6th Infectivology Today

"6th INFECtivology TOday"

"L'infettivologia del 3° millennio: AIDS ed altro"

VI Convegno Nazionale

"Ruolo attuale dei test genotipici per una corretta individualizzazione della terapia antiretrovirale"

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15- 16 -17 maggio 2014

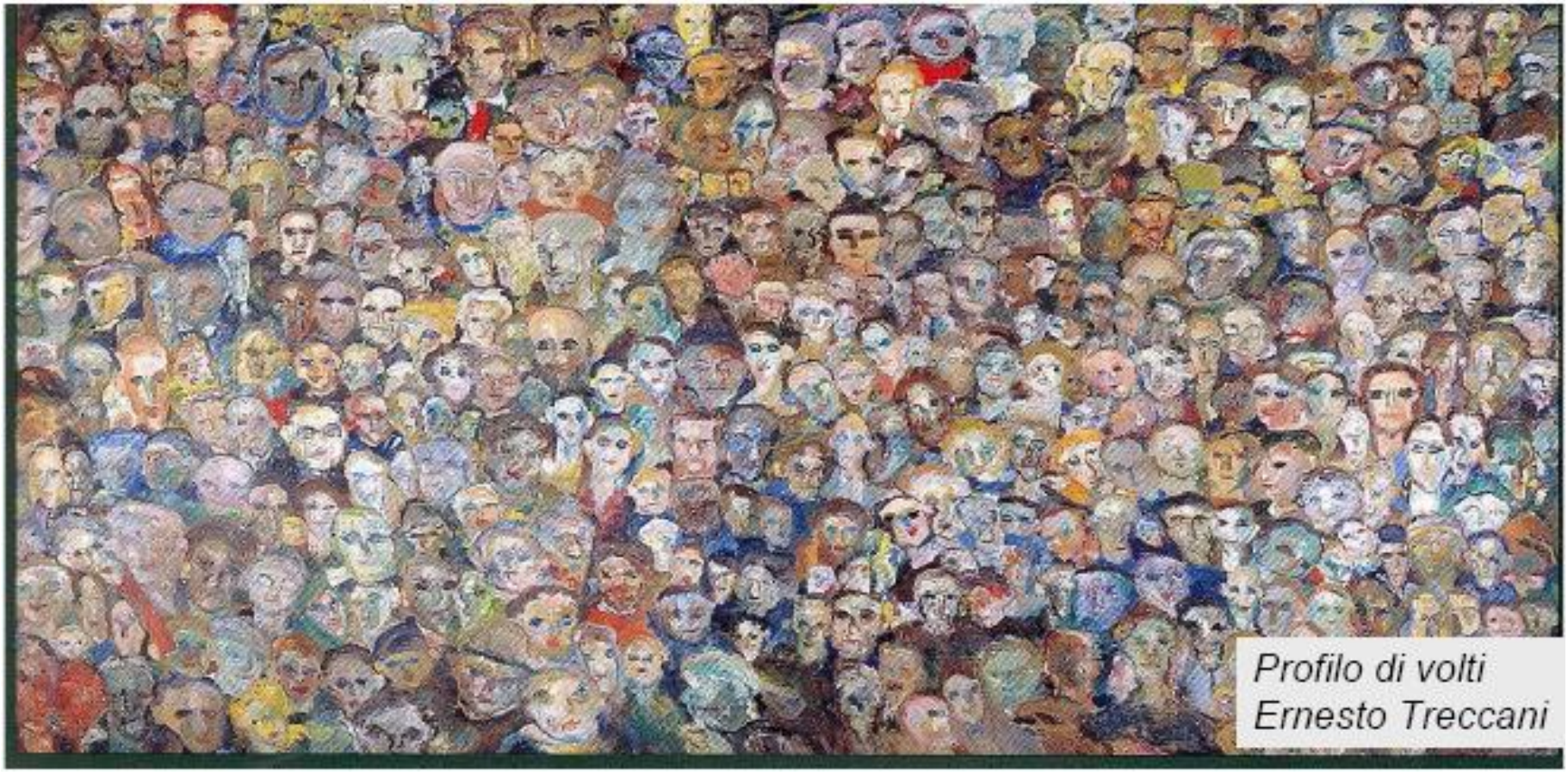
The primary goals for initiating antiretroviral therapy (ART) are to:

- reduce HIV-associated morbidity and prolong the duration and quality of survival
- restore and preserve immunologic function
- maximally and durably suppress plasma HIV viral load
- prevent HIV transmission

Optimal viral suppression is generally defined as a viral load persistently below the level of detection (<20– 75 copies/mL, depending on the assay used).

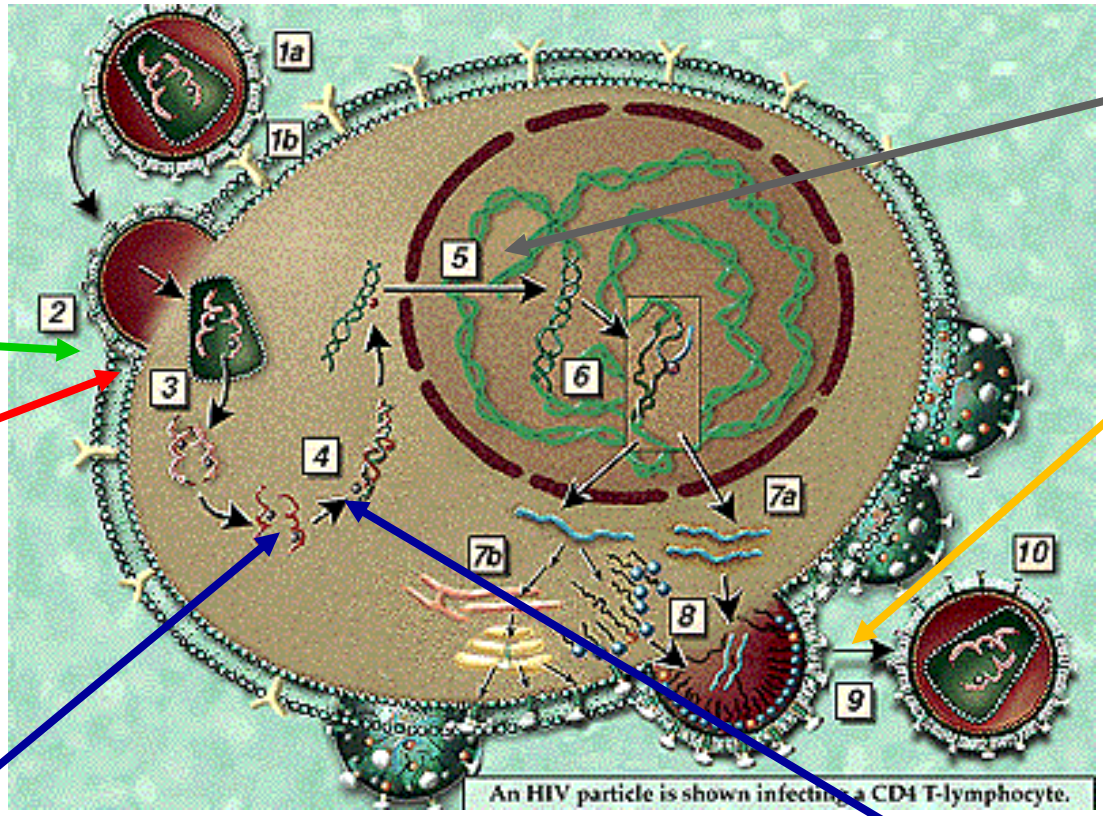
The personalized medicine

All international guidelines focus on the importance of **tailoring antiretroviral therapy** to the individual patient, on the basis of **HIV-1 genetic data**, **integrated with clinical, laboratory and therapeutic information**.



Almost every step of HIV replication is target of at least one drug

(1) Binding & fusion – (2) Entry – (3) Uncoating – **(4) Reverse transcription – (5) Integration** – (6) Transcription – (7) Translation - (8) Assembly & budding – **(9) Maturation**



1 Entry inhibitor:
MVC

1 Fusion inhibitor (FIs): **T20**

3 Integrase inhibitors (INIs)
RAL, EVG, DTG

9 Protease inhibitors (PIs)
SQV, IDV, RTV, NFV, fAPV, LPV, ATV, TPV, DRV

8 Nucleoside reverse transcriptase inhibitors (NRTIs):
AZT, ddI, ddC, d4T, 3TC, ABC, TDF, FTC

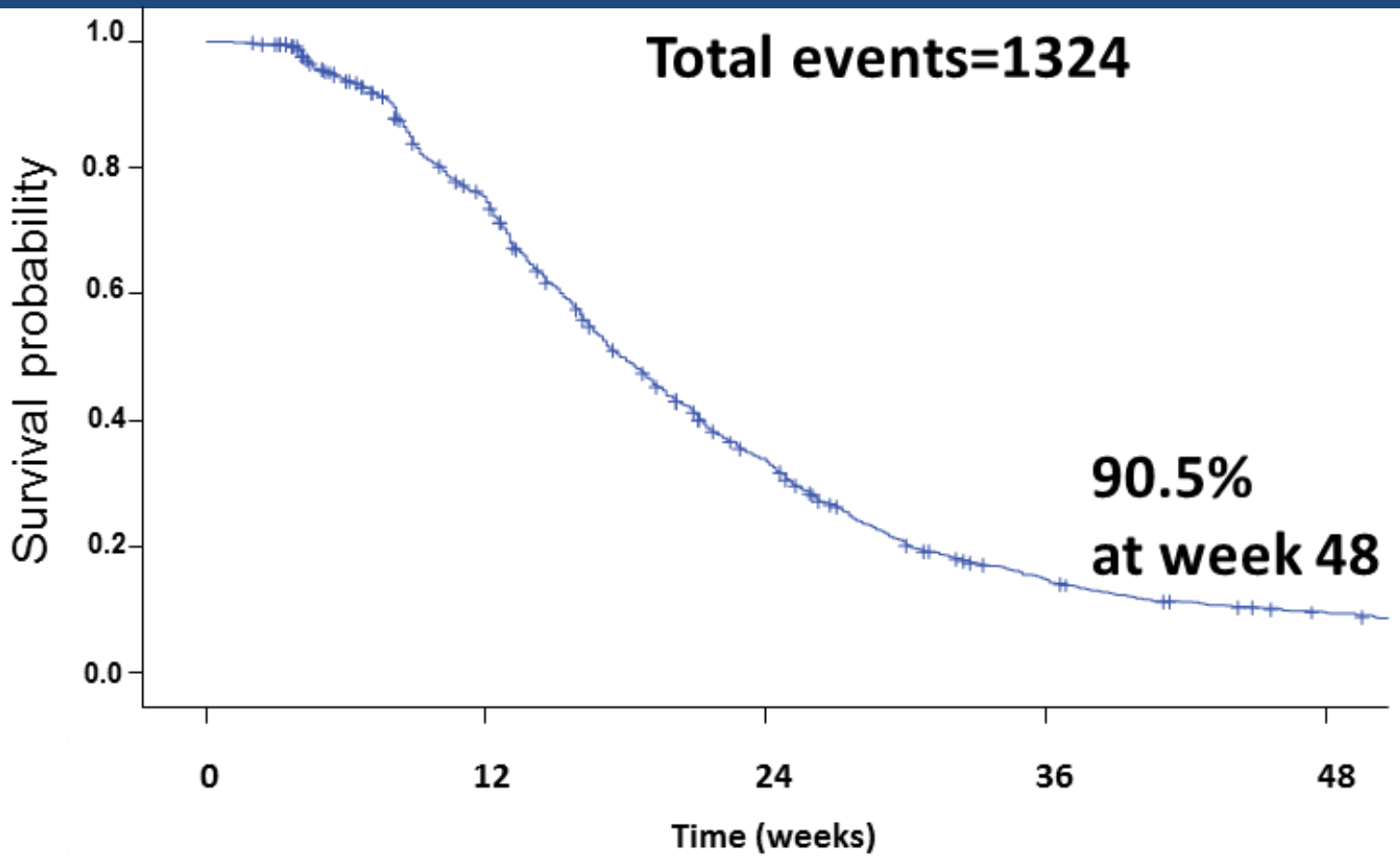
5 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
EFV, NVP, DLV, ETR, RPV

•Over the past 15 years there has been significant progress in the treatment of HIV-1 infection, starting with the use of highly active antiretroviral therapy.

•To date **about 90%** of HIV-1 infected patients who start a first line regimen achieve virological undetectability.

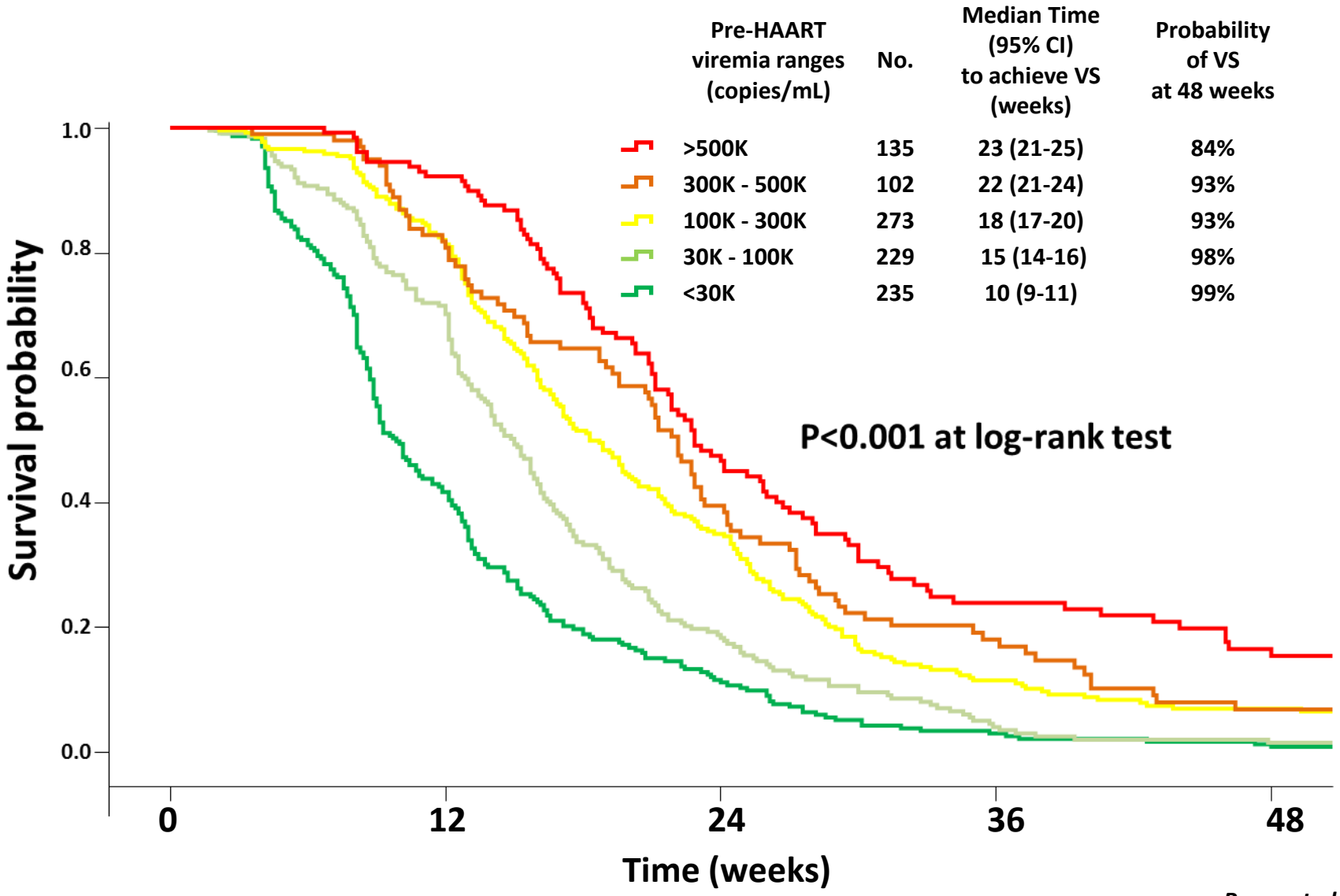
Overall more than 90% of patients achieve virologic suppression at week 48 after starting HAART

Full SET analysis: The median time (95% CI) to achieve VL<50 cps/mL in 1430 ART-naive patients starting HAART treatment is 18 (17-19) weeks



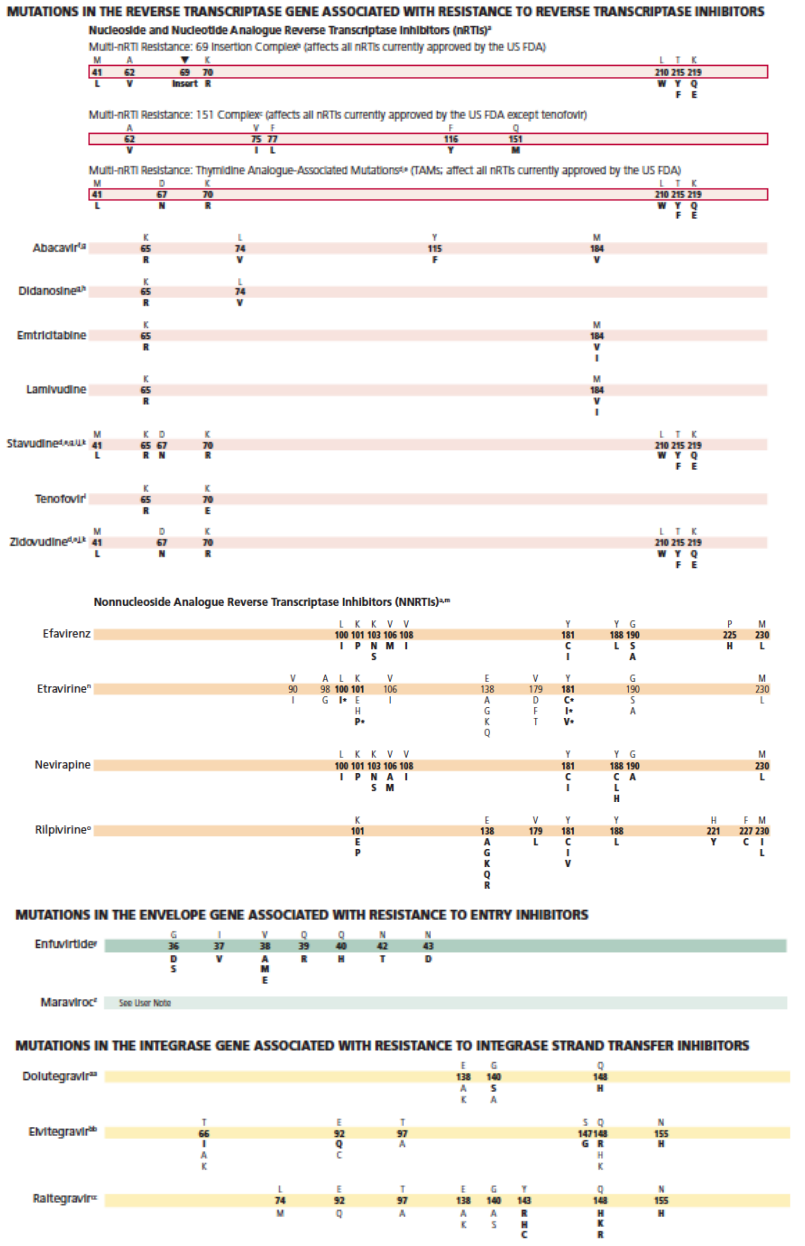
Santoro et al. Antivir Ther 2013

The time to achieve virological undectability and the rate of success at 48 week are pre-HAART viremia dependent

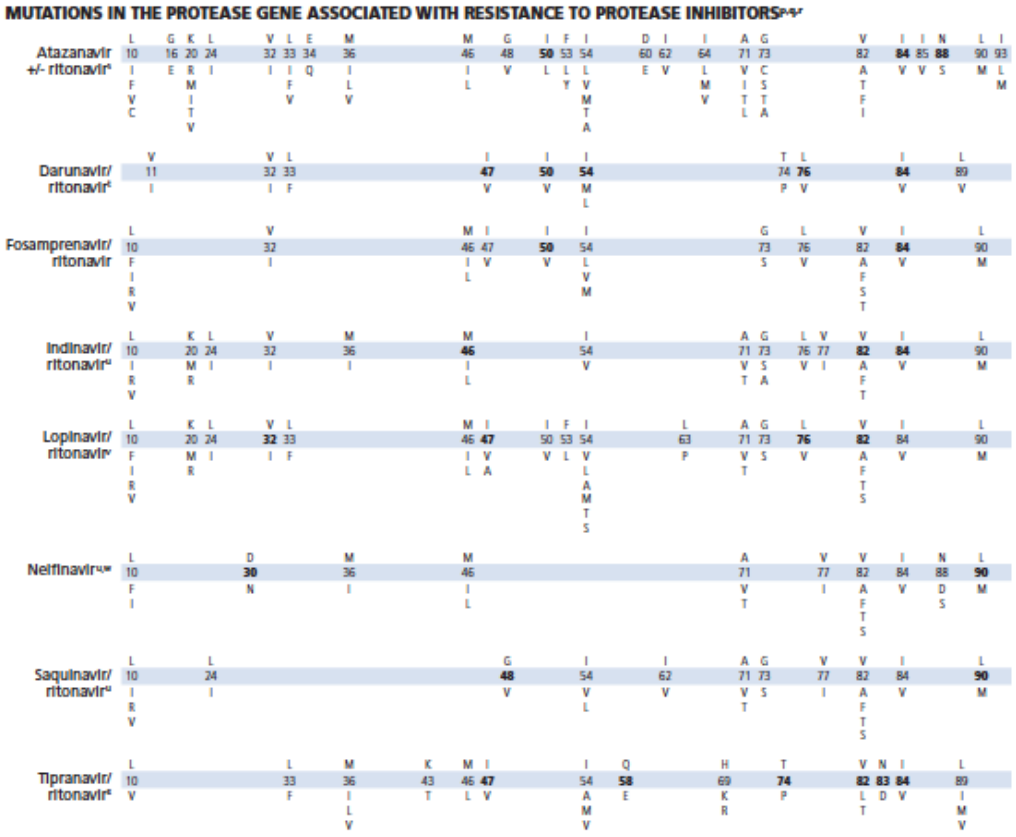


Perno et al., EACS 2011
Santoro et al. Antivir Ther 2013

Today more than 100 mutations…



IAS February/March 2013



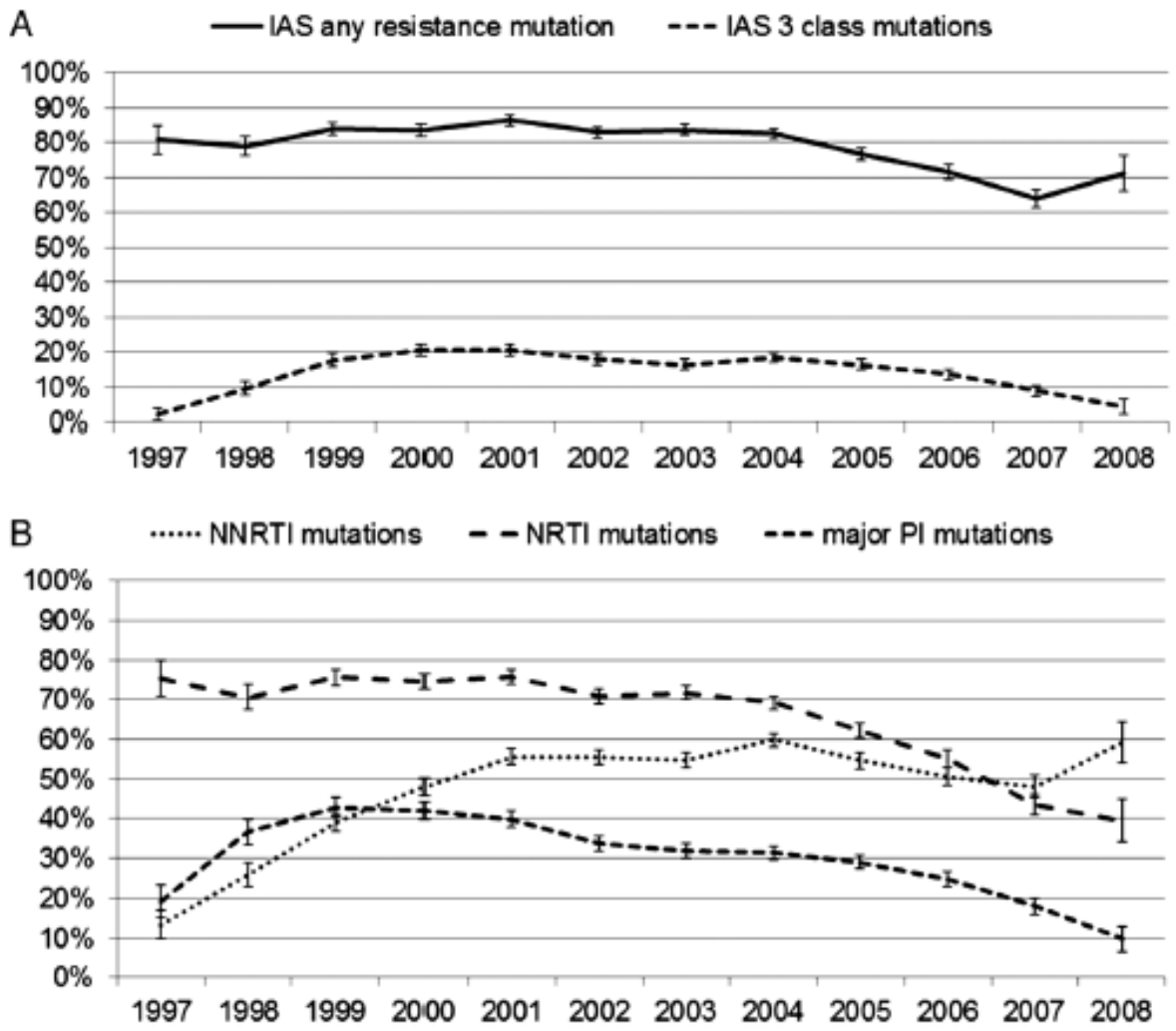
Johnson VA, et al. Top HIV Medicine 2013

Declining Prevalence of HIV-1 Drug Resistance in Antiretroviral Treatment-exposed Individuals in Western Europe

Andrea De Luca,[1,14] David Dunn,[2] Maurizio Zazzi,[3] Ricardo Camacho,[4,15] Carlo Torti,[5,16] Iuri Fanti,[1] Rolf Kaiser,[6] Anders Sönnerborg,[7] Francisco M. Codoñer,[8] Kristel Van Laethem,[9] Anne-Mieke Vandamme,[9,15] Loveleen Bansi,[10] Valeria Ghisetti,[11] David A. M. C. van de Vijver,[12] David Asboe,[13] Mattia C. F. Prosperi,[1,17] and Simona Di Giambenedetto[1] for the SEHERE collaboration in Chain

HIV-1 drug resistance represents a major obstacle to infection and disease control. This retrospective study analyzes trends and determinants of resistance in antiretroviral treatment (ART)-exposed individuals across 7 countries in Europe. Of 20 323 cases, 80% carried at least one resistance mutation: these declined from 81% in 1997 to 71% in 2008. Predicted extensive 3-class resistance was rare (3.2% considering the cumulative genotype) and peaked at 4.5% in 2005, decreasing thereafter. The proportion of cases exhausting available drug options dropped from 32% in 2000 to 1% in 2008. Reduced risk of resistance over calendar years was confirmed by multivariable analysis.

The Journal of Infectious Diseases 2013;207:1216–20



There was a clear evidence of a reduction of overall resistance mutations and of mutations to NRTI and PI over calendar years, in particular after 2001 ($P < .001$ for all comparisons).
The probability of detecting NNRTI resistance mutations initially increased, peaking in 2004, and later declined ($P < .001$).

Evolution of the (A) overall and (B) class-specific resistance mutations over calendar years (vertical bars represent 95% confidence intervals).

The Journal of Infectious Diseases 2013;207:1216–20

DRUG NAÏVE PATIENTS

DHHS Guidelines: October 2013 Update on Integrase Inhibitors

	Preferred Regimens	Alternative Regimens
NNRTI	▪ EFV/TDF/FTC	▪ EFV + ABC/3TC ▪ RPV/TDF/FTC or RPV + ABC/3TC
Boosted PI	▪ ATV/RTV + TDF/FTC ▪ DRV/RTV + TDF/FTC	▪ ATV/RTV + ABC/3TC ▪ DRV/RTV + ABC/3TC ▪ FPV/RTV + (TDF/FTC or ABC/3TC) ▪ LPV/RTV + (TDF/FTC or ABC/3TC)
INSTI	▪ **RAL + TDF/FTC** ▪ **EVG/COBI/TDF/FTC** ▪ **DTG + ABC/3TC** ▪ **DTG + TDF/FTC**	▪ **RAL + ABC/3TC**

- All 3 integrase inhibitors are now part of preferred first-line regimens

DHHS. Guidelines. February 2013. DHHS. Recommendation on INSTIs. October 2013.

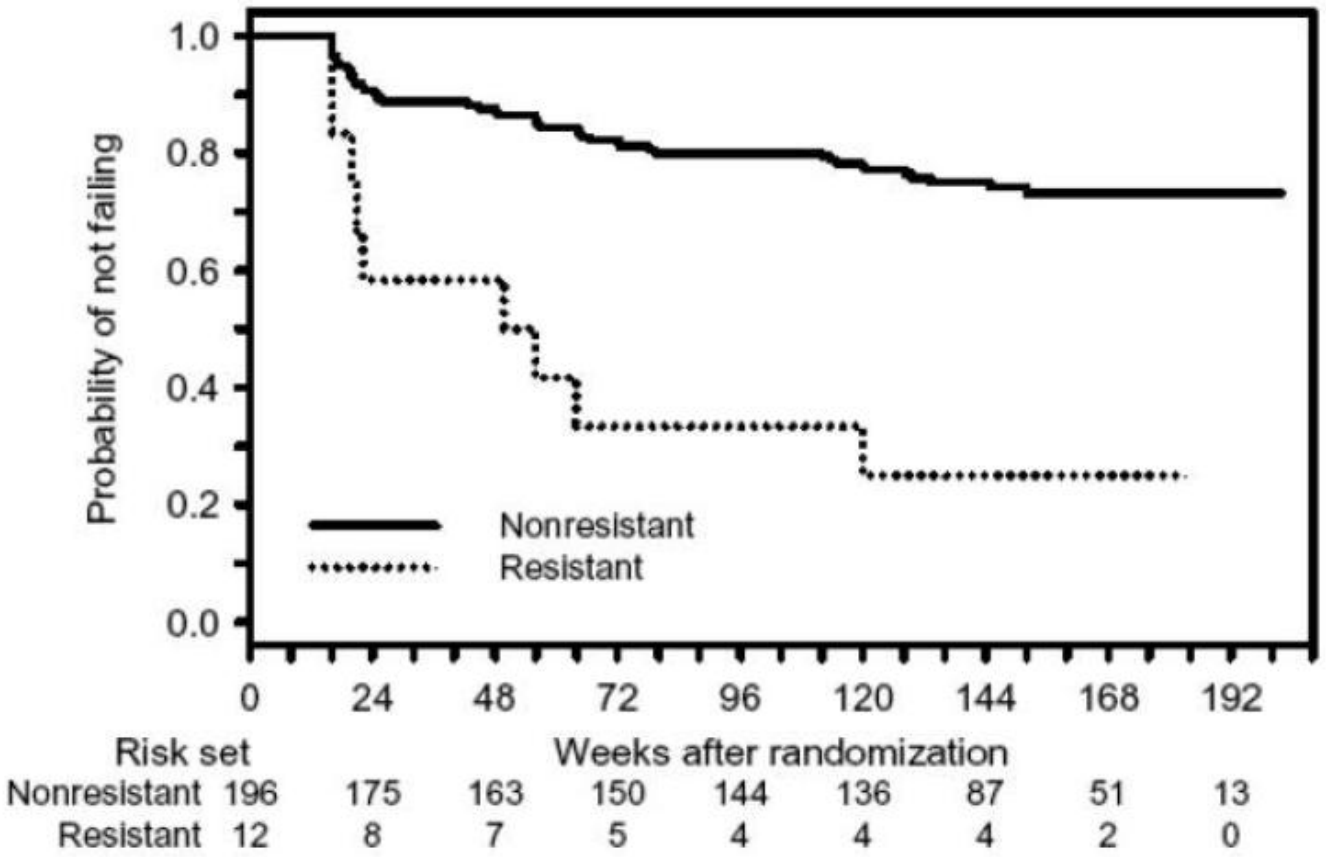
Remember…..

- Due to the intrinsic characteristics of HIV, the **selection** of the **first therapeutic regimen** is **crucial for the success of the following regimens**

Virological factors to be considered for a correct approach to first line therapies

- Limit as much as possible the use of drugs against whom the virus has already selected primary mutations

Time to first virologic failure in the subcohort was substantially shorter for subjects with preexisting NNRTI-resistant virus than for those without



Weighted Cox proportional hazard models including baseline NNRTI resistance showed a significantly increased risk of virologic failure for subjects with NNRTI-resistant virus at baseline compared with those without (intent-to-treat: HR, 2.27 [95% CI, 1.15–4.49]; *P .018) (as-treated: HR, 2.61 [95%* CI, 1.30 –5.20]; *P .007)*

Kuritzkes et al JID 2008

Consider preexisting resistance prior to start antiviral therapy

Resistance testing is recommended before starting antiviral therapy

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug resistance testing is recommended, regardless of whether treatment will be initiated immediately (**AIII**). A genotypic assay is generally preferred (**AIII**).	If treatment is to be initiated, drug resistance testing will determine whether drug-resistant virus was transmitted and will help in the design of initial or changed (if therapy was initiated prior to test results) regimens.
If therapy is deferred, repeat resistance testing should be considered at the time ART is initiated (**CIII**).	If treatment is deferred, testing still should be performed because of the potentially greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection; results of testing may be important when treatment is eventually initiated. Repeat testing at the time ART is initiated should be considered because of the possibility that the patient may have acquired drug-resistant virus.
In chronic HIV infection: Drug resistance testing is recommended at the time of entry into HIV care, regardless of whether therapy will be initiated (**AIII**). A genotypic assay is generally preferred (**AIII**).	Transmitted HIV with baseline resistance to at least one drug may be seen in 6%–16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations.
If therapy is deferred, repeat resistance testing should be considered at the time ART is initiated (**CIII**).	Repeat testing at the time ART is initiated should be considered because of the possibility that the patient may have acquired drug-resistant virus.

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. November 3, 2008

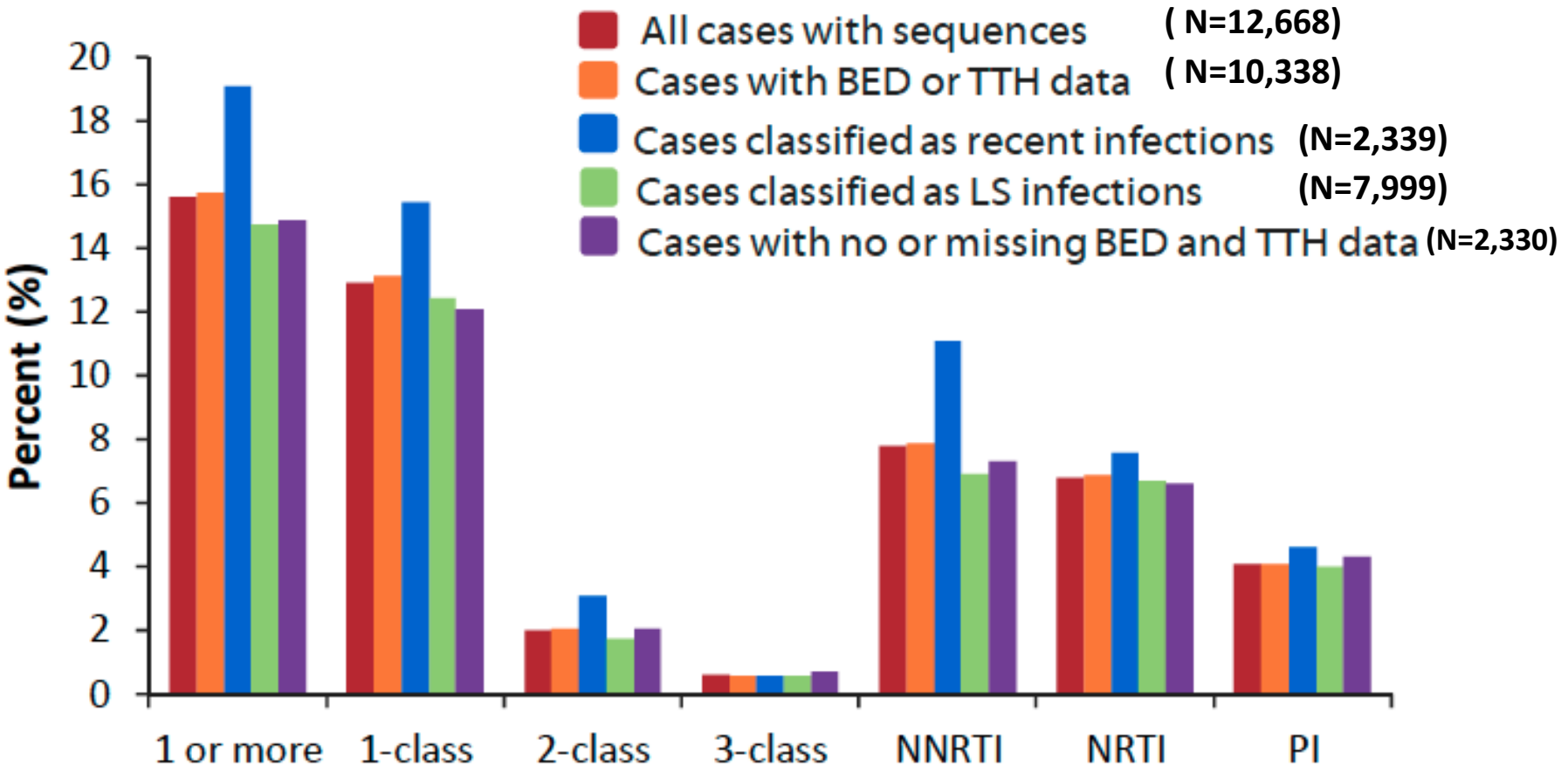
Transmitted drug resistance

- Studies report prevalence of drug resistance in ARV-naïve patients in USA and Europe:
  - **5 to 15% in newly diagnosed persons**
  - **10 to 25% in acutely infected persons**
- Persistence of transmitted resistant virus (median follow-up 2.1 years)
  - NNRTI resistance in 10/14 patients
  - Resistant virus persistently detectable in 13/14 patients
  - Mean time to first detectable wt/resistant mixture was 103 weeks (95% CI: 49–216)
- **Response to therapy in patients with transmitted resistance**
  - **NNRTI (n=67), PI (n=18), NRTI (n=25): some with MDR virus**
  - **45% (38/84) failed to suppress, best response in those receiving >2 active drugs (p=0.01)**

Little S, *et al. 14th CROI*, Los Angeles 2007, #60

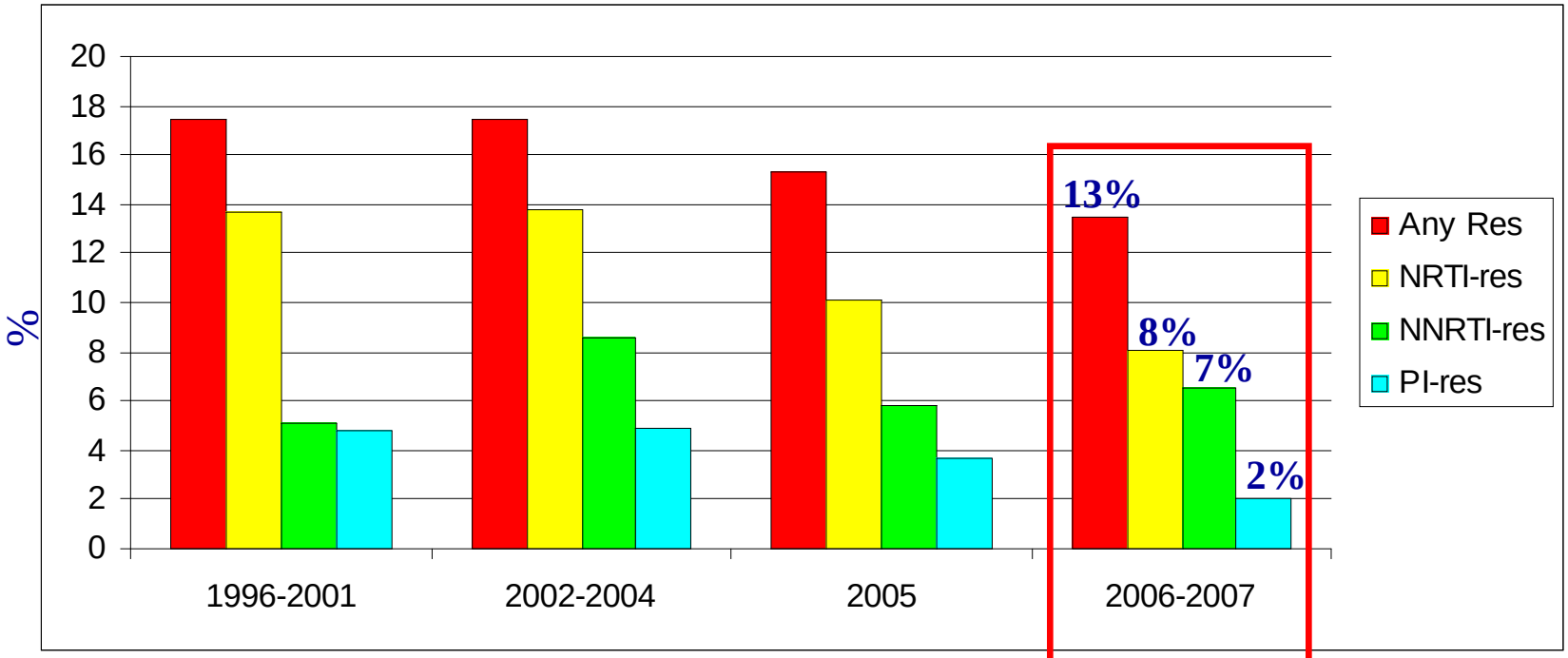
Prevalence and Trends of Transmitted Drug Resistance-associated Mutations by Duration of Infection among Persons Newly Diagnosed with HIV-1 Infection: 5 States and 3 Municipalities, US, 2006 to 2009

Cheryl Banez Ocfemia*1, D Kim1, R Ziebell2, J Prejean1, N Saduvala2, D Pieniazek1, W Heneine1, R Kline1, I Hall1, and the Variant, Atypical, and Resistant HIV Surveillance Group 1CDC, Atlanta, GA, US and 2ICF Intl, Atlanta, GA, US



Ocfemia, et al CROI 2012

Evolution of HIV-DR in drug-naive patients in Italy (by year of testing, ARCAdb)



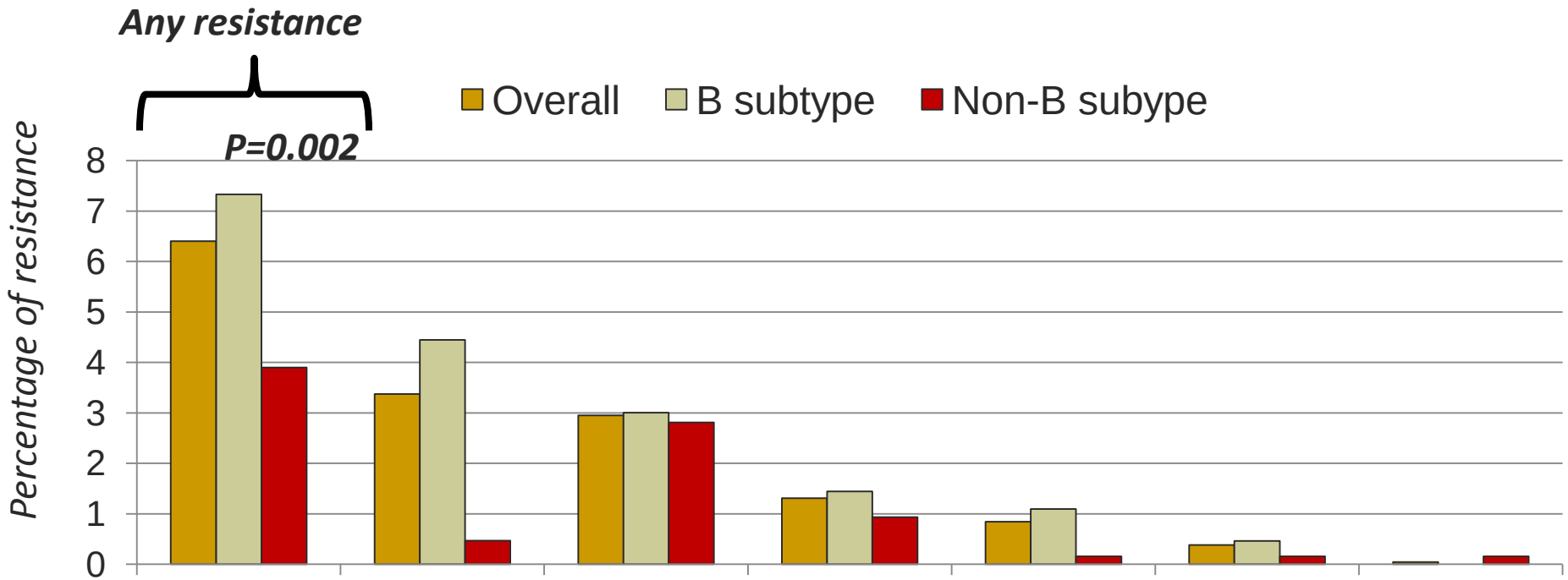
n. patients	350	464	326	550

Prevalence of HIV-DR to any drug showed a trend towards a decline over calendar years (p=0.058), after 2004; HIV-DR to NRTI (p=0.0019) and PI (p=0.0091) declined while NNRTI-DR prevalence remained stable (with a peak during 2002-2004).

Bracciale L JAC 2009

Prevalence of transmitted drug resistance (TDR) in 2464 HIV-1 infected patients enrolled in Sendih project

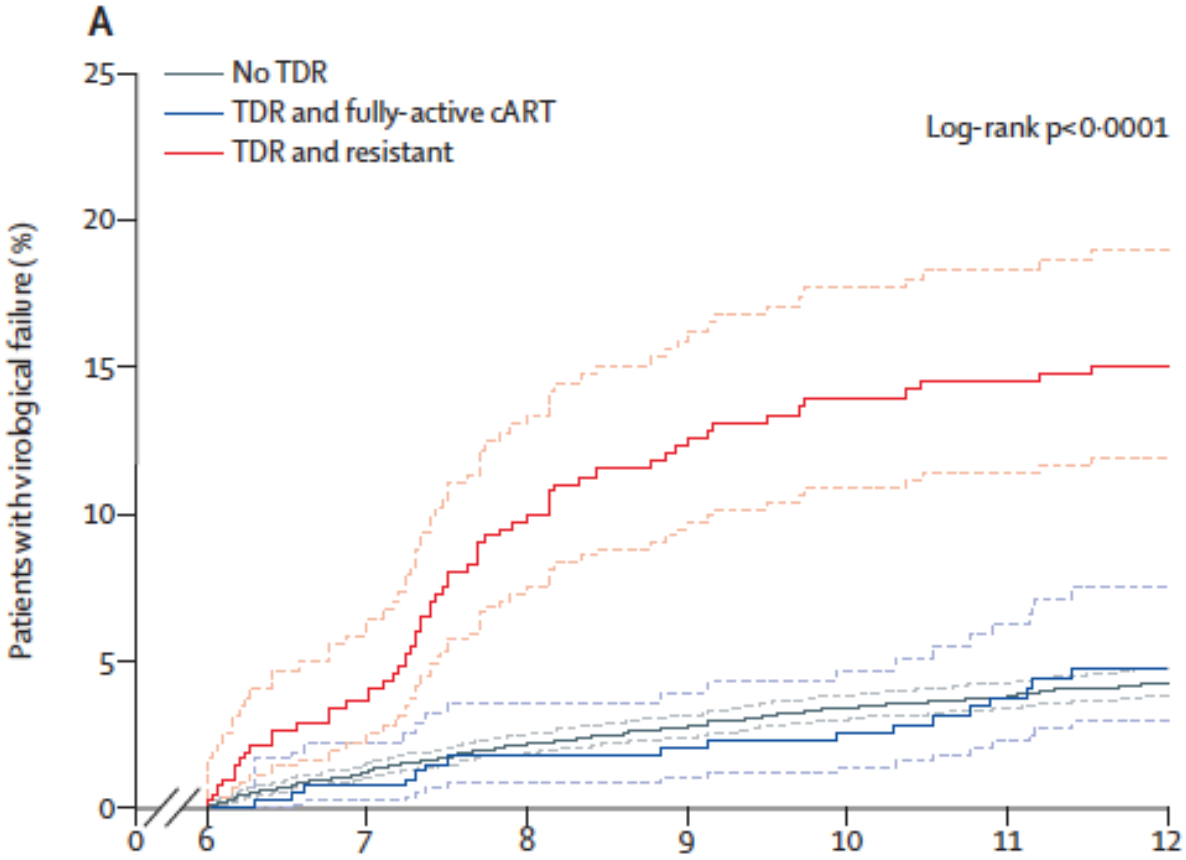
Santoro, unpublished data



- The proportion of patients infected with resistant virus is of 6.4%
- In patients infected by B subtype the proportion of resistant viruses is significantly higher (7.3% vs. 3.9%, p=0.002).

Sendih : Studio Epidemiologico Nuove Diagnosi Infezione HIV-1

Transmitted drug resistance is associated with a poorer virological response when patients received cART containing ≥1 drug not fully active



Number at risk							
No TDR	8086	7701	7367	7066	6717	6346	5786
TDR and fully-active cART	427	403	383	361	337	312	284
TDR and resistant	420	394	356	331	310	298	269

VF rates at M12 were 6.0% (95% confidence interval [CI]: 5.5; 6.5), 6.3% (4.2; 9.3) and 16.2% (13.0; 20.1) for no TDR group, TDR and fully active group and TDR and resistant group, respectively.

Wittkop et al Lancet 2011

When an active regimen was used with TDR, the use of a 2NRTI/NNRTI combination was associated with a higher risk for VF, possibly due to the presence of minority resistant species

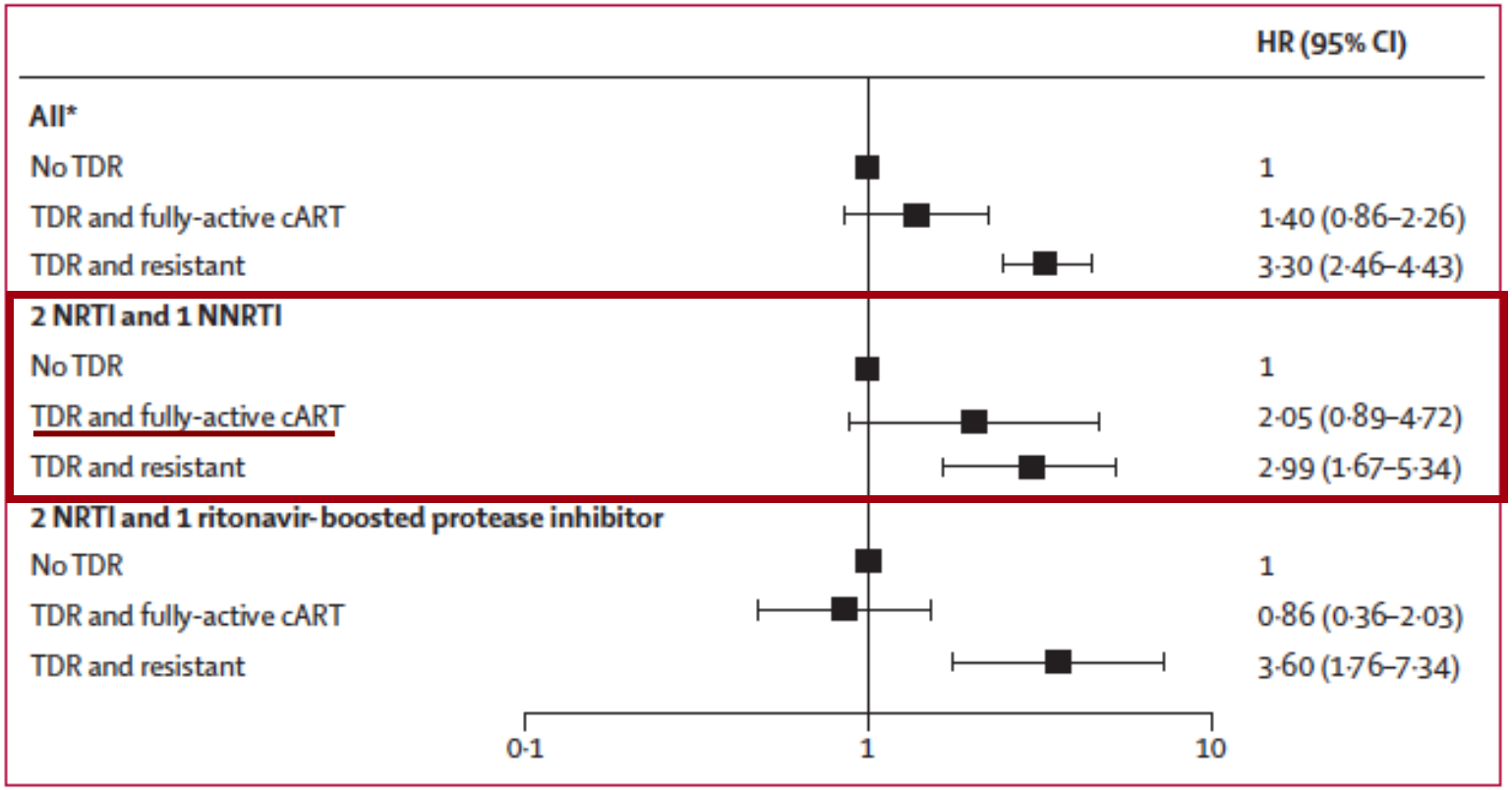


Figure 2: **Adjusted HRs in all patients and patients starting a regimen containing two NRTIs plus either one NNRTI or one ritonavir-boosted protease inhibitor**

HR=hazard ratio. NRTI=nucleotide reverse transcriptase inhibitor. NNRTI=non-nucleotide reverse transcriptase inhibitor. TDR=transmitted drug resistance. cART=combination antiretroviral therapy. *With the following categories for year of treatment start: 1998–99, 2000–05, and 2006–08 in the multivariable model.

Wittkop et al Lancet 2011

Low-Frequency HIV-1 Drug Resistance Mutations and Risk of NNRTI-BasedAntiretroviral Treatment Failure
A Systematic Review and Pooled Analysis

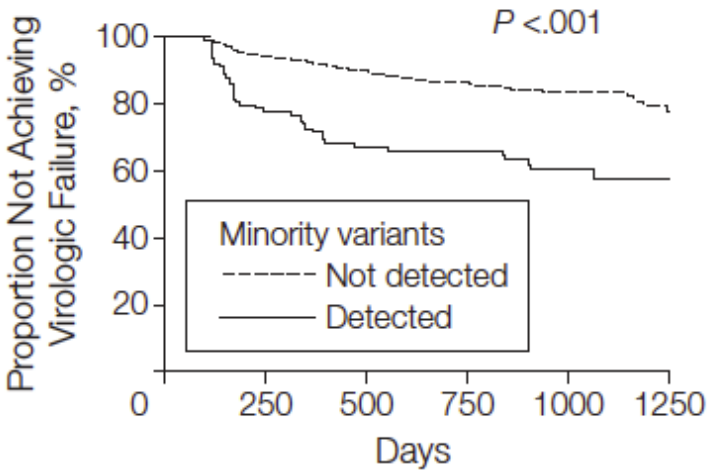
Systematic Review and Baseline Characteristics

Ten studies with 985 patients were identified as meeting the inclusion and exclusion criteria.

The median CD4 cell count was 229 cells/mm3 and mean plasma HIV-1 RNA level was 5.0 log10 copies/mL.

All studies evaluated the presence of K103N. Other commonly evaluated minority variants included Y181C (N=435) and the NRTI mutations M184V (N=228) and K65R (N=163).

Figure 2. Kaplan-Meier Curves for Proportion of Patients Without Virologic Failure by Presence of Drug-Resistant HIV-1 Minority Variants



No. at risk

Minority variants						
Not detected	691	620	455	398	344	46
Detected	117	86	60	53	37	7

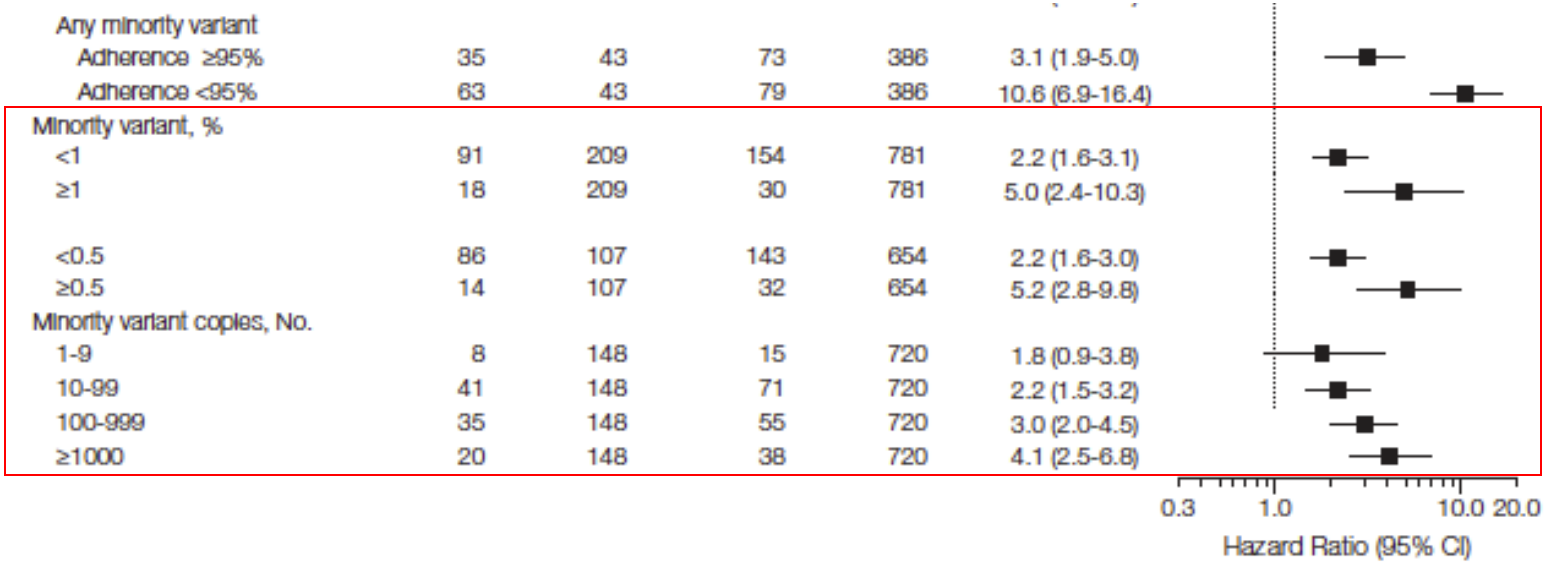
- Minority drug-resistant variants were found in 14% (117/808).
- 35% of those with detectable minority variants experienced virologic failure as compared to 15% of those without minority variants.

Li et al JAMA 2011

Figure 3. Effect of Minority Variants and Antiretroviral Therapy Adherence on Virologic Failure

Presence of minority variants at ≥1% conferred a significantly higher risk of virologic failure as compared to minority variants present at ≤1%.

A dose-dependent effect on the risk of virologic failure was found when subjects were categorized by the absolute copy numbers of minority variants per mL of plasma.



Li et al JAMA 2011

Clinical Case: ID_14827 Patient infected with HIV-1 CRF17_BF subtype	Age: 65	Sex: M	1st Seropositivity: April 2013

April 2013: ART Naive
VL: 1079920 cps/ml; CD4: 591 cells/ul

GRT
- **PR: K20RT M36I L63T**
- **RT: K101E E138K**
- **V3: None**

Tropism: R5 (FPR*: 69,8%)

Other mutations:
- *PR: T12EK I15V E35D R41K K43R R57K D60E Q61N I72T*
- *RT: K20R V35I T39A V111VI K122KEQ D123DE I142V T165I I202V E204K R211KQ F214L A272P K281R T286A A288APT V292VIM I293VI E297K I326V*

Presence of natural resistance to all NNRTI in a naive patient infected with CRF17_BF subtype HIV-1

Mutation scoring* for the protease

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
K20RT	0	0	0	0	0	10	0	0
Total:	0	0	5	0	0	10	0	0

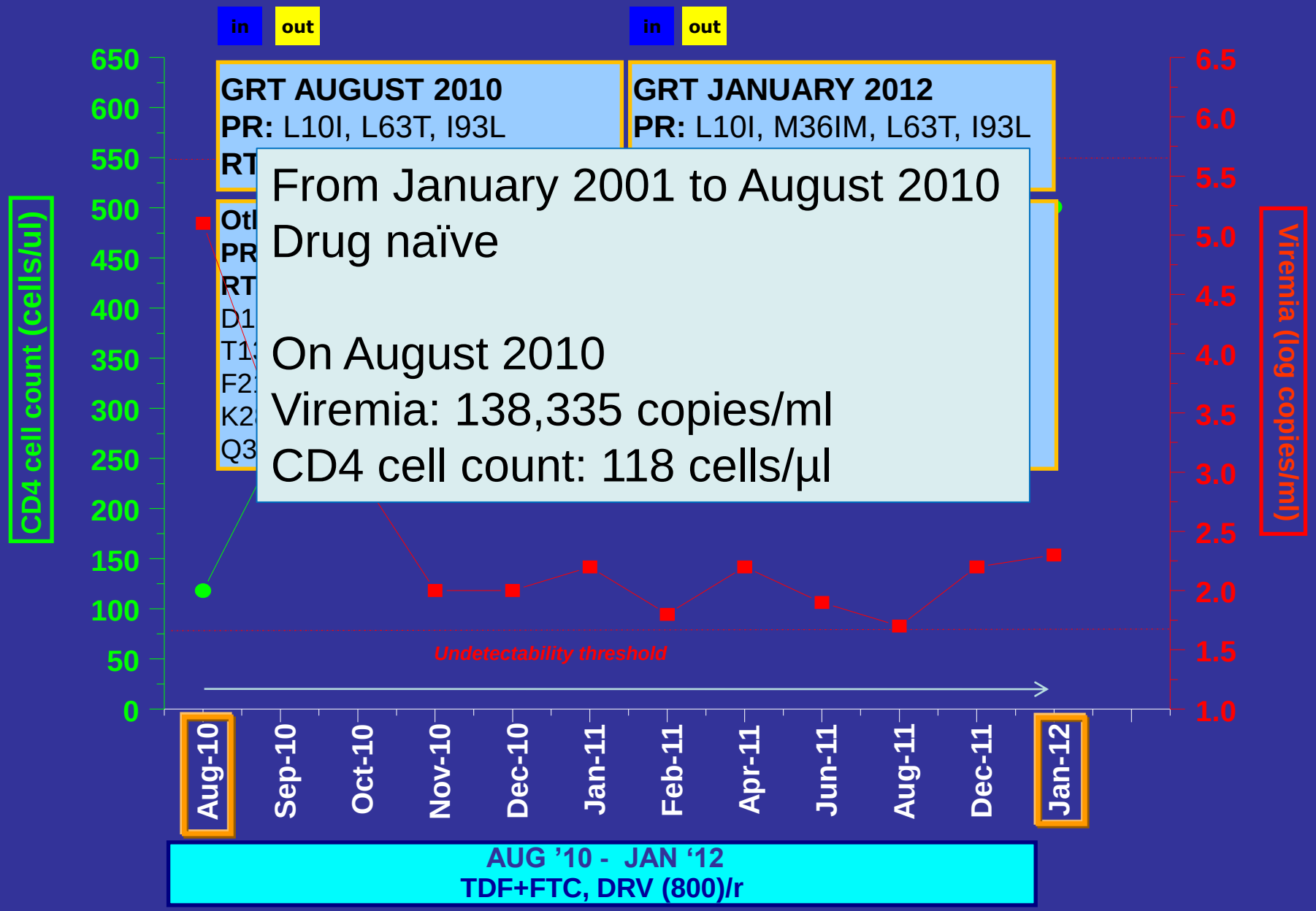
Mutation scoring* for the reverse transcriptase

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
K101E	0	0	0	0	0	0	0	15	10	30	30
E138K	0	0	0	0	0	0	0	10	10	10	30
Total:	0	0	0	0	0	0	0	25	20	40	60

- Susceptible virus
- Potential low resistance
- Low level of resistance
- Intermediate resistance
- High level of resistance

** Stanford Algorithm (http:hivdb.stanford.edu)*

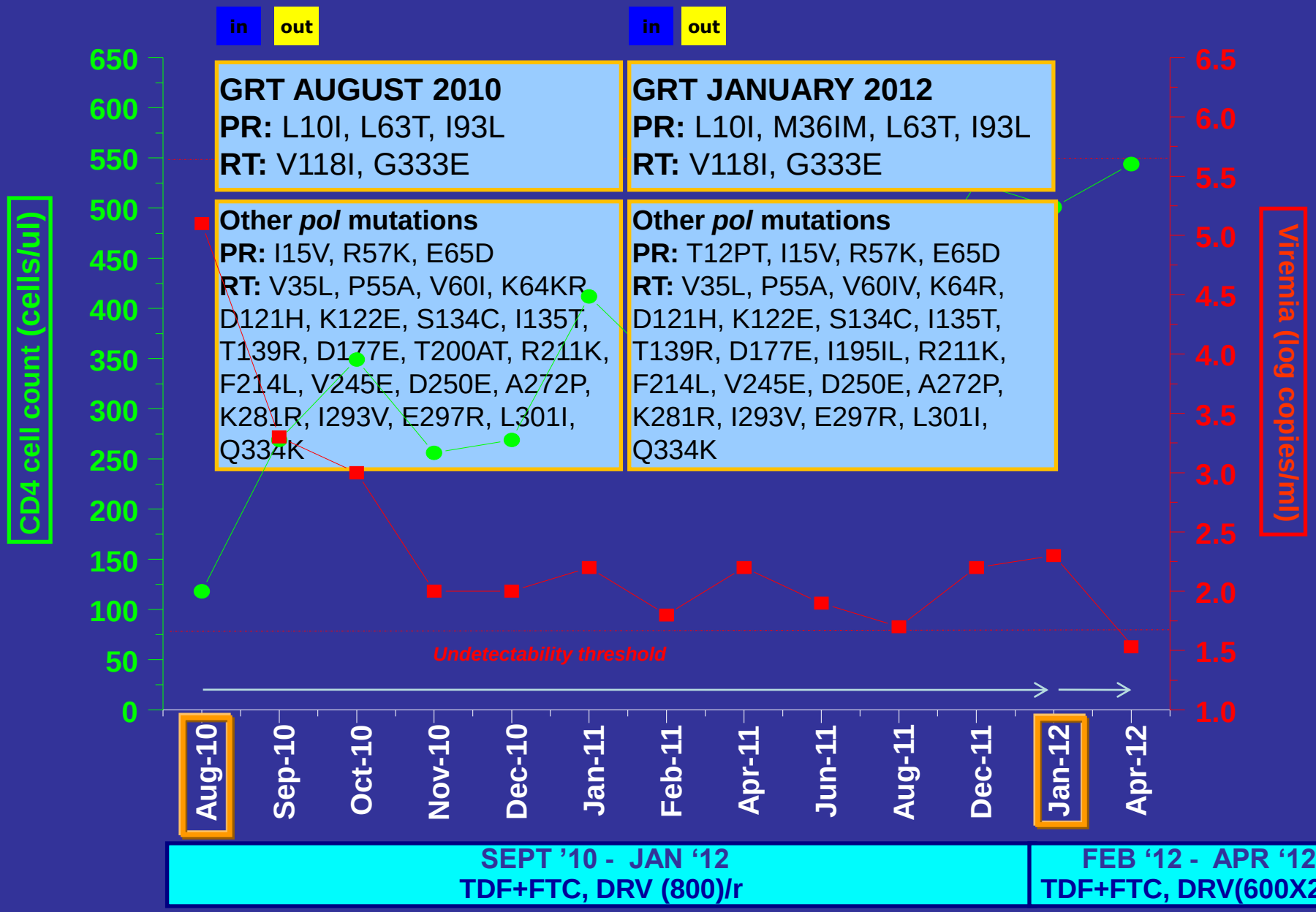
Clinical Case: ID 6784 Patient infected with HIV-1 B subtype	Age 33	Sex M	Risk Factor MSM	I Seropositivity January 2001	CDC stage B2



What to do?

- Maintain the same regimen?
- Change to an NNRTI-based regimen?
- Add another drug?

Clinical Case: ID 6784 Patient infected with HIV-1 B subtype	Age 33	Sex M	Risk Factor MSM	I Seropositivity January 2001	CDC stage B2



Clinical Case: ID 9380 - Patient infected with HIV-1 B subtype	Age: 42	Sex: F	Risk Factor: Heterosexual	CDC: A2	First Seropositivity: May-2009

- **On May 2009** (VL 124,000 cps/ml; CD4 297 cells/mm^3)

  GRT:

  PR: V77I

  RT: None

  Other PR-RT mutations:

  PR: T12TN K14R I15V L19I R41K

  RT: K49R K122E I135T T165I T200 F214L V276VI Q278QH I293V

Therapeutic failure at low level viremia in line with appearance of drug resistance mutations to all drugs administered

- **On January 2014** (VL 503 cps/ml; CD4 470 cells/mm^3)

  GRT:

  PR: V77I

  RT: A62AV K103N M184V

  Other PR-RT mutations:

  PR: T12N K14R I15V L19I R41K

  RT: K49R K122E I135T T165IL T200A F214L L228LR I293V

• **This highlights the need to set up a highly potent antiretroviral regimen particularly in patients with high pre-HAART viremia in order to achieve and mantain virological success.**

Integrase Strand Transfer Inhibitors

- **Raltegravir** (pyrimidinone analogue, formerly known as MK-0518)[1]

  First approved integrase inhibitor. Originally approved for use in treatment-experienced patients; currently approved/recommended for treatment-naive patients (400 mg twice a day).

- **Elvitegravir** (diketoacid derivative of dihydroquinoline-3-carboxylic acid, formerly known as GS-9137)[2] Highly active in drug naïve and drug experienced patients.

  FDA approved on 2012, in Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate), a new once-a-day fixed-dose combination pill to treat HIV-1 infection in antiretroviral treatment-naïve patients.

  Both offer a low-to-moderate genetic barrier to resistance and continued activity is dependent upon the presence of a supportive background regimen.

- **Dolutegravir** (previous S/GSK1349572)[3]
  - **New integrase inhibitor active against raltegravir- and elvitegravir-resistant isolates in vitro. Currently in phase III studies**. Recently approved for clinical use. QD.

- **S/GSK1265744**[4] new INI in clinical development as a long-acting parenteral based potential for a higher genetic barrier to resistance demonstrated through *in vitro* testing and a pharmacokinetic (PK) profile allowing low-dose, oral, once-daily dosing or parenteral once-monthly dosing (or longer) without the need for coadministration with a cytochrome P4503A (CYP3A) isozyme inhibitor such as ritonavir. Currently in phase II clinical trials.

1. Markowitz M, et al. J Acquir Immune Defic Syndr. 2006;43:509-515. 2. DeJesus E, et al. J Acquir Immune Defic Syndr. 2006;43:1-5. 3. Lalezari J, et al. IAS 2009. Abstract TUAB105. 4. Ford SL et al AAC 2013.

The new once-a-day fixed-dose combination of EVG/COBI/FTC/TDF was non inferior to EFV/FTC/TDF single tablet in HIV-1 drug-naïve patients

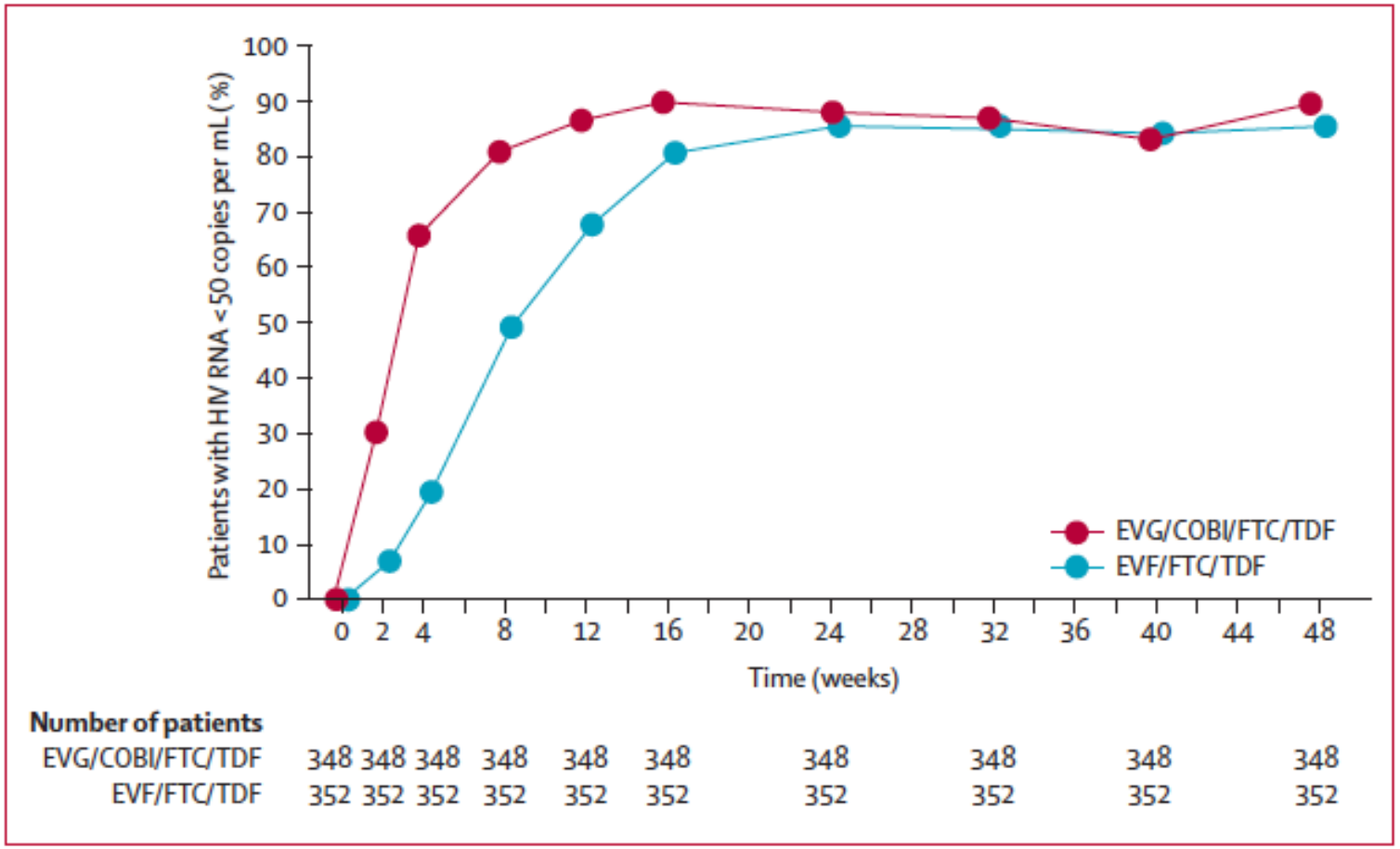


Figure 2: **Proportions of patients with HIV-1 RNA concentrations of fewer than 50 copies per mL**
Patients with missing data were classed as failures. Data are for the intention-to-treat population.
EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz.

Sax et al Lancet 2012

- **SPRING-2** is an ongoing phase III, randomized, double-blind, multicenter study evaluating once-daily dolutegravir versus twice-daily raltegravir in 822 HIV-infected treatment-naïve adult patients (Raffi et al., Lancet 2013a; Raffi et al., Lancet 2013b).

The proportion of patients achieving the HIV-1 RNA <50 copies/ mL (FDA snapshot) by week 48 and week 96 in the dolutegravir group was similar to that in the raltegravir group

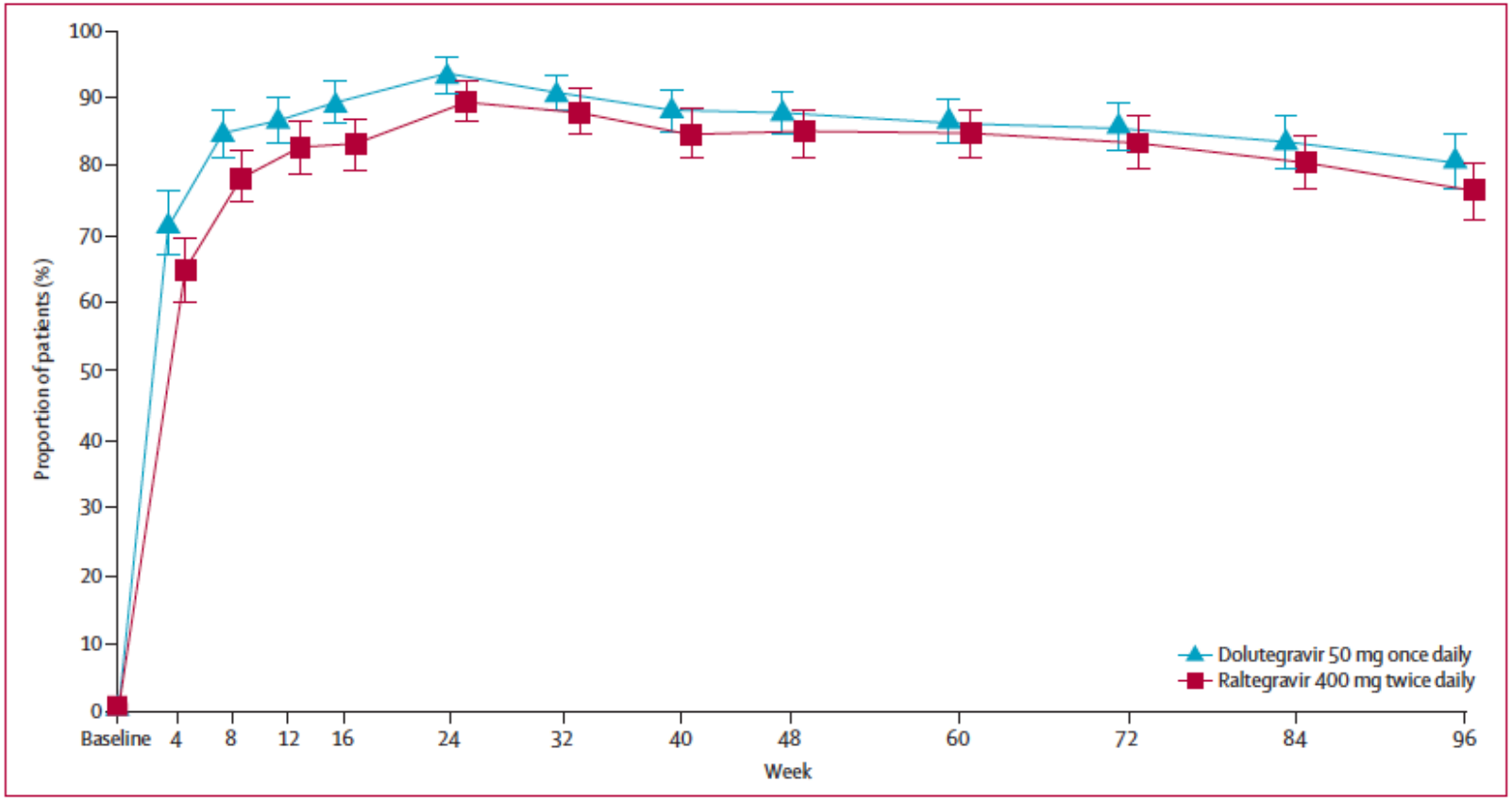


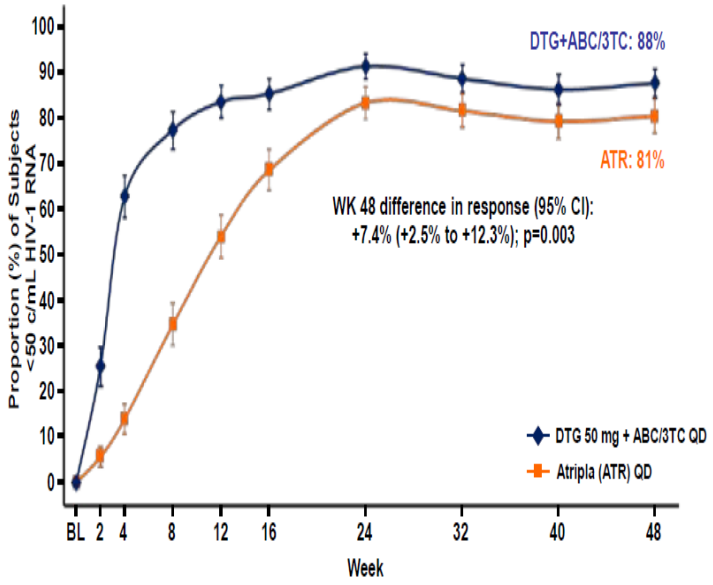
Figure 2: **Proportion of patients with less than 50 copies of HIV-1 RNA per mL, by visit**
Data are % (95% CI). Snapshot (missing, switch, discontinuation=failure) analysis.

Raffi et al., Lancet 2013

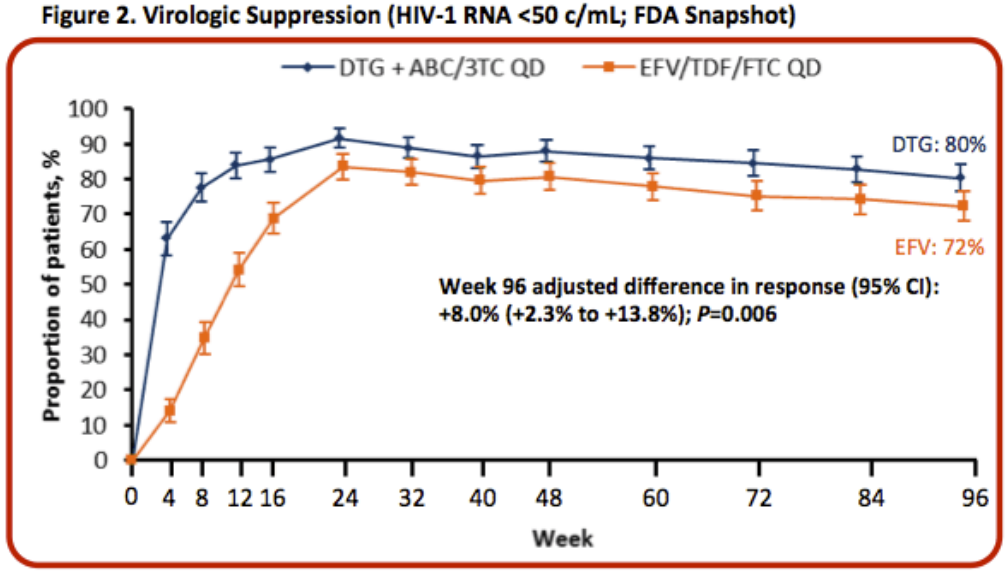
- **SINGLE** is a randomized, double-blind, double dummy, active-controlled, multicenter, phase III study evaluating dolutegravir (50mg QD) plus abacavir/lamivudine (Kivexa) versus the single tablet regimen efavirenz/emtricitabine/tenofovir disoproxil fumarate in 833 HIV-infected treatment-naïve patients (Walmsley et al., ICAAC 2012).

Non-inferiority of the dolutegravir-based regimen compared to the single tablet regimen efavirenz/tenofovir/emtricitabine, and met the pre-specified criteria for superiority.

Subjects receiving the dolutegravir-based regimen achieved virologic suppression faster than efavirenz/tenofovir/emtricitabine, with a median time to HIV-1 RNA <50 copies/mL of 28 days versus 84 days (p<0.001).



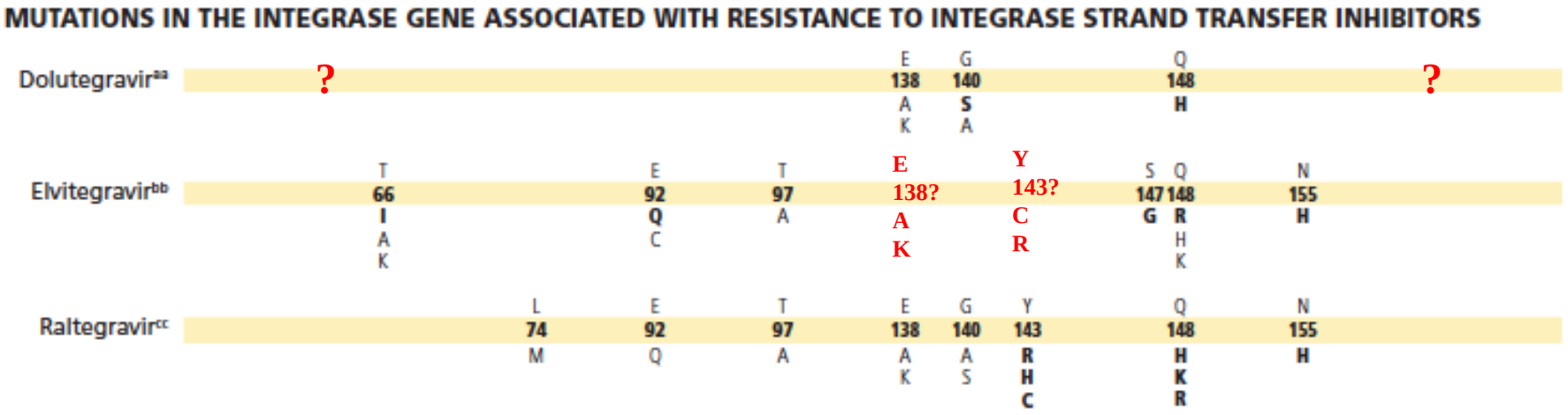
Walmsely et al., ICAAC 2012



- Overall, the statistically higher responses on DTG + ABC/3TC vs EFV/TDF/FTC were driven by withdrawals due to AEs (3% vs 11%, respectively), irrespective of viral load strata.
- Differences in time to viral suppression favored DTG + ABC/3TC (28 vs 84 days, *P*<0.0001).

Walmsley et al., abstract 543, CROI 2014

Knowledge of HIV-1 resistance is continuously evolving

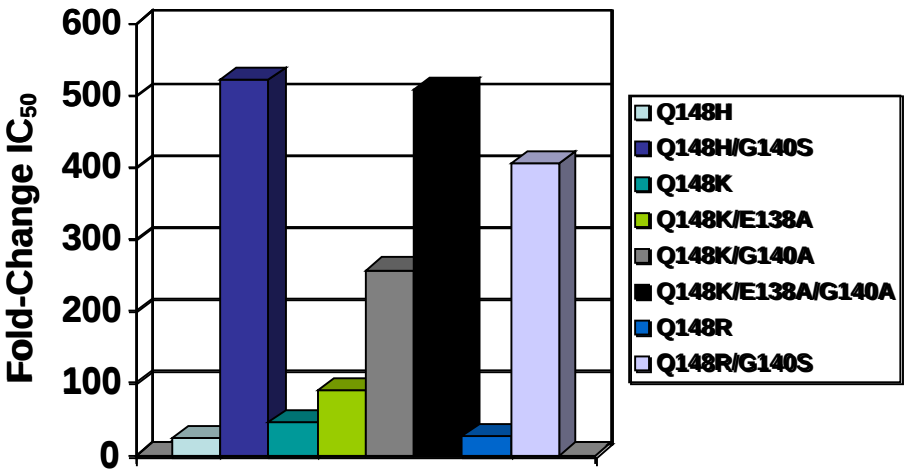


Cross-resistance studies with raltegravir- and elvitegravir-resistant viruses in vitro indicate that **Q148H and G140S** in combination with mutations **L74I/M, E92Q, T97A, E138A/K, G140A, or N155H are associated with 5-fold to 20-fold reduced dolutegravir susceptibility** and reduced virologic suppression in patients. Results of the phase III dolutegravir study in antiretroviral treatment-naive patients are expected to provide additional resistance information.

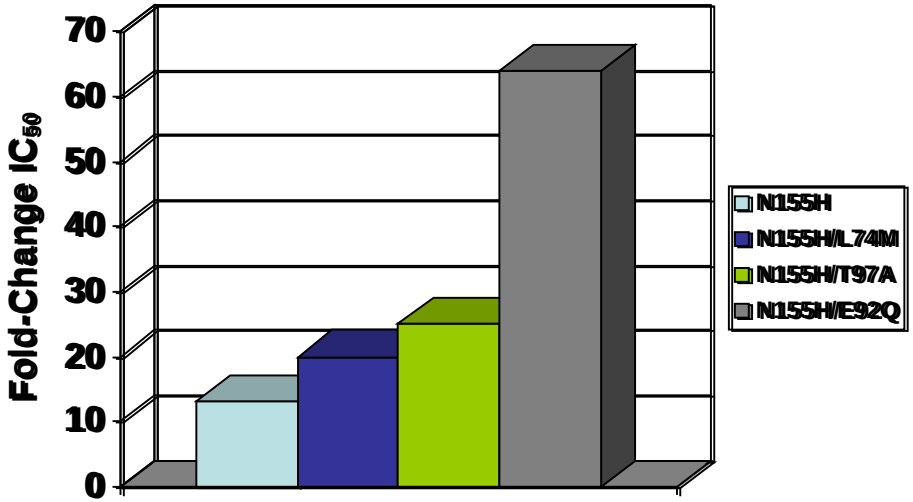
Johnson VA, et al. Top HIV Medicine 2013

Effect of signature and secondary mutations on raltegravir resistance

Q148 Pathway



N155 Pathway



As for the other drug classes, the continuous accumulation of mutations in the integrase during a failing treatment may select a virus with greater replicative capacity and full cross-resistance to the current (and perhaps also future) integrase inhibitors

Cross resistance between raltegravir and elvitegravir

Table 4. EVG and RAL Phenotypes of Site-Directed Mutant HIV-1

Fold Change of Mutant Viruses: Single IN Mutations									
Drug	T66I	E92Q	E138K	G140S	S147G	Q148H	Q148K	Q148R	N155H
EVG	15	33	0.7	5.0	8.0	6.4	67	118	38
RAL	1.4	6.0	0.9	2.0	1.0	20	34	30	23
TFV	0.9	1.0	1.0	0.8	0.8	0.9	0.8	0.7	1.0
LPV	1.0	1.0	0.9	0.8	0.8	0.7	0.9	0.7	1.0

Fold Change of Mutant Viruses: Clinical EVG-R Mutation Patterns					
Drug	T66I S147G	T66I E92Q	E92Q N155H	G140S Q148H	E138K S147G Q148R
EVG	46	145	166	> 1000	175
RAL	2.5	33	135	> 1000	34
TFV	1.1	0.9	0.9	0.9	0.9
LPV	1.0	1.0	0.7	0.9	0.8

EVG: elvitegravir; RAL: raltegravir; TFV: tenofovir; LPV: lopinavir
Green: FC ≤ 2.5; Yellow: FC > 2.5 ≤ 10; Orange: FC > 10
All data based on at least n=3 independent experiments

DJ McColl, et al. XVI International HIVDrug Resistance Workshop 2007

Specific resistance mutations for elvitegravir

Table 4. EVG and RAL Phenotypes of Site-Directed Mutant HIV-1

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RAL	1.4	6.0	0.9	2.0	1.0	20	34	30	23
TFV	0.9	1.0	1.0	0.8	0.8	0.9	0.8	0.7	1.0
LPV	1.0	1.0	0.9	0.8	0.8	0.7	0.9	0.7	1.0

Fold Change of Mutant Viruses: Clinical EVG-R Mutation Patterns					
Drug	T66I S147G	T66I E92Q	E92Q N155H	G140S Q148H	E138K S147G Q148R
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RAL	2.5	33	135	> 1000	34
TFV	1.1	0.9	0.9	0.9	0.9
LPV	1.0	1.0	0.7	0.9	0.8

EVG: elvitegravir; RAL: raltegravir; TFV: tenofovir; LPV: lopinavir
Green: FC ≤ 2.5; Yellow: FC > 2.5 ≤ 10; Orange: FC > 10
All data based on at least n=3 independent experiments

DJ McColl, et al. XVI International HIVDrug Resistance Workshop 2007

The rate of resistance development to STB was low (2.3% treated) All patients with phenotypic resistance to a component of STB had a primary resistance-associated mutation. The most common pattern of resistance was M184V in RT and E92Q in IN

HIV-1 RNA < 50 c/mL through Week 96 STB 86-87% vs 83-85% ATR-ATV/r+TVD		STB (n = 701)	ATR (n = 352)	ATV/r + TVD (n = 355)
Resistance Analysis Population [a] % (n)		5.1% (36)	6.5% (23)	4.5% (16)
Developed Any Primary Resistance to Study Drugs % (n)		2.3% (16)	2.8% (10)	0% (0)
Baseline to Week 48		1.9% (13)	2.3% (8)	0% (0)
>Week 48 to Week 96		0.4% (3)	0.6% (2)	0% (0)
Emergent Primary Resistance Mutations % (n)	NRTI-R	FTC/TDF 2.1% (15)	FTC/TDF 0.9% (3)	FTC/TDF 0% (0)
		M184V/I 2.1% (15) K65R 0.7% (5)	M184V/I 0.9% (3) K65R 0.9% (3)	M184V/I 0 K65R 0
	3rd agent	EVG (INSTI) 2.0% (14)	EFV (NNRTI) 2.8% (10)	ATV/r (PI/r) 0% (0)
		E92Q 1.3% (9) N155H 0.7% (5) Q148R 0.4% (3) T66I 0.3% (2)	K103N 2.6% (9) K101E 0.9% (3) V108I 0.6% (2) Y188F/H/L 0.6% (2) M230L 0.6% (2) V90I 0.3% (1) G190A 0.3% (1) P225H 0.3% (1)	I50L 0 I84V 0 N88S 0
	Primary PI-R	0% (0)	0.6% (2) [b]	0% (0)

a. Virologic failure Population: Patients who experience either suboptimal virologic response (two consecutive visits with HIV-1 RNA ≥50 c/mL and <1 $\log_{10}$ below baseline after week 8), virologic rebound (two consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50, or >1 $\log_{10}$ increase from nadir), or had HIV-1 RNA ≥400 c/mL at Week 48, Week 96, or their last visit.

b. One patient had emergent I50I/L and one patient had emergent Q58E in protease.

White K et al CROI 2013 #poster 596

Dolutegravir (previous S/GSK1349572) **new integrase inhibitor active against raltegravir- and elvitegravir-resistant isolates in vitro. Currently in phase III studies. Recently approved for clinical use. QD.**

Table 2. S/GSK1349572 and RAL Mean FC Against Q148 pathway Double/Triple Mutation SDMs

Viruses	Mean FC	
	S/GSK1349572	Raltegravir
E138A/Q148R	2.6	110
E138K/Q148H	0.89	17
E138K/Q148K	19	330
E138K/Q148R	4.0	110
G140C/Q148R	4.9	200
G140S/Q148H	2.6	>130
G140S/Q148K	1.5	3.7
G140S/Q148R	8.4	200
E138A/S147G/Q148R	1.9	27

3 ≤ FC< 5

5 ≤ FC < 10

10 ≥ FC

Seki et al CROI 2010

Table 3. S/GSK1349572 and RAL Mean FC Against N155 pathway and Other Double Mutation SDMs

Viruses	Mean FC	
	S/GSK1349572	Raltegravir
L74M/N155H	0.91	28
E92Q/N155H	2.5	>130
T97A/N155H	1.1	26
Y143H/N155H	1.7	38
Q148R/N155H	10	>140
N155H/G163K	1.4	23
N155H/G163R	1.1	17
N155H/D232N	1.4	20
T66I/L74M	0.35	2.0
T66I/E92Q	1.2	18
T66K/L74M	3.5	40
F121Y/T125K	0.98	11

- ***Virus continues to evolve if kept under pressure of failing antiviral therapy…***

This may increase cross-resistance, and then decrease chances of efficacy of subsequent drugs and regimens.

In the frame of a correct therapeutic sequencing, first failing therapies should be changed as soon as possible after definition of virological failure.

Different outcome for a multiexperiencing patient with high viremia treated with raltegravir….

Patient	Time (months)	HIV RNA (log_{10} copies/mL)	Mutations	Fold Change Elvitegravir	Fold Change Raltegravir
12	0	4.9	**T97A**	1.22	1.2
	1	5.0	**T97A, Y143R**	**5.2**	**33.1**
	3	5.2	**T97A, Y143R**	**4.2**	**30.9**
	7	5.1	**T97A, Y143R,** T112A/T, S119S/T	**6.7**	**43.7**
	9	4.8	**T97A, Y143R,** T112A/T	**7.5**	**96.1**
	12	4.8	**T97A, Y143R,** T112A, **I203M**	**14.2**	**205.5**
69	0	4.4	No resistance mutations	0.8	1.2
	2	3.8	E92A, **N155H**	**45.32**	**10.42**
	4	3.8	E92E/A, **N155H**	**27.65**	**7.82**
	5	3.8	E92A, **N155H,** D232D/N	**117.5**	**31.6**
	7	3.6	**E92E/Q**/A/P, **N155H, E138E/K, V151I/V**	**7.0**	**5.3**
78	9	4.3	**G163R**	**4.0**	**3.6**
81	0	5.3	No resistance mutations	1.05	0.77
	3	5.1	**N155H**	**29.49**	**4.52**
27	0	3.5	No resistance mutations	0.46	0.38
	10	3.6	**G140S, Q148H**	**456**	**248.02**
84	-3	5.9	No resistance mutations	1.13	0.66
	0	5.7	No resistance mutations	0.59	0.89
	3	3.2	**Q148Q/R**	0.16	0.4
	4	2.7	**G140S, Q148R**	**50.6**	**34.5**
	5	4.7	**Q148Q/R**	1.1	1.3
	-3	5.4	No resistance mutations	0.5	0.5
	-9	5.8	No resistance mutations	0.6	0.5
229	0	4.7	No resistance mutations	0.8	1.2
	11	4.1	**N155H, Y143C**	**114.4**	**493.2**

In red bold raltegravir primary resistance mutations; In black bold raltegravir secondary resistance mutations

Ceccherini Silberstein et al CROI 2010; Armenia et al JID 2012

Different outcome for a multifailing patient with high viremia treated with raltegravir….

Patient	Time (months)	HIV RNA (log_{10} copies/mL)	Mutations	Fold Change Elvitegravir	Fold Change Raltegravir
12	0	4.9	**T97A**	1.22	1.2
	1	5.0	**T97A, Y143R**	**5.2**	**33.1**
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	7	5.1	**T97A, Y143R,** T112A/T, S119S/T	**6.7**	**43.7**
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	0	5.7	No resistance mutations	0.59	0.89
	3	3.2	**Q148Q/R**	0.16	0.4
	4	2.7	**G140S, Q148R**	**50.6**	**34.5**
	5	4.7	**Q148Q/R**	1.1	1.3
	-3	5.4	No resistance mutations	0.5	0.5
	-9	5.8	No resistance mutations	0.6	0.5
229	0	4.7	No resistance mutations	0.8	1.2
	11	4.1	**N155H, Y143C**	**114.4**	**493.2**

In red bold raltegravir primary resistance mutations; In black bold raltegravir secondary resistance mutations

Ceccherini Silberstein et al CROI 2010; Armenia et al JID 2012

Table 1. Cross-resistance Profile of DTG on RAL-resistant Recombinant Viral Variants

	Recombinant viruses features		Average fold change (95% CI)	
Patient	Week after RAL initiation	Integrase genotype	S/GSK1349572	RAL
1	BL	WT		
	8	Y143K	1.26 (.77–1.75)	10.5 (9.73–10.99)
	8	E138K, Q148R	3.01 (2.89–3.13)	50.12 (47.23–50.24)
	12	G140S, Q148R	8.25 (6.29–10.21)	55.43 (49.14–57.39)
	20	T97A, E138A, Y143K	6.14 (4.38–7.90)	53.3 (48.92–55.06)
	24	G140S, Q148H	17.68 (13.56–21.80)	420 (406.44–424.12)
	48	E138A, G140S, Y143H, Q148H	27.12 (20.26–33.98)	700.44 (580.18–707.3)
2	BL	WT		
	24	T97A, Y143C	1.72 (1.33–2.11)	45.3 (43.97–45.69)
	36	L74M, T97A, Y143G	1.01 (.42–1.60)	52.2 (47.78–56.79)
	37	L74M, T97A, Y143G	1.33 (1.04–1.62)	48.32 (42.28–53.61)
	56	T97A, Y143R	1.09 (.89–1.29)	155.56 (151.67–158.76)
	64	L74M, T97A, E138A,Y143C	1.86 (1.47–2.25)	12.94 (11.47–13.33)
3	BL	V72I, T206S		
	24	V72I, Y143R, T206S	1.92 (1.72–2.12)	72.41 (68.69–74.61)
4	BL	WT		
	24	G140S, Q148H	10.39 (9.41–11.37)	327.84 (318.43–328.82)
5	BL	V201I		
	12	Y143S, V201I	0.63 (.43–.83)	5.23 (4.8–5.43)
	48	T97A, Y143S	0.93 (.54–1.32)	7.13 (6.59–7.52)
6	BL	T112I		
	24	Y143R	0.81 (.32–1.30)	10.97 (10.65–11.46)
	32	T97A, Y143R	1.12 (.83–1.41)	71.6 (67.77–74.89)
7	BL	WT		
	16	G140S, Q148R	9.08 (7.12–11.04)	42.37 (35.25–44.33)
	40	G140S, Q148R, G163R	13.41 (9.49–17.33)	65.5 (56.01–69.42)
	64	T112A, G140S, Q148H, G163R	21.36 (16.26–26.46)	300.11 (283.85–305.21)
8	BL	WT		
	12	V54I, Y143R, N155H	1.05 (.66–1.44)	200.43 (184.77–215.82)
9	BL	WT		
	4	V72I, N155H	1.21 (.92–1.50)	42.46 (37.54–46.75)

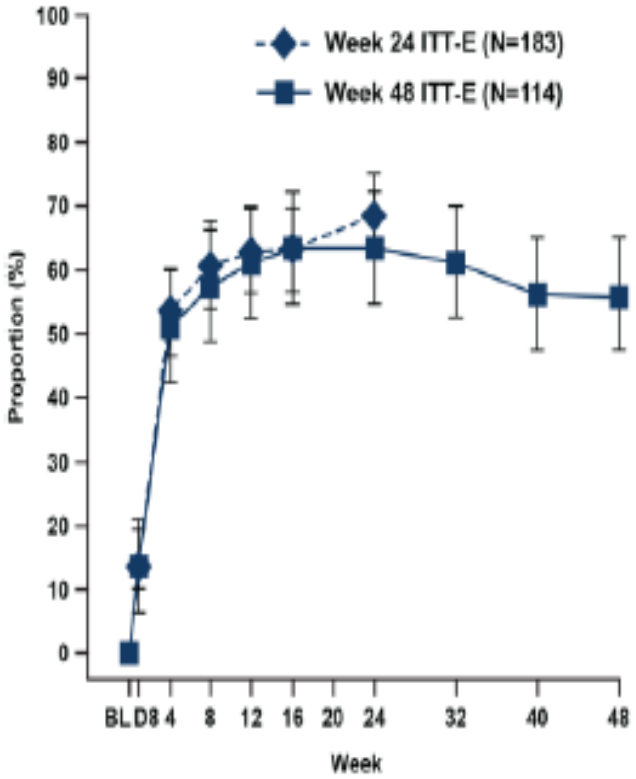
Canducci et al JID 2011

Efficacy data of dolutegravir from the Phase III clinical trial VIKING-3 in treatment-experienced INSTI-resistant patients

At Day 8 of the functional monotherapy of dolutegravir-treatment, 82% of subjects met the primary endpoint (>1 log_{10} HIV-1 RNA decline or HIV-1 RNA <50 copies/mL), the mean HIV RNA decline was of 1.4 log_{10} copies/mL (Nichols et al., 2012).

At week 24, with optimized background regimen, the proportion of participants with HIV-1 RNA <50 copies/mL under dolutegravir-regimen was 69% (126/183)**, and was 56% (64/114) at week 48** (figure 2.8) (Nichols et al., 2013).

Snapshot outcome	DTG 50 mg BID	
	Wk 24 ITT-E (N=183)	Wk 48 ITT-E (N=114)
Virologic success	126 (69%)	64 (56%)
Virologic non-response	50 (27%)	44 (39%)
No virologic data at data cut	7 (4%)	6 (5%)
Discontinued due to AE or death	5 (3%)	5 (4%)
Discontinued for other reasons	2 (1%)	1 (<1%)



Nichols et al., 2013

The best antiviral responses (at both Day 8 and Week 24) were seen in the "No Q148" group. In subjects harboring virus with Q148, a decreased response was observed with increasing numbers of mutations of G140A/C/S, L74I and E138A/K/T.

Derived IN Mutation Groups

- **No Q148**
- **Q148 + 1:** Q148H/K/R with 1 mutation (G140A/C/S, L74I, E138A/K/T)
- **Q148 + ≥2:** Q148H/K/R with 2 or 3 mutations (G140A/C/S, L74I, E138A/K/T)

Table 5. Virologic Response at Day 8 and Week 24 by Derived IN Mutation Groups (VO Population)

	Day 8 response			Week 24 response	
IN mutation group		Decline in VL (log_{10} c/mL)	Full response[a]		<50 c/mL
	N	Median	N (%)	N	N (%)
No Q148	122	-1.65	112 (92%)	72	57 (79%)
Q148 + 1[b]	35	-1.10	25 (71%)	20	9 (45%)
Q148 +≥ 2[b]	20	-0.74	9 (45%)	9	1 (11%)

[a] Full response: decline in HIV-1 RNA >1 log_{10} c/mL or <50 c/mL at Day 8
[b] L74I, E138A/K/T and G140A/C/S

- VIKING-3

A **poorer virologic response to dolutegravir-regimen was observed in subjects with INSTI resistance involving the integrase position Q148, particularly with two or more additional INSTI resistance substitutions.** In subjects harbouring virus with Q148H/K/R, a decreased response was found with an increasing number of secondary mutations among L74I, E138A/K/T and G140A/C/S

Primary INI resistance mutations at baseline	N	Mean HIV-1 RNA (log_{10}) change from baseline (SD) at Day 8	% >1 log_{10} HIV-RNA decline or <50 copies/mL at Day 8 (%)	HIV-1 RNA <50 copies/mL at Week 24 (%)
Total	183	-1.4 (0.61)	82	69
No primary mutations	60	-1.6 (0.55)	95	78
T66	1	-1.9	100	100
Y143	28	-1.7 (0.42)	96	75
N155	33	-1.4 (0.51)	82	88
≥2 Primary mutations	8	-1.4 (0.76)	75	50
Q148 + ≤1 secondary mutation*	32	-1.1 (0.51)	69	59
Q148 + ≥2 secondary mutations*	21	-1.0 (0.81)	48	24

*Key secondary mutations were L74I, E138A/K/T and G140A/C/S.
In multivariate analyses, Q148 + ≥2 mutations and increasing DTG FC were each highly correlated with smaller reductions in HIV-1 RNA at Day 8 (P<0.001).

Nichols et al., 2013

Clinical case_Mo_FS

- **Age: 64 years old**
- **Sex: Male**
- **HIV diagnosis: February 1989**
- **HIV subtype: B**
- **Tropism: R5**
- **The patient started therapy on June 1990**

Drugs administered from June 1990 to July 2011

NRTIs: ABC, AZT, DDI, D4T, TDF, 3TC, FTC

NNRTIs: EFV

PIs: APV/r, DRV/r, FPV/r, IDV, NFV, LPV/r, RTV, SQV/r, TPV/r

INI: RAL

FIs: T20

CCR5-EI: MVC

He had never achieved sustained virological suppression

Clinical case_Mo_FS

- **On may 2011**

Viremia: 247,302 copies/ml; CD4: 9 cells/ul

Genotypic resistance test

Resistance mutations

Pr: L10F K20T V32I L33F M46L I54L Q58E A71V I84V L89V L90M I93L C95F

RT: M41L E44D D67N T69D K101H V118I Y181C M184V G190A L210W T215Y K219NK

IN: Y143R

Other mutations

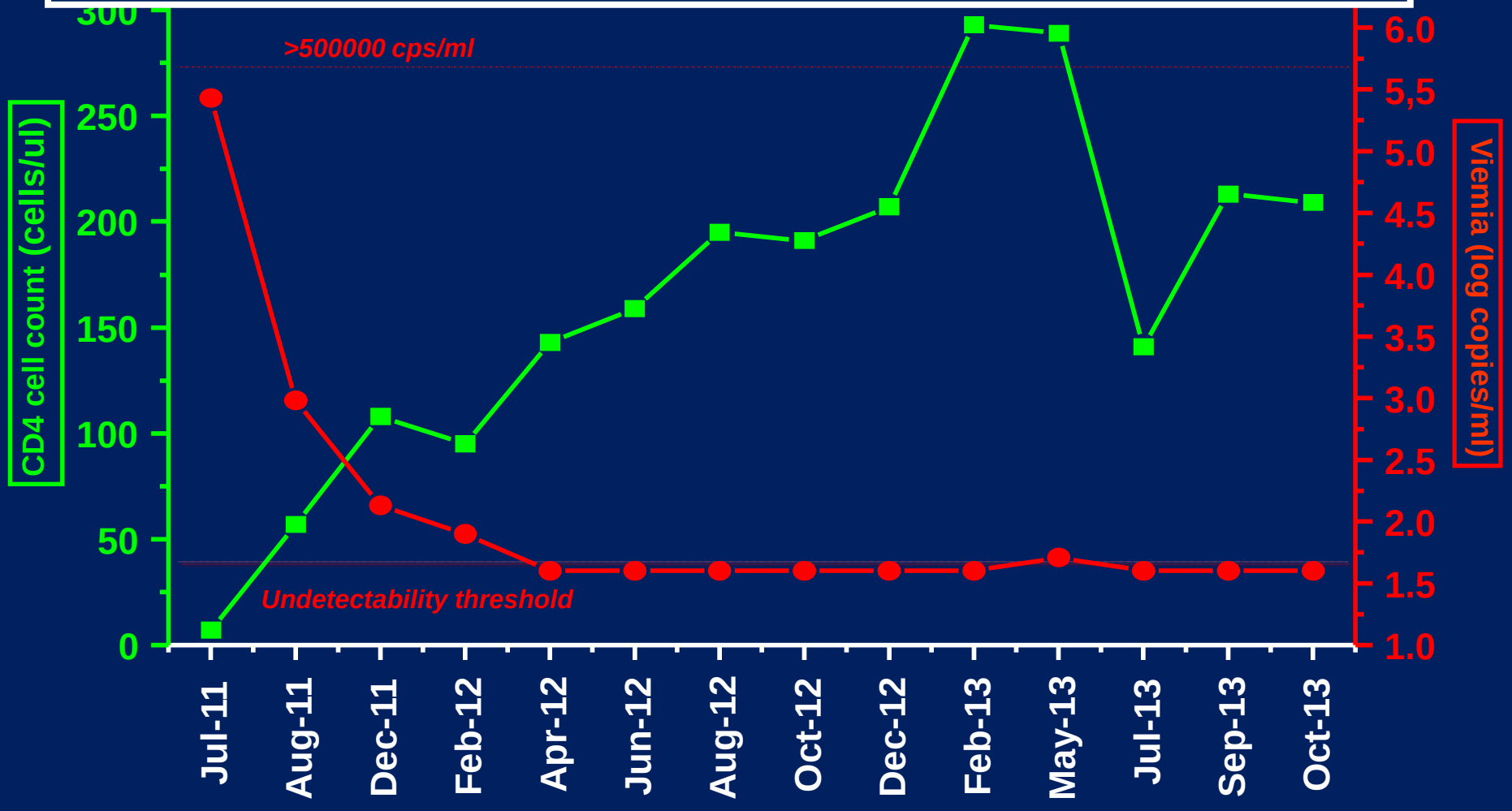
Pr: T12P I13V 14R 19P E34Q E35D M36I K55RK A62V L63P I66V V77IV Q92R

RT: K43QK V60I K122E D123E I142VI G196K Q207E R211K

IN: L101I T112A S119T F181L V201I I208M K211T Q221R L234IL

- **On July 2011 the patient started DTG MVC TPV/r**

Virological success under dolutegravir containing regimen in a pluri-treated ralegravir-experienced patient with Y143R IN mutation



From July-11 to Oct-13 DTG MVC TPV/r

Clinical case_Mo_CR

- **Age: 54 years old**
- **Sex: Male**
- **HIV diagnosis: February 1992**
- **HIV subtype: B**
- **Tropism: X4**
- **The patient started therapy on June 1997**

Drugs administered from June 1990 to July 2013

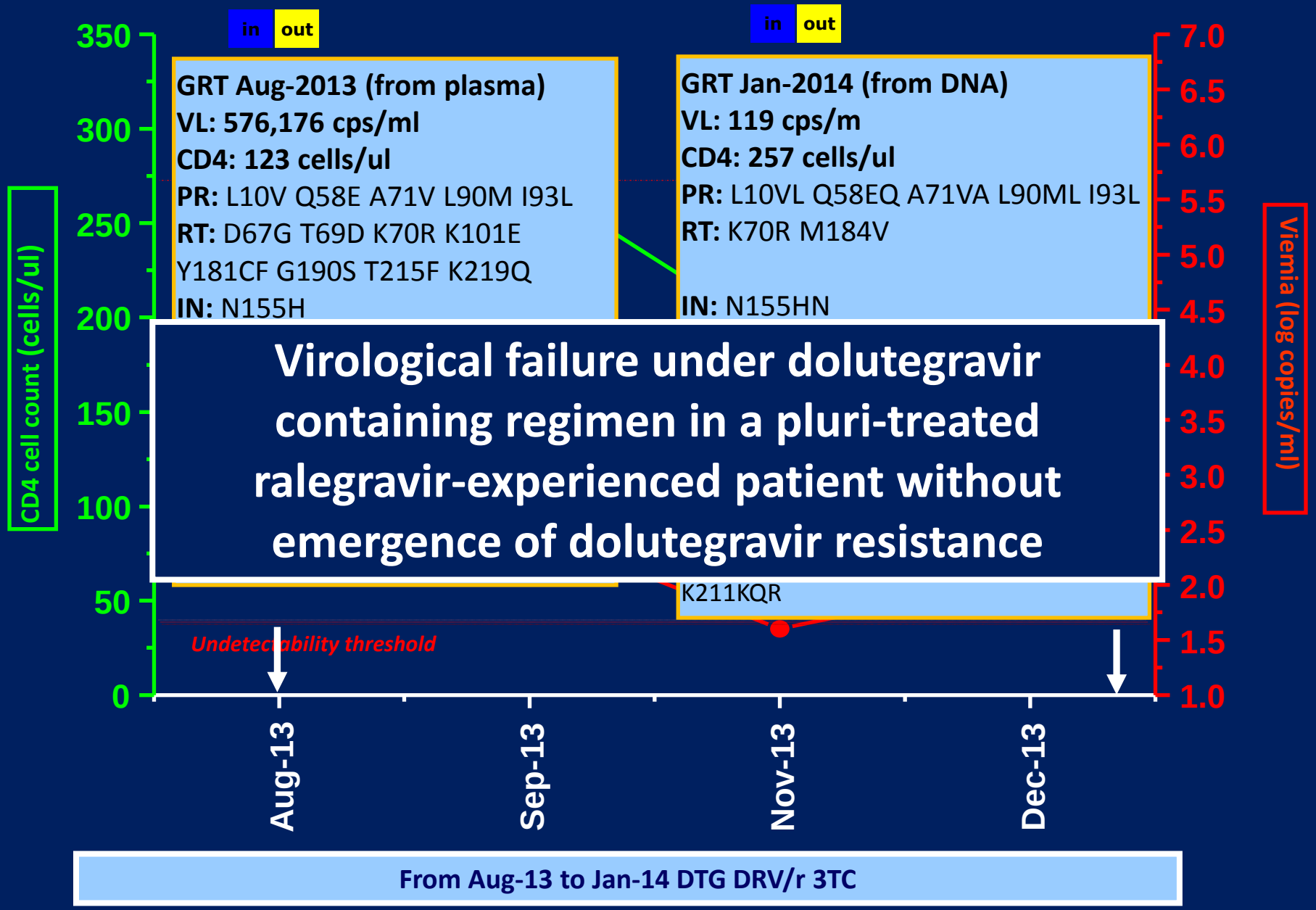
NRTIs: ABC, D4T, DDI, TDF, 3TC

NNRTIs: EFV, ETR

PIs: ATV, FPV/r, DRV/r, LPV/r, SQV/r

INI: RAL

Clinical case_Mo_CR



Conclusions

- **The characteristics of HIV infection have deeply changed, as well as the expectations of antiviral therapy.**
- **The construction of antiretroviral therapy must be designed taking into account a long-term strategy finalized to decrease to the lowest possible level the replication of HIV. The mere short/medium term control of viral replication is no longer a suitable target of antiviral therapy.**
- **The design of regimens able to control the virus over a long-time period must take into account genetic barrier, potency, pharmacokinetics and Interactions.**
- **In this frame, selection of the best therapy, based also on resistance testing, warrants the best result for each single patient.**

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Thank you for your attention !

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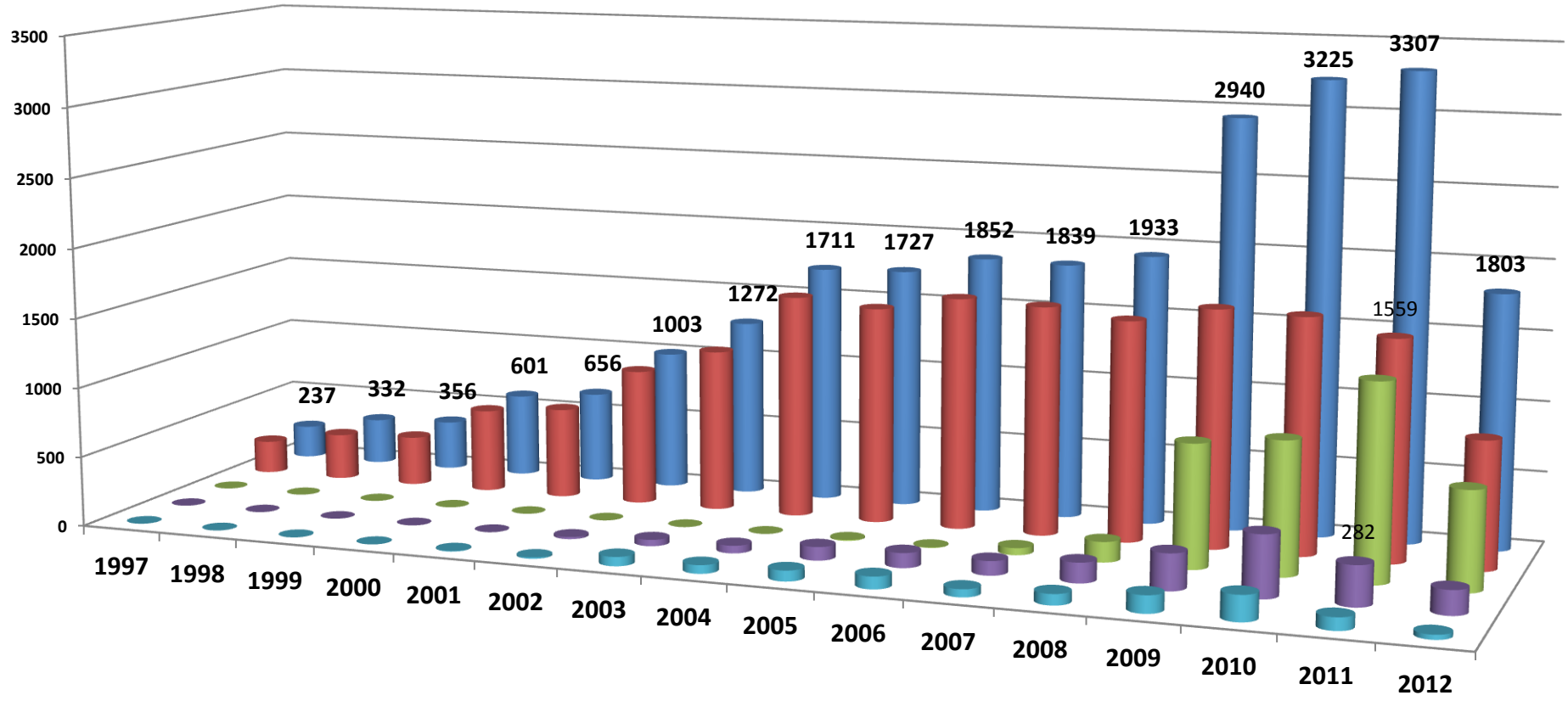
Number of overall plasma genotypes per year*



**From naïve and experienced patients*