Management of HIV resistance in HIV aging patients. Switching to the most suitable regimen.

Daniele Armenia, PhD

COMPREHENSIVE MANAGEMENT OF
AGING IN HIV
INFECTED SUBJECTS

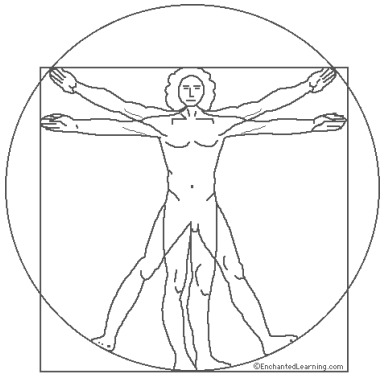
Outline

- Overview of resistance development
- What is resistance today?
- What is changing in antiretroviral therapy?
- Impact of historical resistance at therapy switch
- Impact of resistance in proviral DNA at therapy switch
- Switching to the most suitable regimen

Outline

- **Overview of resistance development**
- What is resistance today?
- What is changing in antiretroviral therapy?
- Impact of historical resistance at therapy switch
- Impact of resistance in proviral DNA at therapy switch
- Switching to the most suitable regimen

Host-virus-drug interaction



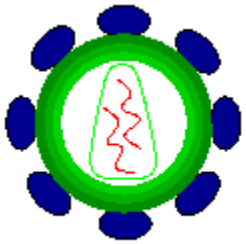
Host: human

infection

immune response

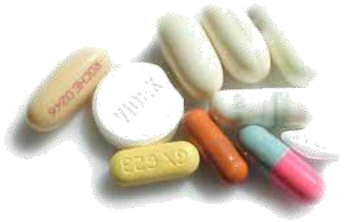
toxicity

degradation, elimination



drug resistance

inhibition



Infectious agent: HIV, HCV, HBV…

Therapy: antiretrovirals

HIV is characterized by a substantial high degree of genetic variability.

Why?

Several factors are known to contribute to the generation of new viral variants and to influence the speed with which the viruses evolve:

i) the **error-prone** nature of the RT, which lacks proofreading functions, generates a lot of mutations in the HIV genome;

ii) the **recombination** between the two strands of the dimeric RNA genome, carried out by the RT enzyme during proviral DNA synthesis;

iii) the **high rate of virus production** that sustains HIV-1 infection in vivo;

iv) the **rapid selection** for viruses with **different fitness**, mainly due to immune pressure, co-receptor selection and antiviral therapy.

Polymorphism population

RT has a high error rate 1:2,000-10,000

HIV genome 9749 nucleotides

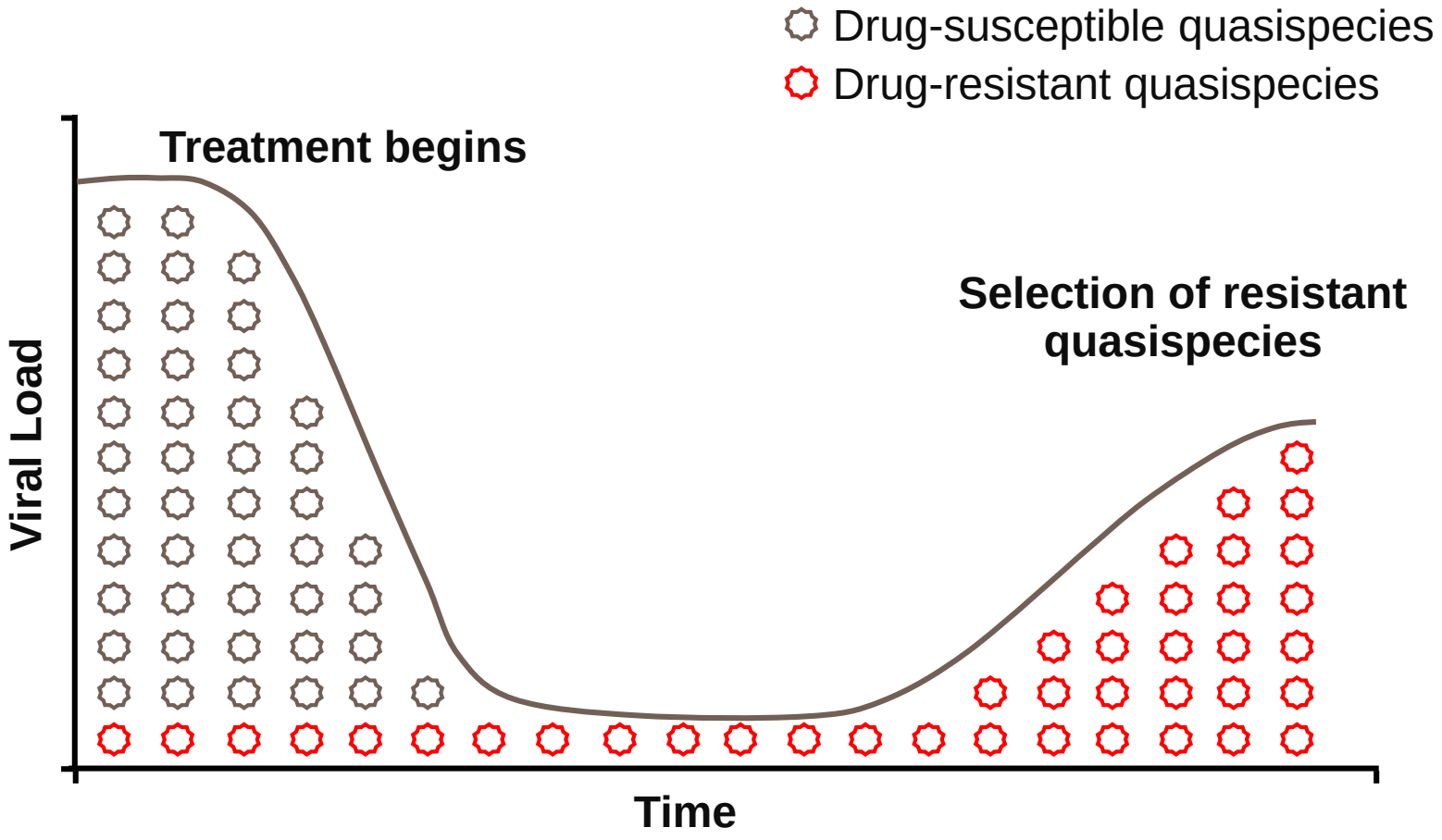
Therefore EVERY new virus has at least one mutation!
Every possible single mutation arises daily
1% of all possible double mutations arise daily

The viral population in an infected person is highly heterogeneous

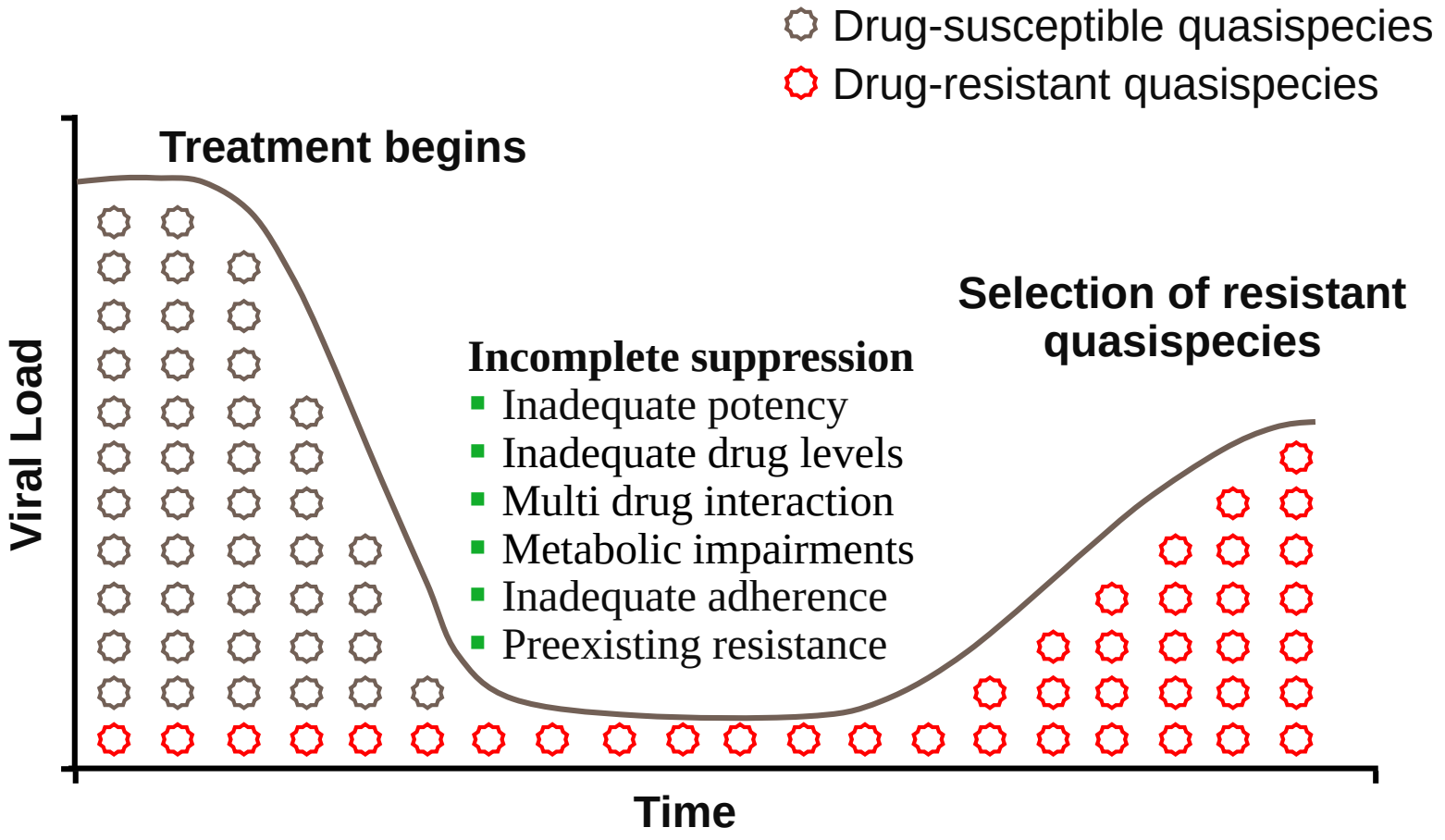
QUASISPECIES!

… CONSEQUENCES?

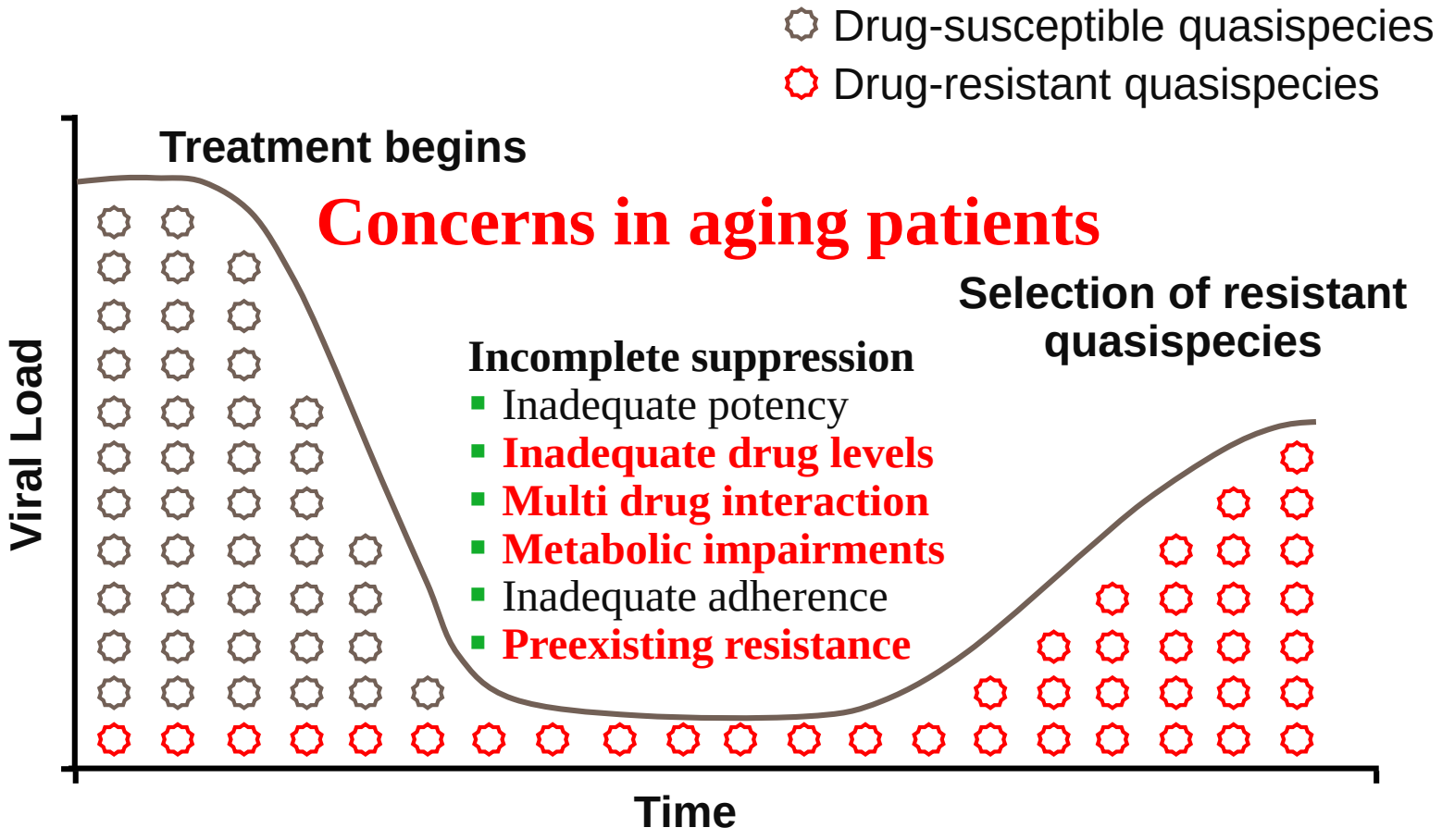
Development of Viral Resistance



Development of Viral Resistance



Development of Viral Resistance



Outline

- Overview of resistance development
- **What is resistance today?**
- What is changing in antiretroviral therapy?
- Impact of historical resistance at therapy switch
- Impact of resistance in proviral DNA at therapy switch
- Switching to the most suitable regimen

Once upon a time in 1989…

Drug-resistant strains of AIDS virus found [news]

Science. 1989 Mar 24;243(4898):1551-2. Unique Identifier : AIDSLINE MED/89186893

Marx JL

Keywords: Acquired Immunodeficiency Syndrome/*DRUG THERAPY *Drug Resistance, Microbial Human HIV/*DRUG EFFECTS Zidovudine/*THERAPEUTIC USE

890730
M8970408

Science 1 December 1989:
Vol. 246 no. 4934 pp. 1155-1158
DOI: 10.1126/science.2479983

Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT)

BA Larder and SD Kemp

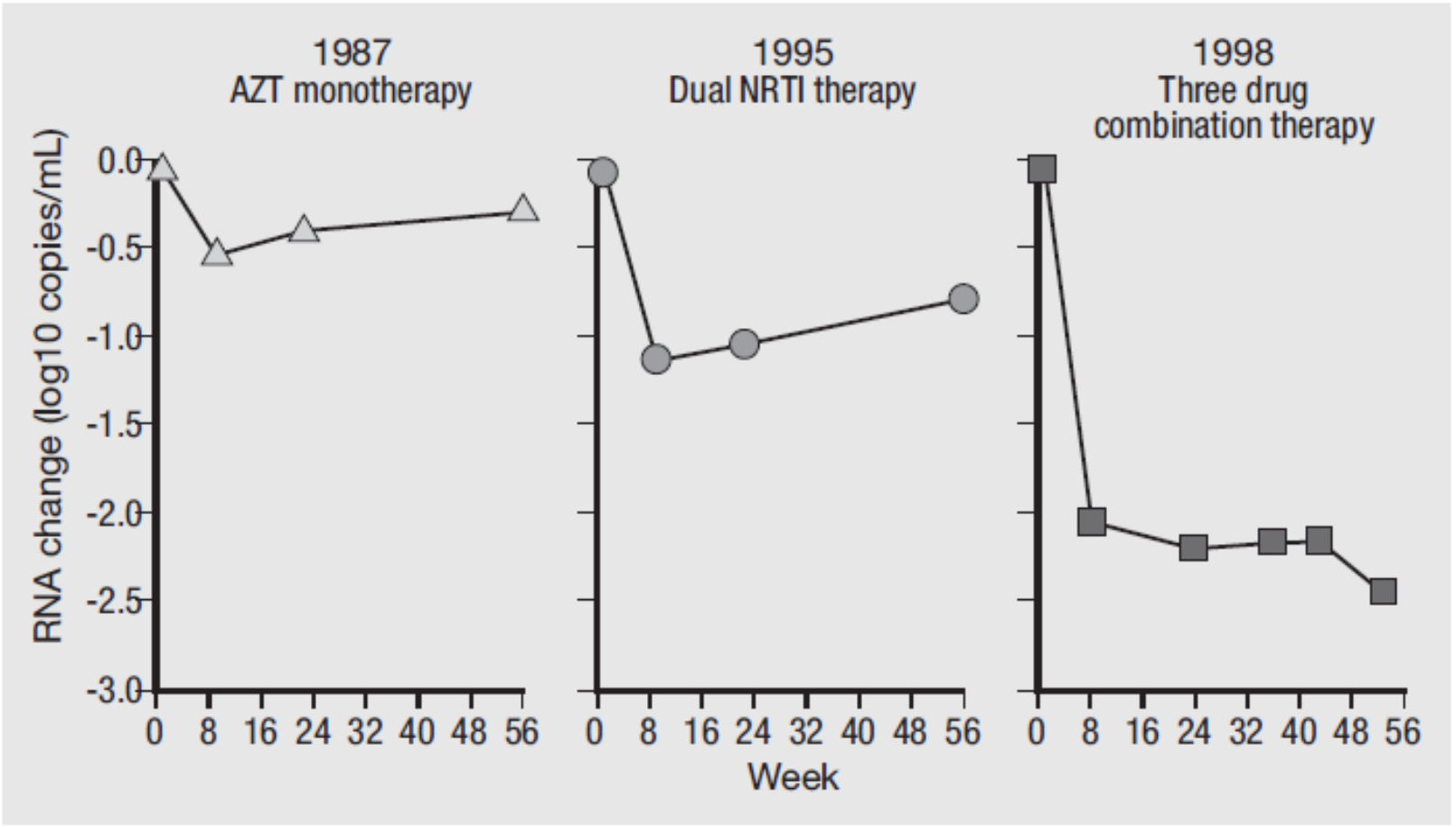
Author Affiliations

ABSTRACT

Human immunodeficiency virus (HIV) isolates with reduced sensitivity to zidovudine (3'-azido-3'-deoxythymidine, AZT) from individuals with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex were studied to determine the genetic basis of their resistance. Most were sequential isolates obtained at the initiation of and during therapy. Comparative nucleotide sequence analysis of the reverse transcriptase (RT) coding region from five pairs of sensitive and resistant isolates identified three predicted amino acid substitutions common to all the resistant strains (Asp67----Asn, Lys70----Arg, Thr215----Phe or Tyr) plus a fourth in three isolates (Lys219----Gln). Partially resistant isolates had combinations of these four changes. An infectious molecular clone constructed with these four mutations in RT yielded highly resistant HIV after transfection of T cells. The reproducible nature of these mutations should make it possible to develop rapid assays to predict zidovudine resistance by performing polymerase chain reaction amplification of nucleic acid from peripheral blood lymphocytes, thereby circumventing current lengthy HIV isolation and sensitivity testing.

4 RT mutations were associated with drug-resistance

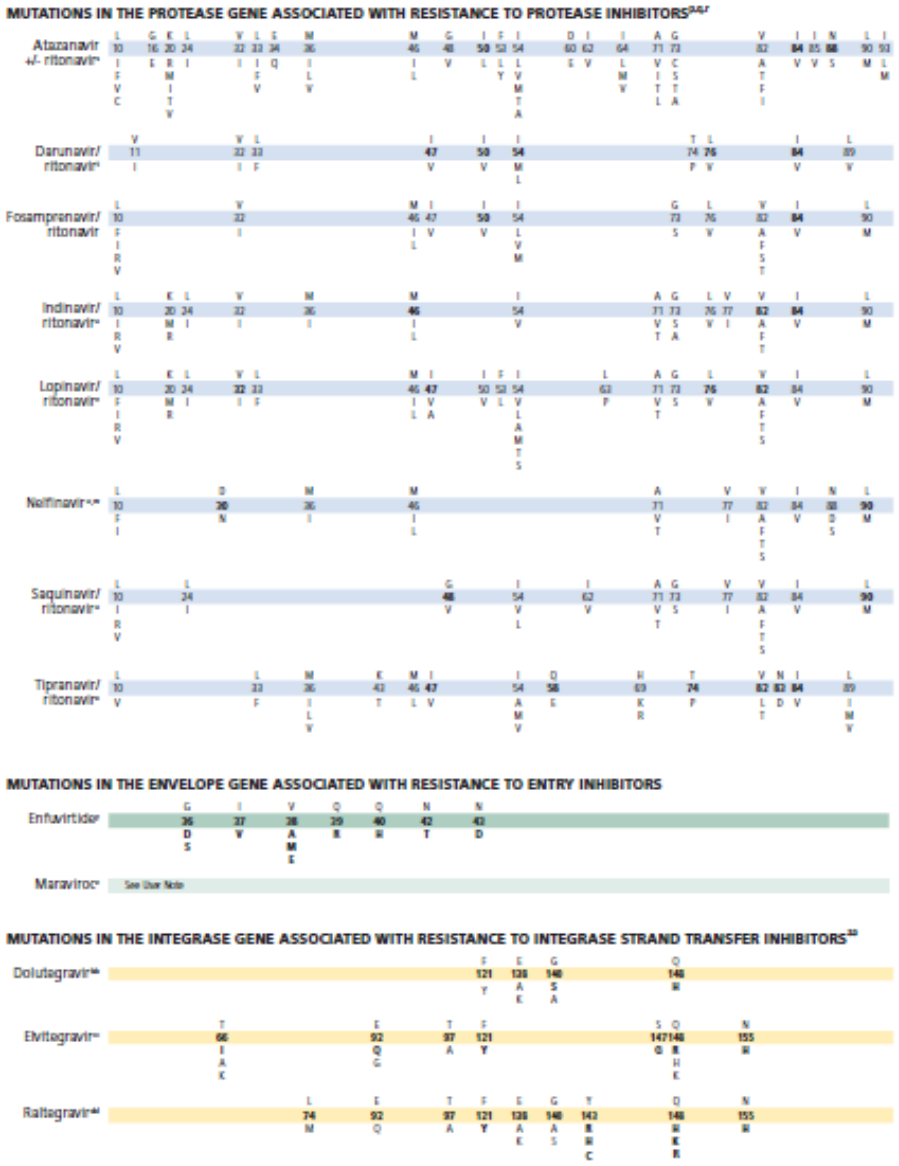
Improved drug-use

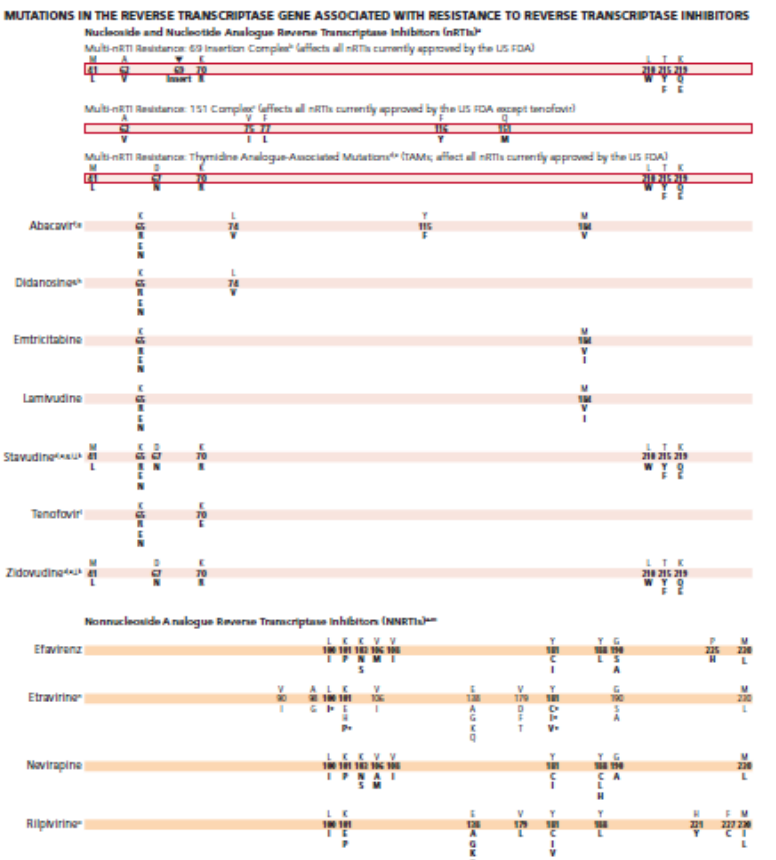


Effect of monotherapy, dual therapy, and Highly Active Antiretroviral Therapy
(HAART) on viremia over time

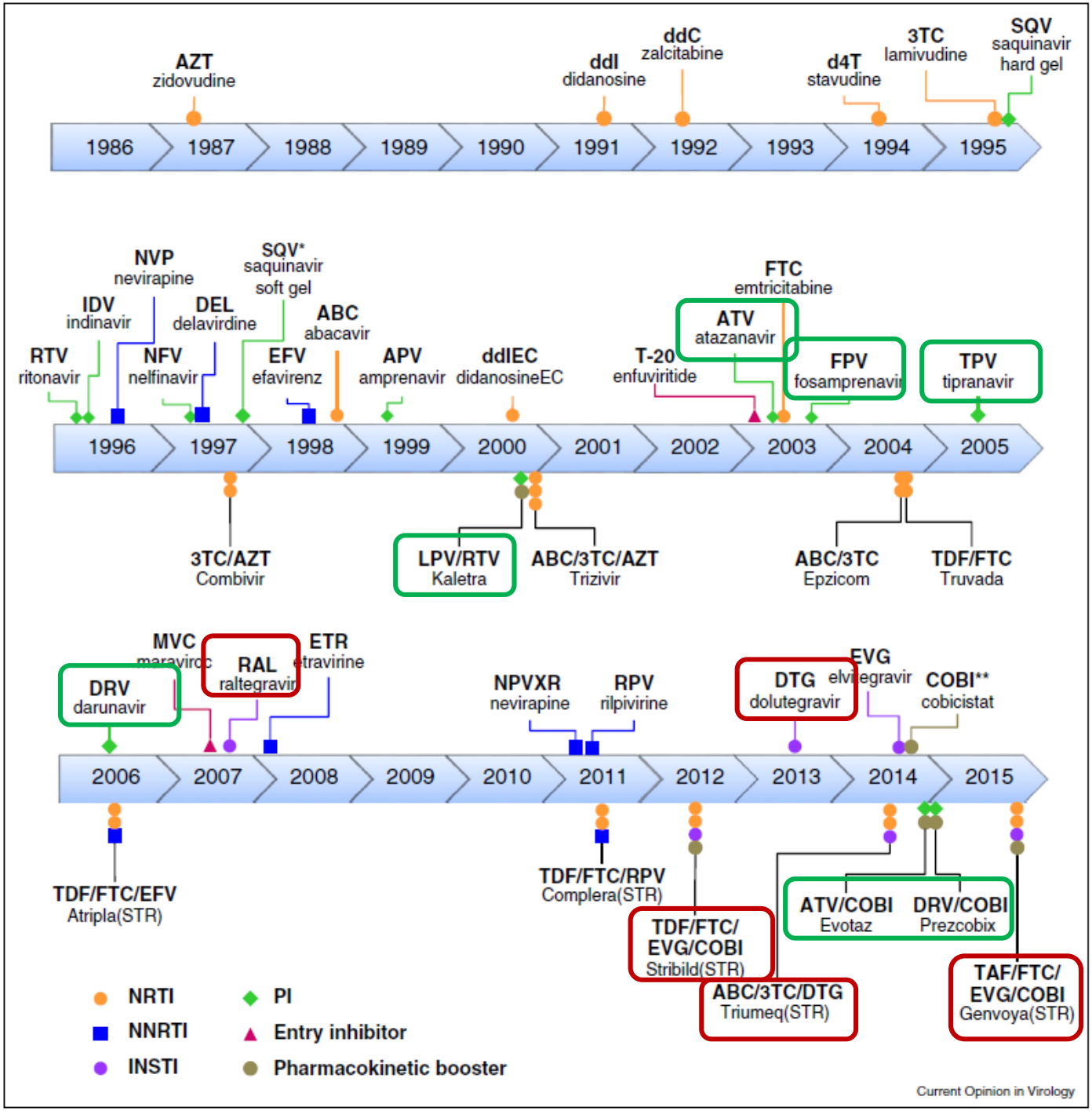
Today more than 100 mutations…

IAS Oct/Nov 2015





Wensing AM, et al. Top HIV Medicine 2015



FDA approval individual antiretroviral drugs and drug combinations

Two milestones in antiretroviral treatment:

Ritonavir-boosted PI

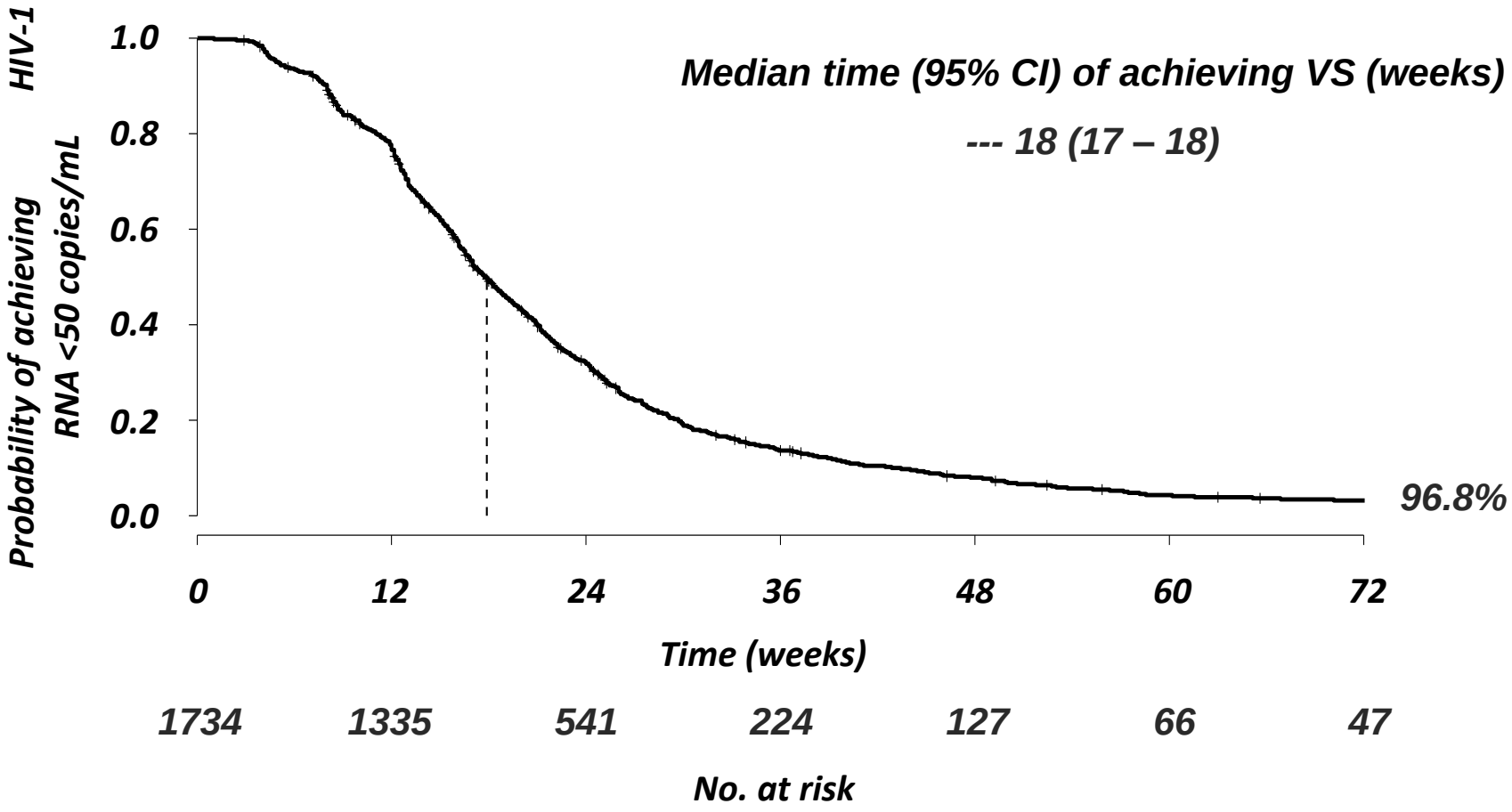
INSTI based

T Cihlar and M Fordyce Current opinion in Virol 2016

Today, thanks to the modern potent regimens, more than 90% of patients starting a first-line regimen achieve virological suppression

Indeed…….

By 72 weeks of therapy, the probability of virological success was 96.8%.



Patients (N=1,734) followed after HAART starting regardless therapy changes or interruptions. CI: confidence interval. HAART: highly active antiretroviral therapy. VS: virological success.

Di Carlo, Armenia and Santoro, unpublished data

Emergence of acquired HIV-1 drug resistance has almost been stopped in Switzerland: a 15 year prospective cohort analysis

Alexandra U. Scherrer, Viktor von Wyl, Wan-Lin Yang, Roger Kouyos, Jürg Böni, SabineYerly, Thomas Klimkait, Vincent Aubert, Matthias Cavassini, Manuel Battegay, Hansjakob Furrer, Alexandra Calmy, Pietro Vernazza, Enos Bernasconi, Huldrych F. Günthard, and theSwiss HIV Cohort Study

Background: Drug resistance is a major barrier to successful antiretroviral treatment (ART). Therefore, it is important to monitor time trends at a population level.

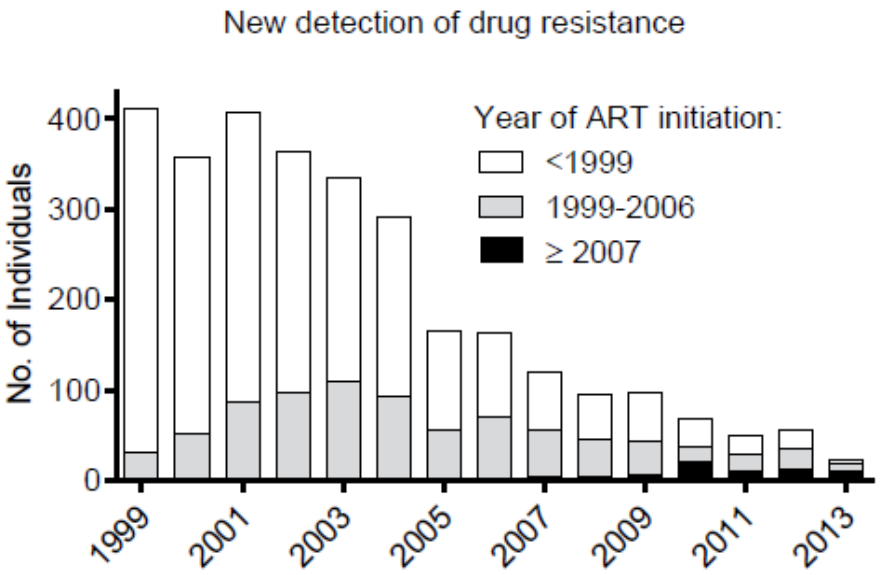
Methods: We included 11,084 ART-experienced patients from the Swiss HIV Cohort Study (SHCS) between 1999 and 2013. The SHCS is highly representative and includes 72% of patients receiving ART in Switzerland. Drug resistance was defined as the presence of at least one major mutation in a genotypic resistance test. To estimate the prevalence of drug resistance, data for patients with no resistance test was imputed based on patient's risk of harboring drug resistant viruses.

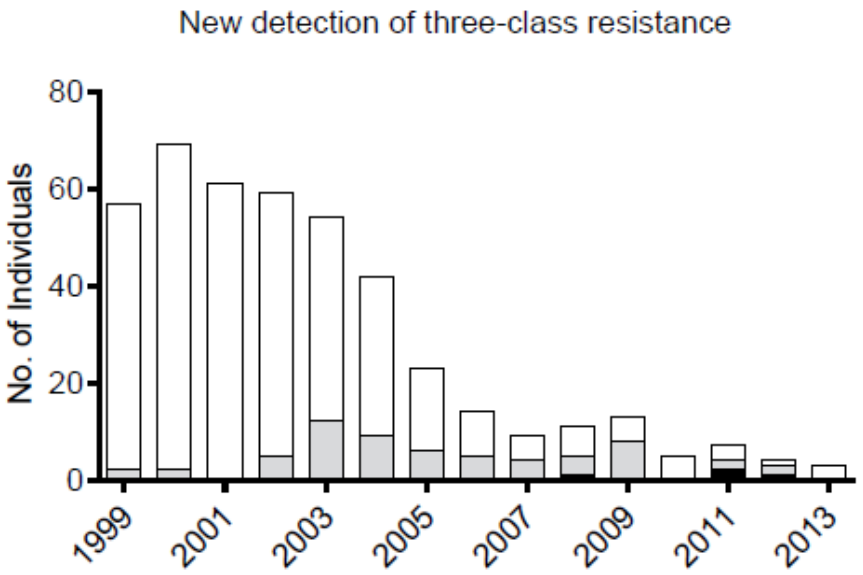
Results: The emergence of new drug resistance mutations declined dramatically from 401 to 23 patients between 1999 and 2013. The upper estimated prevalence limit of drug resistance among ART experienced patients decreased from 57.0% in 1999 to 37.1% in 2013. The prevalence of three-class resistance decreased from 9.0% to 4.4% and was always <0.4% for patients who initiated ART after 2006. Most patients actively participating in the SHCS in 2013 with drug resistant viruses initiated ART before 1999 (59.8%). Nevertheless, in 2013, 94.5% of patients who initiated ART before 1999 had good remaining treatment options based on Stanford algorithm.

Conclusion: HIV-1 drug resistance among ART-experienced patients in Switzerland is a well-controlled relic from the pre-combination ART era. **Emergence of drug resistance can be virtually stopped with new potent therapies and close monitoring.**

Clinical Infectious Diseases published March 8, 2016

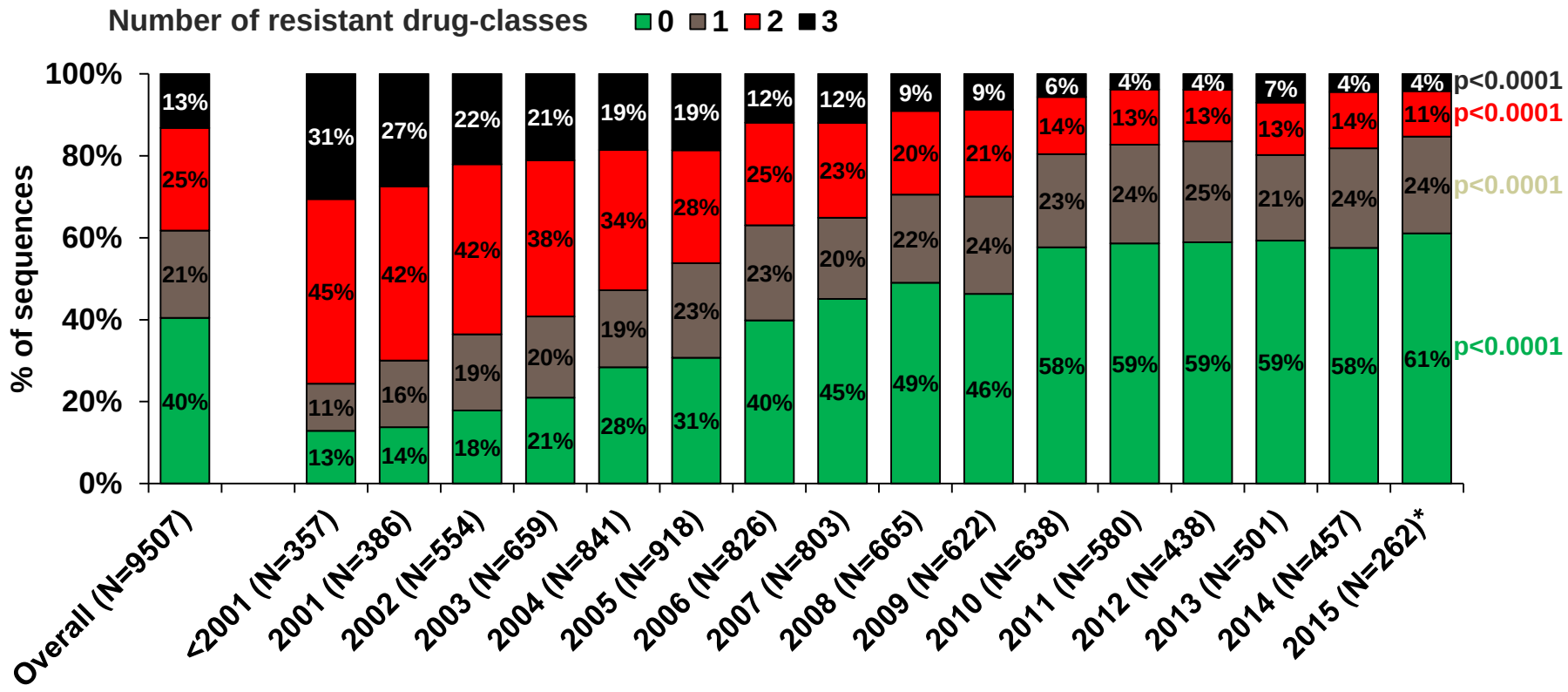
The emergence of new drug resistance mutations declined dramatically from 401 to 23 patients between 1999 and 2013





Scherrer et al CID 2016

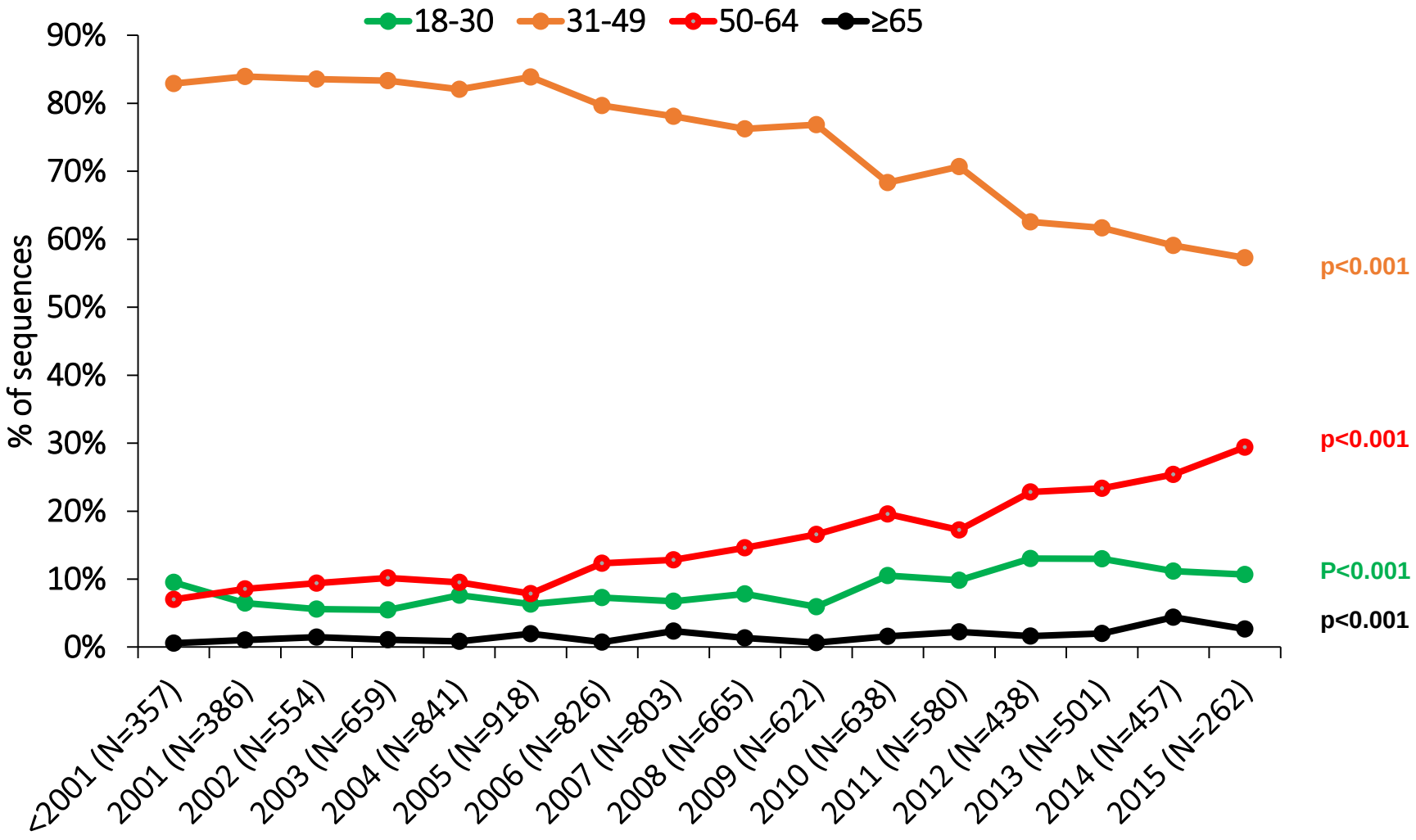
The prevalence of resistance to 3 classes significantly decreased over the years, from 30.5% before 2001 to 4.2% in 2015, while the prevalence of sequences without resistance significantly increased from 12.9% before 2001 to 61.1% in 2015.



Analysis performend on 9,507 sequences of treated HIV-1 infected patients from protease and reverse transcriptase genes. P-values by Chi-squared test for trend. *Update July 2015.

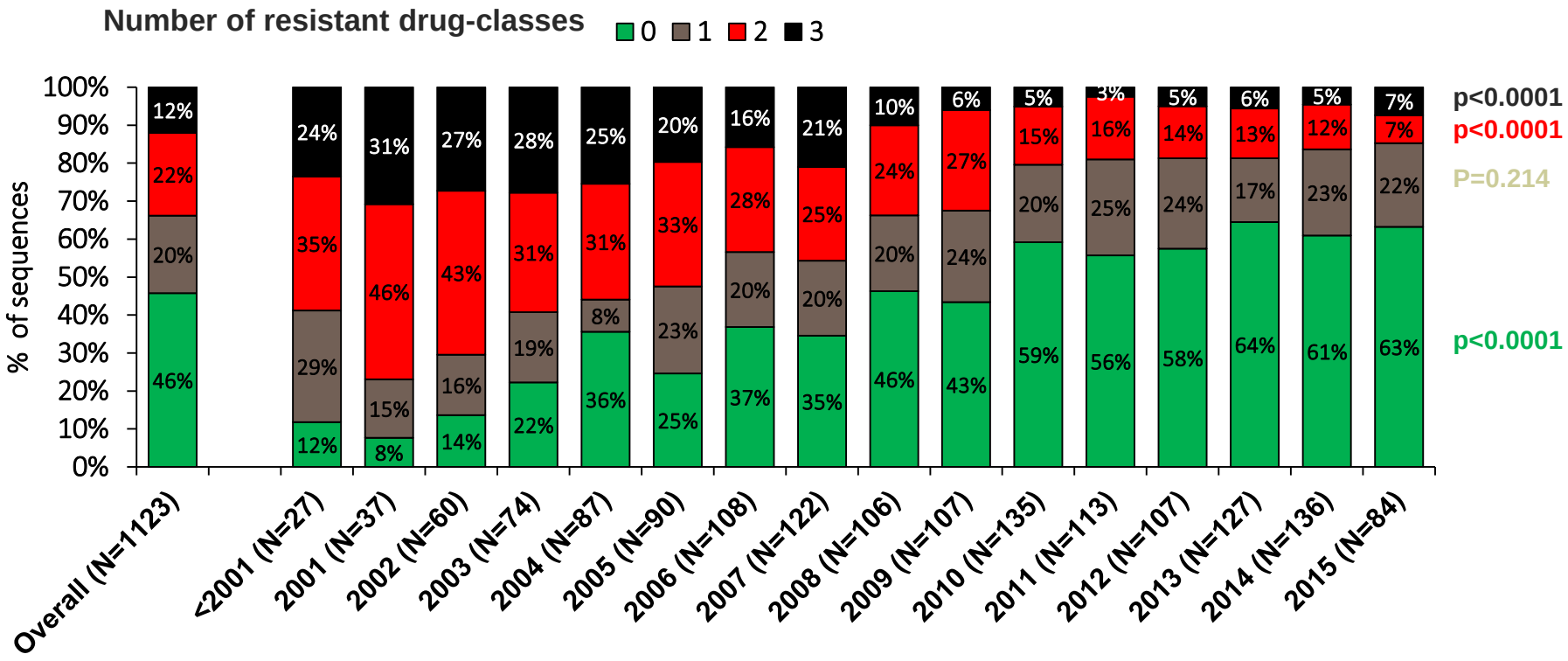
Di Carlo, Armenia, and Santoro, unpublished data

The proportion of patients >50 years old are significantly increasing over time



Di Carlo, Armenia, and Santoro, unpublished data

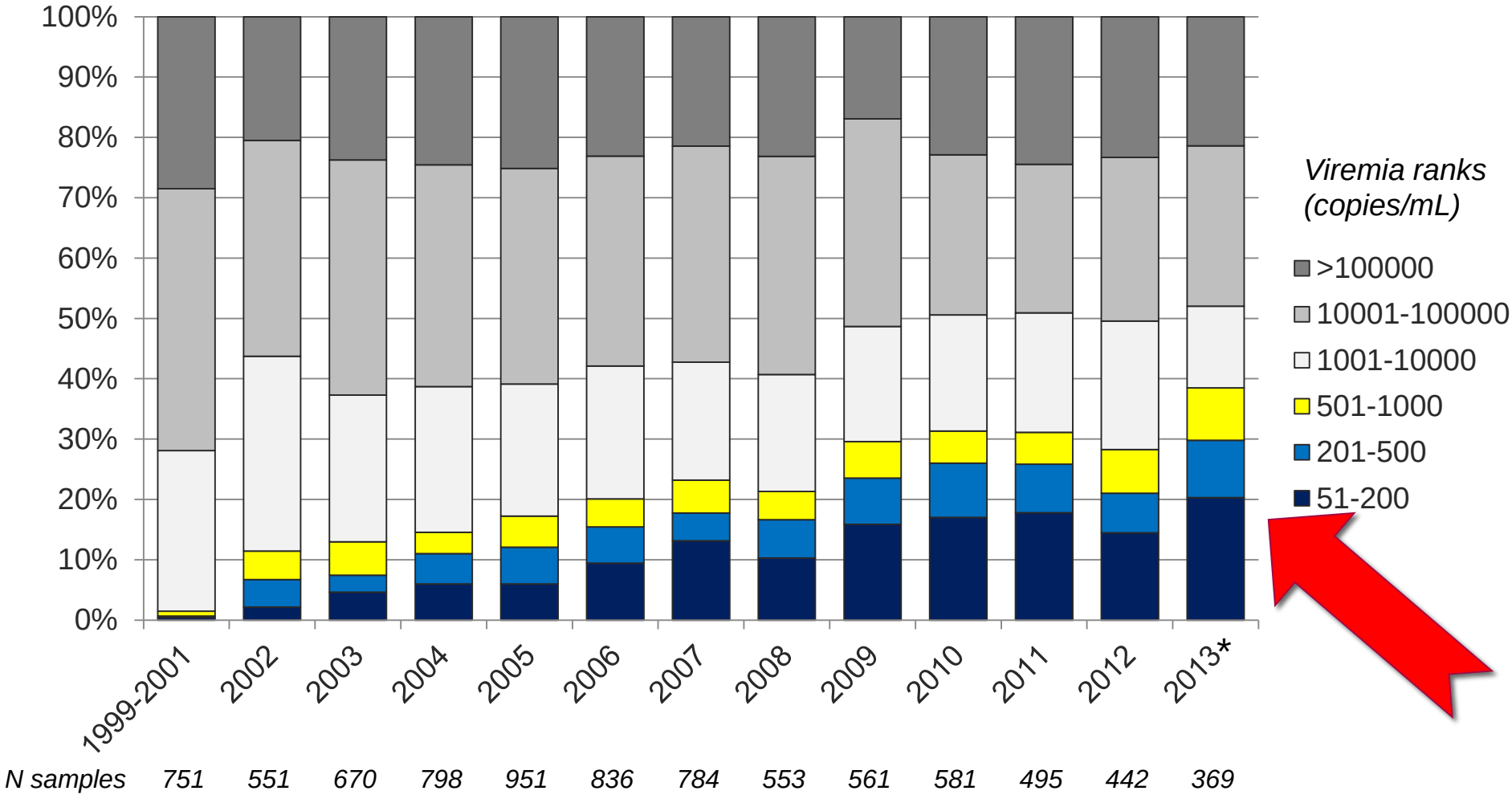
A similar trend of class resistance was observed also in sequences from patients older than 50 year with the exception of 1 class resistance that is stable over time



Analysis performend on 1123 sequences of treated HIV-1 infected patients (age >50 years) from protease and reverse transcriptase genes. P-values by Chi-squared test for trend. *Update July 2015.

Di Carlo, Armenia, and Santoro, unpublished data

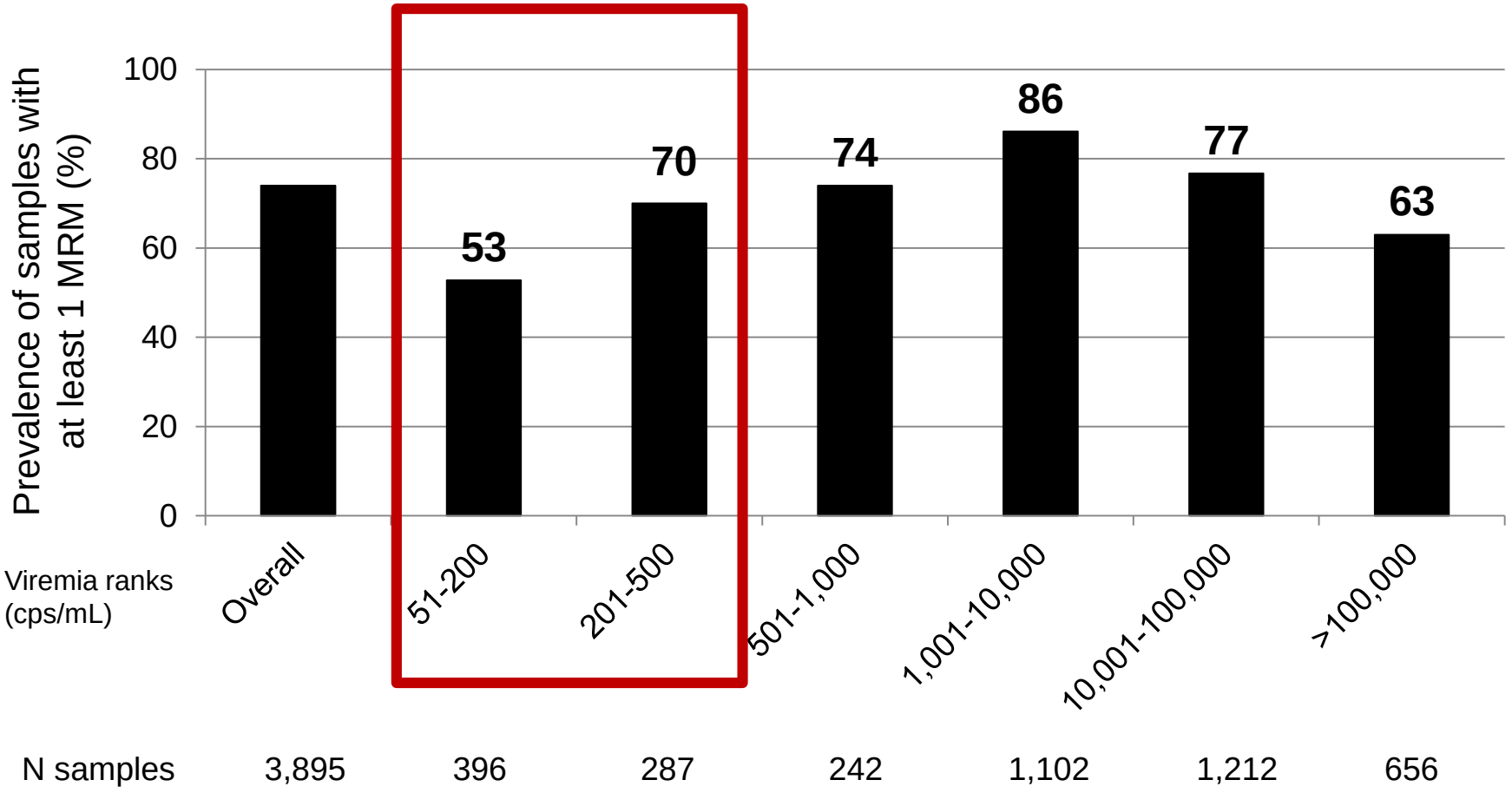
An increased number of plasma GRTs have been requested over the years for patients failing with low viremia values



8,342 genotypic requests from plasma samples of treatment experienced patients stratified by viremia and years. ** Update to October 2013.*

Santoro et al., update from CID 2014

A **considerable resistance** is observed **also at low levels of viremia in PR/RT.**

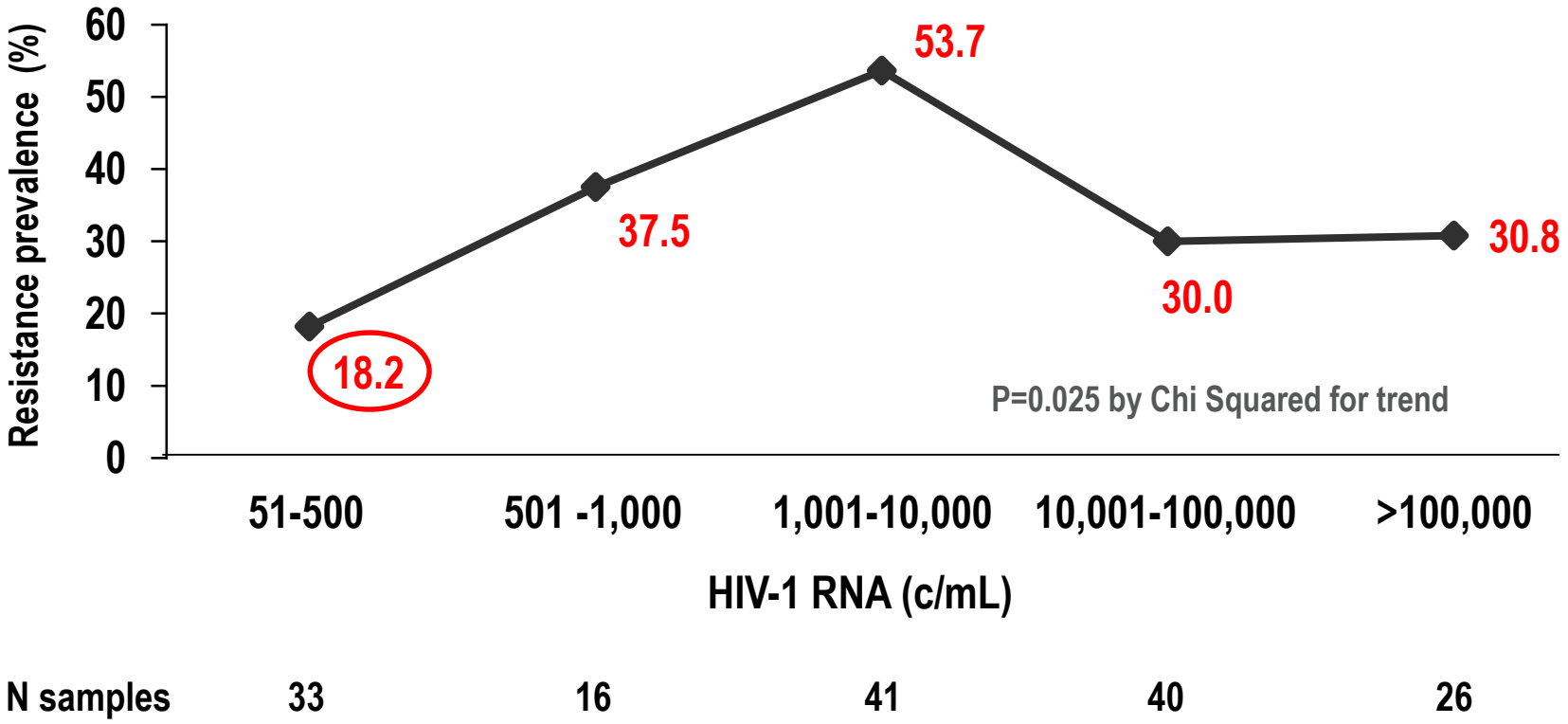


P <0.001 (Chi-squared test for trend)

Prevalence of samples with at least one major resistance mutation in patients failing PIs (boosted or unboosted), NRTIs or NNRTIs, stratified by viremia.

Santoro et al., CID 2014

Considerable levels of resistance are also observed in integrase at low levels of viremia in patients failing ral-containing regimens



Overall proportion of samples with least one major RAL mutation at RAL failure: 54/156 (34.6%)

Armenia, J Antimicr Chemother, 2015

HIV drug resistance detected during low-level viraemia is associated with subsequent virologic failure

Luke C. Swenson[a], Jeong Eun Min[a], Conan K. Woods[a], Eric Cai[a], Jonathan Z. Li[b], Julio S.G. Montaner[a], P. Richard Harrigan[a] and Alejandro Gonzalez-Serna[a]

Background: **The clinical implications of emergent HIV drug resistance on samples with low-level viraemia (LLV <1000 copies/ml) remain unclear**. We undertook the present analysis to evaluate the impact of emergent HIV drug resistance at LLV on the risk of subsequent virologic failure.

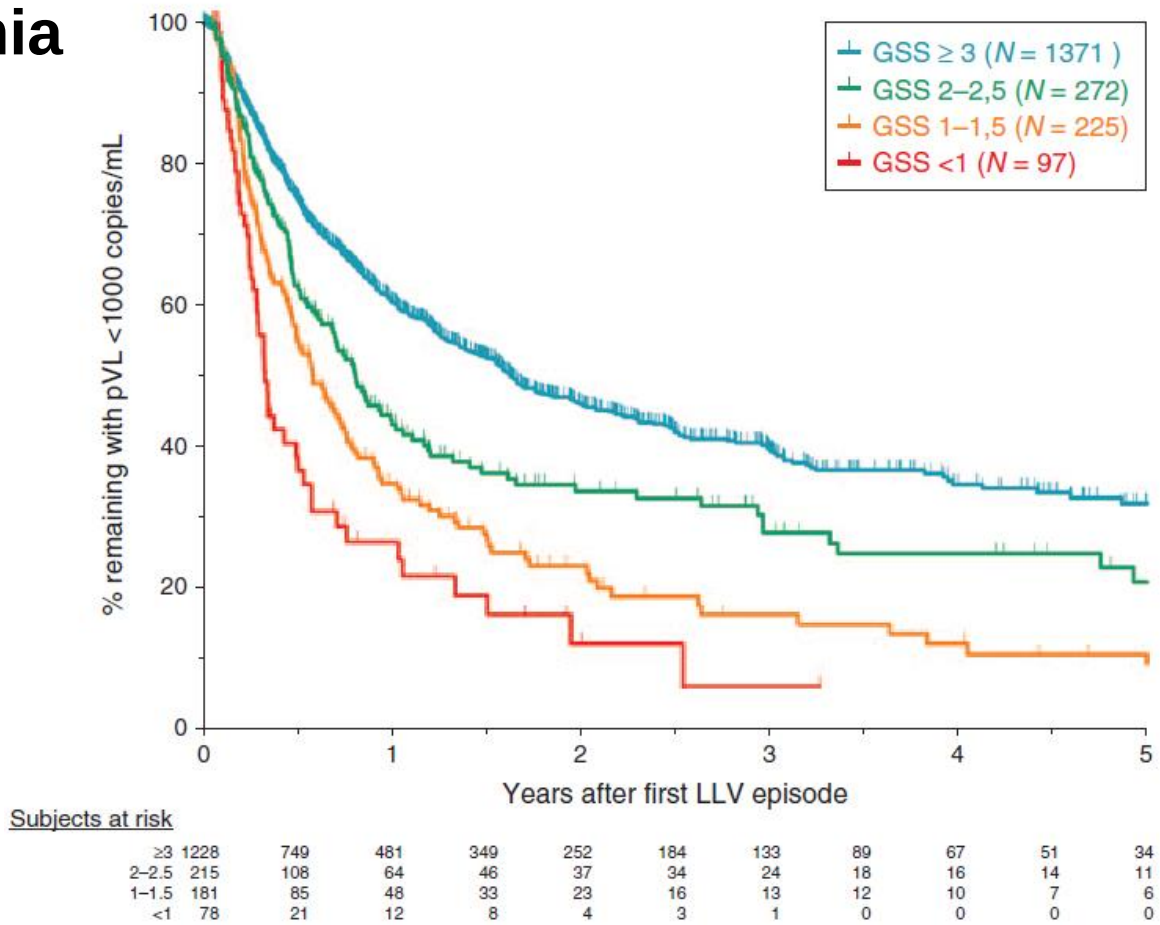
Methods: One thousand nine hundred and sixty-five patients had genotype results at LLV. **Risk of virologic failure (1000 copies/ml) after LLV was evaluated by Kaplan–Meier analysis and Cox proportional hazards regression**. Resistance was assessed using the Stanford algorithm or virtual phenotypes. Patients were grouped into four susceptibility categories ('GSS' or 'vPSS') during LLV, corresponding to the number of 'active' drugs prescribed: <1; 1–1.5; 2–2.5; and 3.

Results: A total of **1702 patients** with follow-up on constant therapy were eligible for analysis. Participants excluded due to changing therapy or loss to follow-up before their next observation had mostly similar characteristics to included participants. **There was a 'dose-dependent' increase in the hazard ratio for virologic failure with susceptibility categories at LLV**. Compared with a GSS of at least 3, hazard ratios for virologic failure were 1.4 for GSS 2–2.5; 2.0 for GSS 1–1.5; and 3.0 for GSS less than 1 (P<0.001). Numerous sensitivity analyses confirmed these findings.

Conclusion: **Our results demonstrate that emergent HIV drug resistance at LLV is strongly associated with subsequent virologic failure.** Furthermore, we uncovered a 'dose-dependent' increase in the hazard ratio for virologic failure with decreasing GSS estimated at the time of LLV. **On the basis of these findings, we propose that resistance genotyping be encouraged for HIV-infected individuals on antiretroviral therapy experiencing low-level viraemia.**

AIDS 2014, **28**:000–000

Virologic failure was faster and more common in patients with lower genotypic susceptibility scores during low-level viraemia



Kaplan–Meier curves for the proportion of patients remaining on the same therapy with viral loads <1000 copies/ml following their first low-level viraemia (LLV) episode. Patients are divided into four groups according to their GSS, and followed for up to 5 years while remaining on constant therapy.

Swenson et al., AIDS 2014

Outline

- Overview of resistance development
- What is resistance today?
- What is changing in antiretroviral therapy?
- **Impact of historical resistance at therapy switch**
- Impact of resistance in proviral DNA at therapy switch
- Minority variants
- Switching to the most suitable regimen

To ensure a maintenance of virological success after a therapy switch/simplification an accurate evaluation of previous resistance (in historical plasma or proviral DNA) is mandatory

Pre-existent NRTI- and NNRTI-resistance impacts on maintenance of virological suppression in HIV-1 infected patients who switch to tenofovir/emtricitabine/rilpivirine single tablet regimen

D. Armenia, D. Di Carlo, A. Calcagno, G.Vendemiati, F. Forbici, A. Bertoli, G. Berno, S. Carta, F. Continenza, V. Fedele, R. Bellagamba, S. Cicalini, A. Ammassari, R. Libertone, M. Zaccarelli, V. Ghisetti, M. Andreoni, F. Ceccherini-Silberstein, S. Bonora, G. Di Perri, A. Antinori, CF. Perno, MM. Santoro

Objectives: **To evaluate the maintenance of virological suppression (VS)** in antiretroviral-treated HIV-1 suppressed patients **switching to tenofovir/emtricitabine/rilpivirine (TDF/FTC/RPV)** single-tablet regimen, by considering pre-existent resistance (pRes).

Methods: pRes was evaluated according to resistance on all previous plasma genotypic resistance tests. Probability and predictors of virological rebound (VR) were evaluated.

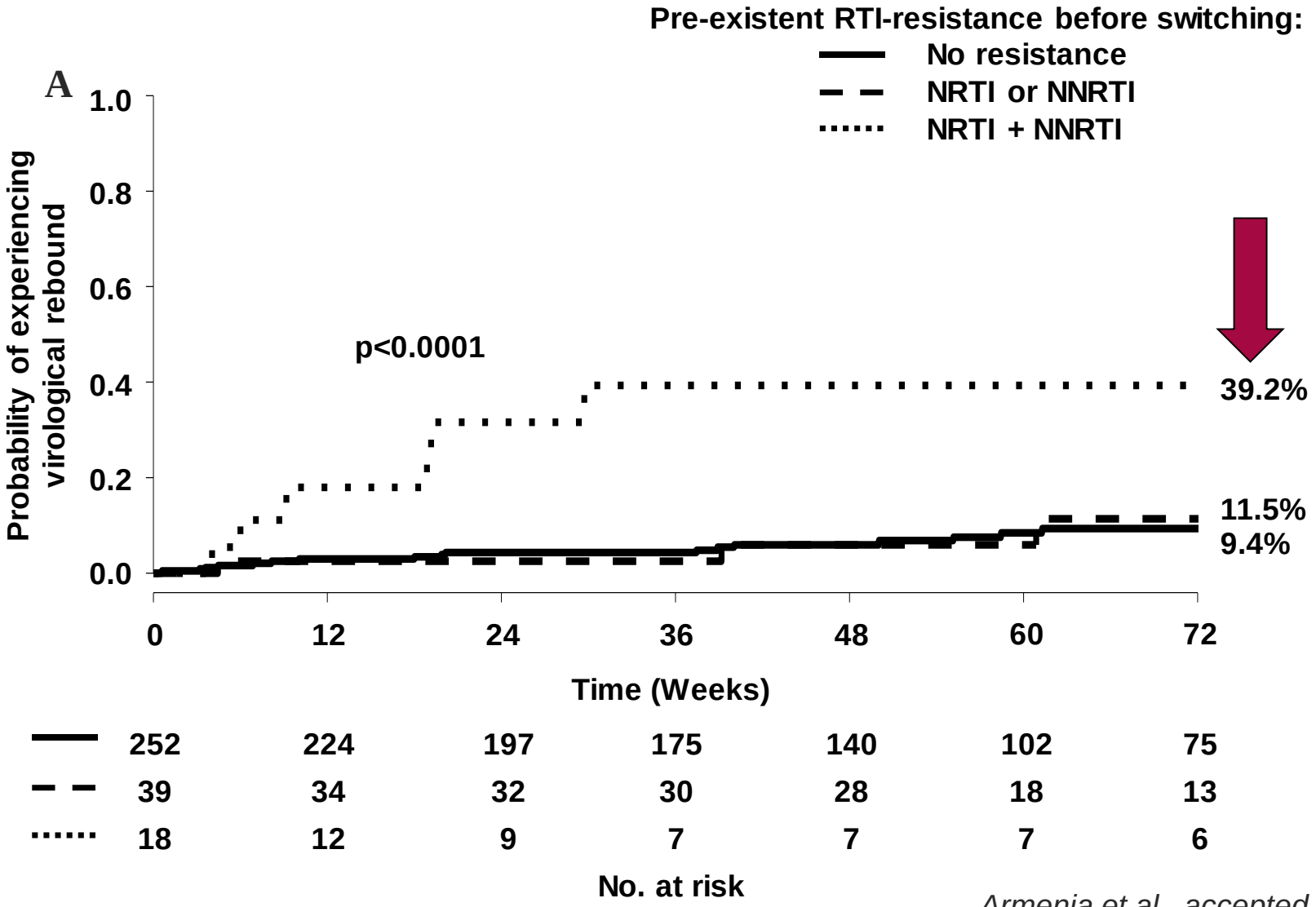
Results: 309 patients were analyzed, 5.8% of them showed resistance to both nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and non-NRTIs (NNRTIs), while 12.6% showed resistance to only one of these drug-classes.

By 72 weeks, the probability of VR was 11.3%. A higher probability of VR was found in the following groups: i) patients with NRTI+NNRTI pRes, compared to those harboring NRTI or NNRTI pRes and to those without RTI pRes (39.2% versus 11.5% versus 9.4%, $p<0.0001$); ii) patients with a virus with full/intermediate resistance to both tenofovir/emtricitabine and rilpivirine, compared to those having a virus with full/intermediate resistance to tenofovir/emtricitabine or rilpivirine, and those having a virus fully susceptible to TDF/FTC/RPV (36.4% versus 17.8% versus 9.7%, $p<0.001$); iii) patients with pre-therapy viremia >500,000 copies/mL compared to those with lower viremia levels (>500,000: 16.0%; 100,000-500,000: 9.3%; <100,000 copies/mL: 4.8%, $p=0.009$). pRes and pre-therapy viremia >500,000 copies/mL were independent predictors of VR by multivariable Cox regression.

Conclusions: TDF/FTC/RPV as a treatment simplification strategy show a very high rate of VS maintenance. The presence of pRes to both NRTIs and NNRTIs and a pre-therapy viremia >500,000 copies/mL are associated with an increased risk of VR, highlighting the need for an accurate selection of patients before simplification.

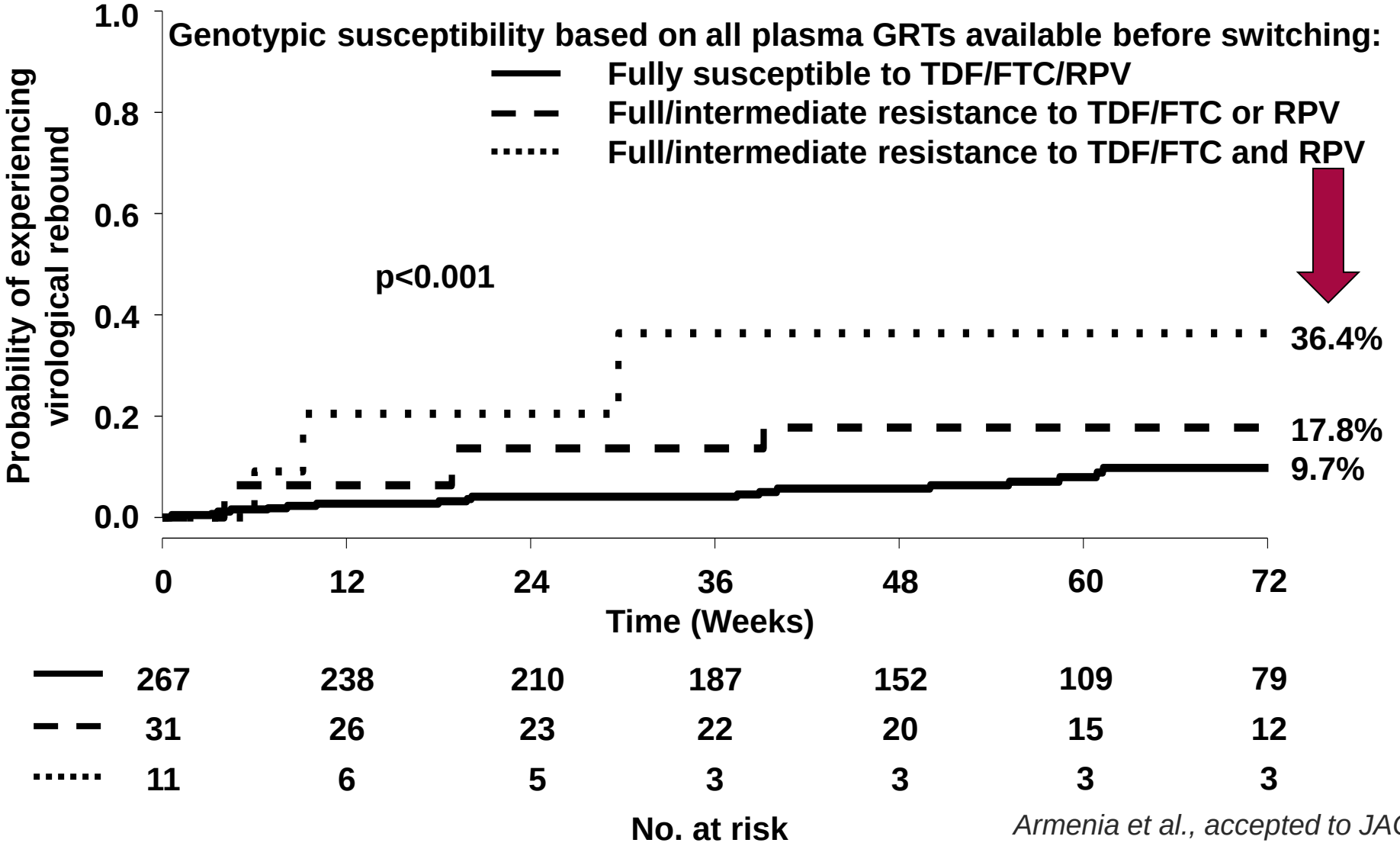
Accepted on JAC

Patients with pre-existent NRTI+NNRTI resistance had a higher probability of experiencing VR compared to those harboring pre-existent NRTI or NNRTI reistance and to those without pre-existent RTI resistance.



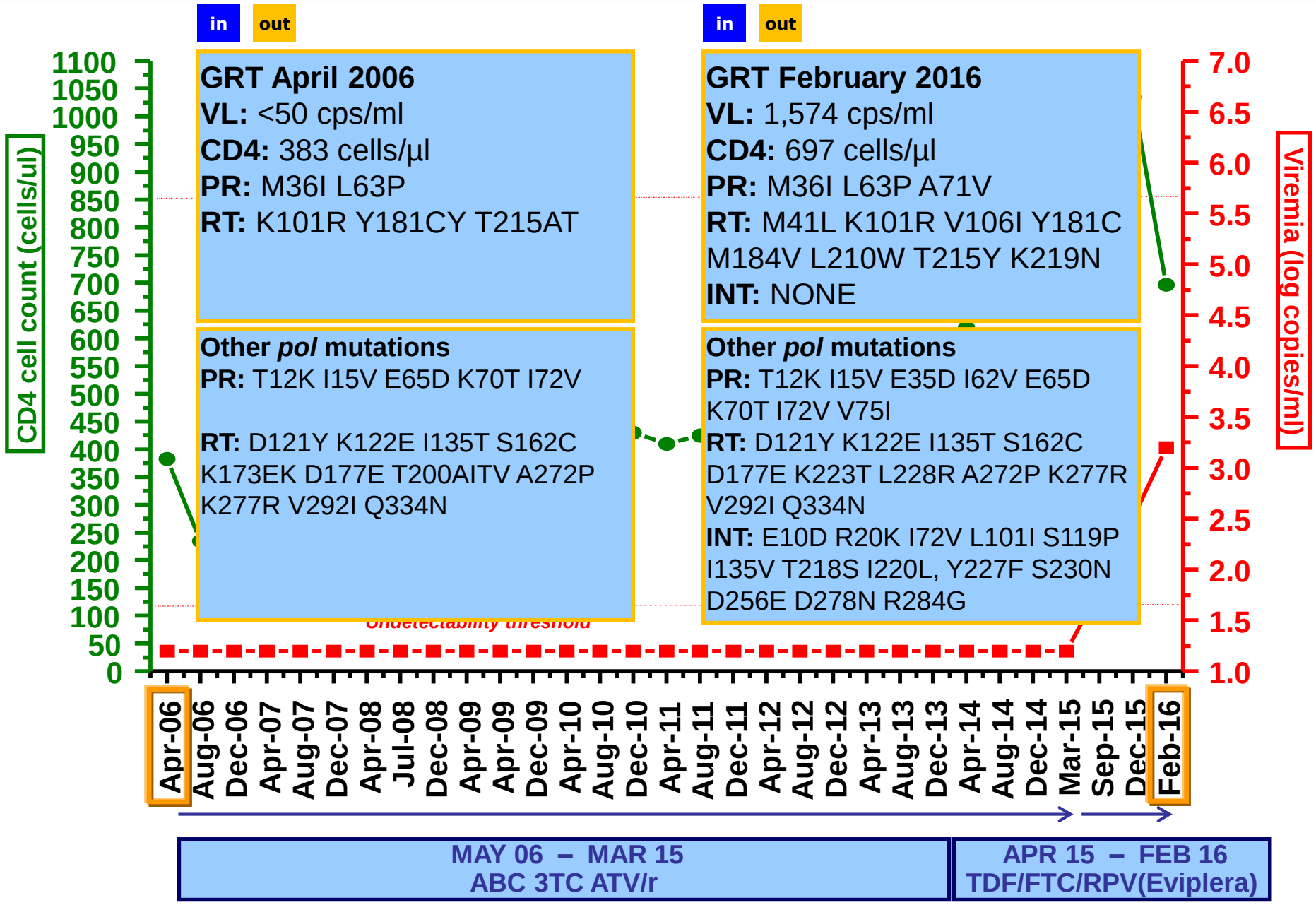
Armenia et al., accepted to JAC

Patients with a virus with full/intermediate resistance to both TDF/FTC and RPV had a higher probability of experiencing VR compared to those having a virus with full/intermediate resistance to tenofovir/emtricitabine or rilpivirine, and those having a virus fully susceptible to TDF/FTC/RPV



Armenia et al., accepted to JAC

Clinical Case: ID 1463 Patient infected with HIV-1 B subtype	Age: 41	Sex: M	Risk Factor: Sexual	CDC: B2	1st Seropositivity: January 1995



Outline

- Overview of resistance development
- What is resistance today?
- What is changing in antiretroviral therapy?
- Impact of historical resistance at therapy switch
- **Impact of resistance in proviral DNA at therapy switch**
- Switching to the most suitable regimen

Resistance in PBMC should be considered for patients with undetectable HIV-RNA needing a treatment switch

Genotypic resistance test in proviral DNA can identify resistance mutations never detected in historical genotypic test in patients with low level or undetectable HIV-RNA☆

Mauro Zaccarelli[a,1], Maria Mercedes Santoro[b,*,1], Daniele Armenia[b], Vanni Borghi[c], William Gennari[c], Caterina Gori[a], Federica Forbici[a], Ada Bertoli[b], Lavinia Fabeni[a], Alberto Giannetti[a], Stefania Cicalini[a], Rita Bellagamba[a], Massimo Andreoni[d], Claudio Maria Mastroianni[e], Cristina Mussini[c], Francesca Ceccherini-Silberstein[b], Carlo Federico Perno[a], Andrea Antinori[a]

[a] *National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy*
[b] *University of Rome Tor Vergata, Rome, Italy*
[c] *Modena University Hospital, Modena, Italy*
[d] *University Hospital Tor Vergata, Rome, Italy*
[e] *La Sapienza University, Polo Pontino, Latina, Italy*

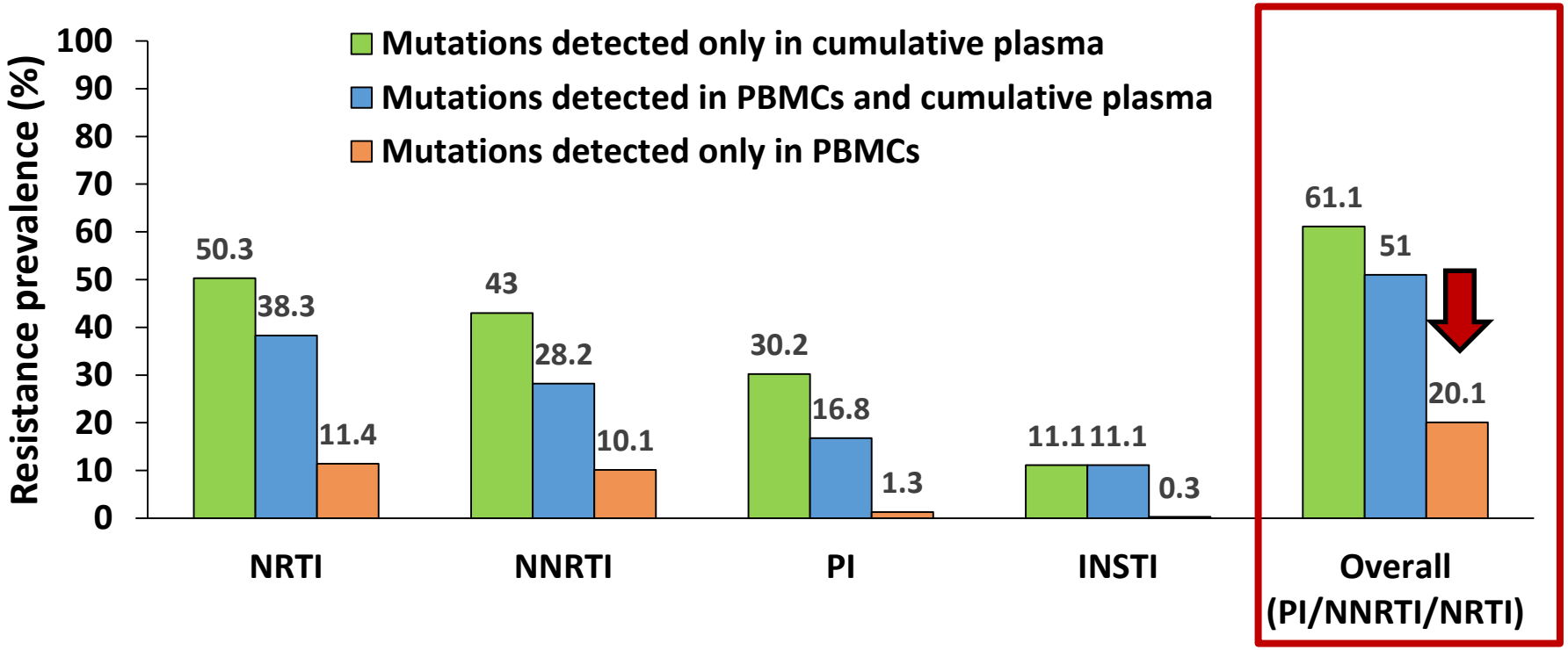
A B S T R A C T

Background: Beyond the detection of resistant HIV strains found in plasma samples, archival HIV-DNA in peripheral blood mononuclear cells (PBMCs) might represent a reservoir of additional resistance.
Objective: To characterize the HIV-1 resistance in PBMCs from patients with suppressed or low-level viremia (50–1000 copies/mL) and evaluate its added value compared to the resistance detected in previous plasma genotypic resistance tests (GRTs).
Study design: HIV-1 infected patients selected for treatment change despite low/undetectable viremia were tested. Number and type of primary resistance mutations (PRMs) detected in PBMCs were compared to those detected in previous plasma GRTs. Logistic regression assessed factors associated with presence of at least one PRM in PBMCs.
Result: 468 patients with a PBMC GRT were analyzed; 149 of them had at least 2 plasma GRTs performed before PBMC genotyping. 42.3% of patients showed at least one PRM in PBMCs. The highest proportion of PRMs in PBMCs was observed for NRTI class (30.6%), followed by NNRTI (22.2%), PI (14.1%) and INI (4.9%). In 20.1% of patients, PRMs were detected only in PBMCs and not in any of the plasma GRT previously performed. By using multivariable analysis, a higher number of previous regimens, injecting drug-use route and a lower nadir CD4 were associated with significantly higher risk of detecting PRMs in PBMCs.
Conclusion: Our findings support the usage of PBMC GRT in addition to the current recommended plasma RNA test, especially when therapeutic and/or resistance information is not available.

Journal of Clinical Virology 2016

By exploring plasma cumulative resistance for any class and resistance detected in PBMC, 20.1% of patients harboured major resistance mutations (MRMs) not detected in any of previous GRTs performed in plasma.

Proportion of Patients with MRM in PBMCs and Cumulative Plasma
(149 Patients with DNA GRT and ≥2 Plasma GRTs, 9 Patients for INSTI)



	NRTI	NNRTI	PI	INSTI	Overall (PI/NNRTI/NRTI)
Mean (±SD) number of MRM,	1.29 (±1.67)	0.74 (±1.00)	0.77 (±1.39)	0.11 (±0.33)	2.79 (±3.26)
	1.03 (±1.66)	0.38 (±0.72)	0.34 (±8.84)	0.44 (±1.33)	1.75 (±2.57)
	0.13 (±0.37)	0.14 (±0.47)	0.02 (±0.18)	0.00 (±0.00)	0.29 (±0.71)

Zaccarelli et al., JCV2016

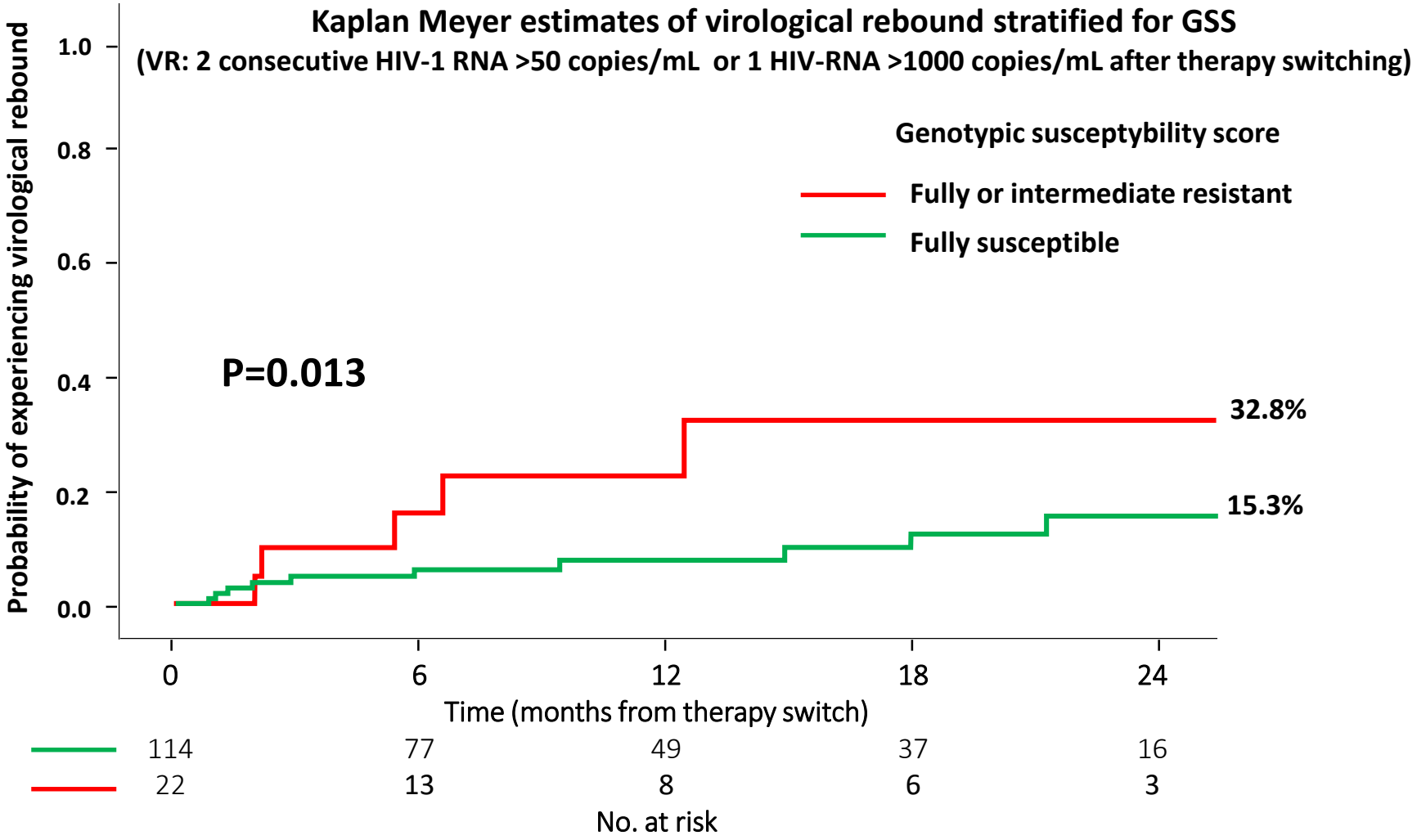
Poster # 42

Resistance in PBMCs Can Predict Virological Rebound after Therapy Switch in cART-Treated Patients with Undetectable HIV-RNA

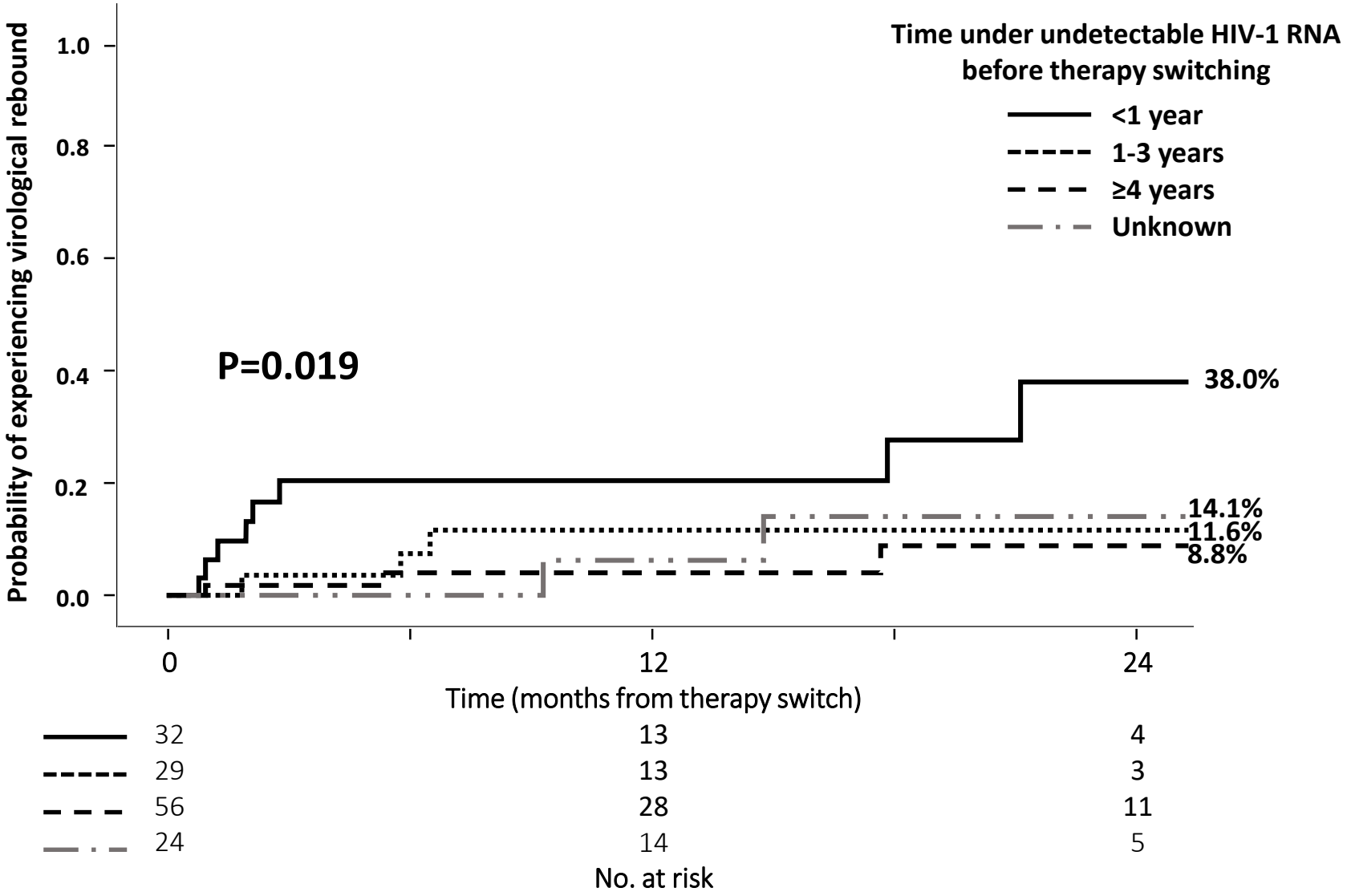
D Armenia[1], M Zaccarelli[2], V Borghi[3], W Gennari[3], A Giannetti[2], F Forbici[2], C Pinnetti[2], F Ceccherini Silberstein[1], C Mussini[3], CF Perno[2], A Antinori[2], and MM Santoro[1]

1 University of Rome Tor Vergata, Rome, Italy; 2 L. Spallanzani Hospital, Rome, Italy; 3 Polyclinic of Modena, Modena, Italy.

Twenty-four months after therapy switching, the overall probability of VR was 18%. Patients showing in PBMCs an intermediate or fully resistant GSS to the regimen administered had a higher probability of experiencing VR compared to those showing full susceptibility.



Patients virologically suppressed for less than one year before therapy switching showed the highest probability of experiencing VR compared to those with a longer time of virological suppression.



Outline

- Overview of resistance development
- What is resistance today?
- What are changing in antiretroviral therapy?
- Impact of historical resistance at therapy switch
- Impact of resistance in proviral DNA at therapy switch
- **Switching to the most suitable regimen**

P054

Safety and efficacy of dolutegravir plus rilpivirine (DTG/RPV) in treatment-experienced HIV-infected patients: preliminary results at 24 weeks of the DORIVIR study

Rosario Palacios[1]; Marisa Mayorga[2]; Carmen-María González-Domenech[1]; Carmen Hidalgo-Tenorio[3]; Carmen Gálvez[4]; Leopoldo Muñoz-Medina[3]; Javier de la Torre[5]; Ana Lozano[6]; Manuel Castaño[2]; Mohamed Omar[7] and Jesús Santos[1]

Introduction: DTG/RPV is a two-pill nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI)-sparing regimen with very good tolerance. It is currently in phase 3 clinical trials being developed as two-drug ''maintenance therapy''. The aim of this study is to analyze the efficacy and safety of this regimen in HIV-infected patients who switched from any other ART combination.

Methods: Open-label, multicentre, non-controlled study in seven hospitals from Andalusia, southern Spain. Patients who switched from any regimen to DTG/RPV from February 2015 to February 2016 were included. Epidemiological, clinical and antiretroviral data in addition to immediate reasons for switching were collected. Lipids, liver and renal tests were measured at baseline and at 24 weeks. The primary endpoint was the proportion of patients with plasma HIV RNA B50 copies/mL at 24 weeks (missingfailure), and secondary endpoints included adverse events and rate of discontinuation related with adverse events of dual therapy after switching and metabolic changes at 24 weeks.

Results: Hundred and five patients started DTG/RPV during the study period: 82 (78.1%) virologically suppressed, 22 (20.9%) non-virologically suppressed (eight failures and 14 restart of ART) and one naive, who was not included for analysis. There were 70.5% men, mean age was 51.9 years, mean time of HIV infection 214.7 (IQR 140.4288.9) months, and mean time on the prior ART was 37.0 (IQR 7.868.2) months. The most frequent reasons for switching were toxicity or intolerance (41.9%), convenience (27.6%) and drugs interactions (17.1%). Prior regimens were based on PI (56.9%), integrase inhibitors (26.5%) or non-NRTI (16.7%). **At this time 85 patients have completed 24 weeks and all were still taking the same regimen, 82 (96.5%) of them with undetectable viral load; the three cases with detectable HIV RNA (532, 316 and 75 copies/mL, respectively) were not considered virological failures.** Mean CD4 cells count increased (622 vs. 552 cells/mL; p0.008), and a mean decrease in fasting triglycerides (34.6 mg/dL; p0.005) and glomerular filtration (5.2 mL/min; p0.004) were observed, with no changes detected in total cholesterol, HDL-c, LDL-c, creatinine and GPT. No patient stopped DTG/RPV due to adverse events.

Conclusions: **DTG/RPV is effective and safe in a cohort of patients with long time of HIV infection and prior ART.** Most patients changed from more complex regimens. Toxicity, intolerance, convenience and interactions were the main reasons for changing. At 24 weeks lipid profile improved with a decrease in triglycerides.

Disposition at 24 weeks*	N (%)
Patients on same regimen	85 (100)
Viral suppression**	82 (96.5)

*At this time, 85 patients have reached 24 weeks
**The three cases with detectable HIV RNA (532, 316, 75 cop/mL, respectively) were not considered virological failures.

Changes from baseline to week 24

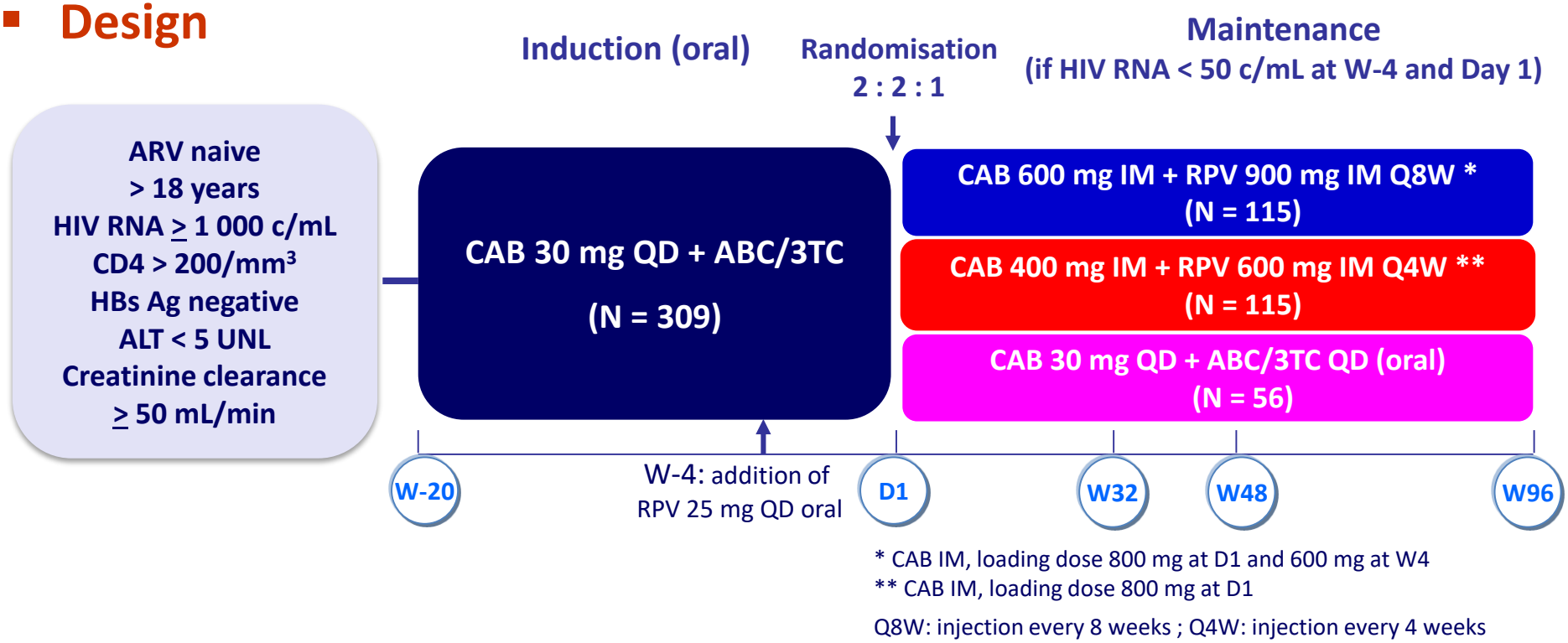
	Baseline	Week 24	P
TC (mg/dL)	183 (153-223)	177 (153-214)	0.4
HDL-c (mg/dL)	46 (36-56)	46 (38-54)	0.9
LDL-c (mg/dL)	105 (82-138)	105 (82-131)	0.6
TG (mg/dL)	**149 (107-224)**	**128 (84-173)**	**0.005**
GFR (ml/min)	**88 (71-90)**	**80 (65-90)**	**0.004**
GPT (UI/L)	28 (20-40)	29 (20-39)	0.7
CD4 (cells/µL)	**536 (316-735)**	**591 (370-851)**	**0.008**

Variables are expressed as median (IQR)
TC, total cholesterol; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TG, triglycerides; GFR, glomerular filtration rate

Palacios et al. HIV Drug therapy 2016, Glasgow Abs. P054

LATTE-2 Study: switch to cabotegravir LA + rilpivirine LA IM

- **Design**



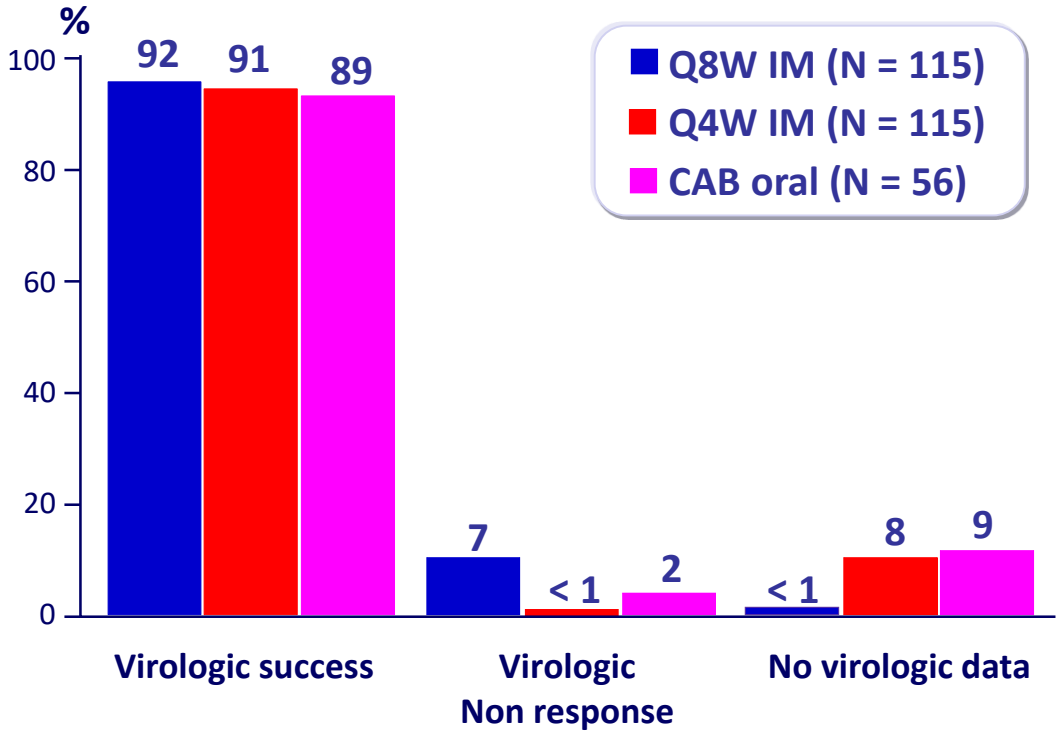
Induction phase: HIV RNA < 50 c/mL (ITT-E) after 20 weeks = 91.3 % ; discontinuation in 18/309 patients, including 6 for adverse event and 2 for lack of efficacy

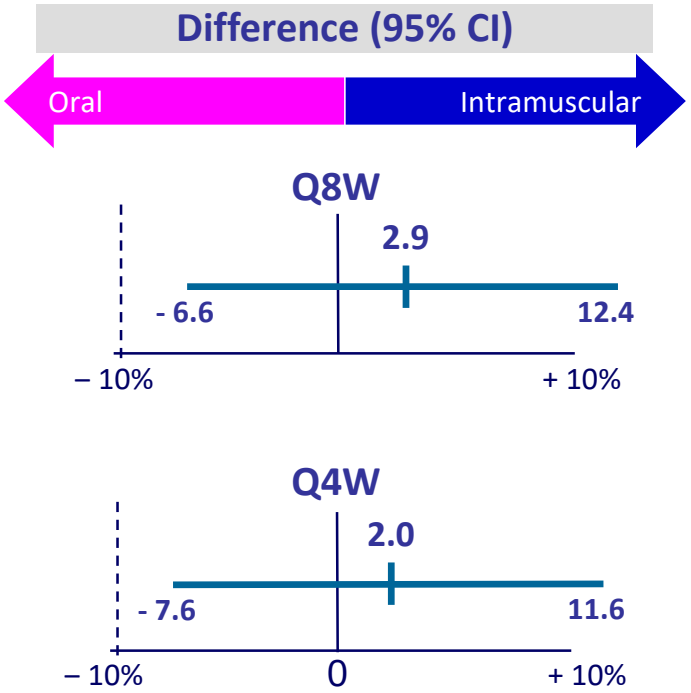
- **Objective**
  - Primary: % HIV RNA < 50 c/mL at W32 of maintenance phase: selection of dosing schedule for phase III studies (confirmation of dose on W48 analysis) ; safety

Margolis DA. AIDS 2016, Durban, Abs. THAB0206LB

LATTE-2 Study: switch to cabotegravir LA + rilpivirine LA IM

HIV RNA < 50 c/mL at W48 (snapshot analysis, ITT-ME)





- Non inferiority of the 2 IM regimens vs oral CAB
- Protocol-defined virologic failure: 2 in Q8W group, 1 in oral group
- **Emergence of resistance at failure (genotype): N = 1 (Q8W group): NNRTI (K103N, E138G, K238T), INSTI (Q148R)**

LATTE-2

Margolis DA. AIDS 2016, Durban, Abs. THAB0206LB

P090

Dolutegravir and unboosted atazanavir: a dual NRTI- and booster-free antiretroviral regimen simplification in HIV-1 infected patients with viral suppression

Agostino Riva[1]; Andrea Poli[2]; Stefano Rusconi[3]; Stefano Bonora[4]; Anna Maria Cattelan[5]; Eugenia Quiros Roldan[6]; Micol Ferrara[4]; Vincenzo Spagnuolo[2]; Layla Pagnucco[7]; Silvia Cavinato[5]; Dario Cattaneo[8]; Roberto Gulminetti[7] and Antonella Castagna[2]

[1]III Division of Infectious Diseases, ASST FBF-Sacco, Milan, Italy. [2]Infectious Diseases Unit, San Raffaele Scientific Institute, Milan, Italy. [3]Department of Biomedical & Clinical Sciences, University of Milan, Milan, Italy. [4]Infectious Diseases Unit, University of Turin,

HIV Drug Therapy GLASGOW 2016

Introduction: There are increasing concerns about long-term toxicity of antiretroviral treatment. NRTIs have the potential for long-term toxicities and ritonavir has negative metabolic consequences and drug-drug interactions. **The combination of dolutegravir (DTG) with unboosted atazanavir (uATV) is an intriguing new NRTI- and boosterfree regimen. We report a real-life experience of the simplification of different antiretroviral regimens to DTG+ATV.**

Methods: A total of 61 patients were enrolled in our observational study; 58 subjects with at least one follow-up visit. We evaluated several laboratory parameters including CD4 T cell, HIV RNA and metabolic values. We measured ATV and DTG trough concentrations after a minimal 2-week interval from the start of the new regimen.

Results: Patients enrolled in the study were predominantly males (63%), CDC stage C was 22%, HCV-Ab positivity was 28% and the previous regimen included more frequently 3 drugs, mainly Pis (90%). Patients had a median time since first HIV-positive test of 16.1 years (10.223.6) and a median time of ART exposure of 14.3 years (9.019.0). The reasons for switching to uATV DTG were several: mainly toxicities, comorbidities and simplification (Table 1). As far as uATV: 55 patients were administered 400 mg QD, two patients 300 mg QD and one patient 200 mg BID; DTG was dosed 50 mg QD, but one patient received 50 mg BID. **Patients had a median follow-up of 4.9 months (IQR 2.37.8). At last visit, all patients on treatment had undetectable HIV RNA. Two patients presented a viral blip during follow-up (91 and 98 copies/mL), subsequently HIV RNA returned negative without treatment modification. There were three treatment discontinuations: one severe hyperbilirubinemia (grade 3), one G-I intolerance and one patient was lost to follow-up.** No differences were found in laboratory parameters between baseline and the last follow-up including immuno-virologic variables, except for a significant decrease in tryglicerides (Table 2). ATV and DTG mean concentrations were 310 ng/mL (95% CI 116504) and 3216 ng/mL (95% CI 24363996) respectively. ATV concentration was below 150 ng/mL in 11 out of 28 patients.

Conclusions: **ART switch towards this dual-drug regimen NRTI and booster-sparing, although in a short follow-up, appears to be well tolerated and safe.** Virologic suppression was maintained in all patients despite long-lasting HIV infection and ART treatment. DTG concentrations are high in the majority of the patients as expected from previous pharmacokinetics study. Despite low ATV concentrations in several patients, no virologic failures were observed. This NRTI- and RTV-sparing regimen appears an attractive new strategy in patients with metabolic disorders and NRTI-related toxicities.

Randomized, Open-label Trial to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide plus Darunavir in Treatment-Experienced HIV-1 Infected Adults

Gregory D. Huhn MD, Pablo Tebas MD, Joel Gallant MD, Timothy Wilkin MD, Andrew Cheng MD, Mingjin Yan, Lijie Zhong, Christian Callebaut, Joseph M. Custodio, Marshall W. Fordyce, Moupali Das, Scott McCallister.

Background: HIV-infected, treatment-experienced adults with a history of prior resistance and regimen failure can be virologically suppressed but may require multi-tablet regimens associated with lower adherence and potential resistance development.

Methods: We enrolled HIV-infected, virologically suppressed adults with 2- to 3-class drug resistance and at least 2 prior regimen failures into this phase 3, open-label, randomized study. The primary endpoint was the percentage of participants with HIV-1 RNA <50 copies/mL at week 24 (FDA snapshot algorithm).

Results: For 135 participants (E/C/F/TAF plus DRV, n=89; baseline regimen, n=46), most of whom were taking a median of 5 tablets/day, simplification to E/C/F/TAF plus DRV was noninferior to continuation of baseline regimens at week 24 (plasma HIV-1 RNA <50 copies/mL: 96.6% vs 91.3%, difference 5.3%, 95.001% CI -3.4% to 17.4%). E/C/F/TAF plus DRV met prespecified criteria for noninferiority and superiority at week 48 for the same outcome. E/C/F/TAF plus DRV was well tolerated and had an improved renal safety profile compared with baseline regimens, with statistically significant differences between groups in quantitative total proteinuria and markers of proximal tubular proteinuria. Compared with baseline regimens, participants who switched to E/C/F/TAF plus DRV reported higher mean treatment satisfaction scale total scores and fewer days with missed doses.

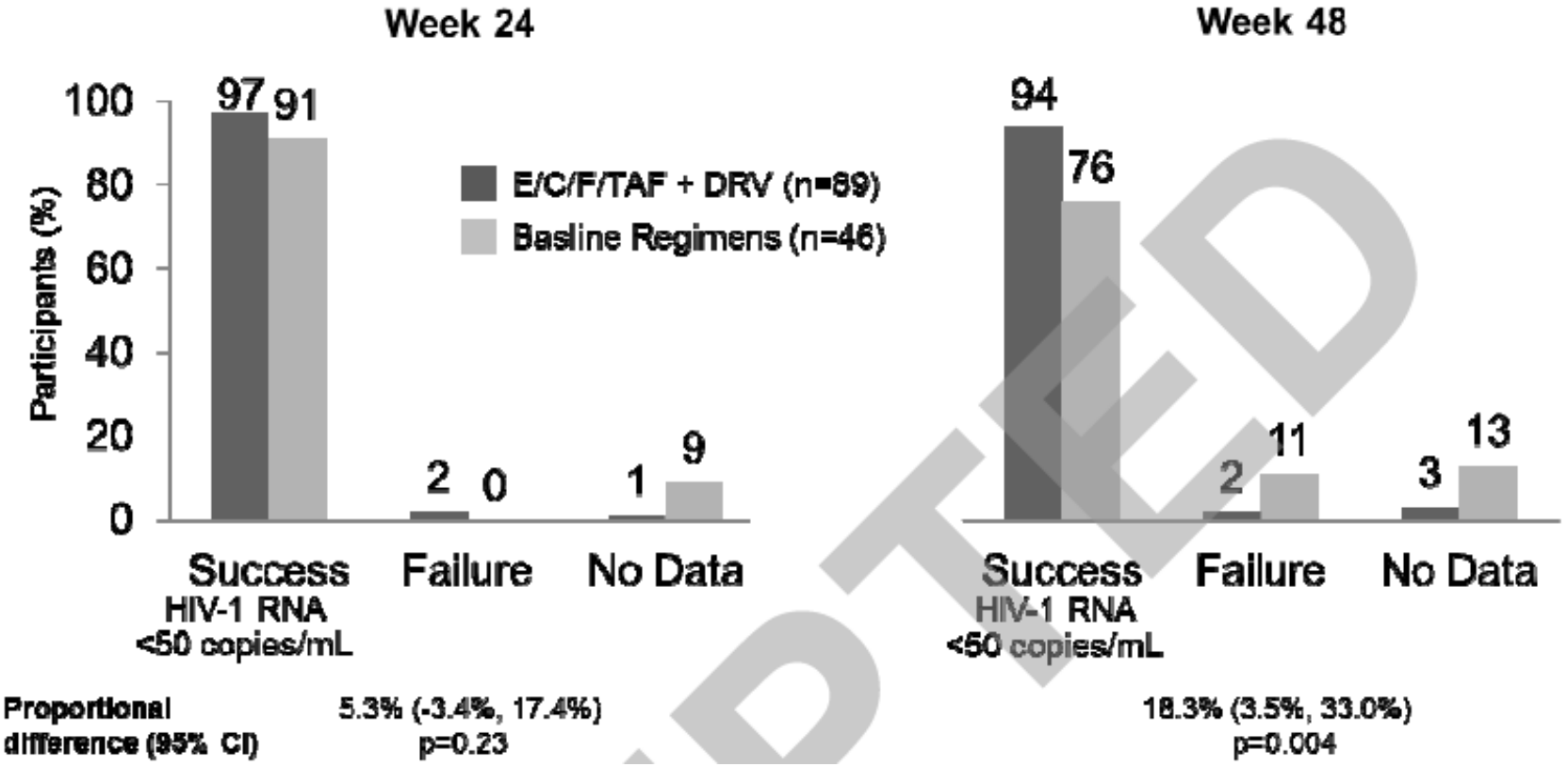
Conclusions: This study demonstrated that regimen simplification from a 5-tablet regimen to the 2-tablet, once-daily combination of E/C/F/TAF plus DRV has durable maintenance of virologic suppression and improvements in specific markers of renal safety. Such a strategy may lead to greater adherence and improved quality of life.

	E/C/F/TAF + DRV (n=89)	Baseline Regimens (n=46)
Baseline Characteristics		
Age, median (range), years	49 (29, 70)	47 (23, 64)
Male	73 (82%)	28 (61%)
Black (or African descent)	35 (39%)	26 (57%)
CD4 count, median (range), cells/µL	519	518
eGFR by Cockcroft-Gault, median (range), mL/min	99	100
Antiretroviral Regimen History		
Number of pills per day, median (range)	5	5
≥ 6 pills per day	36 (40%)	17 (37%)
At least twice-daily dosing	58 (65%)	30 (65%)
Prior regimens containing		
TDF	54 (61%)	25 (54%)
ABC	10 (11%)	5 (11%)
Other NRTIs	11 (12%)	6 (13%)
Resistance History		
2-class Resistance	62 (70%)	34 (74%)
3-class Resistance	23 (26%)	9 (20%)
M184V/I	76 (85%)	36 (78%)
K65R	18 (20%)	14 (30%)
NNRTI-R	79 (89%)	40 (87%)
PI-R	34 (38%)	13 (28%)
TAM	39 (44%)	18 (39%)
GSS at study entry (mean)	2.45	2.56

Thirty-nine percent of participants were taking 6 or more tablets per day. All participants had at least 2-class genotypic resistance per eligibility criteria, with high prevalence of M184I/V and K65R mutations.

Huhn et al, JAIDS2016

E/C/F/TAF plus DRV met pre-specified criteria for non-inferiority at 24 weeks and superiority at week 48.



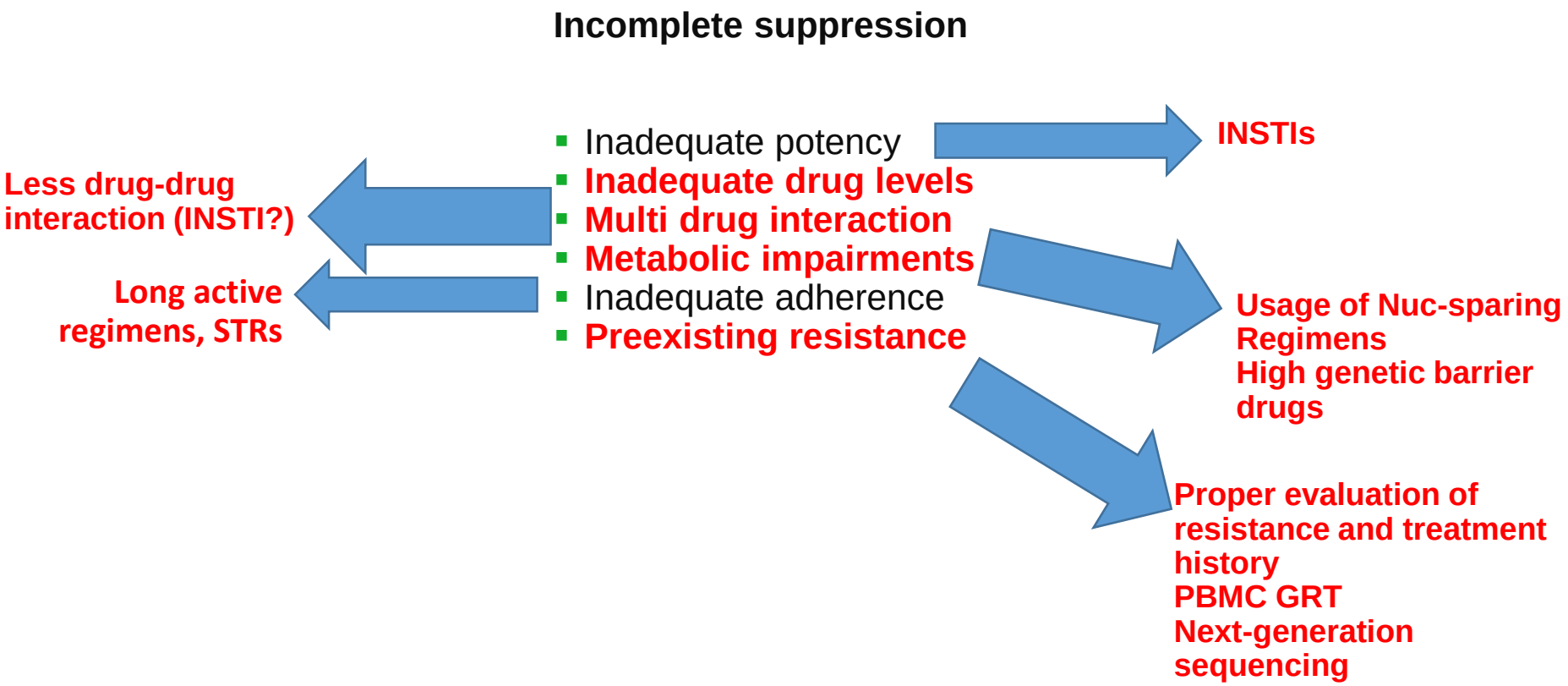
As no participants in the E/C/F/TAF plus DRV group had confirmed virologic rebound with HIV-1 RNA > 400 copies/mL through week 48, none were tested for resistance

One participant in the baseline regimen group, on raltegravir, ritonavir-boosted darunavir, and etravirine, had viral rebound (week 36). Historical genotyping confirmed 2-class resistance, with PR (L10V, M361) and RT (D67N, K70R, K103N, Y181I, T215Y) mutations. **K65R and M184V were newly detected.**

Huhn et al, JAIDS2016

To Avoid Viral Resistance

Concerns in aging patients



CONCLUSIONS

Due to the intrinsic characteristics of HIV, resistance to antiviral drugs represents the rule, not the exception, if the virus is left replicating under the pressure of antivirals

Previous resistance archived in viral reservoir is an important concern in case of switch containing low genetic barrier drugs

Prevention of resistance is easier and far more productive than its treatment

Acknowledgements

AVIRALIA Fondazione

InterOmics CNR

- The Patients

University of Rome Tor Vergata, Rome Italy: **C.F. Perno, F. Ceccherini-Silberstein, V. Svicher, M. M. Santoro, D. Armenia, C. Alteri, D. Di Carlo, A. Bertoli, M.C. Bellocchi, A. Bidditttu, M. Romani, M. Bruni, L. Carioti.**

Policlinic of Rome Tor Vergata, Rome Italy: **M. Andreoni, L. Sarmati, L. Dori, E. Gentilotti, D. Leoni G. Maffongelli. A. Ricciardi, M. Viscione, N. Cesta, S. Gini, C. Cerva, V. Malagnino, P. Sordillo, T. Guenci, F. Stazi, S. Giannella.**

INMI L Spallanzani, Rome, Italy: **G. Ippolito, A. Antinori, G. D'Offizi, N. Petrosillo, U. Visco-Comandini, G. Liuzzi, F. Antonucci, E. Boumis, S. Cicalini, P. De Longis, E. Nicastri, A. Ammassari, R. Bellagamba, M. Zaccarelli, C. Pinnetti, C. Tommasi, S. Cicalini, A. Sanpaoloesi, G. De Carli, F.M. Fusco, L. Lo Iacono, M.L. Giancola, R. Acinapura, P. Scognamiglio, N. Orchi, E. Girardi, P. Scognamiglio, M.R. Capobianchi, L. Fabeni, C. Gori, F. Forbici, S. Carta, V. Fedele, G. Berno, D. Pizzi, F. Continenza, R. D'Arrigo, A. Giannetti, P. Lorenzini, A. Navarra.**

San Gallicano Hospital, Rome, Italy: **A. Latini, M. Giuliani, A. Pacifici, A. Cristaudo. General Hospital Umberto I: V. Vullo, G. D'Ettorre.** ***San Giovanni Addolorata Hospital, Rome, Italy:*** **F. Montella, F. Di Sora, W. Leti.** ***Sant'Andrea Hospital, Sapienza University, Rome, Italy:*** **A. Pennica, E. Teti.** ***Rebibbia, Rome, Italy:*** **S. Marcellini.** ***Bambin Gesù Hospital, Rome Italy:*** **S. Bernardi.** ***Polo Pontino, Sapienza University, Rome, Italy:*** **C. Mastroianni, M. Lichtner, V.S. Mercurio, C. Del Borgo, R. Marocco.** ***Frosinone Hospital, Frosinone, Italy:*** **G. Farinelli, E. Anzalone, M. Limodio, L. Sarracino.** ***Rieti Hospital, Italy:*** **G. Natalini Raponi, M.E. Bonaventura.** ***Viterbo Hospital, Viterbo, Italy:*** **O. Armignacco, G. Bernardini, A. Caterini, F. Ferri, A. Ialungo, E. Liguori, D. Migliorini, R. Monarca, R. Preziosi, E. Rastrelli, G. Starnini, G. Sebastiani.**

Modena Hospital, Modena, Italy: **C. Mussini, V. Borghi, W. Gennari.** ***University of Turin:*** **G. Di Perri, S. Bonora, A. Calcagno.** ***Amedeo di Savoia Hospital, Torino, Italy:*** **V. Gihsetti.** ***Papa Giovanni XXIII Hospital, Bergamo, Italy:*** **F. Maggiolo, AP Callegaro.** ***Sacco Hospital:*** **G. Rizzardini, V. Micheli.** ***San Martino Hospital:*** **B. Bruzzone, A. Di Biagio.** ***University of Milan, Milan, Italy:*** **A. D'Arminio Monforte.** ***Ospedale "S. Gerardo", Monza, Italy*****: A. Gori.**

Careggi Hospital, Florence, Italy: **K. Sterrantino.** ***Pescara General Hospital, Pescara, Italy:*** **G. Parruti, F. Vadini, F. Sozio, E. Mazzott, T. Ursini, E. Polilli, P. Di Stefano, M. Tontodonati, G. Calella.** ***San Salvatore, L'Aquila, Italy:*** **A. Grimaldi, A. Cellini, M. Mariani, G. Picchi.** ***Ancona Hospital, Ancona, Italy:*** **A. Mataloni Paggi.** ***Giuseppe Mazzini Hospital, Teramo, Italy:*** **Di Giammartino, L. Falconi, P. Tarquini.** ***San Salvatore – Muraglia- Hospital, Pesaro, Italy:*** **E. Petrelli, G. Corbelli, P. Tarquini.** ***Avezzano Hospital, Avezzano, Italy:*** **R. Paolini.**

Cotugno Hospital, Naples, Italy: **A. Chirianni, M. Gargiulo.** ***Second University of Naples, Naples, Italy:*** **N. Coppola.** ***Bisceglie-Trani Hospital, Bisceglie, Italy:*** **R. Losappio.** ***University "Magna Graecia", Catanzaro, Italy:*** **C. Torti.** ***Catania Hospital, Catania, Italy:*** **R. La Rosa.** ***Enna Hospital, Enna, Italy:*** **L. Guarneri.** ***Palermo Hospital, Palermo, Italy:*** **F. Di Lorenzo.** ***University of Messina:*** **G. Nunnari.** ***University of Sassari:*** **MS Mura, G. Madeddu.**