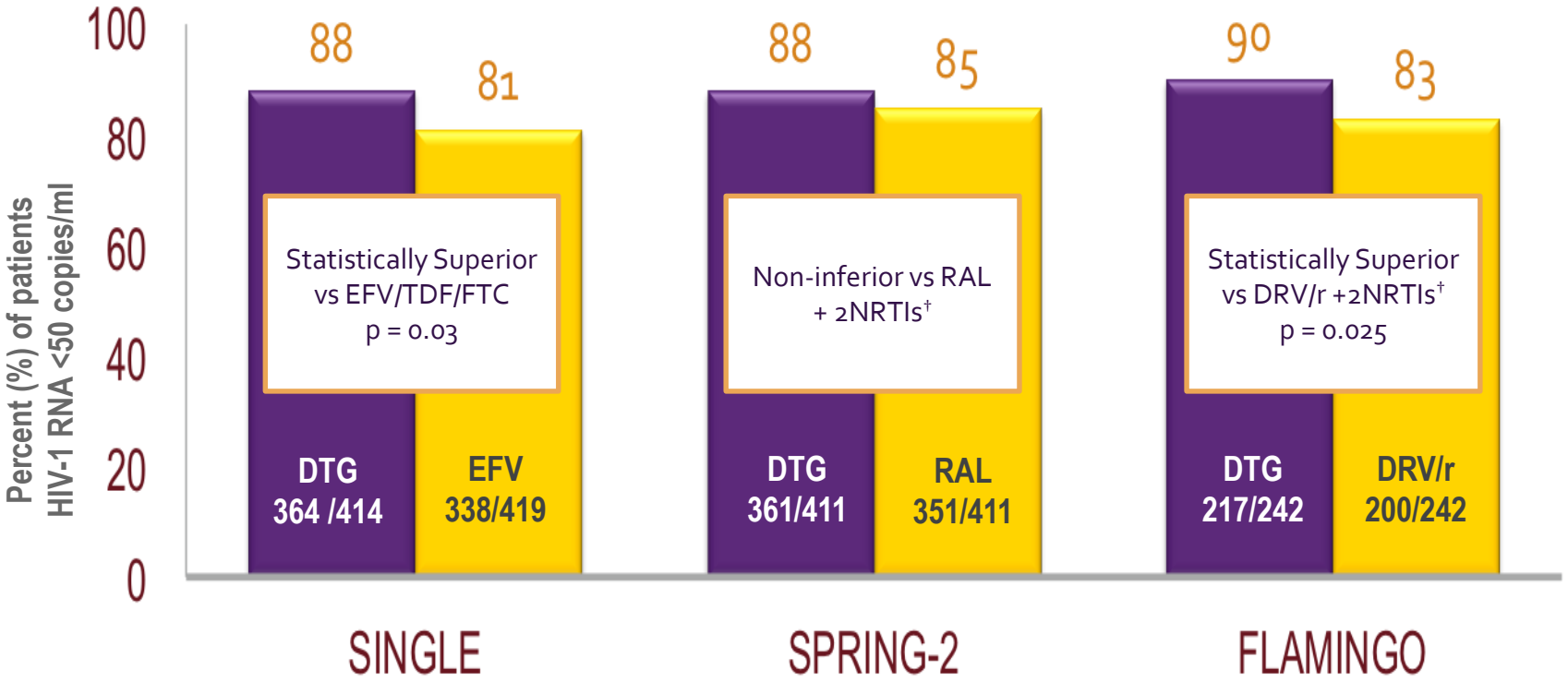
Combined Study GS-102 and -103 – Week 96

Mutation, n (%)	STB (combined, n=701) Wk 48	STB (combined, n=701) Wk 48–96	Mutation	EFV/FTC/TDF (n=352) Wk 48	EFV/FTC/TDF (n=352) Wk 48–96	ATV+RTV+FTC/TDF (n=355) Wk 48	ATV+RTV+FTC/TDF (n=355) Wk 48–96
Resistance analysis population at Week 96		36 (5.1%)			23 (5.1%)		16 (4.5%)
Any emergent resistance	13 (1.9%)	+3 (+0.4%)		8 (2.3%)	+2 (+0.6%)	0	0
Any primary integrase resistance	11 (1.6%)	+3 (+0.4%)	Any NNRTI resistance	8 (2.3%)	+2 (+0.6%)	0	0
E92Q	8	+1	K103N	7	+2		
N155H	3	+2	K101E	0	+3		
Q148R	3	0	V108I	2	0		
T66I	2	0	Y188F/H/L	1	+1		
			M230L	0	+2		
			V90I	0	+1		
			G190A	1	0		
			P225H	0	+1		
Any primary NRTI resistance	12 (1.7%)	+3 (+0.4%)		2 (0.6%)	+1 (+0.3%)	0	0
M184V/I	12	+3		2	+1	0	0
K65R	4	+1		2	+1	0	0

Zolopa A. Presented at CROI 2013, poster 553

DTG Phase III Clinical Trials in Treatment-Naïve Adult Patients

FDA Snapshot Response Rates (48-Week Data; Primary Endpoint)



- In SINGLE, 414 patients received DTG +ABC/3TC.[1]
- In SPRING-2, on Day 1 in the DTG arm, 242 and 169 patients received TDF/FTC or ABC/3TC, respectively; in the RAL arm 247 and 164 patients received TDF/FTC and ABC/3TC, respectively.[2]
- In FLAMINGO, on Day 1 in the DTG arm, 163 and 79 patients received TDF/FTC or ABC/3TC, respectively; in the DRV/r arm 162 and 80 patients received TDF/FTC and ABC/3TC, respectively.[3]

1. Walmsley S, et al. N Engl J Med 2013;369:1807–18; 2. Raffi F, et al. Lancet 2013;381:735–43; 3. Clotet B, et al. Lancet 2014;383:2222–31;

Resistance profile of DTG in treatment-naïve studies

- DTG has demonstrated a favourable resistance profile in several studies to date

Treatment-emergent mutations observed in trials with treatment-naïve patients

SINGLE study (144 weeks)[1]	DTG + ABC/3TC QD (N=414)	EFV/TDF/FTC QD (N=419)
INI resistant mutations	0	0
NRTI-resistant mutations NNRTI-resistant mutations	0 0	1 (K65R) 6 (K101E, K103N, K103K/N, G190G/A)*
SPRING-2 study (96 weeks)[2]	**DTG QD (N=411)**	**RAL BD (N=411)**
INI-resistant mutations	0	1
NRTI-resistant mutations	0	4†
FLAMINGO study (96 weeks)[3]	**DTG QD (N=242)**	**DRV/r QD (N=242)**
Treatment-emergent primary mutations (INI, NRTI, PI)	0	0

SINGLE: *n=1 with K101E, n=2 with K103N, n=2 with K103K/N, n=2 with G190G/A (n=1 with K103N and G190G/A)

SPRING-2: †1 participant had INI-resistance mutations T97T/A, E138E/D, V151V/I, and N155H, and NRTI-resistance mutations A62A/V, K65K/R, K70K/E, and M184V; 1 participant had NRTI-resistance mutation M184M/I; 1 participant had NRTI-resistance mutation A62A/V; and 1 participant had NRTI-resistance mutation M184M/V

1. Pappa K, et al. ICAAC 2014. Abstract H-647a
2. Raffi F, et al. Lancet 2013;381:735–43
3. Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

First ART failure: IIs

- Resistance patterns
  - No resistance (WT virus).
  - 3TC/FTC resistance (M184V/I) following any first-line therapy, including TDF/FTC or ABC/3TC.
  - INI resistance (e.g. K143C/R, Q148R/H, or N155H) and/or 3TC/FTC resistance (following first-line therapy with RAL or ELV-based regimen, including TDF/FTC or ABC/3TC)

- **Options:**
  - **Switch to a bPI-based regimen is optimal**

Thanks

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