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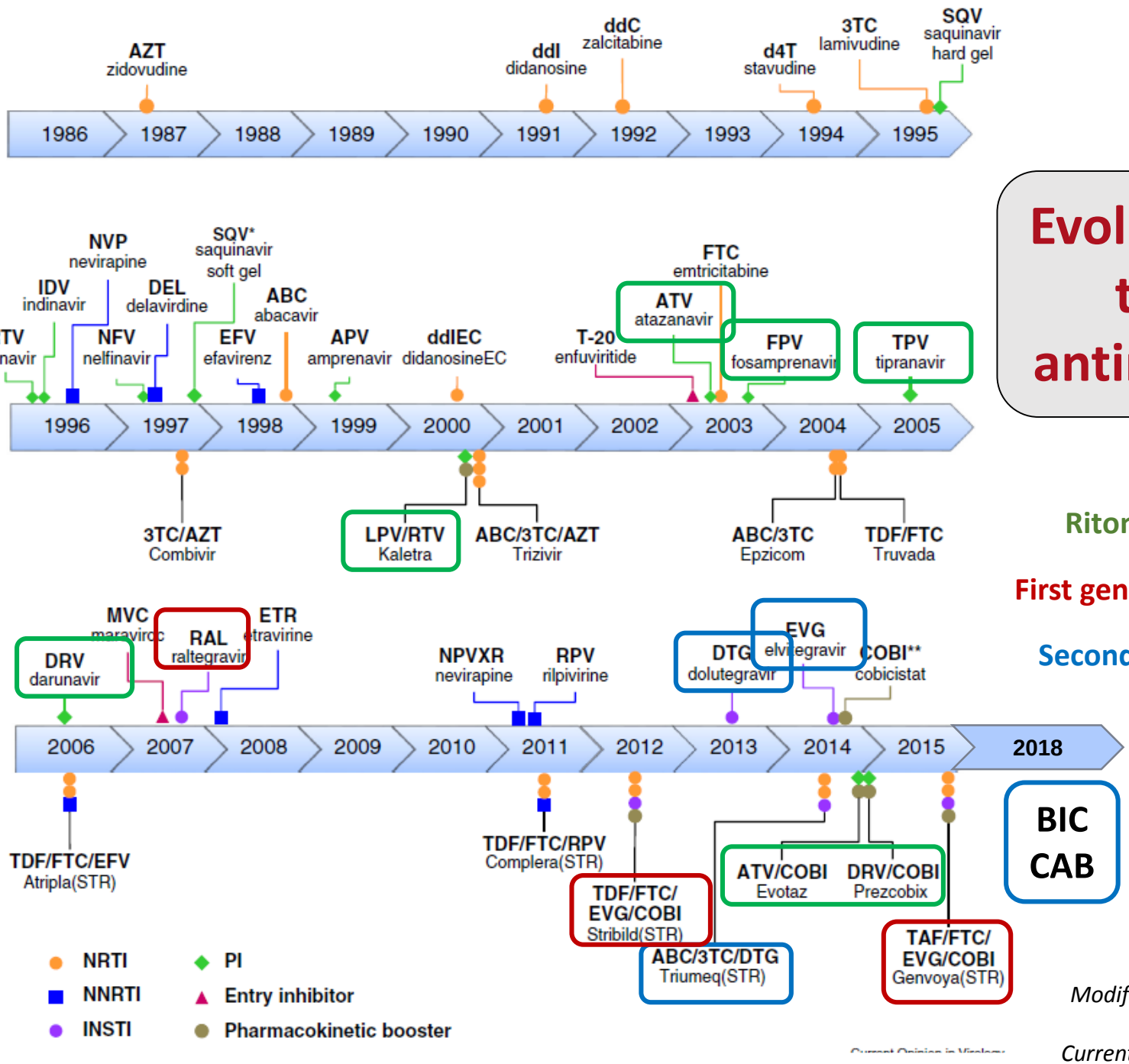
MILANO, 14-15 GIUGNO 2018
OSPEDALE LUIGI SACCO POLO UNIVERSITARIO – ASST FATEBENEFRATELLI SACCO
AULA MAGNA POLO LITA

# La resistenza nell'enzima integrasi

Carlo Federico Perno
*ASST Grande Ospedale Metropolitano Niguarda, Università degli Studi di Milano*

# Evolution over time of antiretrovirals




**Ritonavir-boosted PI**

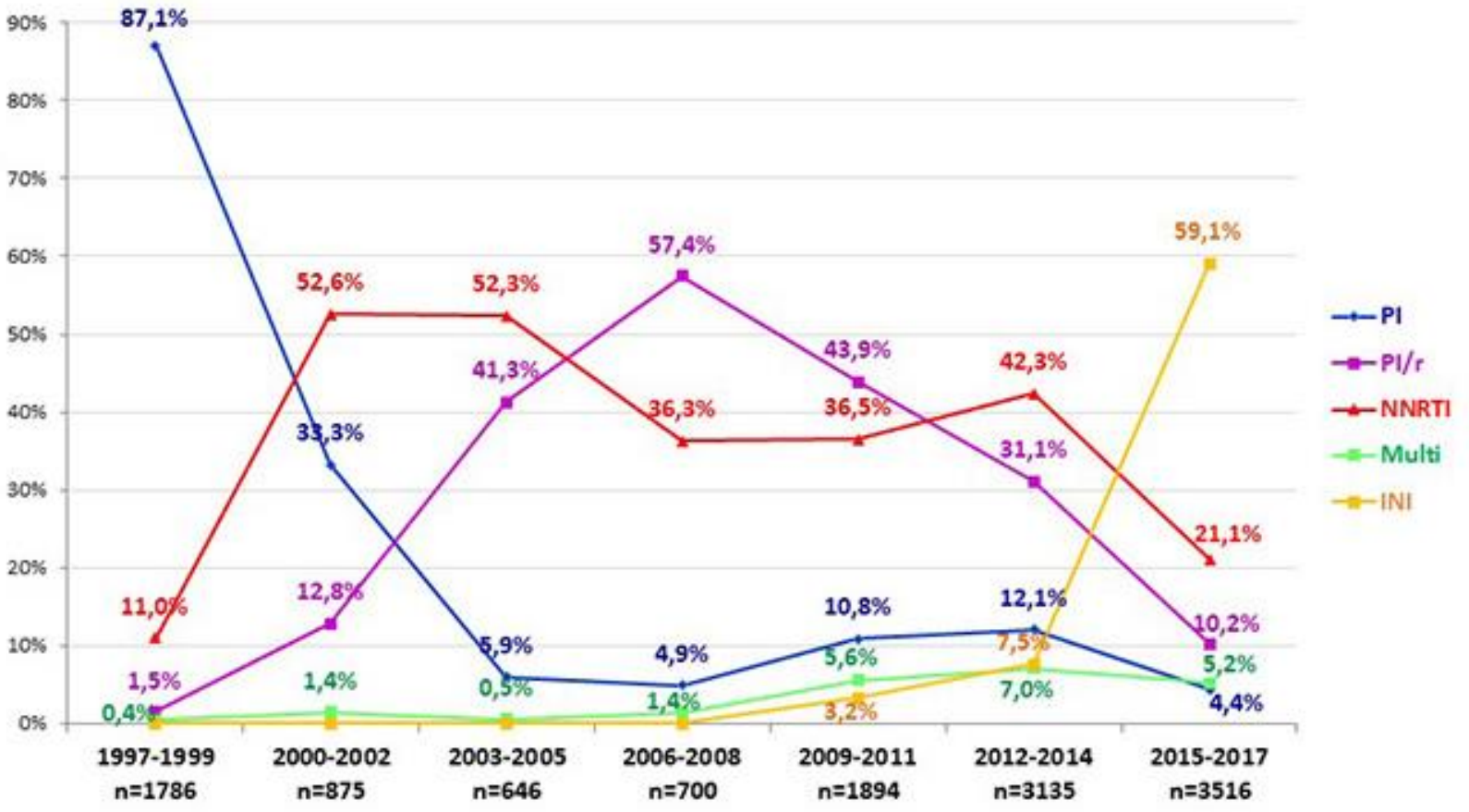
**First generation INSTI based**

**Second generation INSTI based**

*Modified from T Cihlar and M Fordyce*
*Current opinion in Virol 2016*

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

# Proportion of usage of different ART classes as third drug in first line regimen according to calendar period of starting (NRTIs not considered)




Jan 2018 Report

# Outline

- ✓ **Overview of mutations associated with drug resistance to INIs**
- ✓ INI genetic barrier
- ✓ Resistance at first line failure
- ✓ INI transmitted drug resistance
- ✓ Integrase natural polymorphisms
- ✓ Resistance & treatment switch

**In 2009 INI resistance was already a concern due to the medium/low genetic barrier of first generation INIs RAL (and later EVG)**

STANFORD UNIVERSITY
# HIV DRUG RESISTANCE DATABASE

*A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.*

HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVdb PROGRAM

## Integrase Inhibitor Resistance Notes

Last updated on Sep 15, 2009

**Resistance Matrix** Resistance Mutation Comments Resistance Mutation Scores

### Integrase Inhibitor (INI) Resistance Mutations

| | 66 | 92 | 121 | 138 | 140 | 143 | 147 | 148 | 153 | 155 | 263 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Cons* | T | E | F | E | G | Y | S | Q | S | N | R |
| **Raltegravir†** | | **Q** | **Y** | AK | **AS** | **RCH** | G | **HRK** | | **HS** | |
| **Elvitegravir§** | **IAK** | **Q** | **Y** | AK | **AS** | | **G** | **HRK** | Y | **HS** | K |

**LEGEND** INI-resistance mutations selected in persons receiving raltegravir (D Hazuda HIVDRW 2007, I Malet AAC 2008) or elvitegravir (D McColl HIVDRW 2007) are characterized for *in vitro* susceptibility (G Jones CROI 2007, D McColl HIVDRW 2007, C Ren HIVDRW 2007, M Rowley Prog Med Chem 2008). **Mutations in bold red** are associated with >5-10 fold decreased susceptibility.

† Other mutations selected *in vitro* or *in vivo* by raltegravir include L74M, T97A, V151I, E157Q, G163R, I203M, and S230R/N.

§ Other mutations selected *in vitro* or *in vivo* by elvitegravir include the nonpolymorphic mutations H51Y, Q95K, H114Y, P145S, and Q146P (K Shimura JV 2007).

**ADDITIONAL MUTATIONS** Additional integrase mutations selected by other investigational INIs include the nonpolymorphic mutations T125K, A128T, Q146K, N155S, K160D, and the polymorphic mutations V72I, A154I, V165I, and V201I (M Lataillade AVT 2007).

# So far not so many additional resistance associated mutations have been identified

Stanford University
**HIV DRUG RESISTANCE DATABASE**
*A curated public database to represent, store and analyze HIV drug resistance data.*

**HIVdb version 8.5 (last updated 2018-04-16)**

## INSTI Resistance Notes (PI · NRTI · NNRTI)

Sierra version 2.2.5-1 (last updated 2018-0
HIVdb version 8.5 (last updated 2018-0

### Major Integrase Inhibitor (INI) Resistance Mutations

| | 66 | 92 | 118 | 138 | 140 | 143 | 147 | 148 | 155 | 263 |
|---|---|---|---|---|---|---|---|---|---|---|
| *Consensus* | T | E | G | E | G | Y | S | Q | N | R |
| Bictegravir (BIC) | K | Q | R | KAT | SAC | | | HRK | H | K |
| Dolutegravir (DTG) | K | Q | R | KAT | SAC | | | HRK | H | K |
| Elvitegravir (EVG) | AIK | Q | R | KAT | SAC | | G | HRK | H | K |
| Raltegravir (RAL) | AIK | Q | R | KAT | SAC | RCH | | HRK | H | K |

**Major Accessory Resistance Mutations**

- H51Y
- L74M/I
- T97A
- Q95K
- V151I/L/A
- S153Y/F
- E157Q
- G163R/K
- S230R

**Rare Primary INSTI-Resistance Mutations**

- F121Y
- P145S
- Q146P

**Why?**

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- ✓ Resistance & treatment switch

Hôpital général juif
Jewish General Hospital

# IN VITRO SELECTED RESISTANCE TO NEW INTEGRASE INHIBITORS BY B & NON-B SUBTYPE VIRUSES

Bluma G. Brenner[1] , Maureen Oliveira[1] , Ruxandra-Ilinca Ibanescu[1] , Bonnie Spira[1] , Thibault Mesplede[1] , Jean-Pierre Routy[1]
[1] McGill University, Montreal , QC, Canada

McGill UNIVERSITY

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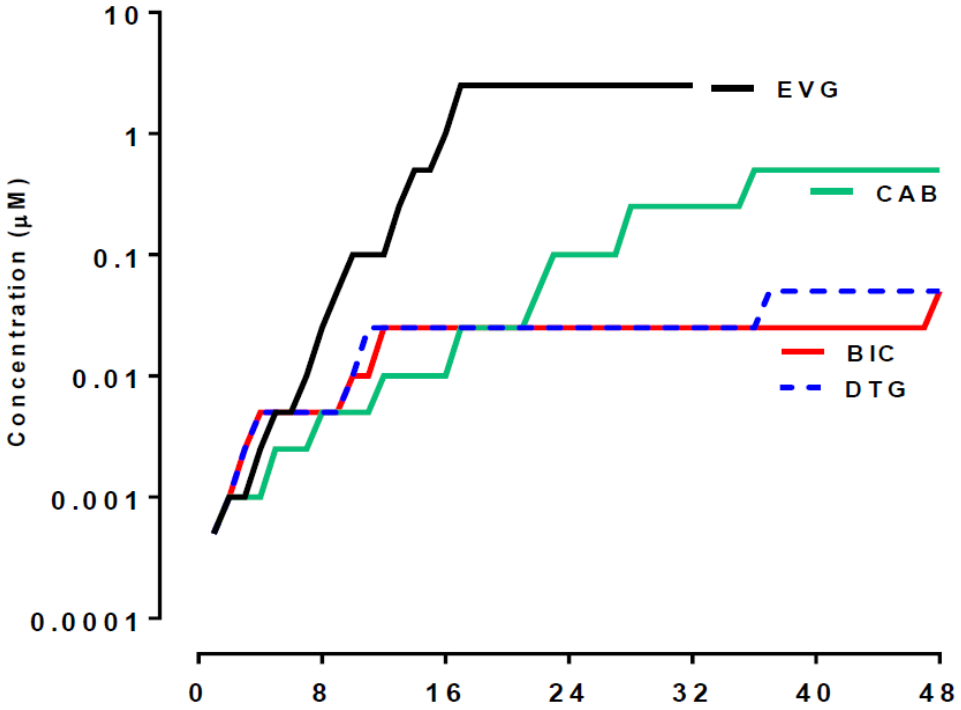
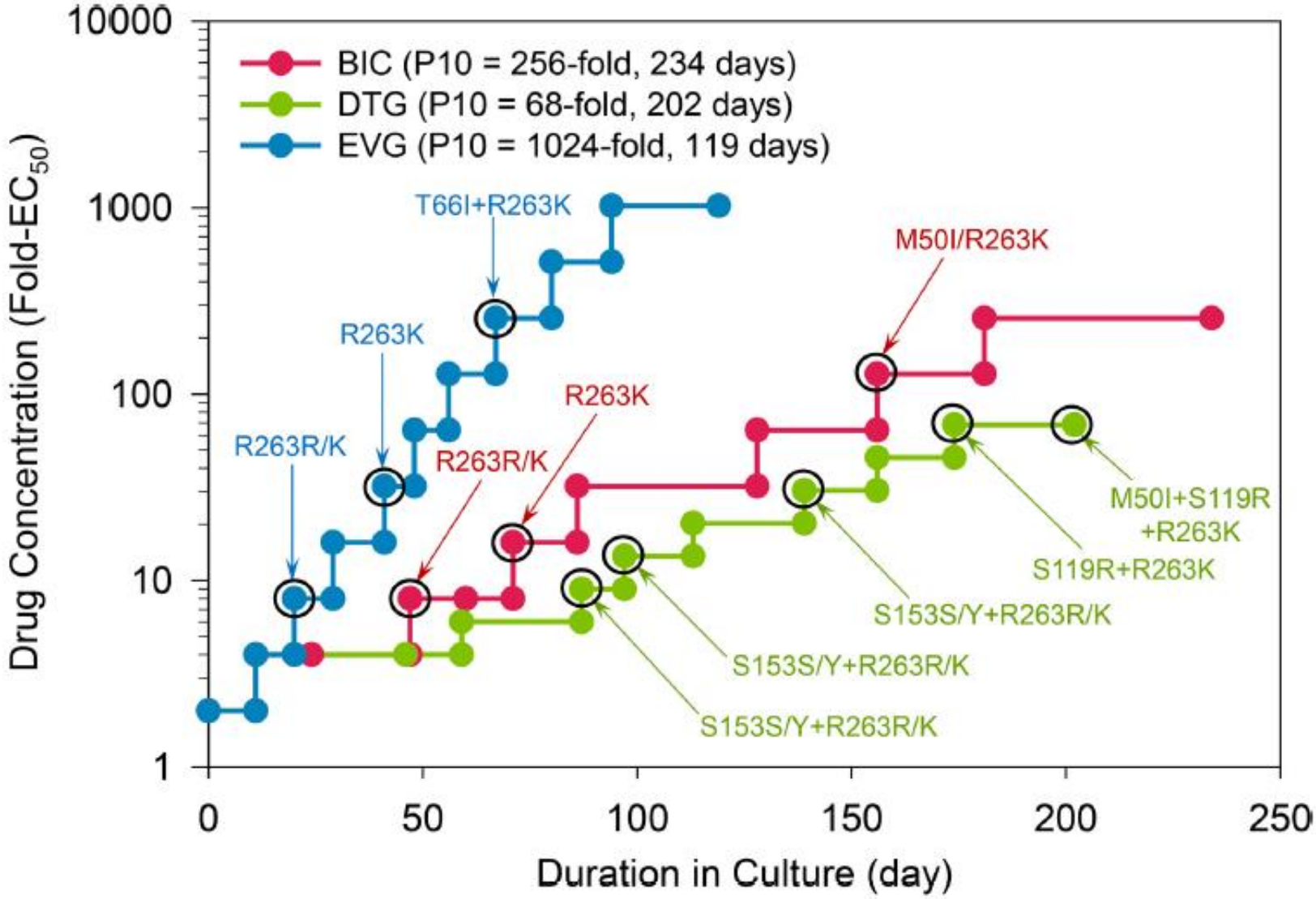
## Delay in the acquisition of resistance to DTG and BIC, compared to CAB and EVG




Growth of 96USSN20 cells in escalating concentrations of dolutegravir (DTG), bictegravir (BIC), cabotegravir (CAB) and elvitegravir (EVG). The rise in drug concentrations is related to the acquisition of resistance mutations.

*Brenner et al. CROI 2018*

**The BIC and DTG resistance selections progressed at a rate that was considerably slower than that of EVG, suggesting that BIC and DTG have a higher barrier to resistance emergence than EVG**




**Tisiang et al. AAC 2016**

# IN VITRO SELECTED RESISTANCE TO NEW INTEGRASE INHIBITORS BY B & NON-B SUBTYPE VIRUSES

Bluma G. Brenner[1] , Maureen Oliveira[1] , Ruxandra-Ilinca Ibanescu[1] , Bonnie Spira[1] , Thibault Mesplede[1] , Jean-Pierre Routy[1]
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Table 1. Selection of drug resistance to dolutegravir (DTG), bictegravir (BIC), cabotegravir (CAB) and elvitegravir(EVG) at the final week of passage

| Virus isolate | Subtype | Acquired mutations at final passage (week 46) of selective drug pressure | | | |
|---|---|---|---|---|---|
| | | DTG | BIC | CAB | EVG |
| 14514 | B | R263K | None | None | T66I |
| 10387 | B | None | None | None | T66I |
| 10249 | B | R263K | None | None | E92Q |
| 14624 | B | none | None | H51HY | T66I |
| 14637 | B | R263K | R263K | R263K | **T66I, E157Q, R263K** |
| 14947 | B | R263K | R263K | R263K, S153A | **T66I, E138EK, S147G, Q148R** |
| 5326 | B | H51H/Y | S153Y | **L74M, G140S, S147G, Q148K** | **R263K, S153A** |
| 4742 | C | None | None | R263K | **E92EG, R263KR** |
| 10947 | C | R263K | R263K | S147G | **E92V, R263K** |
| 6343 | AE | R263K | S153Y | S153Y, G163R | **T66I, R263K** |
| 14515 | AG | None | None | None | T66I, H51HY |
| 96USSN20 | AG | R263K | S153FS, E157EK | **L74M, E138K, Q148R, R263K** | |
| pNL4.3 | B | R263K, M50I | R263K, M50I | S153F | **T66I, T97A, S147G, S119R, S153A** |

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- ✓ **Resistance at first line failure**
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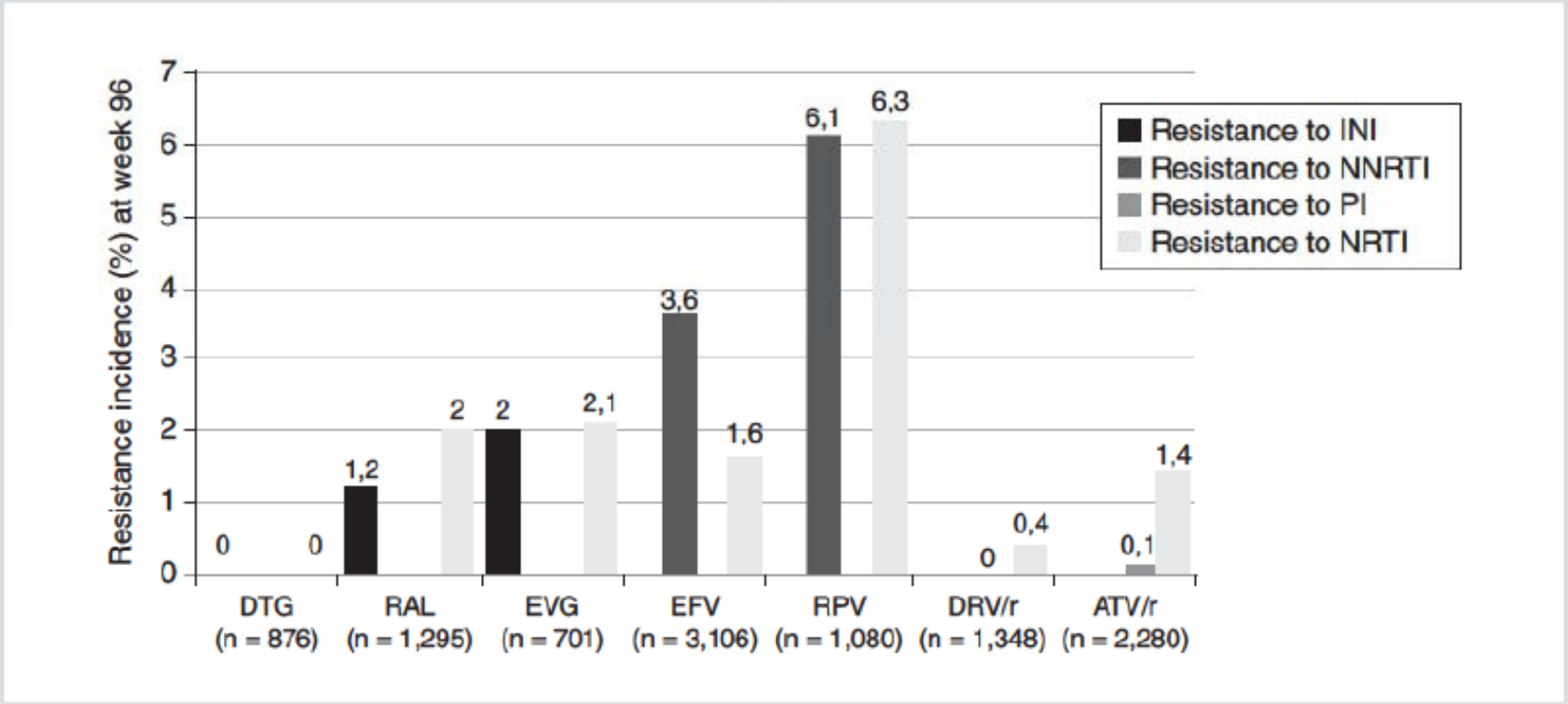
- ✓ Resistance & treatment switch

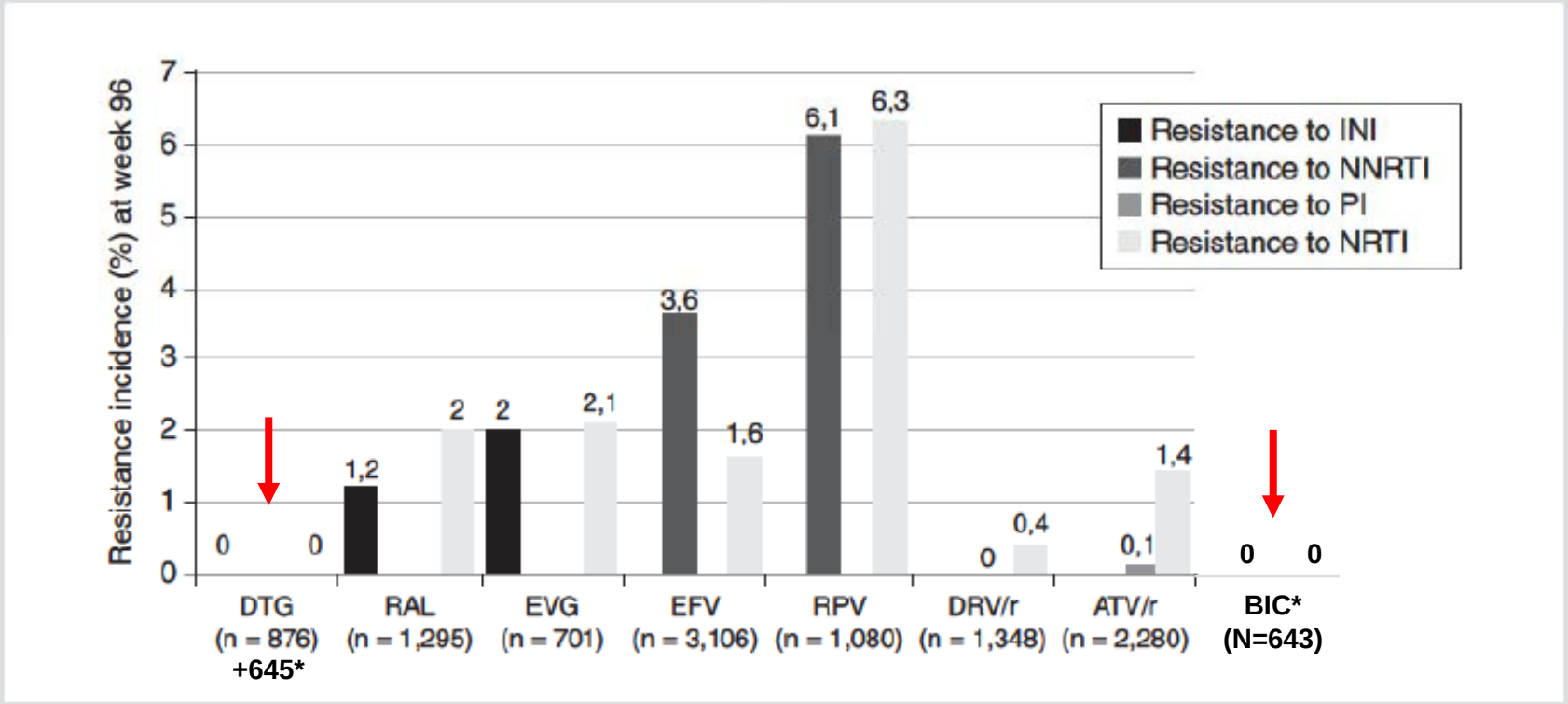
# PIs and DTG show a very low or null emergence of resistance at first-line failure




**Incidence of resistance at week 96 in pivotal clinical trials of antiretroviral therapy in naïve patients**

Libre et al. AIDS rev. 2015

# DTG and BIC show null emergence of resistance at first-line failure




**Incidence of resistance at week 48/96 in pivotal clinical trials of antiretroviral therapy in naïve patients**

Libre et al. AIDS rev. 2015
*Sax et al Lancet 2017
*Gallant et al Lancet 2017

***data at 48 weeks**

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

# Rare emergence of drug resistance in HIV-1 treatment-naïve patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide for 144 weeks☆

Nicolas Margot*, Stephanie Cox, Moupali Das, Scott McCallister, Michael D. Miller, Christian Callebaut

*Background:* The single tablet regimen (STR) composed of elvitegravir (E), cobicistat (C), emtricitabine (F), and tenofovir alafenamide (TAF) (E/C/F/TAF) was compared to the STR composed of E, C, F, and tenofovir disoproxil fumarate (TDF) (E/C/F/TDF) in 2 phase 3 studies in 1733 HIV-1 infected treatment-naïve adults. Superior efficacy of E/C/F/TAF compared to E/C/F/TDF was demonstrated at Week 144 with 84% treatment success compared to 80%, respectively, along with significantly better outcomes of bone and renal safety.

*Objectives:* Analyze the emergence of HIV-1 resistance in treatment-naïve adults receiving E/C/F/TAF for 144 weeks.

*Study design:* We conducted an integrated resistance analysis of the 2 Phase 3 studies, comprising pretreatment HIV-1 sequencing for all participants (N = 1733) and post-baseline HIV-1 resistance analysis for participants with virologic failure (HIV-1 RNA ≥400 copies/mL).

*Results:* Primary resistance-associated mutations (RAMs) were observed pre-treatment in 7.4% (NRTI-RAMs), 18.1% (NNRTI-RAMs), and 3.3% (PI-RAMs) of enrolled subjects. Baseline HIV-1 subtype or pre-existing RAMs did not affect E/C/F/TAF treatment response at week 144. Virologic failure resistance analyses were conducted for 28/866 (3.2%) and 30/867 (3.5%) patients in the E/C/F/TAF and E/C/F/TDF arms, respectively. Over the 3-year study, the rate of resistance emergence remained low at 1.4% in each group (12/866 in E/C/F/TAF; 12/867 in E/C/F/TDF). Resistant virus emerged in 24 patients who developed resistance to antiretrovirals in the regimens (E/C/F/TAF: M184V/I [1.3%], INSTI-RAMs [0.9%], K65R/N [0.2%]; E/C/F/TDF: M184V/I [1.0%], INSTI-RAMs [0.9%], K65R/N [0.5%]).

*Conclusions:* Resistance emergence was rare (1.4%) with similar patterns of emergent mutations in both groups. M184V/I was the most prevalent RAM (1.2% overall).

JCV 2018

| Resistance Category | Number of Subjects n (%) | | P-Value[a] |
|---|---|---|---|
| | E/C/F/TAF (n = 866) | E/C/F/TDF (n = 867) | |
| RAP | 28 (3.2) | 30 (3.5) | 0.89 |
| Final RAP[b] | 22 (2.5) | 22 (2.5) | 1.0 |
| With Data | 22 | 20 | |
| Developed Primary Resistance to Study Drugs | 12 (1.4) | 12 (1.4)[c] | 1.0 |
| No resistance | 10 (1.2) | 8 (0.9) | |
| NRTI-R | 12 (1.4) | 11 (1.3) | |
| E44D | 0 | 1 | |
| A62V | 0 | 1 | |
| K65R/N | 2 | 4 | |
| K70R | 1 | 1 | |
| M184V/I | 11 | 9 | |
| L210W | 0 | 1 | |
| Primary INSTI-R | 8 (0.9) | 8 (0.9) | |
| T66A/I/V | 2 | 0 | |
| E92Q/V | 4 | 4 | |
| Q148R | 1 | 2 | |
| N155H/S | 2 | 3 | |
| Secondary INSTI-R | 5 (0.6) | 3 (0.3) | |
| M50I | 1 | 0 | |
| L68V | 1 | 0 | |
| V72N/S | 1 | 0 | |
| A128T | 1 | 0 | |
| E138K | 1 | 3 | |
| E157K | 0 | 1 | |

RAP: resistance analyses population; NRTI-R: nucleoside RT inhibitor resistance mutations; INSTI-R: Integrase strand transfer inhibitor resistance mutations.

[a] Fisher's exact test.

[b] The final RAP did not include subjects without emerging resistance who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

[c] One participant in the E/C/F/TDF group having HIV-1 with emerging secondary INSTI-R mutations only (E138K E157K) in the absence of primary INSTI-R is not included in this total.

**Twelve participants in each group (24 total) had emerging HIV-1 primary resistance mutations. Among these 24 participants, all 23 participants with available RT genotypic data developed HIV-1 resistance mutations to NRTIs.**

Margot et al. JVC 2018

| Clinical Case: ID 18672 Patient infected with HIV-1 B subtype | Age 63 | Sex M | Risk Factor Sexual | 1st Seropositivity September 2017 | CDC stage C3 |
|---|---|---|---|---|---|

• **Genotyping Resistance Test on 15th September 2017:**

**CD4: 40 cells/µl** **VL: 980,000 cps/ml**

**Test reveals an infection by a subtype B of HIV-1**

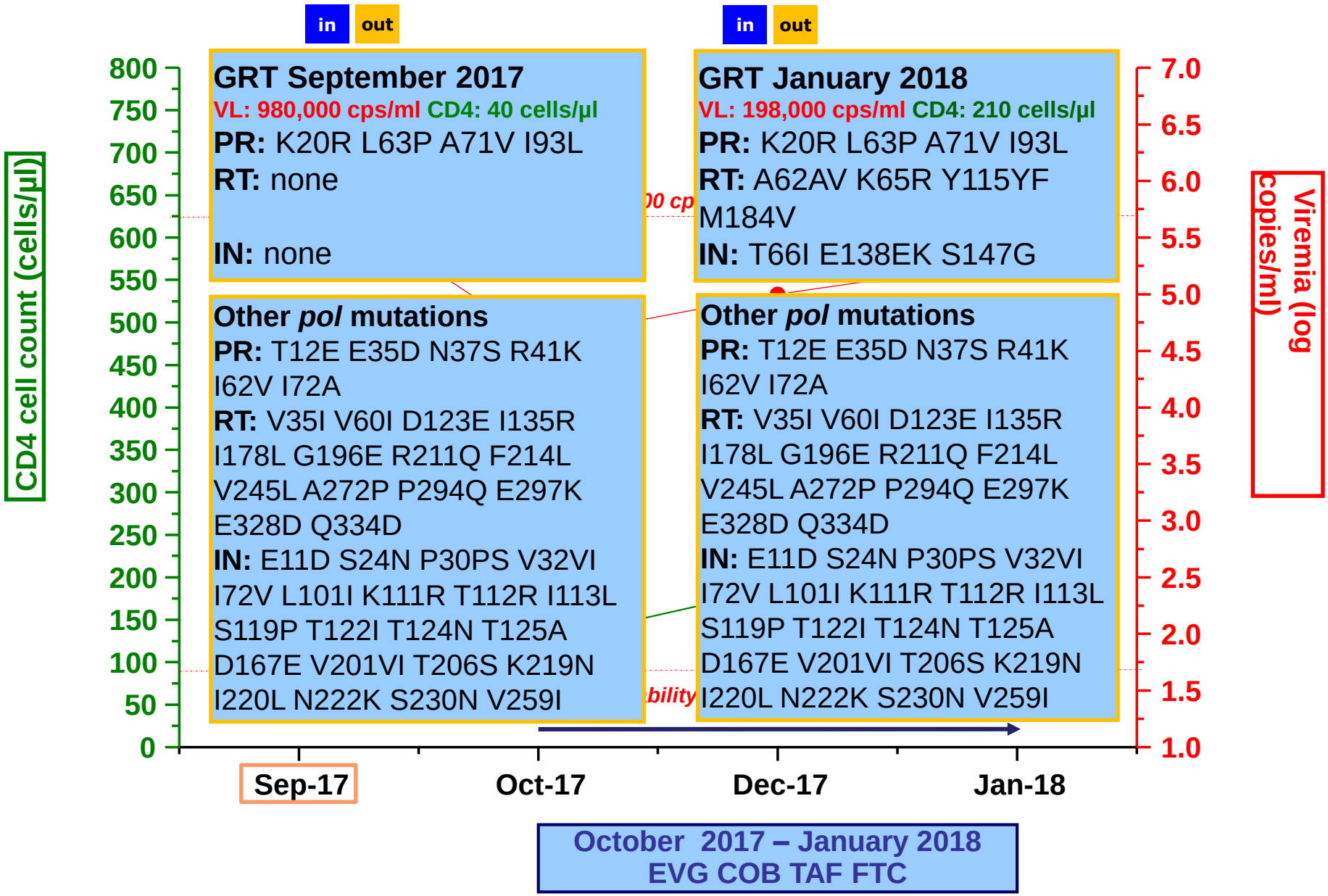
**Resistance mutations:**

**PR: K20R L63P A71V I93L**
**RT: none**
**IN: none**

Other mutations:

**PR:** T12E E35D N37S R41K I62V I72A
**RT:** V35I V60I D123E I135R I178L G196E R211Q F214L V245L A272P P294Q E297K E328D Q334D
**IN:** E11D S24N P30PS V32VI I72V L101I K111R T112R I113L S119P T122I T124N T125A D167E V201VI T206S K219N I220L N222K S230N V259I

| Clinical Case: ID 18672 Patient infected with HIV-1 B subtype | Age 63 | Sex M | Risk Factor Sexual | 1st Seropositivity September 2017 | CDC stage C3 |
|---|---|---|---|---|---|



# Emergent drug resistance with integrase strand transfer inhibitor-based regimens: Incidence and risk factors.

Lepik KJ, Harrigan PR, Yip B, Wang L, Robbins MA, Zhang WW, Toy J, Akagi L, Lima VD, Guillemi S, Montaner JSG, Barrios R.

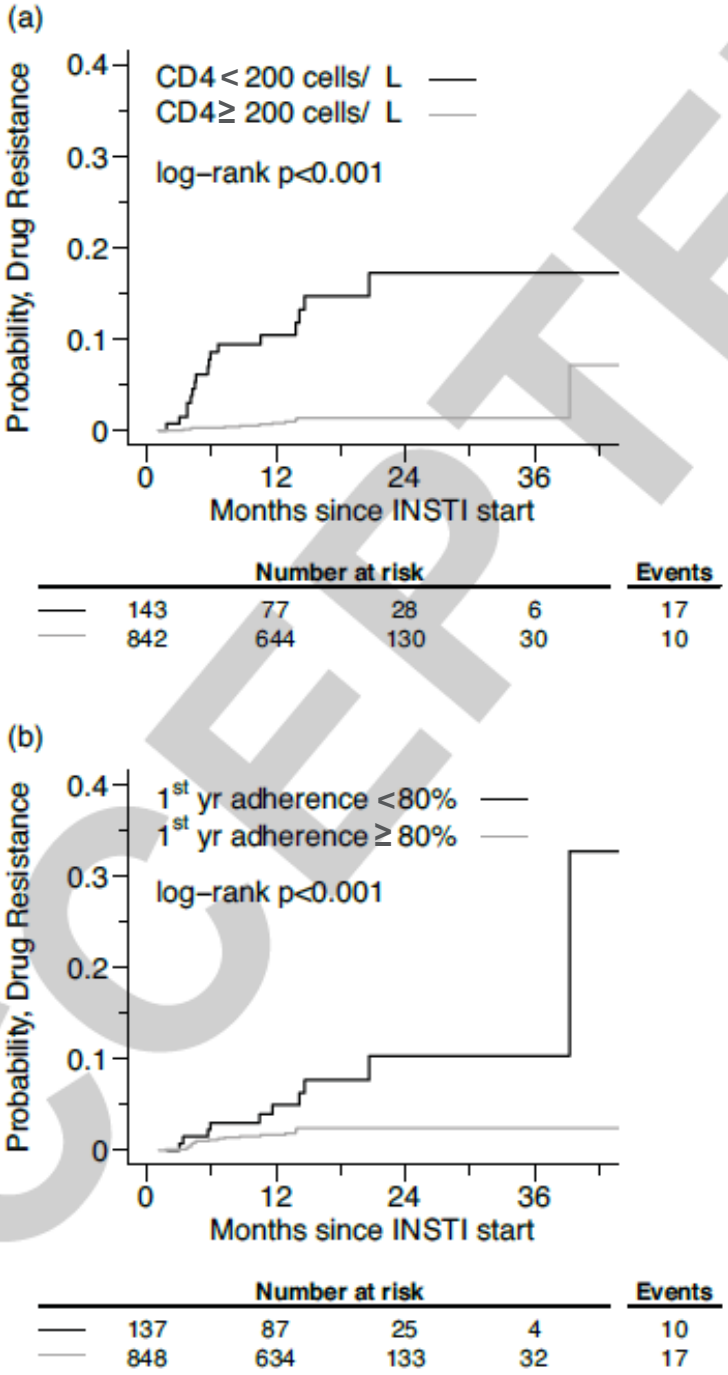
*AIDS 2017*

**Objectives**: To estimate the incidence of and risk factors for emergent resistance to integrase inhibitors (INSTI) and nucleoside(-tide) reverse transcriptase inhibitors (NRTI) in HIV-1- infected adults receiving an INSTI plus two NRTIs.

**Methods:** Persons ≥19 years were included if they received their first prescription for raltegravir, elvitegravir or dolutegravir in British Columbia, Canada in 2012-2014, and were followed to 31-Dec-2015. Emergent resistance was defined as new mutations conferring intermediate-high level NRTI or INSTI resistance (score ≥30, Stanford algorithm v.7.0.1). First-year resistance rates and 95% confidence intervals (CI95%) were estimated for "any" (INSTI or NRTI) resistance using Poisson regression. The relationship between any emergent resistance and explanatory variables was modeled by Cox proportional hazards.

**Results:** There were 270 raltegravir, 323 elvitegravir and 392 dolutegravir-treated persons who were predominantly male (77%), antiretroviral therapy (ART)-experienced (81%), with low prevalence of pre-existing drug resistance (16%). INSTI and NRTI resistance emerged in both ART-experienced and ART-naive persons (including dolutegravir-treated ART-naive), with no statistically significant differences in "any" resistance rates (CI95%) between INSTIs: Raltegravir 3.80 (1.90,7.60), elvitegravir 2.37 (1.06,5.27) and dolutegravir 1.48 (0.62,3.55)/100 person-years. The strongest factors associated with emergent resistance were CD4 <200 cells/μL, adjusted hazard ratio (HR, CI95%) 10.46 (4.67,23.41) and <80% adherence to the INSTI regimen HR 2.52 (1.11,5.71).

Conclusions: Incident drug resistance rates were low with "real-world" use of INSTI-based regimens. However, incomplete ART adherence and low CD4 count were associated with increased resistance rates regardless of which INSTI was prescribed. Provide adherence support and monitor for drug resistance.




## The strongest factors associated with emergent resistance were CD4 <200 cells/μL, and <80% adherence to the INSTI regimen by both Kaplan mayer estimated and by cox multivariable regression

| Variable | Hazard Ratio ($CI_{95\%}$) Emergent drug resistance | |
|---|---|---|
| | Univariable models | Multivariable model |
| Sex | | |
| Male | 1.00 | NS |
| Female | 2.25 (1.04, 4.89) | |
| Pre-INSTI pVL c/mL | | |
| ≤100,000 c/mL | 1.00 | NS |
| >100,000 c/mL | 4.23 (1.90, 9.41) | |
| Pre-INSTI CD4 cells/μL | | |
| ≥200 | 1.00 | 1.00 |
| <200 | 11.84 (5.47, 25.63) | 10.46 (4.67,23.41) |
| INSTI | | |
| raltegravir | 1.00 | NS |
| elvitegravir | 0.54 (0.23, 1.29) | |
| dolutegravir | 0.29 (0.10, 0.80) | |
| % Adherence, INSTI | | |
| ≥80% | 1.00 | 1.00 |
| <80% | 3.61 (1.67, 7.80) | 2.52 (1.11,5.71) |

Hazard ratio and 95% confidence interval ($CI_{95\%}$) calculated by Cox proportional hazards model, using t robust sandwich covariance matrix estimate for clustered data structure. Reference category has HR 1.00. NS variable was not selected for multivariable model (p-value >0.2).

Lepik et al, AIDS 2017

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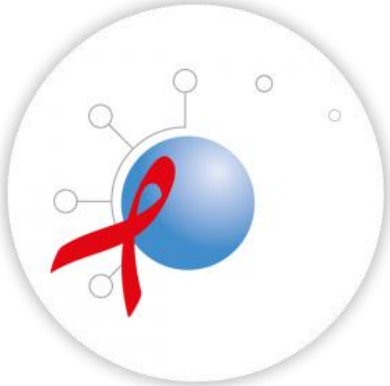
# Factors associated with virological response and resistance profile in HIV-1 infected patients starting first-line integrase inhibitors based regimen in clinical settings

D. Armenia[1], C. Gori[2], A. Bertoli[1], V. Borghi[3], M. Zaccarelli[2], A. Di Biagio[4], B. Bruzzone[4], L. Fabeni[1], W. Gennari[3], D. Pizzi[2], A. Giannetti[2], A. Vergori[2], I. Mastrorosa[2], A. Latini[5], M. Colafigli[5], C. Cerva[6], R. Marocco[7], M. Andreoni[6], C. Mussini[3], A. Antinori[2], F. Ceccherini-Silberstein[1], C.F. Perno[2], **M.M. Santoro[1]**.

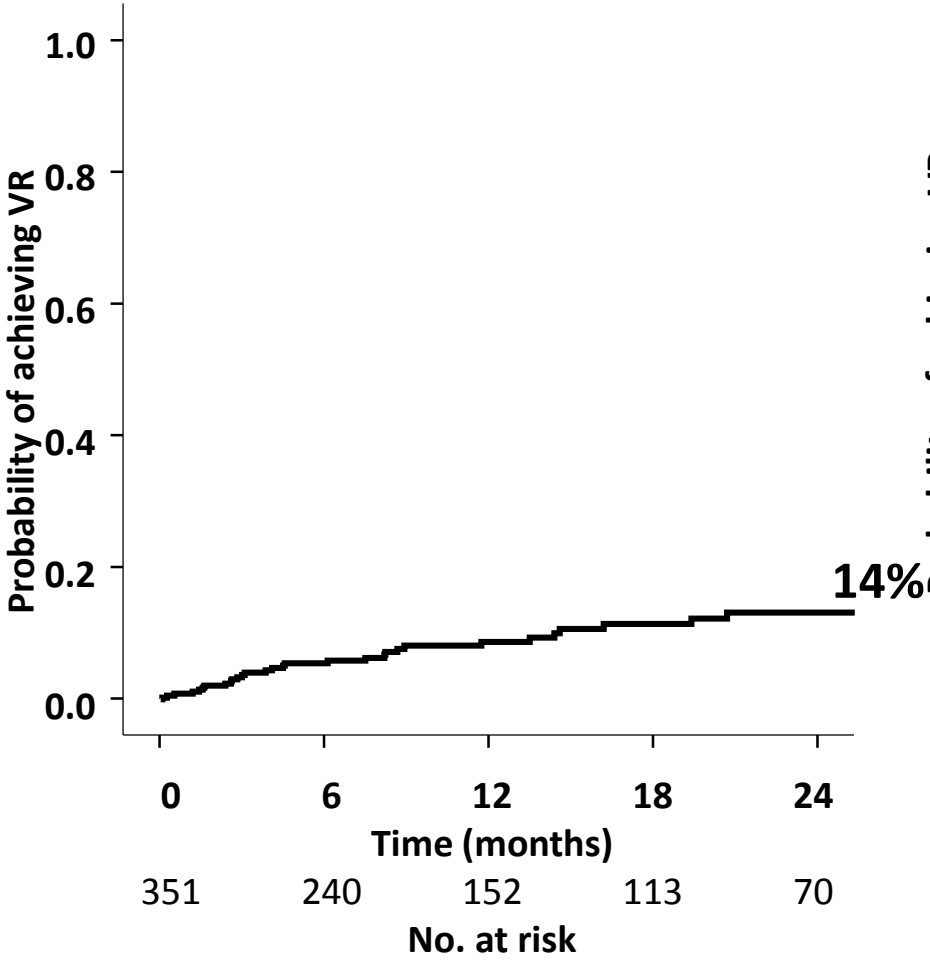
1University of Rome "Tor Vergata", Rome, Italy; 2National Institute for Infectious Diseases L. Spallanzani, IRCCS; 3Polyclinic of Modena, Modena, Italy; 4 Hospital Policlinico San Martino, University of Genoa, Genoa, Italy; 5San Gallicano Dermatological Institute, IRCCS, Rome, Italy; 6Polyclinic of Rome "Tor Vergata", Rome Italy; 7La Sapienza University Polo Pontino, Latina, Italy.



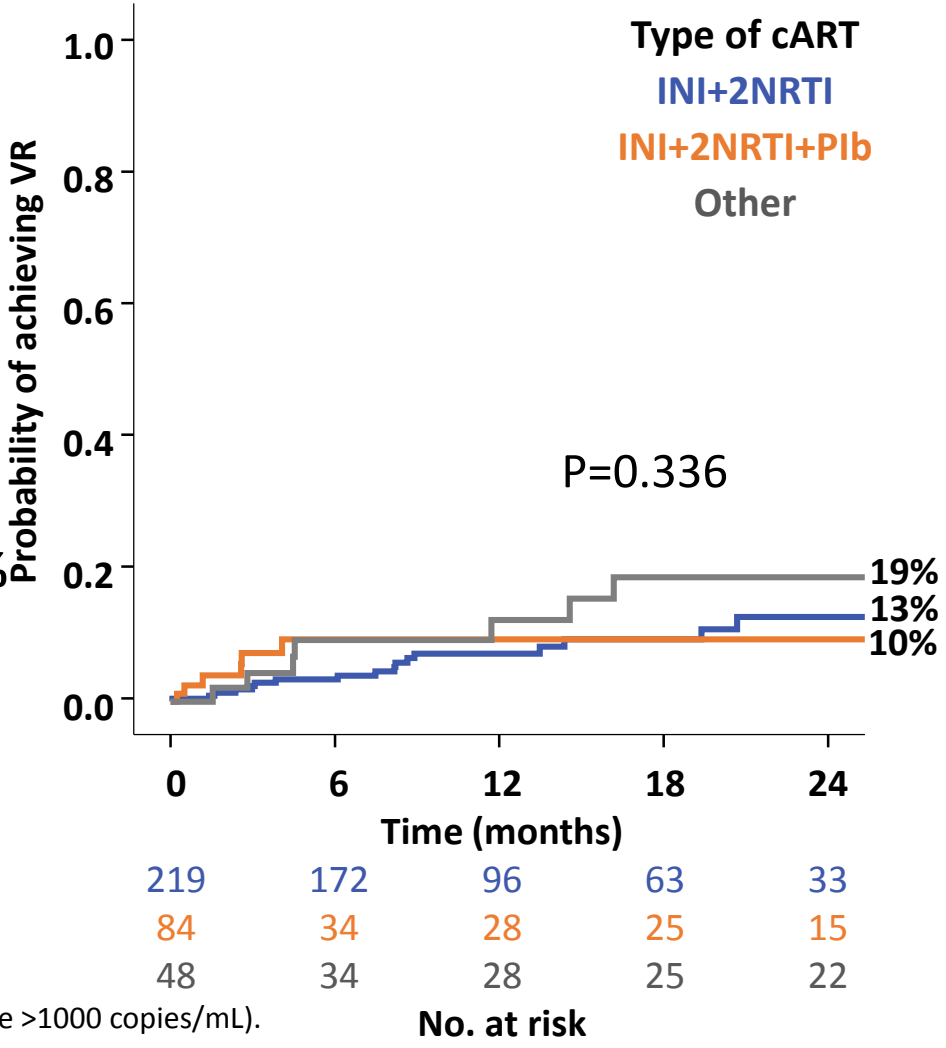
***16th European Meeting on HIV & Hepatitis 2018, abstract # 8***

**By 24 months after achieving virological success, the overall probability of virological rebound was 14%. Patients who received dual-therapy or not recommended ARV-combinations have the highest probability of experiencing virological rebound.**

## Kaplan Meyer estimates of VR




## Kaplan Meyer estimates of VR




VR: virological rebound (two consecutive viremia >50 copies/mL or one >1000 copies/mL).

*Armenia, Santoro et al. 16th European Meeting on HIV & Hepatitis 2018, abstract # 8*

**Twenty patients (3.8%) had an available genotypic resistance test at virological failure. Five patients (25%) harbored at least one INI MRM and 3 patients (15%) developed the MRM M184V and 1 patient (5%) the K70E. No resistance was observed in the unique DTG failing patient.**

| ID | Pre-cART CD4 count (cells/mm³) | Pre-cART viremia (copies/mL) | Transmitted Drug-resistance | cART received | Time to failure GRT (days) | Viremia at GRT (copies/mL) | Resistance mutations detected at failure | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | INI MRM | INI Accessory | PI MRM | NRTI MRM | NNRTI MRM |
| 8635 | <200 | 100-500K | None | RAL + FTC/TDF | 119 | 54,987 | **Y143YCHR, N155NH** | G163K | None | **M184V** | None |
| 18216 | 350-500 | >500K | None | $EVG_C$/FTC/TDF | 115 | 235,745 | **G140A, Q148R** | None | None | **M184V** | None |
| 18528 | <200 | >500K | None | RAL + FTC/TDF | 157 | 102,085 | **Y143R** | None | None | **K70KE, M184V** | None |
| 15464 | <200 | >500K | None | RAL+ DRVb | 196 | 7,802 | **N155H** | None | None | None | None |
| 17640 | <200 | <100k | None | RAL + FTC/TDF | 378 | 92 | **G140GRS** | None | None | None | None |
| 15850 | <200 | <100k | NRTI: M41L, M184V, L210W; NNRTI: V179I/V | RAL+ DRVb | 148 | 2,270 | None | T97TA | None | **M41L** | None |
| 16380 | 350-500 | 100-500K | NNRTI: E138A | RAL+ DRVb | 998 | 408 | None | None | None | None | E138A |

*Armenia, Santoro et al. 16th European Meeting on HIV & Hepatitis 2018, abstract # 8*

**Circulating INI resistance strains might become a problem**

**Indeed…**

# Outline

- ✓ Overview of mutations associated with drug resistance to INIs
- ✓ INI genetic barrier
- ✓ Resistance at first line failure
- ✓ **INI transmitted drug resistance**
- ✓ Integrase natural polymorphisms
- ✓ Resistance & treatment switch

| Clinical Case: ID 18209 Patient infected with HIV-1 B subtype | Age 36 | Sex F | Risk Factor Heterosexual | 1st Seropositivity April 2017 | CDC stage A2 |
|---|---|---|---|---|---|

• **GRT (April 2017)**

**VL: 86,000 cps/ml**
**CD4: 476 cells/mm$^3$**
**Subtype B**
**Therapy status: drug-naïve**

**Resistance mutations**
**PI: L63P**
**NRTI: T215S**
**NNRTI: V108VI E138G H221Y M230L**
**INT: G140S Q148H**
**Tropim: R5 (FPR: 46.5%)**

Other mutations
PR: L19V I62V E65D H69N
RT: K46Q V60I L109M V118I D123E I142K S162C I178L V179I G196E F214L A272P K277R R284K T286A I293V P294A E297R
INT: K34KR T124N M154L V201I T206S I208L

• **GRT (October 2016)** (from a patient infected with a virus phylogenetically related):

**VL: 160,100 cps/ml**
**CD4: 202 cells/mm$^3$**
**Subtype B**
**Therapy status:**
**May 16 - January 17: ETR RAL**

**Resistance mutations**
**PR: L63P**
**NRTI: T215S K219KE**
**NNRTI: V108VI E138G H221Y M230L**
**INT: G140S Q148H**
**Tropim: R5 (FPR: 46.5%)**

Other mutations
PR: L19V I62IV E65D H69N
RT: K46KQ V60I S68SG V106VI L109LV V118I D123E I142K S162SC I178L G196E F214L L234LI A272P K277R R284RK T286A I293V P294A E297R
INT: VM50MV K111KQ T124N M154MIL V201VI T206TS I208L

# Outline

- ✓ Overview of mutations associated with drug resistance to INIs
- ✓ INI genetic barrier
- ✓ Resistance at first line failure
- ✓ INI transmitted drug resistance
- ✓ **Integrase natural polymorphisms**
- ✓ Resistance & treatment switch

# Which accessory resistance mutations might be a concern for INSTI susceptibility?

## New data:

### T97A (Kuriakose et al CROI 2018, )

**Isolated emergence of the T97A mutation led to high level DTG resistance with >10 fold increases in DTG $IC_{50}$**

- **E157Q (Charpentier et al CROI 2018; Saladini et al AIDS 2017)**

**This mutations was mainly prevalent in non-B subtype infected patients. Some concern about EVG susceptibility. The most recommended INI in patients with E157Q mutation might be dolutegravir.**

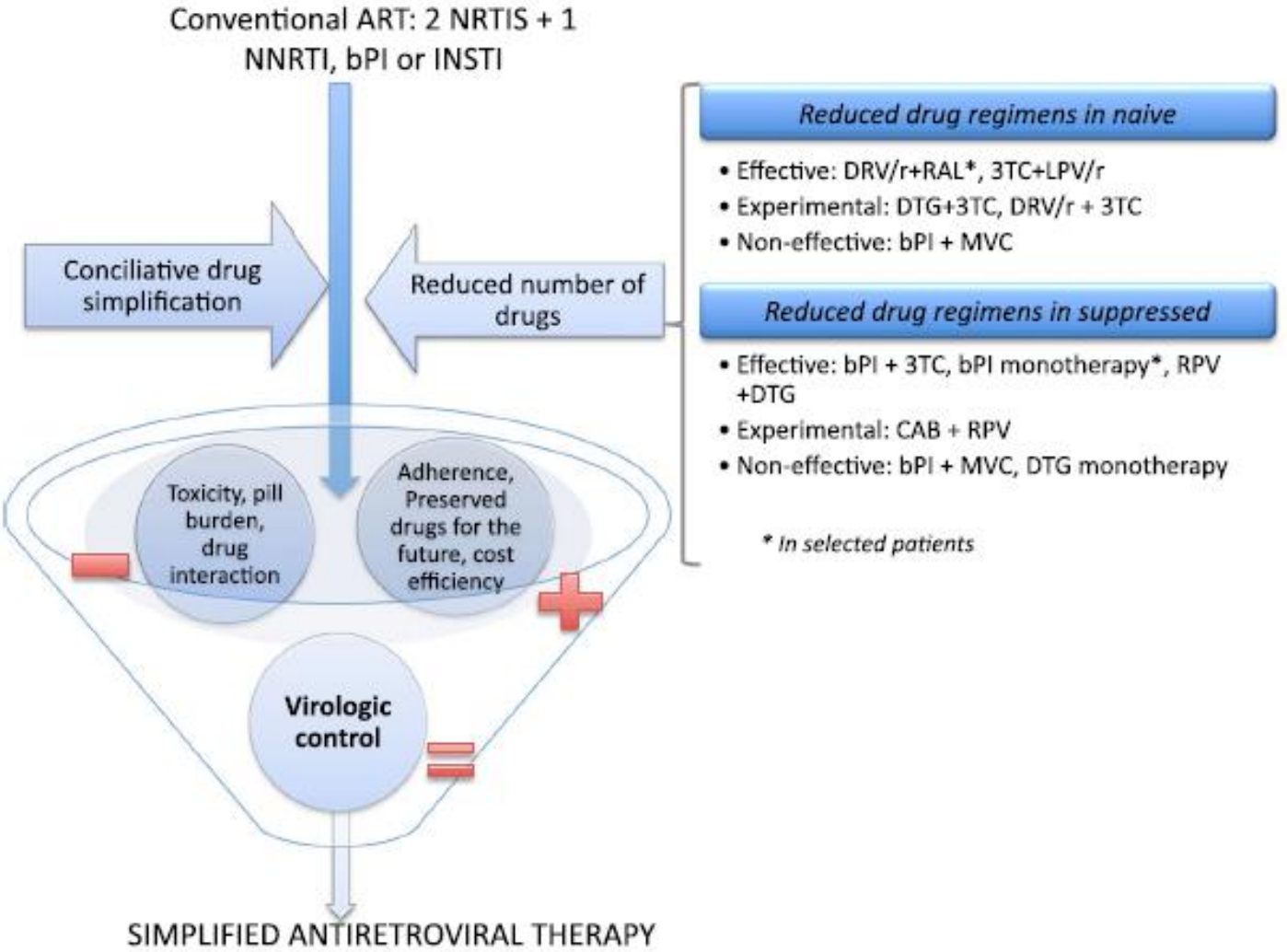
- **S230N (Pham et al CROI 2018)**

**Virological failure under DTG monotherapy can occur through the development of S230R mutation without the need for high levels DTG resistance**

# Outline

- ✓ Overview of mutations associated with drug resistance to INIs
- ✓ INI genetic barrier
- ✓ Resistance at first line failure
- ✓ INI transmitted drug resistance
- ✓ Integrase natural polymorphisms
- ✓ **Resistance & treatment switch**

# Long-life treatment dictates the switch. But patients should be carefully selected!!!




Buckley et al, Current HIV/AIDS Reports 2018

**We know that monotherapy is risky!!!**

# Comprehensive Assessment of Resistance Mutations Selected by Dolutegravir (DTG) in Subjects Failing DTG-Monotherapy after Switching from other Therapies (Redomo Study)

Blanco JL[1], Oldenbuettel C[2], Thomas R[3], Mallolas J[1], Wolf E[2],

Brenner BG[4],Spinner CD[2], Wainberg MA[4], Martinez E[1]

1 Hospital Clinic, Barcelona, Spain. 2 MVZ Karlsplatz, HIV Research and Clinical Care Centre, Munich, Germany. 3 Clinique Actuel, Montreal, Quebec, Canada. 4 McGill AIDS Centre Montreal, Quebec, Canada

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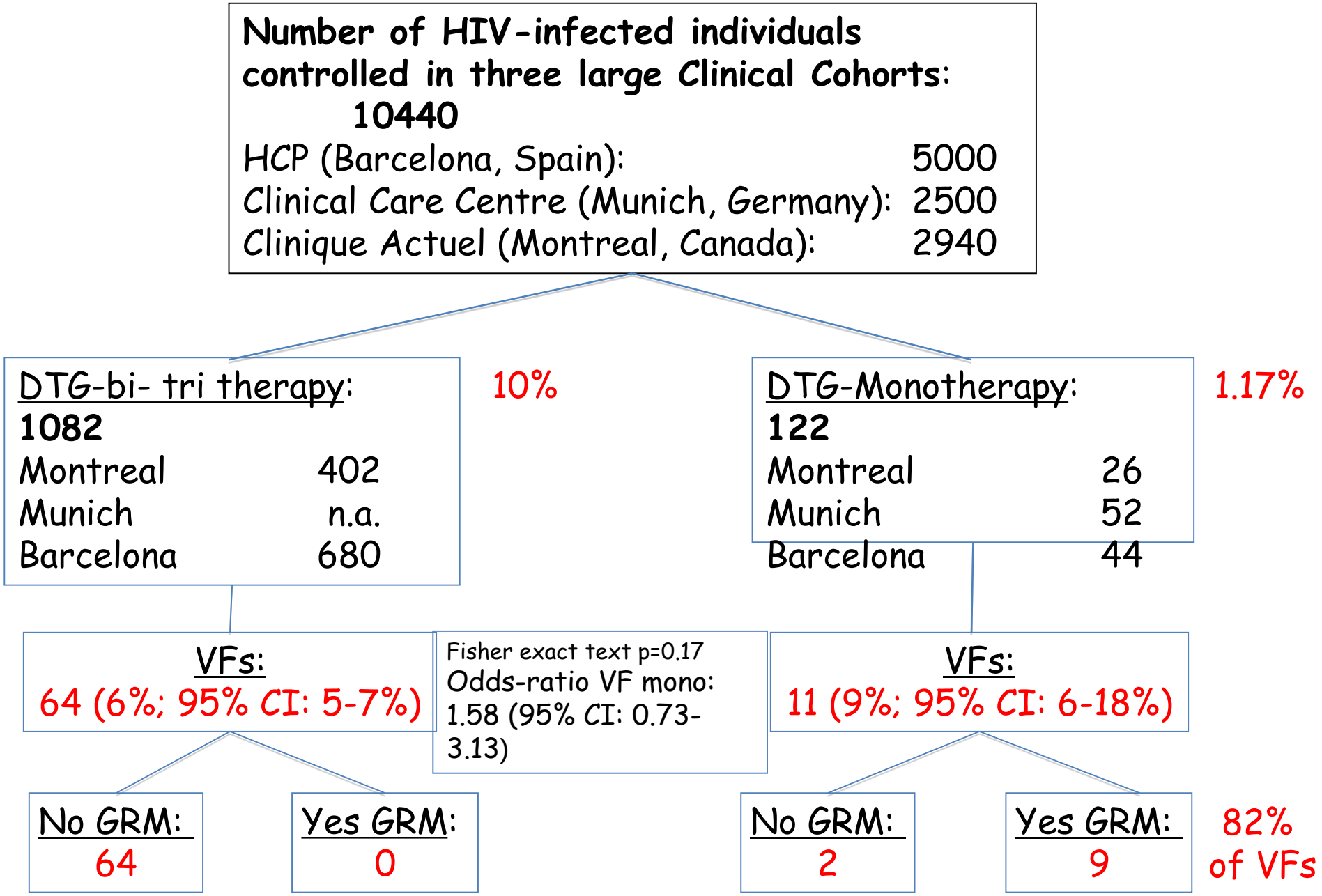
MVZ Karlsplatz

l'Actuel CENTRE D'EXCELLENCE VIH · ITS · HÉPATITES

Jewish General Hospital Lady Davis Institute for Medical Research




GRM: Genotypic resistance mutations

Blanco JL et al CROI 2017

We know that monotherapy is risky!!!

**But attention should be deserved also for the tailoring of dual therapies!!!**

# PS1/4 - Antiretroviral Resistance Selected at Failure in HIV Infected Patients Treated by Triple and Dual Therapies

V. Calvez[1,2], C. Charpentier[3,4], M. Wirden[1,2], D. Descamps[3,4], A.-G. Marcelin[1,2] [1]Pitie-Salpetriere Hospital, Dpt of Virology, Paris, France, [2]Sorbonne University, UPMC Univ Paris 06, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique (IPLESP UMRS 1136), Paris, France, [3]Bichat-Claude Bernard Hospital, Inserm UMR 1137, Paris, France, [4]Université Paris - Diderot Sorbonne Paris-Cité, Paris, France

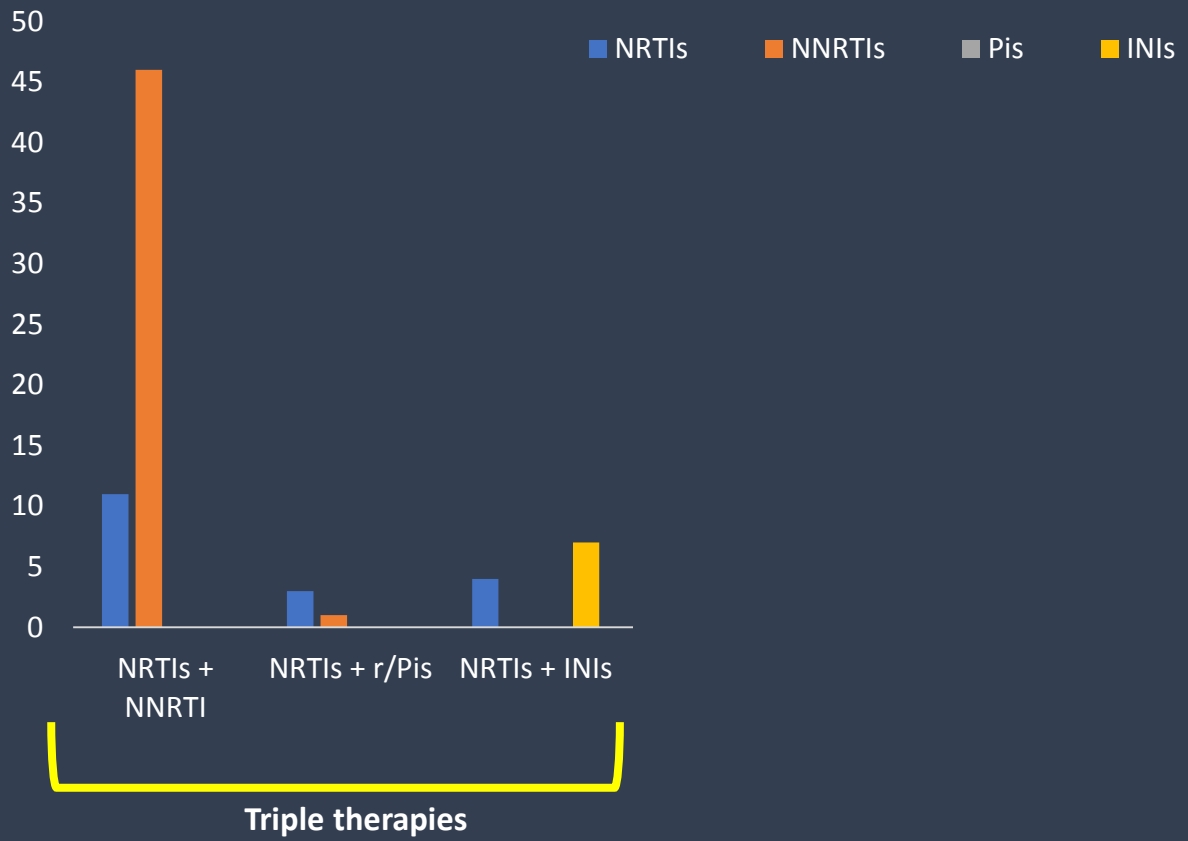
# Aim of the study

- To measure resistance selected in patients treated by triple and dual regimen experiencing virologic failure

- 465 patients where studied
  - 300 receiving triple combinations
    - NRTIs + NNRTI (EFV or RPV)
    - NRTIs + INI (RAL or c/EVG or DTG)
    - NRTIs + r/PI (r/DRV or r/ATV)
  - 165 receiving dual combinations
    - DTG based regiment: DTG + RPV (n=14) ; DTG + 3TC (n= 11); DTG + r/PI (n = 21)
    - RAL based regiment: RAL + r/DRV (n= 55); RAL + ETR (n= 15)
    - r/Pis based regiment: r/PI + 3TC (n= 49)

- None of these patients have failed to drugs of these classes in their therapeutic histories

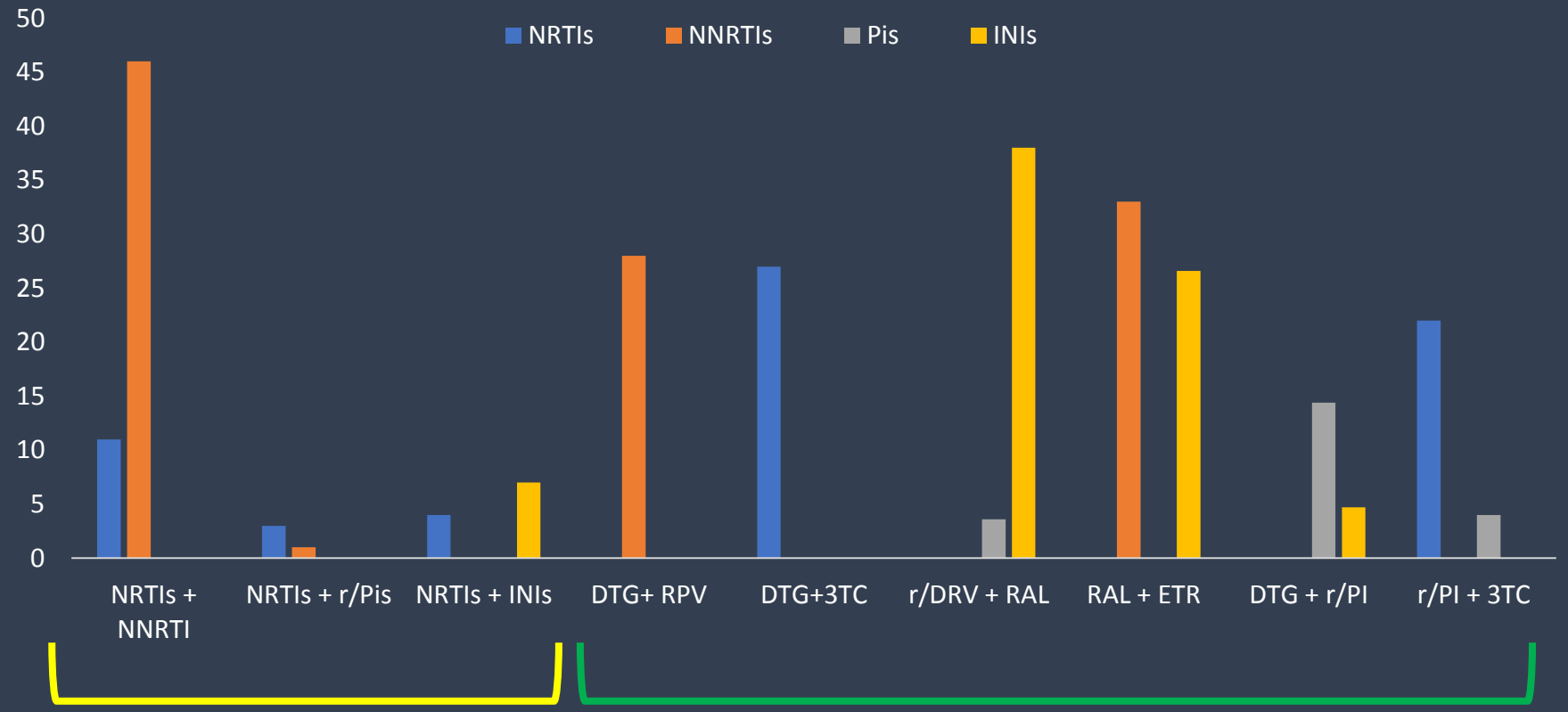
# PI & DTG based triple therapies are more protective than NNRTI based treatments




No DTG resistance in triple

Resistance selected with only RAL and c/EVG

Failure to dual regimen is associated globally with higher resistance selection. When r/PI or DTG are used in dual combinations, a weaker resistance protection is observed as compared when used in triple combination




DTG does not protect for RPV or 3TC resistance in case of failure
r/DRV does not protect RAL
No cross protection between RAL and ETR
DTG does not protect resistance to r/ATV
r/DRV or r/ATV does not protect resistance to 3TC

# Summary & conclusions

- Some natural polymorphisms may contribute to lowering INI efficacy or favor resistance development.
- A surveillance of integrase resistance should be guaranteed to improve the knowledge about “viral evolution” in the new era of INIs.
- Treatment simplifications strategies, even though very effective, seem to be associated with a high propensity of developing resistance at failure.
- A careful selection of an INI containing regimen based on treatment personalization in conjunction with integrase resistance testing (in both drug naïve and drug-experienced patients) can avoid resistance selection with loss of treatment options.

## The Patients

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