Simplifying Antiretroviral Therapy Regimens: It's not so simple…

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Disclosures

- No Financial Disclosures
- Parts of this talk are adapted from Clinical Care Options (HIV) webinar: Evolving Switch Strategies for Virologically Suppressed HIV-Infected Patients

Objectives

1. Understand the rationale for guideline based ART switch strategies in virologically suppressed HIV patients and become familiar with trial data guiding these decisions
2. Identify patients who are the best candidates for undertaking an ART switch
3. Develop strong working knowledge of pros/cons for each potential switch scenario

Summary of cases

1. **Case 1:** 45 y.o. Jamaican woman on TDF/FTC/ATV/r now with jaundice

1. **Case 2:** 50 y.o. AA gentleman on TDF/FTC/LPV/r with hypertriglyceridemia and GI intolerance

1. **Case 3:** 53 y.o. Peruvian woman with newly diagnosed TB is on TDF/FTC/LPV/r

1. **Case 4:** 50 y.o. Caucasian on AZT/TDF/FTC/DRV/r with HTN, DM, worsening CKD and virologic failure.

BACKGROUND ON SWITCH STRATEGIES

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Regimen Switching In the Setting of Virologic Suppression (Last updated May 1, 2014; last reviewed May 1, 2014)

With use of currently available antiretroviral therapy (ART), most HIV-infected patients are able to achieve sustained HIV viral suppression. Furthermore, advances in treatment and better understanding about drug resistance make it possible to consider switching an effective regimen to an alternative regimen in some situations (see below). When contemplating such a switch, clinicians must consider several key principles to maintain viral suppression while addressing concerns with the current treatment.

Panel on Antiretroviral Guidelines for Adults and Adolescents. DHHS. H13-16.

Reasons to switch

- Simplify regimen
  - dosing frequency / pill burden
- Enhance tolerability and decrease toxicities
- Minimize or address drug interactions
- Pregnancy (anticipated or ongoing)
- Reduce costs
  - To patient
  - To healthcare system

Panel on Antiretroviral Guidelines for Adults and Adolescents. DHHS. H13-16.

Cardinal Principle:
Maintain Viral Suppression

- Review full ART history:
  - Drugs
  - Adverse effects
  - Virologic response
  - Resistance profiles
    - Archived mutations
    - Infer mutations based on prior failed regimens
- Increase intensity of monitoring for 3 months
  - Adherence, tolerability, viral suppression, laboratory monitoring

Panel on Antiretroviral Guidelines for Adults and Adolescents. DHHS. H13-16.

Potential Drawbacks of Switching
"If it ain't broke, don't fix it"

- Risk of new toxicities
- Emergence of archived resistance
- STRs don't allow for dosage adjustments
- Errors
  - MD, pharmacy, patient
  - Difficult follow-up
- Potential increase in cost

Case 1

45 y.o. woman with HIV/AIDS diagnosed 3 years prior (2012) started on TDF/FTC/ATV/r prior to initial genotype result

- Baseline: CD4 116/8%; VL 103,500; HLA-B*5701 negative
- Genotype: WT

Medical / Surgical History

- Cerebral Toxoplasmosis
- Adjustment disorder: no MDD, no suicidality

Case 1 Labs

	Diagnosis (7/2012)	8/2012	1/2013	7/2013	1/2014	12/2014
HIV-1 RNA (copies/mL)	103,500	< 40	ND	ND	ND	ND
CD4 T cell count (cells/µL)	116 / 8%	242/10%	311/10%	260/11%	207/12%	208/12%
HIV Genotyping	WT					
ART Regimen	TDF/FTC/ATV/r					

GFR > 70
AST 16, ALT 17, AP 109, T bili 7.2 (direct 0.6)
TC 162, TG 79, LDL 111, HDL 35
HepBsAb (-) sAg (-) cAb (-): immunized

- Jaundice notable. Friends asking why eyes are yellow
- Patient wants to switch regimens

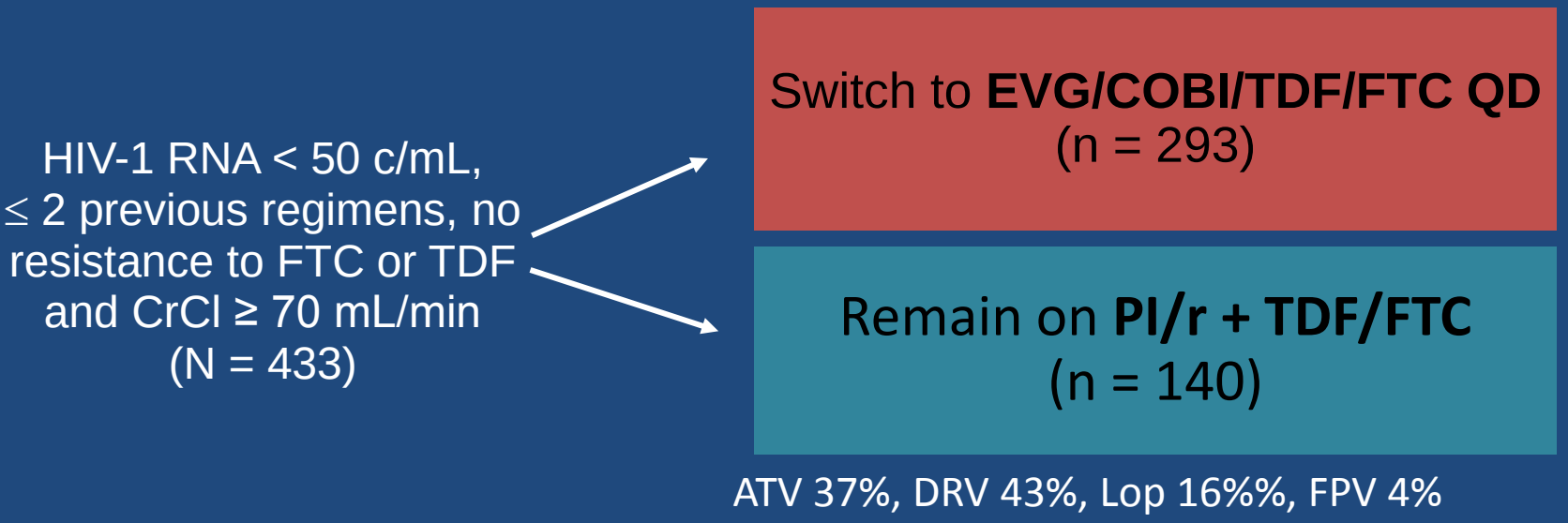
What do you switch to?

A. TDF/FTC/EFV
B. TDF/FTC/EVG/Cobi
C. TDF/FTC/RPV
D. ABC/3TC/DTG

STRATEGY-PI

Switch from PI based regimen to Stribild

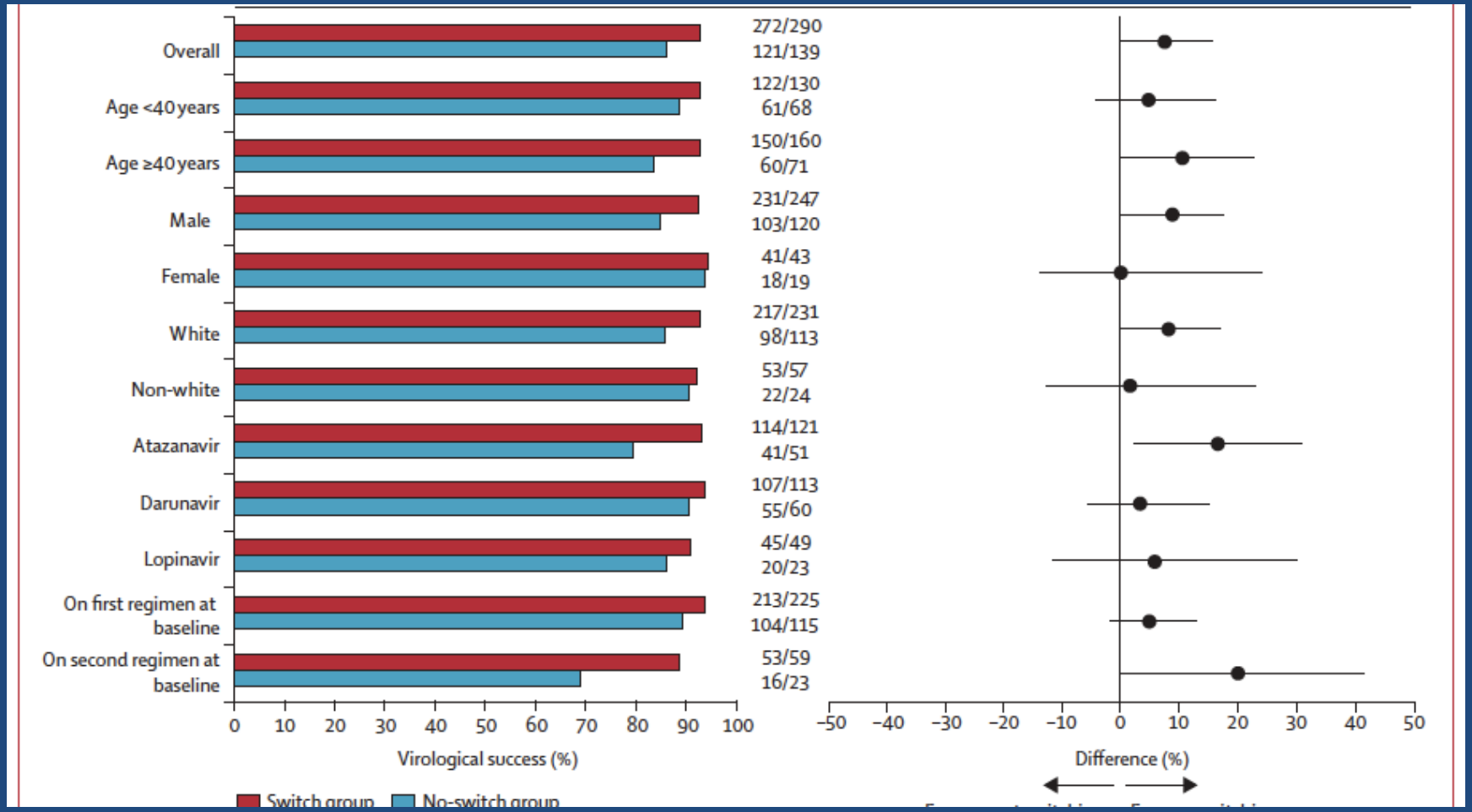
- RCT, open label switch study: patients virologically suppressed ≥ 6months on PI/r + TDF/FTC regimen
- Primary endpoint: HIV-1 RNA <50 copies/mL at wk 48



Arribas J et al. *LancetID* 2014. 14(7): 581-89

STRATEGY-PI

PI/r → EVG/COB/TDF/FTC



Arribas J et al. *LancetID* 2014. 14(7): 581-89

STRATEGY-NNRTI

Modified Intention to Treat

Details from the Study

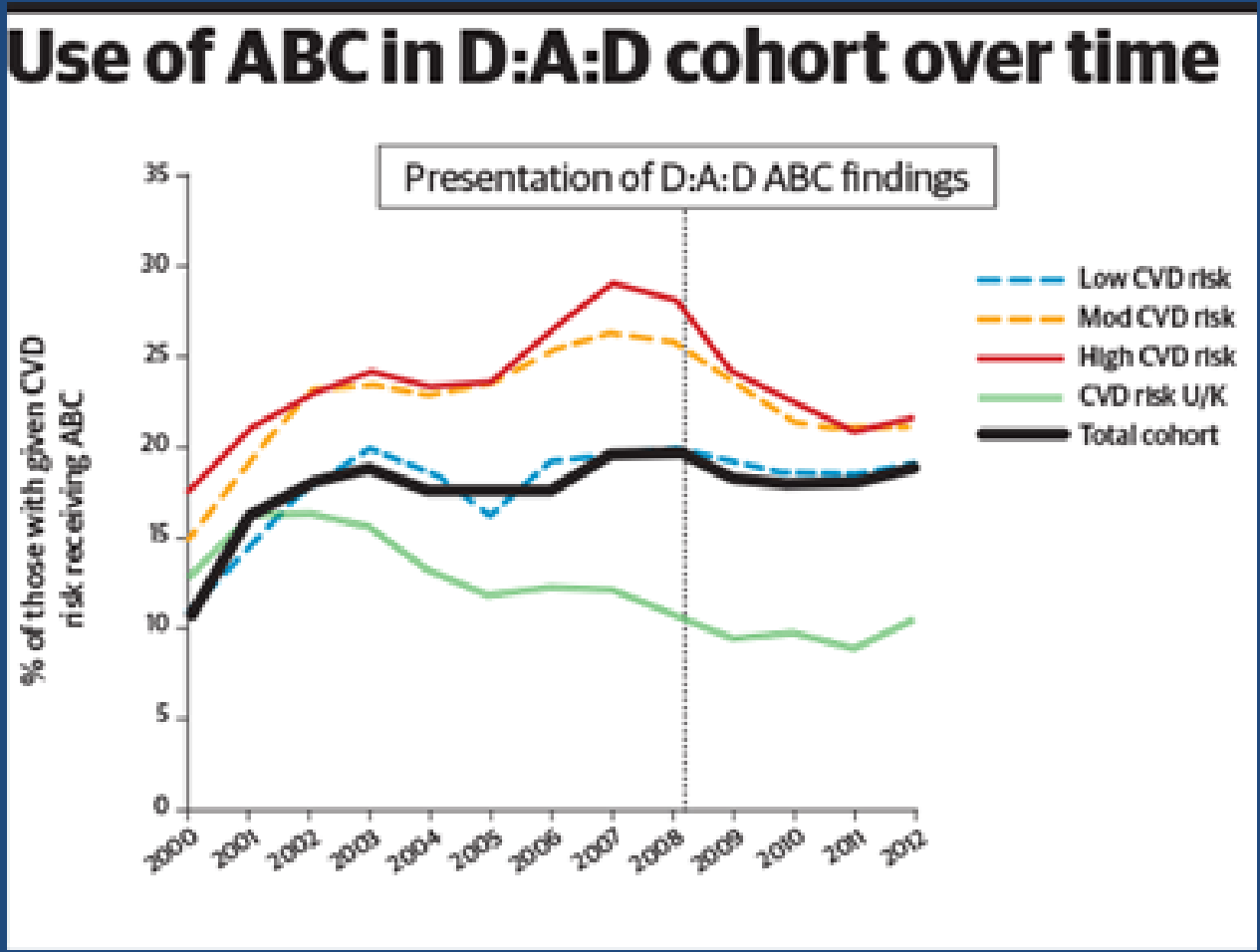
- EFV 78%, NVP 17%, RPV 4%, ETV < 1%
- Plasma HIV-1 RNA > 50 copies/ml
  - Switch = 3 (1%)
  - NNRTI = 1 (1%)
- Discontinued drug but last VL <50 copies/mL
  - Switch = 11(4%)
  - NNRTI = 13 (9%)
- Discontinued study due to AE or death
  - Switch = 5 (2%)
  - NNRTI = 1 (1%)
- No drug resistance in patients with virologic failure
- Patients switch from EFV had higher treatment satisfaction scores at week 24 and fewer neuropsychiatric symptoms at week 48 compared to baseline

Pozniak, A. et al. *Lancet ID*. July 2014;14(7): 590-99

Would you switch our patient to ABC/3TC/DTG?

A. Yes
B. No
C. I don’t know

Why not switch all patients to ABC/3TC/DTG?



ACTG 5202

ABC/3TC had worse lipid profile than TDF/FTC, whether used with EFV or ATV/r

- Higher TC, LDL and TG

- Sabin C et al. Is there continued evidence for an association between abacavir and myocardial infarct risk? CROI 2014. Boston. Abstract 747LB
- Daar E et al. CROI 2010. Abstract59LB
- Sax et al. Abacavir/lamivudine versus tenofovir/emtricitibine as part of combinations regimens for initial treatment of HIV: Final Results. JID 2011 204:1191-201

Case 2

50 y.o. gentleman with HIV/AIDS (dx in 2003), chronic hepatitis B, and HTN currently virologically suppressed on TDF/FTC/LPV/r. Presents with new hypertriglyceridemia and complains of vague ongoing abd bloating and diarrhea

- Baseline: CD4 85/6%, VL 320,000, HLA-B*5701 negative
- ART History:
  - AZT/3TC/LPV/r (2/2004 → 9/2008)
  - TDF/FTC/LPV/r (9/2008 → present)

Medical / Surgical History

- Elevated Cr baseline 1.3 – 1.5 (GFR 58 – 75)
- Dyslipidemia
- MDD

Case 2 Labs

ART start

	Diagnosis (2003)	12/2004	2006	11/2007	2/2008	6/2012
HIV-1 RNA (copies/mL)	320,000	< 50	ND	251	ND	ND
CD4 T cell count (cells/µL)	85/6%	53 /12%	244/18%	344/20%	353/22%	444/25%
HIV Genotyping	**NONE**					
ART Regimen		AZT/3TC/ LPV/r	→	→	9/2008 TDF/FTC/ LPV/r	↑

- Patient requesting simpler regimen / something that won't upset his stomach

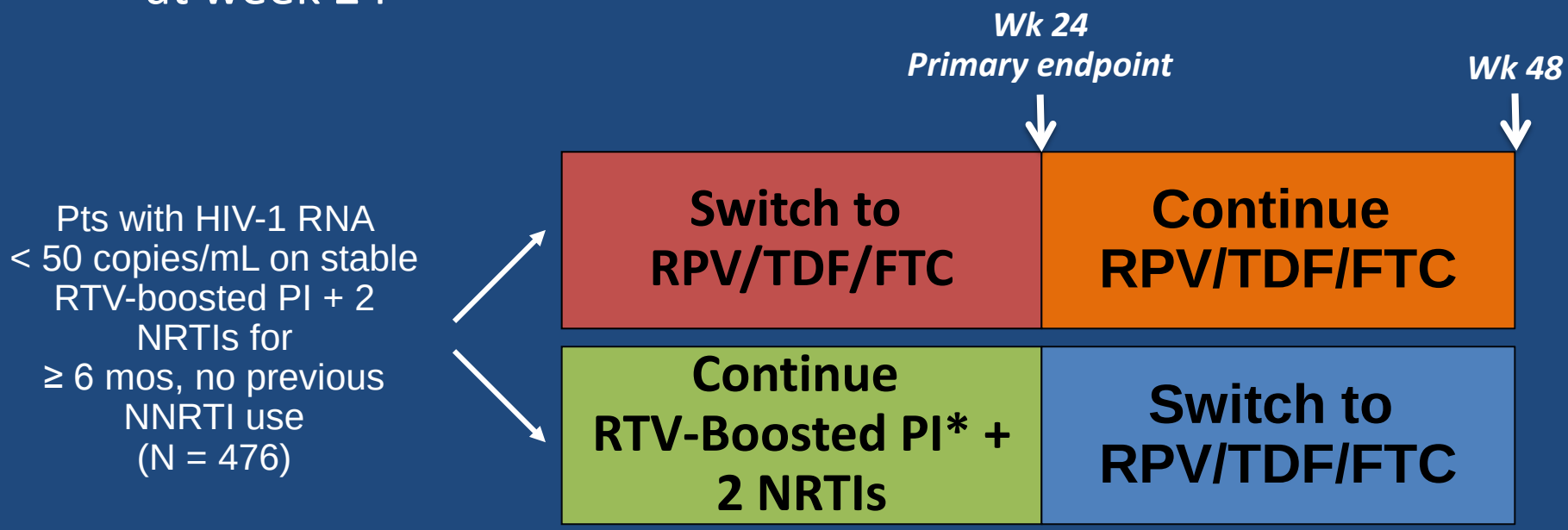
GFR ~ 55-60
AST 41, ALT 37, AP 59, T bili 0.6
TC 262, TG 1039, LDL 93, HDL 41

What do you switch to?

A. TDF/FTC/DRV/r
B. TDF/FTC/RAL
C. TDF/FTC/RPV
D. ABC/3TC/ATV/r

SPIRIT
PI/r to Rilpivirine

- RCT, open label switch trial
- Primary endpoint: maintenance of HIV-1 RNA < 50copies/mL at week 24



*PIs: ATV/RTV, 37%; LPV/RTV, 33%; DRV/RTV, 20%; FPV/RTV, 8%; SQV/RTV, 2%

Palella, F. et al. *AIDS* 2014. 28:335-344

SPIRIT: Analysis

	Immediate Switch to RPV/TDF/FTC (D1 to W24) N = 317	PI/r + 2 NRTIs (D1 to W24) n = 159	Delayed Switch to RPV/TDF/FTC (W24 to W48) n = 159	Immediate RPV/TDF/FTC D1 to W48 n = 317
VS, % HIV-1 RNA <50 copies/mL	**93.7%**	**89.9%**	**92.1%**	**89.3%**

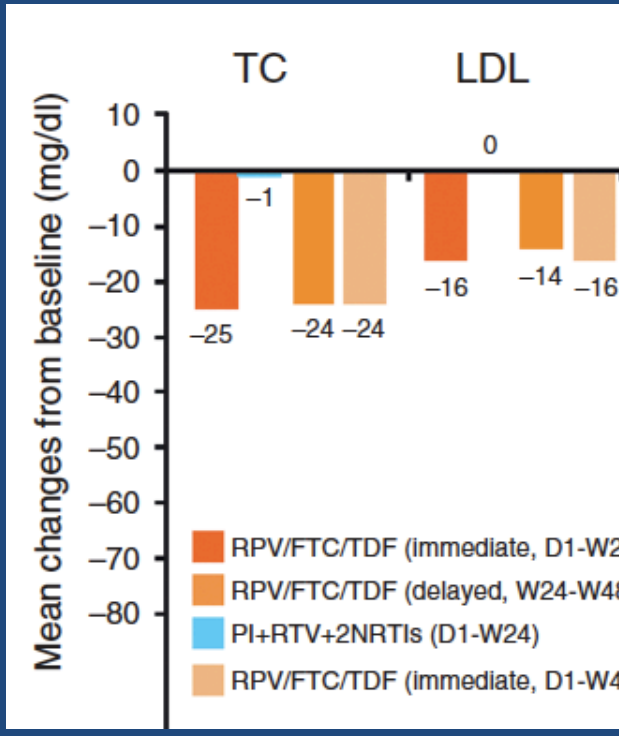
A Few More Points

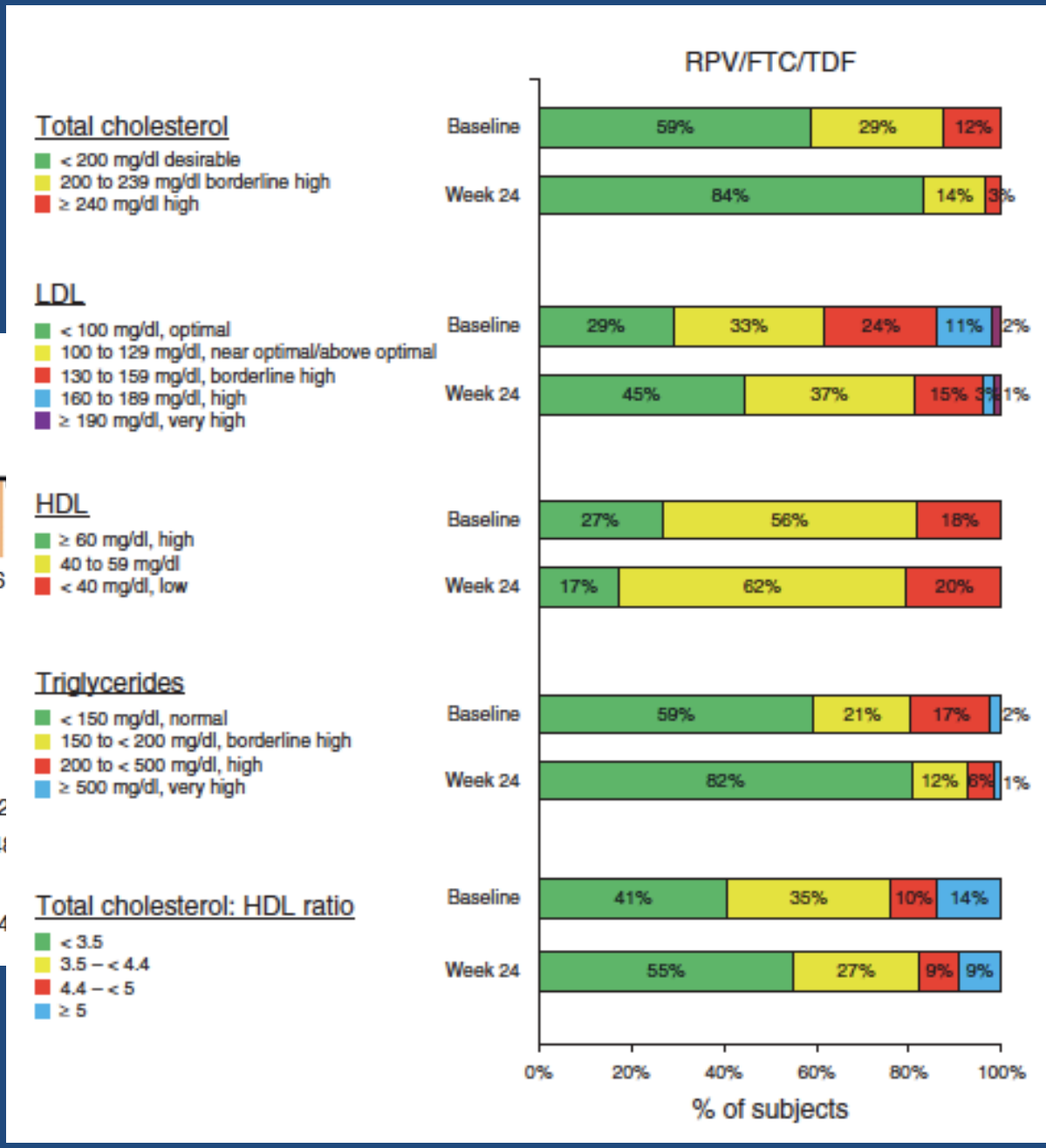
- 24 had K103N while treatment naïve. 18 in immediate switch arm and none with VF
- No difference in the pretreatment HIV-1 RNA of ≥100,000 or <100,000 groups

Palella, F. et al. *AIDS* 2014. 28:335-344

SPIRIT

A big "FAT" bonus





- Improved lipid profiles with RPV/FTC/TDF switch at 24 and 48 weeks

Palella, F. et al. *AIDS* 2014. 28:335-344

Interim Summary

- Patient currently virally suppressed with no history of virologic failure
  - Wants to switch due to medication side effects or to make dosing easier (decrease pill burden or number of times/day)
- Evidence for
  - NNRTI → TDF/FTC/EVG/Cobi
  - PI/r → TDF/FTC/RPV
  - PI/r → TDF/FTC/EVG/Cobi

Case 3

53 y.o. woman with HIV/AIDS diagnosed 15 years prior, currently on TDF/FTC/LPV/r with undetectable VL and CD4 of 378/19%. Presents with new diagnosis of pulmonary Tuberculosis

Medical / Surgical History

- HTN
- DM poorly adherent to therapy (A1C 7.5)

Case 3

- Baseline HIV data: CD4 75/5%; VL 170,000; HLA-B*5701 negative
- ART History:
  - AZT/3TC/EFV x 5 years (~ 2002 – 2007)
    - Genotype: D67N, K70R, K103N
  - TDF/FTC/LPV/r 2008 - current
- Current labs: CBC, CMP within normal limits, TC 220, TG 320, LDL 118, HDL 45
- You decide to start patient on RIPE for tuberculosis therapy…

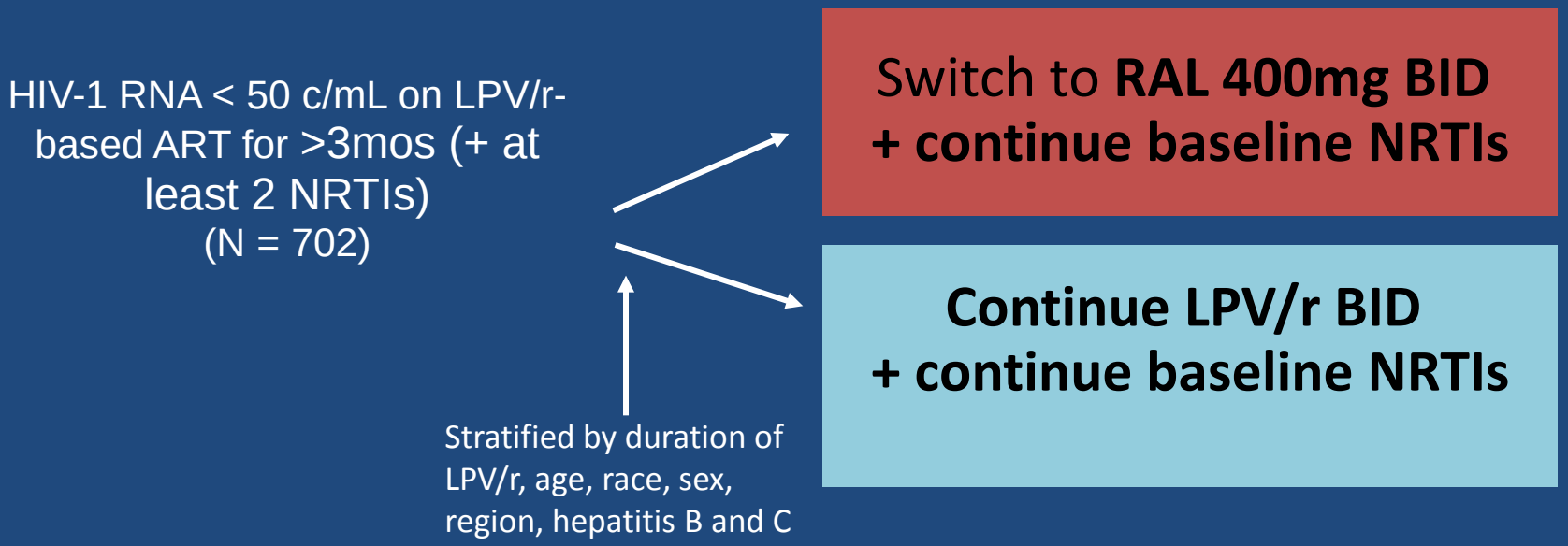
Case 3

What do you do with ART?

A. Continue TDF/FTC/LPV/r
B. Change to TDF/FTC/EFV
C. Change to TDF/FTC/EVG/Cobi
D. Change to TDF/FTC/RAL

SWITCHMRK Trials
LPV/r → RAL

- RCT, double-blinded, multicenter switch trial
  - OK if previous virologic failure as long as currently suppressed for time specified
- Primary endpoint: maintenance of HIV-1 RNA < 50copies/mL at week 24



Eron J et al. *Lancet* 2010; 375: 396-407.

SWITCHMRK: Analysis

- Study terminated at wk 24 because RAL did not meet noninferiority, BUT….

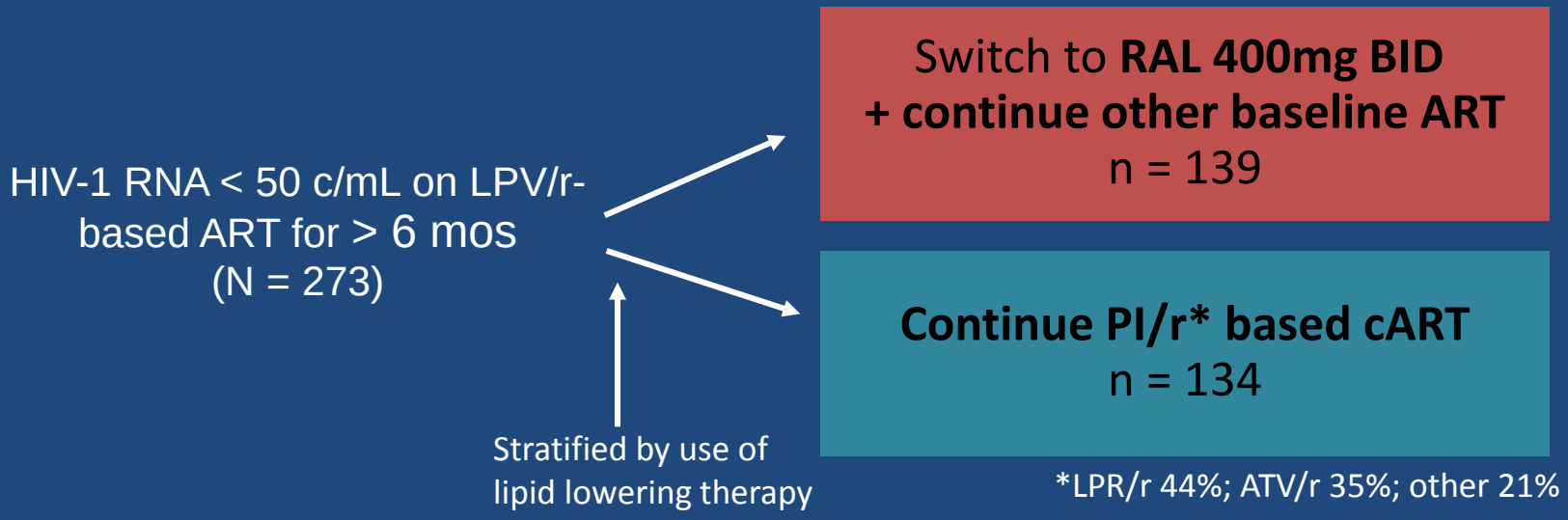
Category	Study	Raltegravir		Lopinavir-r		Treatment difference
		n/N	%*	n/N	%*	
All Patients	Combined	293/347	84%	319/352	91%	-6.2% (-11.2 - -1.3)
Patients On LPV/r as first regimen	Combined	112/128	88%	117/130	90%	-2.5% (-10.6 to 5.4)
Previous Virologic failure	**Combined**	**85/111**	**77%**	**113/123**	**92%**	**-15.3% (-25 to -6)**

Eron J et al. *Lancet* 2010; 375: 396-407.

* The percentages were rounded

SPIRAL
PI/r → RAL

- RCT, open-labeled, multicenter switch trial
  - OK if previous virologic failure as long as currently suppressed for time specified
  - Median duration of virologic suppression prior to switch: 6.6. yrs
- Primary endpoint: maintenance of HIV-1 RNA < 50copies/mL at week 48



Martinez E et al. *AIDS* 2010. 24:1697 – 1707.

SPIRAL: Analysis

- Raltegravir switch group non-inferior to boosted PI

Maintained Viral Suppression at Week 48	Raltegravir		PI/r		Treatment difference
	n/N	%	n/N	%	% (95% CI)
All patients	127/142	90	122/140	87	+2.3% (-5.4 to 10)
Patients with prior VF	50/55	91	40/48	83	+7.6% (-5.6 to 21.5)
Patients with prior VF or suboptimal therapy	70/79	89	54/65	83	+5.5% (-5.9 to 17.6)

- Improved lipids with Raltegravir

Martinez E et al. *AIDS* 2010. 24:1697 – 1707.

NRTI SPARING REGIMENS: ARE THEY AN OPTION?

Why consider NRTI sparing regimens?

- Avoid long term toxicities:
  - Cardiovascular
  - Kidney
  - Bone
- D:A:D: cardiovascular risk with abacavir
- EuroSIDA: progression to CKD
- D:A:D: declining GFR with tenofovir
- Increased BMD with TDF → RAL switch

Mocroft A et al. *AIDS*. 2010;24:1667-1678. Ryom L et al. *JID*. 2013;207:1359-1369. Bloch et al. *HIV med*. 2014 Jul;15(6):373-80

Case #4

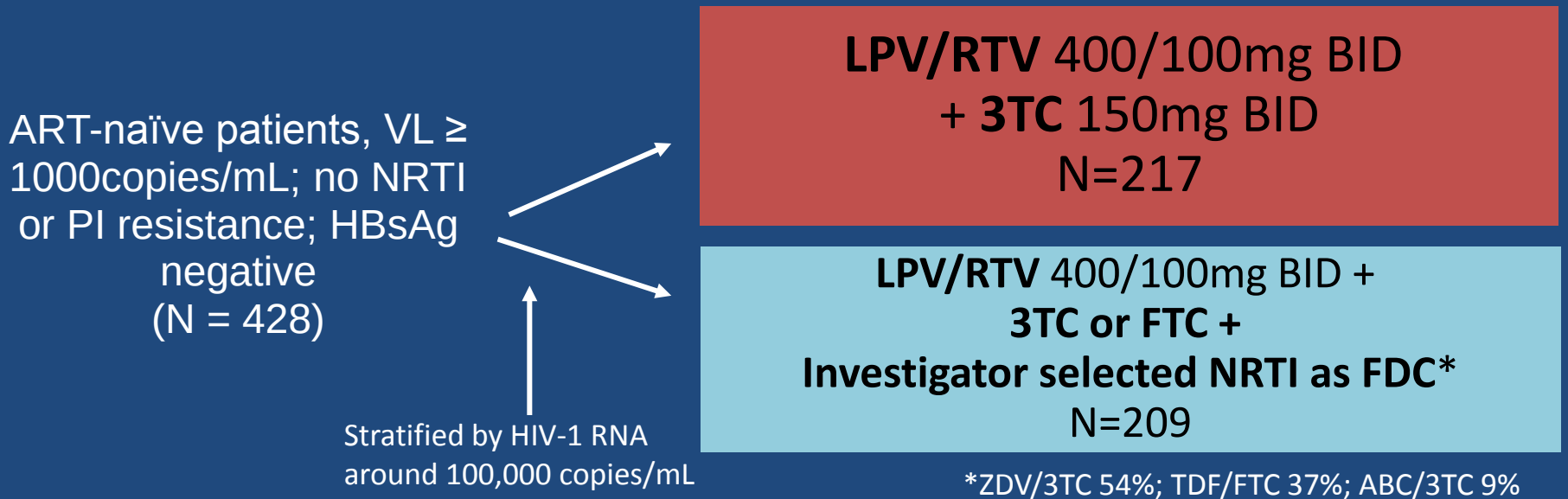
57 yo Caucasian gentleman with HIV/AIDS (dx 2000), HTN, DM, CAD.

- Baseline HIV data: CD4 120; VL 65,000; genotype WT, HLA-B*5701 positive

- ART History:
  - 2004 – 2008: TDF/FTC/EFV
    - Poorly adherent w/ VF
    - Genotype M184V, K103N.
  - 2009 – present: AZT/TDF/FTC/DRV/r
    - Adherent now and VS for 18 months
    - HBsAg negative, HBsAb positive

GARDEL
Dual ART (single NRTI) versus Triple ART

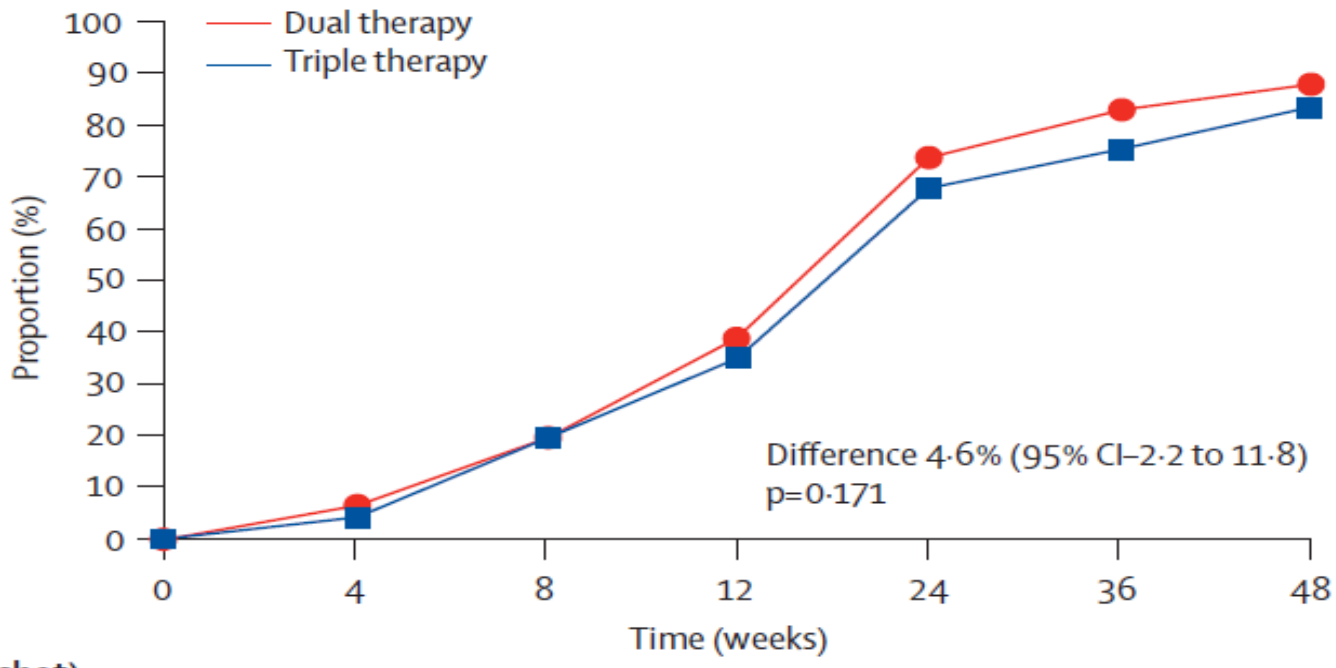
- RCT, open-labeled
- Primary endpoint: proportion of patients with HIV-1 RNA < 50copies/mL at week 48



*ZDV/3TC 54%; TDF/FTC 37%; ABC/3TC 9%

Cahn P et al. *Lancet Infect Dis*. 2014; 14: 572-80

GARDEL Analysis



Number of patients (snapshot)						
Dual therapy	214	214	214	214	214	214
Triple therapy	202	202	202	202	202	202

- Dual ART noninferior to triple ART at week 48
- CD4 count increases equivalent
- Grade 2/3 adverse events more frequent in triple ART arm (88 v 65)
- 22 patients not virally suppressed at week 48
  - 2 had m184v – both in dual ART arm

Cahn P et al. *Lancet Infect Dis*. 2014; 14: 572-80

Other supporting nucleoside sparing data in naïve Populations

- PROGRESS: 96 wk randomized pilot
  - RAL/LPV/r Vs. TDF/FTC/LPV/r
  - 206 patients randomized
  - Wk 96 response: RAL 66% vs LPV/r 69%
  - Comparable safety

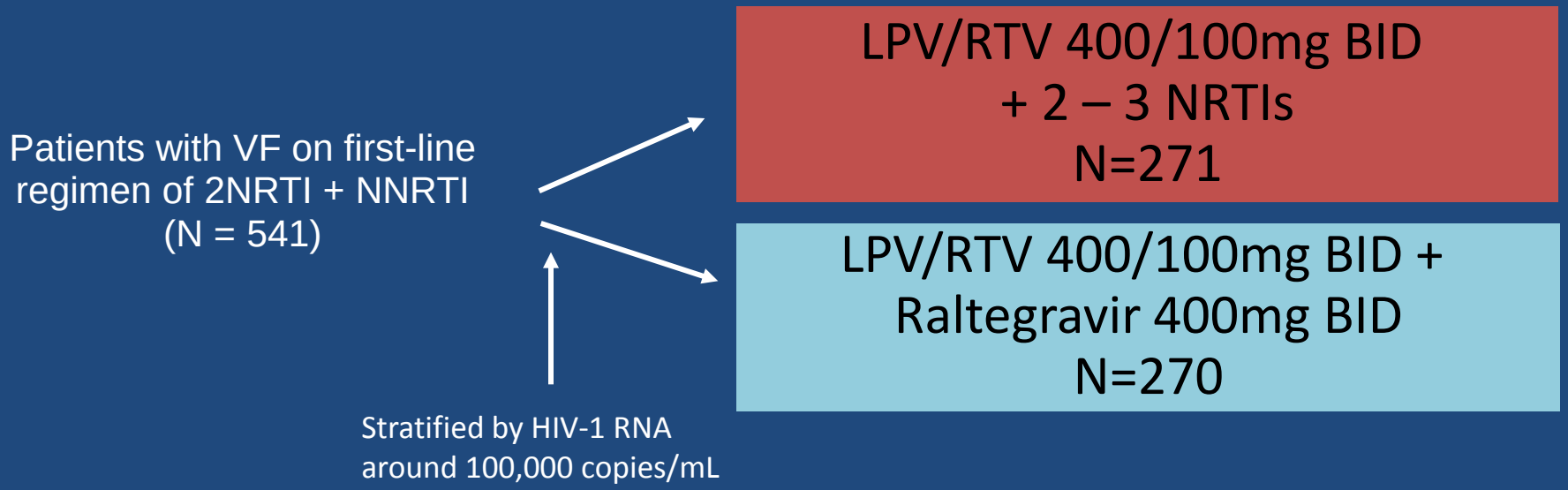
- ACTG 5262 (Phase 2b)
  - DRV/r once daily + RAL 400mg twice daily
  - 112 ART naïve patients
  - 84% virologicaly suppressed at wk 24
  - Failure associated with baseline VL > 100,000 copies/mL

Reynes J et al. *AIDS Res and Hum Retroviruses.* 2013;29(2):256-265.
Taiwo B et al. *AIDS*. 2011;25(17): 2113-2122.

SECOND-LINE

In patients with VF: LPV/r + NRTIs vs LPV/r + RAL

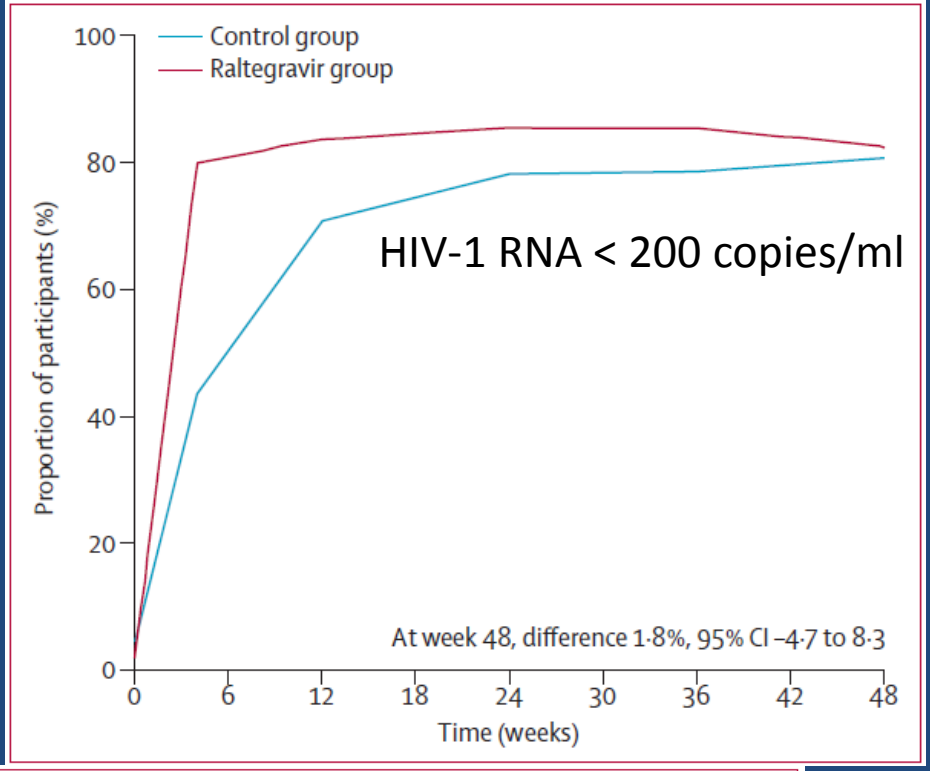
- RCT, open-labeled
- Primary endpoint: proportion of patients with HIV-1 RNA < 200 copies/mL at week 48



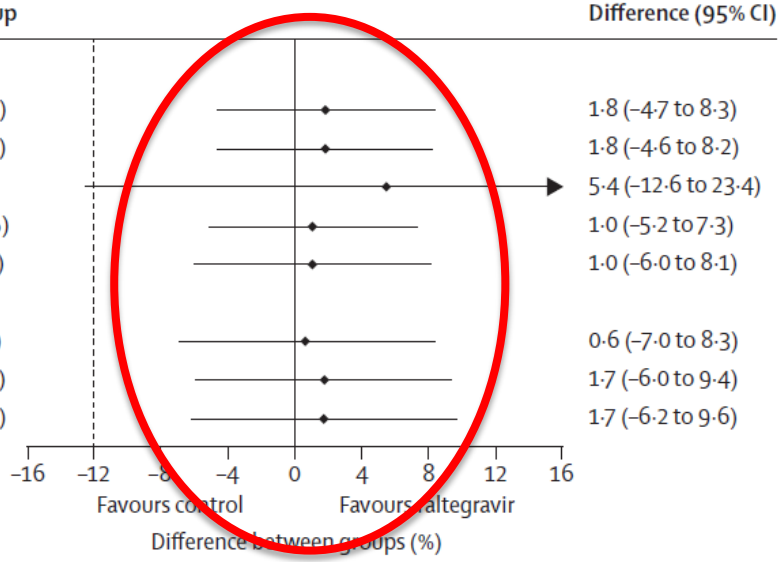
Boyd M et al. *Lancet*. 2013;381:2091-99

SECOND-LINE Results

- RAL non-inferior to the NRTIs
- New mutations in those with VF
  - RAL: 17%
  - Control: 14%



	Control group	Raltegravir group	Difference (95% CI)
Plasma viral load <200 copies/mL			
Modified intention-to-treat (primary outcome)	219/271 (80·8%)	223/270 (82·6%)	1·8 (−4·7 to 8·3)
Baseline viral load ≤100 000 copies per mL*	188/219 (85·8%)	184/210 (87·6%)	1·8 (−4·6 to 8·2)
Baseline viral load >100 000 copies per mL*	31/52 (59·6%)	39/60 (65·0%)	5·4 (−12·6 to 23·4)
Per protocol	211/249 (84·7%)	211/246 (85·8%)	1·0 (−5·2 to 7·3)
Non-completer classed as failure†	208/271 (76·8%)	210/270 (77·8%)	1·0 (−6·0 to 8·1)
Plasma viral load <50 copies per mL			
Modified intention to treat	191/271 (70·5%)	192/270 (71·1%)	0·6 (−7·0 to 8·3)
Per protocol	183/249 (73·5%)	185/246 (75·2%)	1·7 (−6·0 to 9·4)
Non-completer classed as failure†	180/271 (66·4%)	184/270 (68·1%)	1·7 (−6·2 to 9·6)



Boyd M et al. *Lancet*. 2013;381:2091-99

Any difference with newer generation Protease Inhibitors?

- NEAT Trial:
  - Randomized treatment naïve patients to DRV/r + RAL or TDF/FTC/RAL
  - Overall non-inferior

But higher rates VF with low CD4

CD4 T Cells	RAL + DRV/r	TDF/FTC/RAL
< 200 cells/µL	43.2%	20.9%
≥ 200 cells/µL	13.7%	12.3%

Raffi F et al. *Lancet.* 2014; 384: 1942 – 51.

Case 4 overview

50 y.o. man with h/o VF (m184V, K103N)

- HTN, DM and worsening CKD (Cr 1.2 – 2.4)
- Hemoglobin 9
- Currently on AZT/TDF/FTC/DRV/r and virologically suppressed x 18 months

Switch to which regimen?

A. AZT/3TC/DRV/r
B. ABC/3TC/DTG
C. TDF/FTC/RAL
D. LPV/r + RAL

Dropping NRTIs Altogether?
The story of boosted PI monotherapy

Study	Design	N	Therapy	Primary Endpoint
KalMo 2009 Nunes EP	96-week, open label, randomized trial; Patients on cART* ≥ 6 months and VL < 80 copies/mL prior to randomization	60	LPV/r versus cART	**Endpoint:** VL < 80 copies/mL LPV/r: 80.0% cART: 86.6%
MONOI 2012 Valantin MA	96-week, randomized, open-label, non-inferiority trial; Patients on cART with VL < 400 copies/mL ≥ 18 months and screening VL < 50 copies/mL prior to randomization	225	DRV/r versus cART	**Endpoint:** VL < 50 copies/mL DRV/r: 88% cART: 86%
OK04 2009 Arribas JR	96-week, randomized, open-label, non-inferiority trial; Patients on cART with VL < 50 copies/mL for > 6 months prior to randomization	205	LPV/r versus cART	**Endpoint:** VL < 50 copies/mL LPV/r: 77% cART: 78%
MONET 2011 Arribas JR	144-week, randomized, open-label, non-inferiority trial; Patients on cART for ≥ 6 months with screening VL < 50 copies/mL prior to randomization	256	DRV/r versus cART	**Endpoint:** VL < 50 copies/mL DRV/r: 72% cART: 78%
MODAT 2013 Castagna A	48-week, randomized, open-label, non-inferiority trial, interim analysis; Patients on cART for ≥ 48 weeks with viral suppression for ≥ 24 weeks prior to randomization	103	ATV/r versus cART	**Endpoint**: Efficacy, where treatment failure was considered virologic failure[$] or discontinuation for any reason ATV/r: 73% cART: 85%

- Some achieved non-inferiority, others didn't
- Large variability with regard to prior therapy
  - Virologic failure, amount of time virally suppressed
- Patients on PI/r monotherapy who failed virologically tended to not acquire resistance and re-suppressed with addition of NRTI

Colasanti J et al. *AIDS*. 2014 Apr 24;28(28(7):943-7

Conclusions

- Possibilities exist even for patients on older/complex/toxic regimens with prior VF
- After a switch, ensure follow up and maintenance of viral suppression
  - Allows for re-broadening of regimen
- Patients with well documented ART history, and longer duration of viral suppression are probably best suited for any reductive approach

Select patients carefully!

References

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