Etat des résistances du VIH-1 en France à l'ère du Test & Treat

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Test & Treat : Quelles molécules possibles?

Tritherapie

- TDF FTC/3TC r/DRV
- TDF FTC/3TC DTG
- TAF FTC BIC
- ABC non (HLA)
- NNRTI non (TDR)

Bithérapie ?

- DTG 3TC/FTC ?
- r/DRV 3TC/FTC ?

Clinical Infectious Diseases

MAJOR ARTICLE

2018

Human Immunodeficiency Virus Drug Resistance: 2018 Recommendations of the International Antiviral Society–USA Panel

Huldrych F. Günthard,[1] Vincent Calvez,[2] Roger Paredes,[3,4] Deenan Pillay,[5] Robert W. Shafer,[6] Annemarie M. Wensing,[7] Donna M. Jacobsen,[8] and Douglas D. Richman[9]

[1]University Hospital Zürich and Institute of Medical Virology, University of Zurich, Switzerland; [2]Pierre et Marie Curie University and Pitié-Salpêtrière Hospital, Paris, France; [3]Infectious Diseases Service and IrsiCaixa AIDS Research Institute, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [4]Africa Health Research Institute, KwaZulu Natal, South Africa; [5]University College London, United Kingdom; [6]Stanford University Medical School, California; [7]University Medical Center Utrecht, The Netherlands; and [8]International Antiviral Society–USA, San Francisco, and [9]Veterans Affairs San Diego Healthcare System and University of California San Diego

Background. Contemporary antiretroviral therapies (ART) and management strategies have diminished both human immunodeficiency virus (HIV) treatment failure and the acquired resistance to drugs in resource-rich regions, but transmission of drug-resistant viruses has not similarly decreased. In low- and middle-income regions, ART roll-out has improved outcomes, but has resulted in increasing acquired and transmitted resistances. Our objective was to review resistance to ART drugs and methods to detect it, and to provide updated recommendations for testing and monitoring for drug resistance in HIV-infected individuals.

Methods. A volunteer panel of experts appointed by the International Antiviral (formerly AIDS) Society–USA reviewed relevant peer-reviewed data that were published or presented at scientific conferences. Recommendations were rated according to the strength of the recommendation and quality of the evidence, and reached by full panel consensus.

Results. Resistance testing remains a cornerstone of ART. It is recommended in newly-diagnosed individuals and in patients in whom ART has failed. Testing for transmitted integrase strand-transfer inhibitor resistance is currently not recommended, but this may change as more resistance emerges with widespread use. Sanger-based and next-generation sequencing approaches are each suited for genotypic testing. Testing for minority variants harboring drug resistance may only be considered if treatments depend on a first-generation nonnucleoside analogue reverse transcriptase inhibitor. Different HIV-1 subtypes do not need special considerations regarding resistance testing.

Conclusions. Testing for HIV drug resistance in drug-naive individuals and in patients in whom antiretroviral drugs are failing, and the appreciation of the role of testing, are crucial to the prevention and management of failure of ART.

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Conclusions. Testing for HIV drug resistance in drug-naive individuals and in patients in whom antiretroviral drugs are failing, and the appreciation of the role of testing, are crucial to the prevention and management of failure of ART.

Recommendations	When to Test	Gene to be Sequenced: Protease	Reverse Transcriptase[a]	Integrase	Strength/ Evidence	Comments
HIV resistance testing is recommended for all individuals with HIV infection:						
• who are newly diagnosed and presumably ART-naïve;	As soon as an individual is diagnosed with HIV-1 infection. In any case, before ART is started.	Yes	Yes	(Yes)[b]	AIIa	To detect transmitted RAM. Early testing increases the chances of detecting TDR before mutations are potentially replaced by wild-type virus (particularly relevant for high–fitness cost mutations, eg, M184V, K65R, T215Y, and others). Many resistance mutations can still be detected even years after infection; in particular, low–fitness cost mutations (eg, K103N, L90M, etc). InSTI TDR is currently rare.
• who are on antiretroviral treatment and have plasma HIV RNA that is rising to above 200 copies/mL by confirmed measurements after they have been suppressed to below 50 copies/mL;	Preferably while on failing ART.	Yes	Yes	Yes	AIIa	To detect acquired drug resistance in patients who initially responded to ART and, later on, failed. InSTI RAM should be tested in all treatment failures.
• who have not achieved full virus suppression after initiating ART;	≥6 months after ART initiation.	Yes	Yes	Yes	AIIa	To detect acquired drug resistance in patients who did not achieve successful viral suppression to antiretroviral treatment. InSTI RAM should be tested in all treatment failures.
• who have interrupted ART containing an NNRTI with a long half-life (eg, efavirenz); or	As soon as virus rebounds above 500 HIV-RNA copies/ mL, respectively, before re-initiation of ART.	Yes	Yes	Yes	AIIa	Treatment interruption of such regimens can lead to virtual monotherapy with rapid emergence of resistance.
• who have a significant increase in viral load in a drug-naive individual not on treatment.[c]	After confirmation of increase in plasma viremia.	Yes	Yes	(Yes)[b]	AIII	Superinfection with drug-resistant virus may occur (consider also tropism testing, because a switch from CCR5- to CXCR4 tropic virus may have occurred).

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RNA, ribonucleic acid; TDR, transmitted drug resistance.

[a]Sequencing of first half of the reverse transcriptase up to at least nucleotide 215 is sufficient.

[b]Currently, evidence of InSTI TDR is rare. Thus "Yes" in brackets (YES) means that InSTI testing should be considered if certain circumstances are given (see comments).

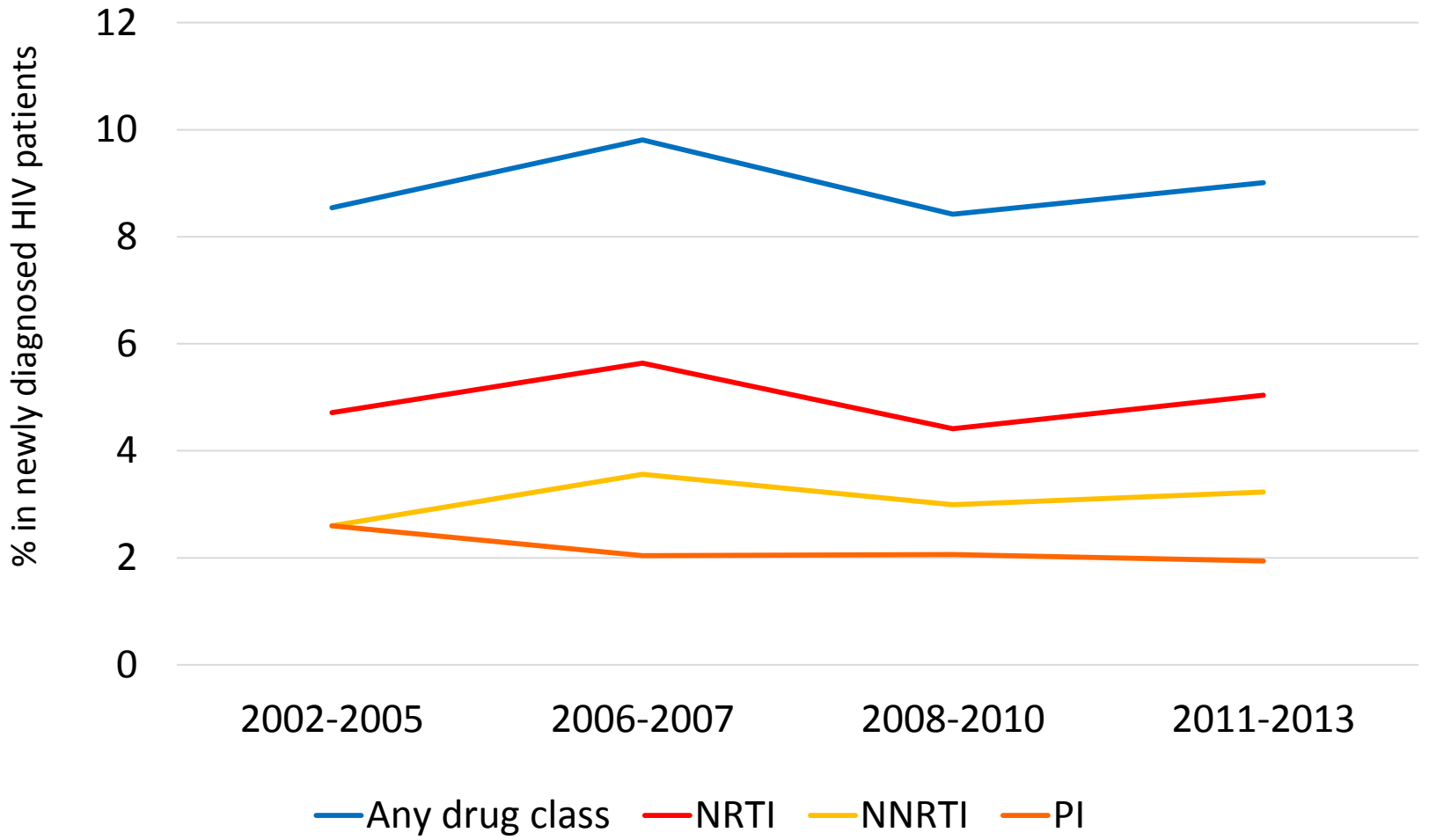
[c]Increase of plasma viremia of >0.5 $\log_{10}$ within approximately 3–6 months that is confirmed by a second HIV-1 RNA measurement.

Recommendations for Resistance Testing in Clinical Practice:

Who and When to Test ?

Günthard et al., CID 2018

The prevalence of TDRM is stable in Europe

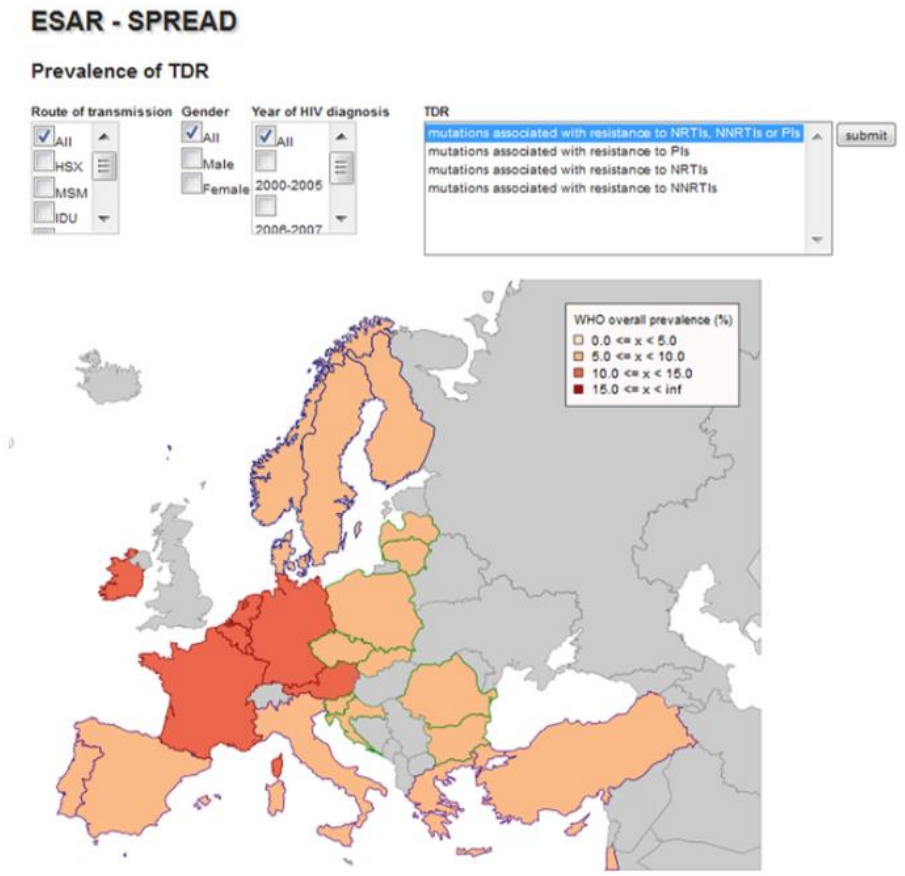


Hofstra et al, IDRW 2016, CID 2016

SPREAD 2011-2013
The prevalence of HIV drug resistance mutations in Europe: interactive monitoring

- Overall prevalence of TDRM in Europe : **8.6%**
  - Northern and Central EU: **5.7%**
  - Mediterranean Europe : **7.4%**
  - Western Europe : **12.2%**, driven by a higher prevalence of NRTIs (7.5%) and non-NRTIs (4.2%)
  - Protease inhibitors low in all regions (2.1%)
  - Lower in heterosexual contact (7.8%) vs MSM (10.2%) in all regions.

Figure 1. The online interactive map with figures on the prevalence of transmitted drug resistance.



Hofstra et al. Journal of the International AIDS Society, submitted

Clinical Infectious Diseases

MAJOR ARTICLE **2018**

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Trends in the Molecular Epidemiology and Genetic Mechanisms of Transmitted Human Immunodeficiency Virus Type 1 Drug Resistance in a Large US Clinic Population

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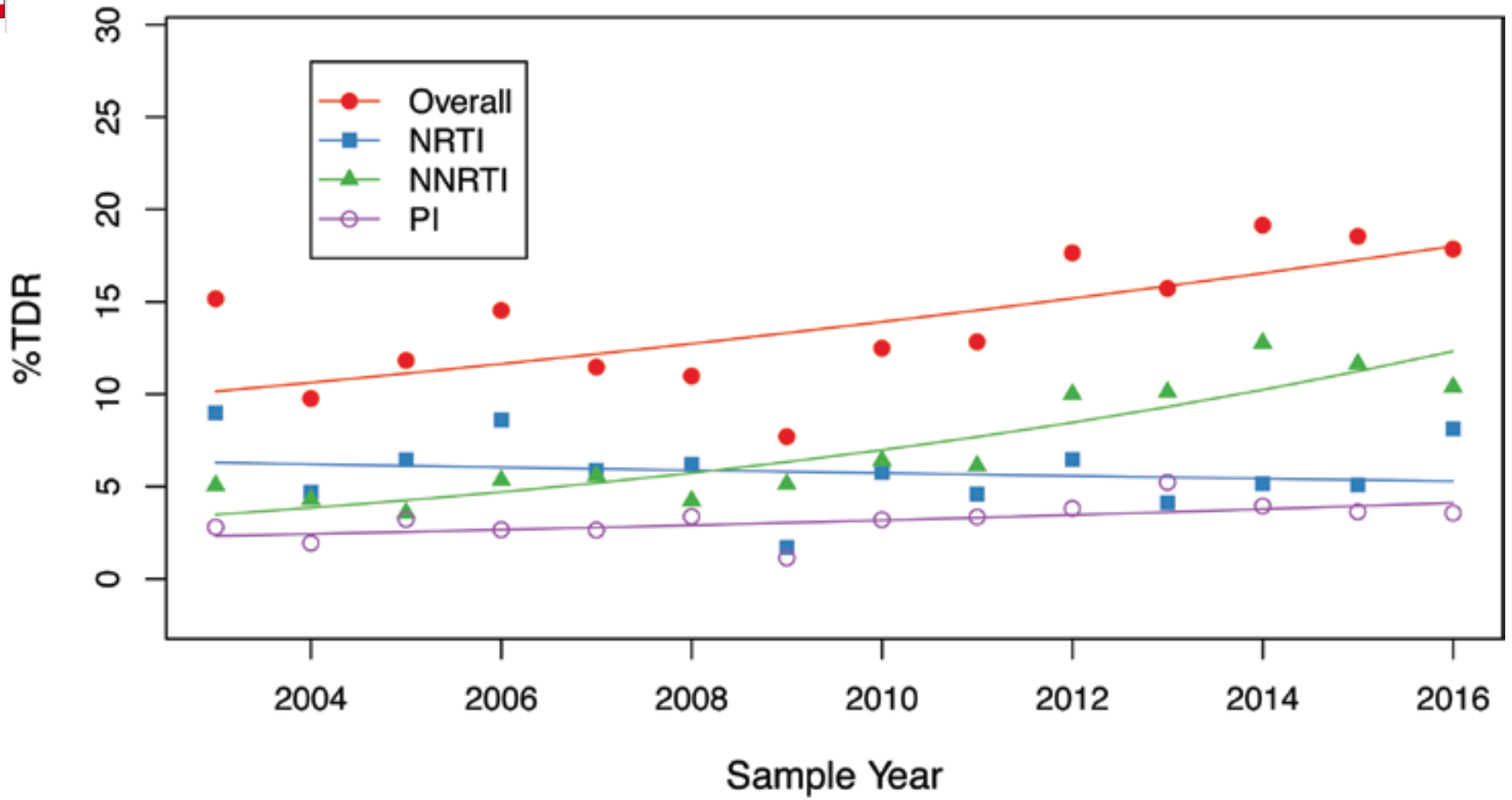
Background. There are few large studies of transmitted drug resistance (TDR) prevalence and the drug resistance mutations (DRMs) responsible for TDR in the United States.

Methods. Human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) and protease sequences were obtained from 4253 antiretroviral therapy (ART)–naive individuals in a California clinic population from 2003 to 2016. Phylogenetic analyses were performed to study linkages between TDR strains and selection pressure on TDR-associated DRMs.

Results. From 2003 to 2016, there was a significant increase in overall (odds ratio [OR], 1.05 per year [95% confidence interval {CI}, 1.03–1.08]; $P < .001$) and nonnucleoside RT inhibitor (NNRTI)–associated TDR (OR, 1.11 per year [95% CI, 1.08–1.15]; $P < .001$). Between 2012 and 2016, TDR rates to any drug class ranged from 15.7% to 19.2%, and class-specific rates ranged from 10.0% to 12.8% for NNRTIs, 4.1% to 8.1% for nucleoside RT inhibitors (NRTIs), and 3.6% to 5.2% for protease inhibitors. The thymidine analogue mutations, M184V/I and the tenofovir-associated DRMs K65R and K70E/Q/G/N/T accounted for 82.9%, 7.3%, and 1.4% of NRTI-associated TDR, respectively. Thirty-seven percent of TDR strains clustered with other TDR strains sharing the same DRMs.

Conclusions. Although TDR has increased significantly in this large cohort, many TDR strains are unlikely to influence the activity of currently preferred first-line ART regimens. The high proportion of DRMs associated with infrequently used regimens combined with the clustering of TDR strains suggest that some TDR strains are being transmitted between ART-naive individuals.

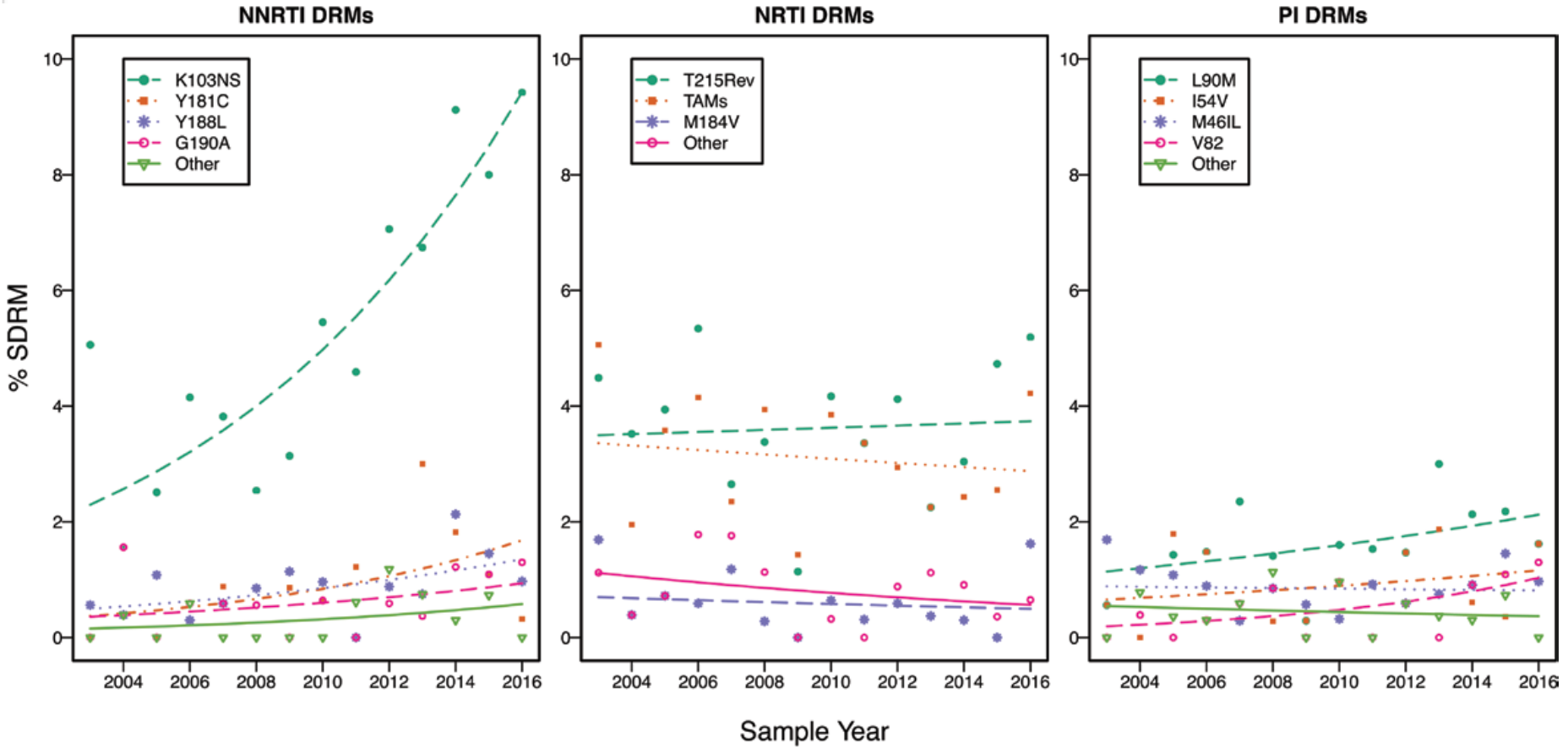
Temporal trends in the yearly proportion of individuals with transmitted drug resistance in US, by drug class.



The fitted lines show the effect of sample years in generalized binomial logistic regression models. Abbreviations: NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDR, transmitted drug resistance.

Soo-Yon Ree, CID 2018

Temporal trends in the yearly proportion of individuals with the most commonly detected NRTI, NNRTI, and PI surveillance TDRAMs



The fitted lines show the effect of sample years in generalized binomial logistic regression models. Abbreviations: DRM, drug resistance mutation; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SDRM, surveillance drug resistance mutation; TAM, thymidine analogue mutation.

Soo-Yon Ree, CID 2018

Poster 529

High prevalence of NNRTI and INI-resistant polymorphic virus in primary HIV infection

ML Chaix[1,2], M Grude[3], H Delagrèverie[1,2], C Roussel[4], H Pere[5], H Le Guillou-Guillemette[6], J Dina[7], A Signori-Schmuck[8], MJ Carles[9], L Morand-Joubert[10], J Izopet[11], L Meyer[12], L Assoumou[3], D Descamps[13] on behalf the AC11 ANRS Resistance Group

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Objective

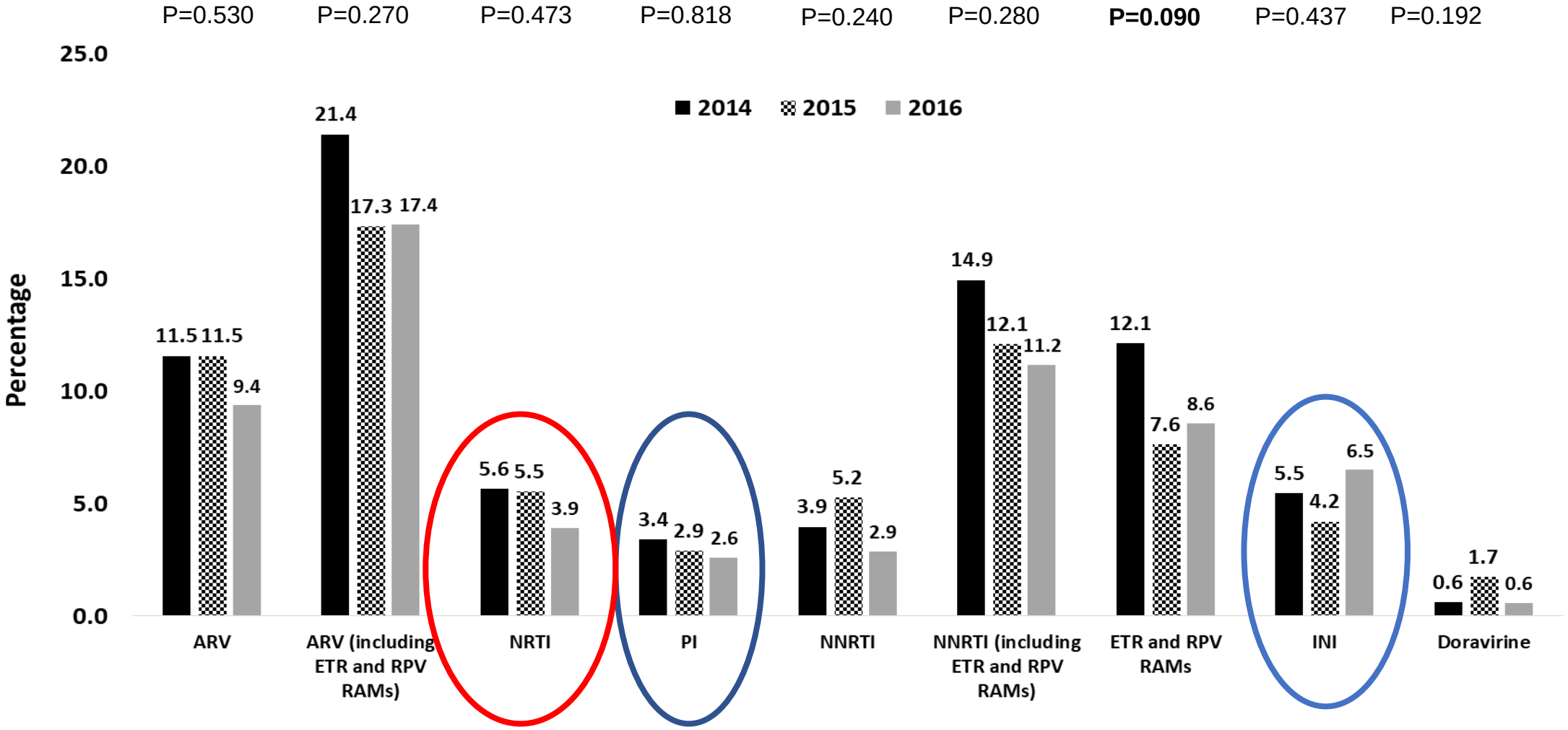
According to the French ANRS program for HIV-1 resistance surveillance, we estimated the prevalence of transmitted drug resistance associated mutations (TDRAMs) in primary infected patients (PHI) diagnosed in France in 2014-2016.

Table 2. RAMs according to the Stanford list and the ANRS algorithm 2017

At least 1 RAM using WHO list	**10.8%**
At least 1 NRTI RAM using Stanford list	5.0%
At least 1 NNRTI RAM using Stanford list	4.0%
At least 1 PI RAM using Stanford list	2.9%
At least 1 RAM using Stanford + ANRS (2017)	**18.6%**
At least 1 NNRTI RAM using Stanford list + ANRS (2017)	12.7%
At least 1 II RAM (ANRS 2017)	5.3%

Chaix ML et al. CROI, 2018

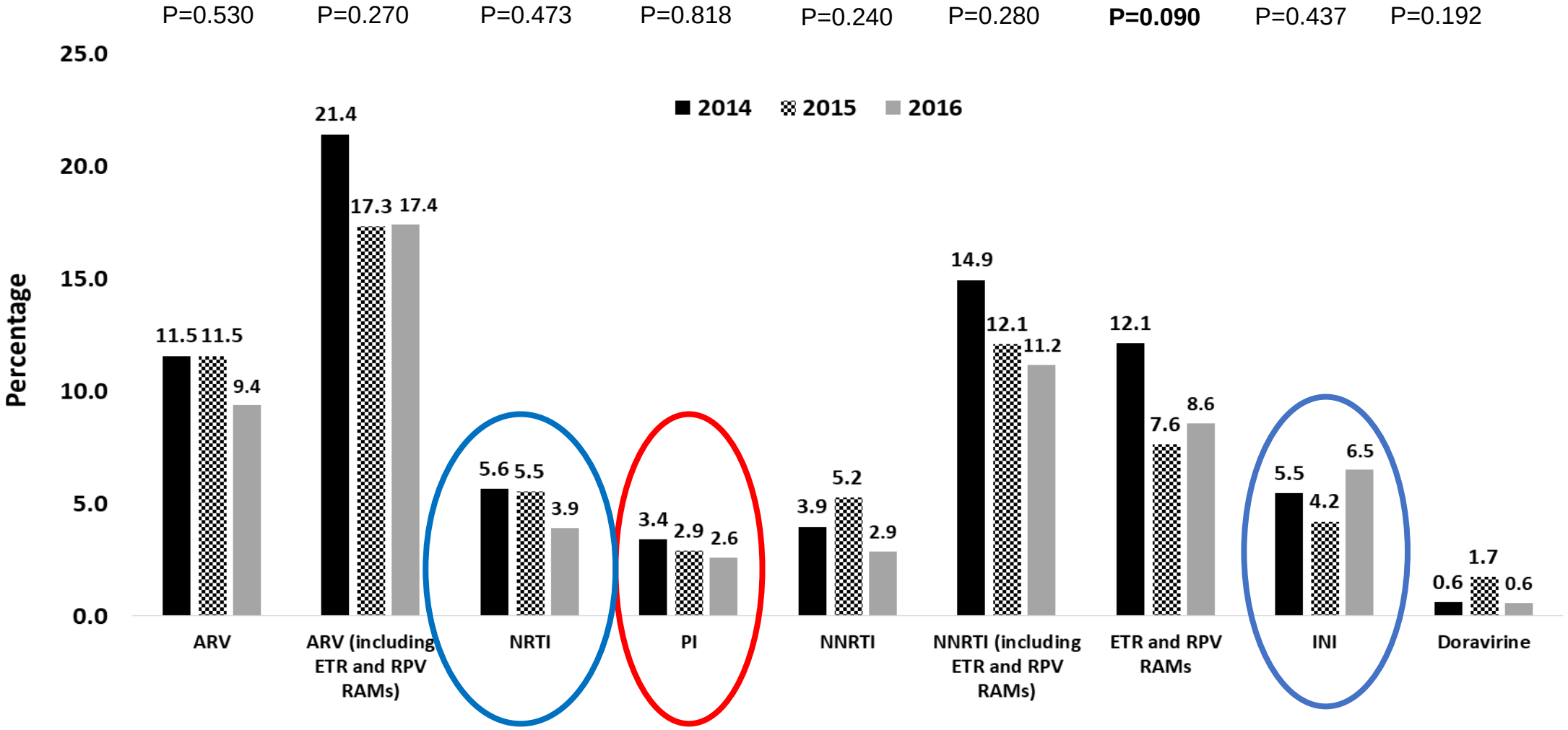
Frequency of virus with at least one TDRAMs in each category



215 revertants (2.9%) and other TAMs (M41L, (1.4%), K219Q/E (0.5%), D67N/E (0.5%), L210W (0.3%), T215F (0.2%), K70R (0.09%)

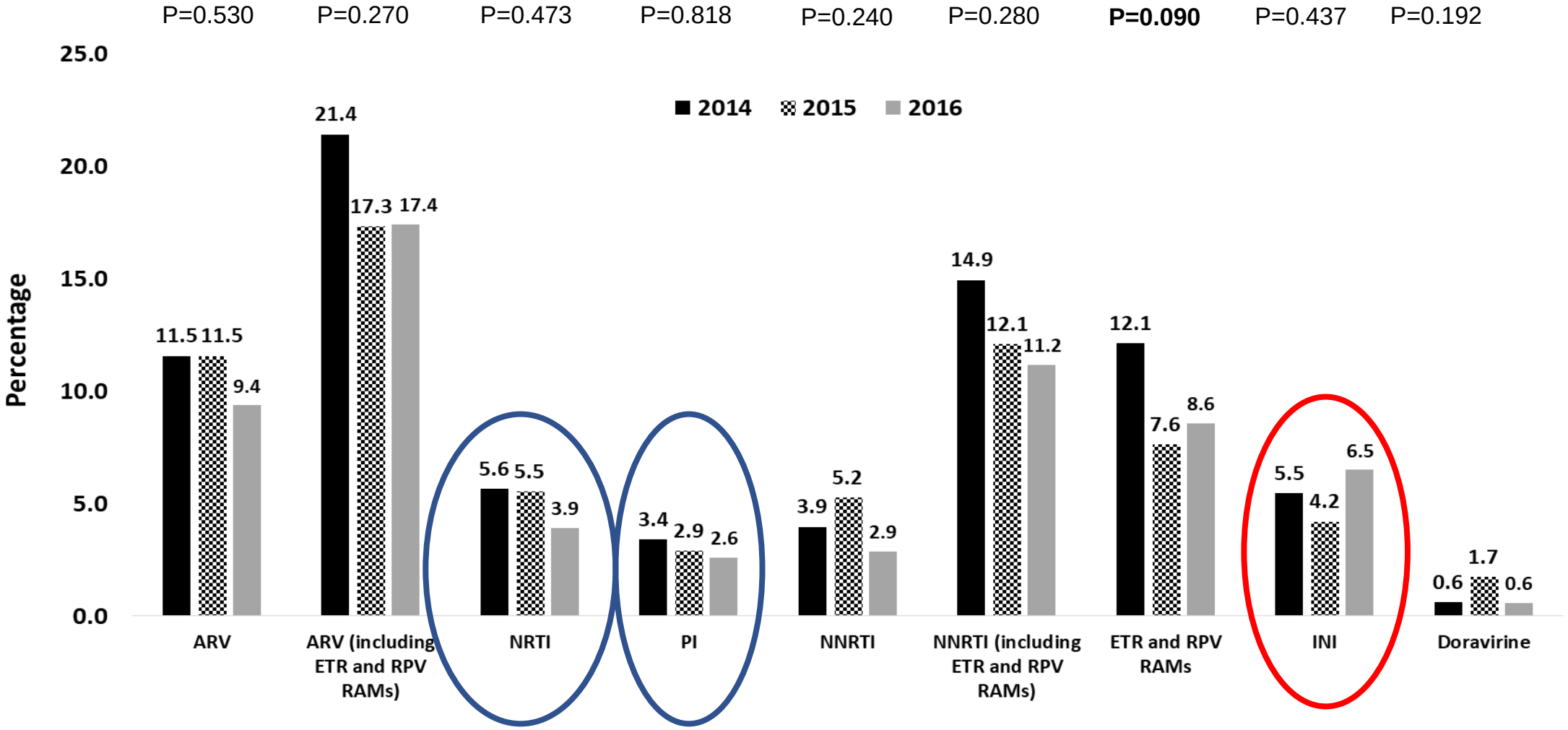
M184V/I in 6 cases (**0.5%**), T69D in 2 (0.2%), Y115F in 2 (0.2%) and **K65R in 1 case (0.09%)**

Frequency of virus with at least one TDRAMs in each category



L90M in 11 cases (1%), I85V/I 0.8%, L76V in 0.6%, M46I/L in 0.5%, V32I, V82A/T, I54L/S in 0.3%, N88D, I47V, I50V, F53Y/L in 0.2% and L23I, L24I in 0.09%

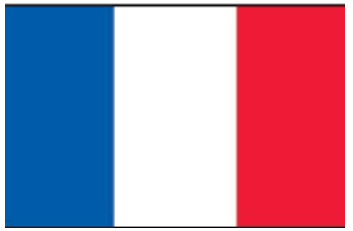
Frequency of virus with at least one TDRAMs in each category



L74M n=8, E92Q/G n=1, **T97A n=12,** E138K n=3, **E157Q n=17**, S230R n=2, R263K n=1.
Double mutants E92Q+T97A and L74M+T97A were observed in 1 patient, respectively.

Stable Prevalence of Transmitted Drug Resistance Mutations and Increased Circulation of non-B subtypes in Antiretroviral-Naive Chronically HIV-Infected Patients in 2015/2016 in France

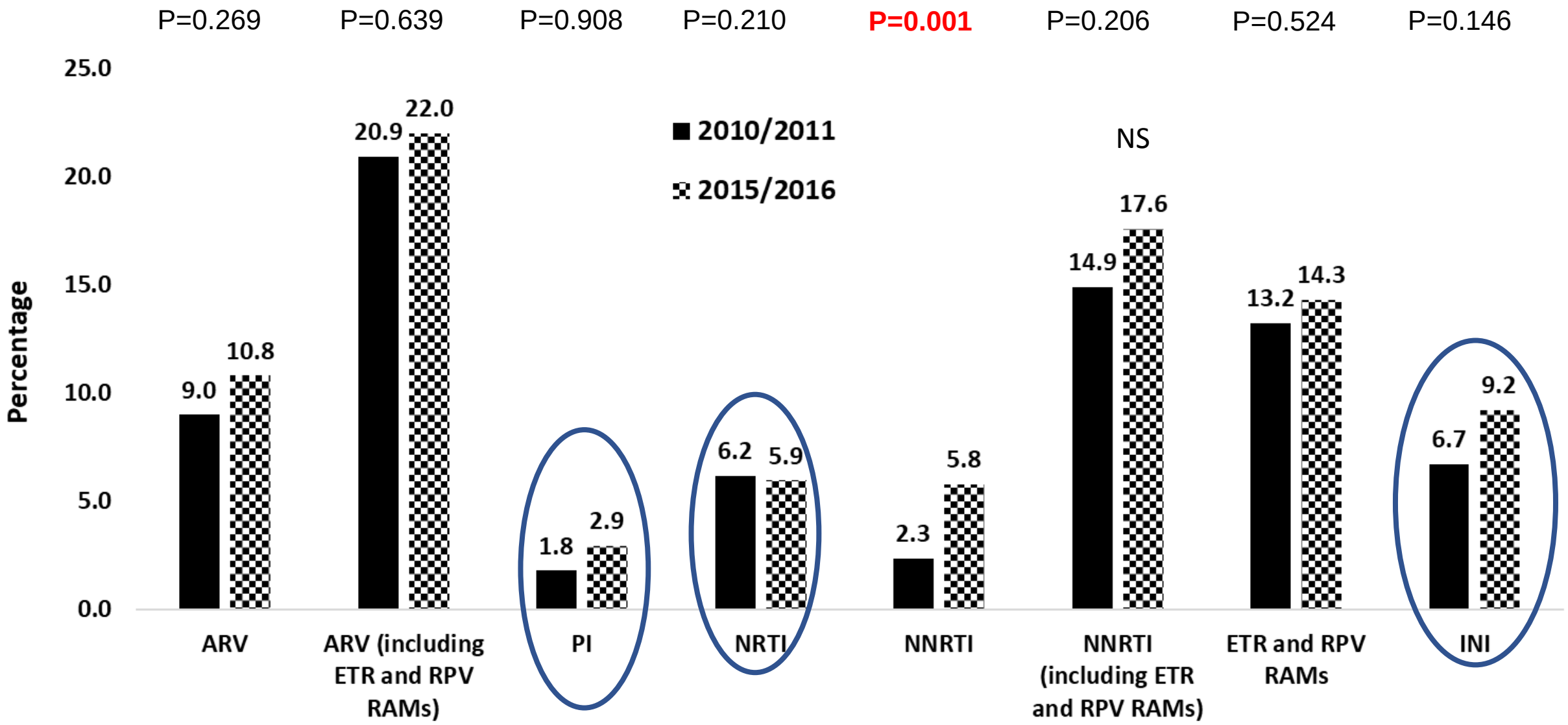
Lambert Assoumou[1], Laurence Bocket[2], Coralie Pallier[3], Maxime Grude[1], Rachid Ait-Namane[1], Jacques Izopet[4], Stéphanie Raymond[4], Charlotte Charpentier[5,6], Benoit Visseaux[5,6], Marc Wirden[1,7], Mary-Anne Trabaud[8], Hélène Le Guillou-Guillemette[9], Chakib Allaoui[10], Cécile Henquell[11], Anne Krivine[12], Georges Dos Santos[13], Catherine Delamare[14], Magali Bouvier-Alias[15], Brigitte Montes[16], Virginie Ferre[17], Anne De Monte[18], Anne Signori-Schmuck[19], Anne Maillard[20], Laurence Morand-Joubert[21], Camille Tumiotto[22], Samira Fafi-Kremer[23], Corinne Amiel[24], , Francis Barin[25], Stéphanie Marque-Juillet[26], Laurence Courdavault[27], SophieVallet[28], Agnès Beby-Defaux[29], Alexis de Rougemont[30], Honorine Fenaux[31], Véronique Avettand-Fenoel[32], Annick Allardet-Servent[33], Jean-Christophe Plantier[34], Gilles Peytavin[6,35], Vincent Calvez[1,7,36], Marie-Laure Chaix[37] and Diane Descamps[5,6], and the ANRS AC-43 Resistance Study Group, France



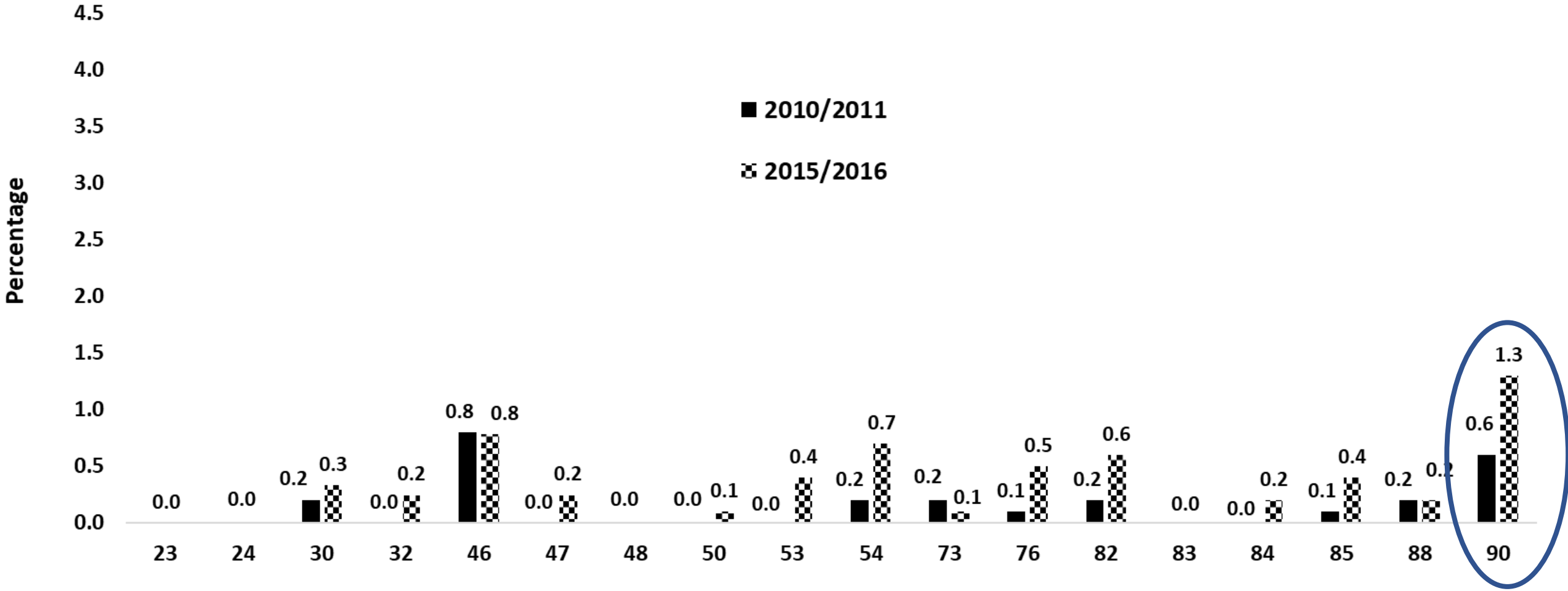
Overall prevalence of TDRAMs was **10.8%** and stable compared 2005/2006 & 2010/2011 surveys.

Descamps D et al .JAC 2010, Descamps D et al. JAC 2013, Assoumou L et al. IAS 2017 & JAC, submitted

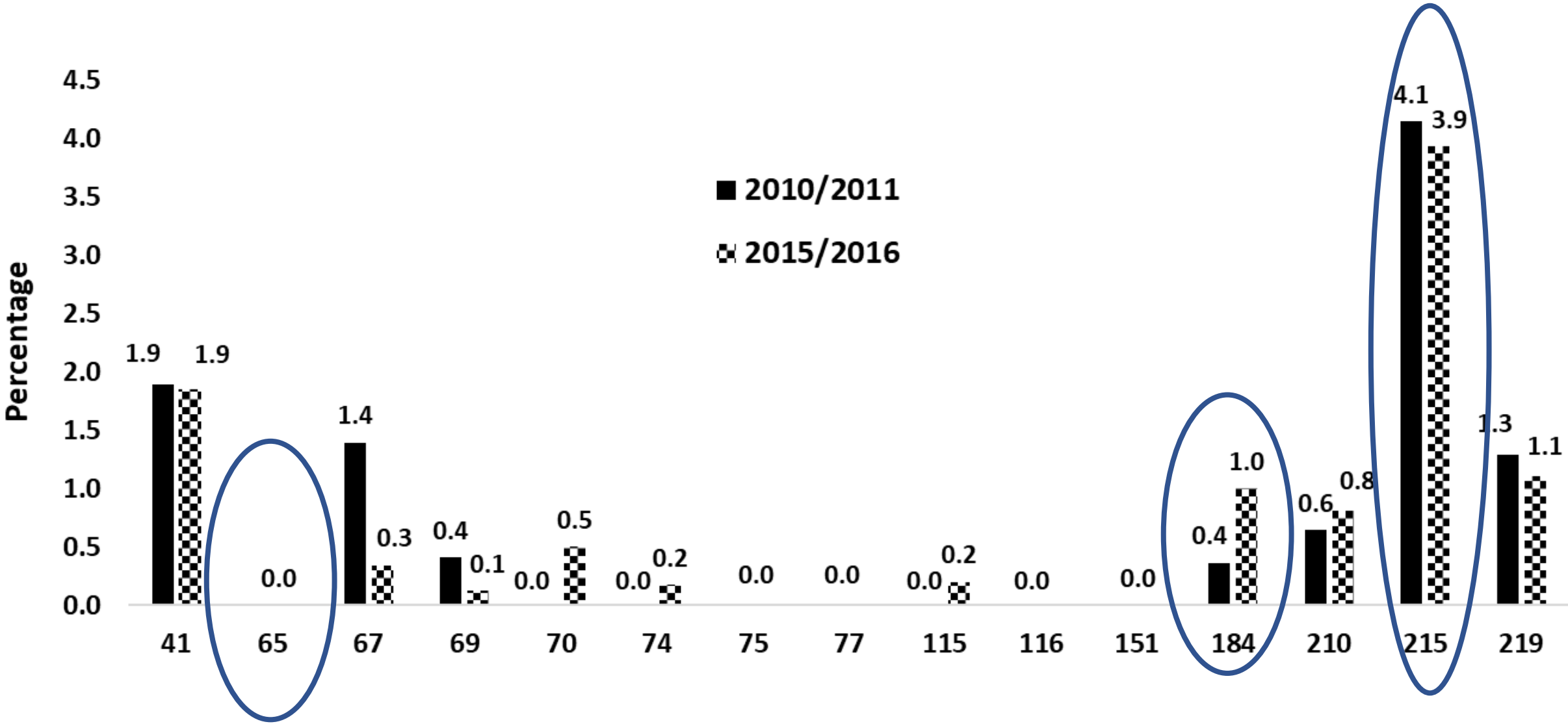
Frequency of virus with at least one TDRAMs in each category



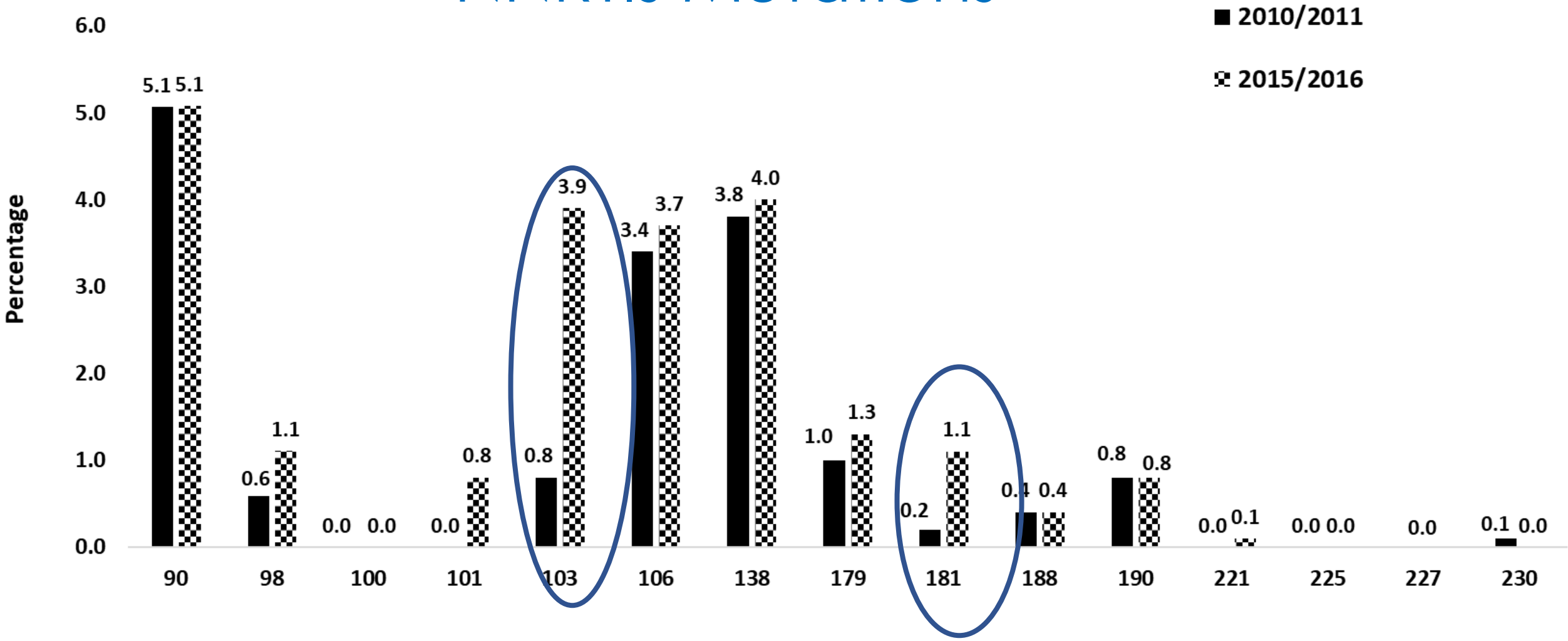
PIs Mutations



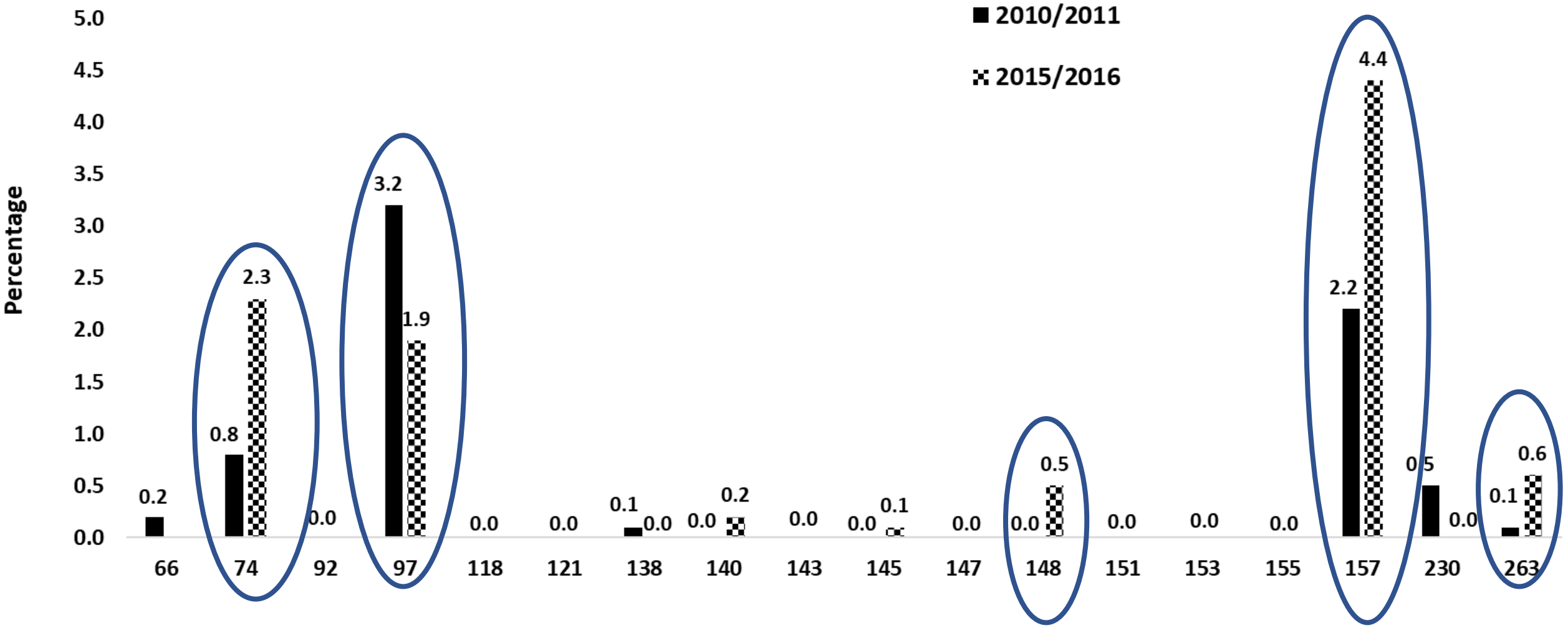
Mutations NRTIs



NNRTIs Mutations



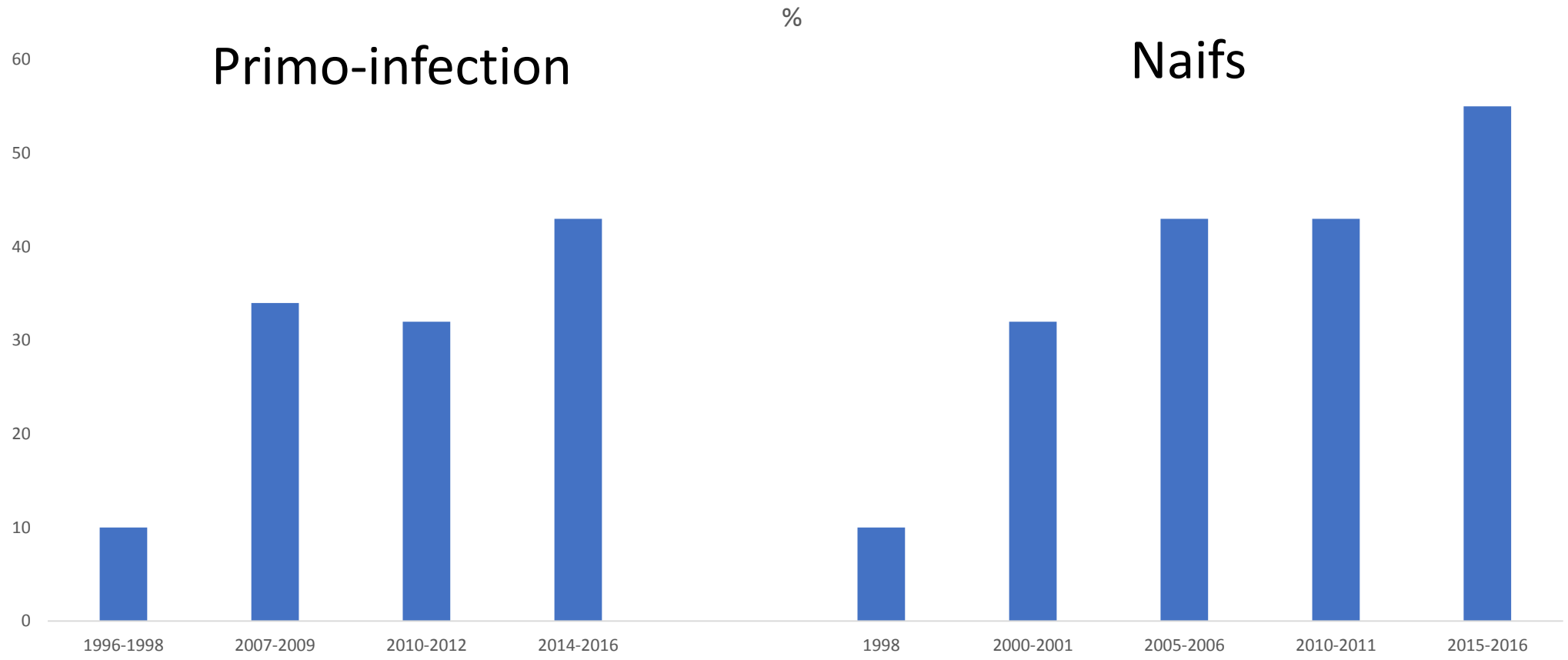
INIs Mutations



2010-2011 : 1 major INI mutation (T66I)

2015-2016 : 3 major INI mutations (Q148K & G140A+Q148R)

Primo & Odyssee : Sous-types non B



Chaix et al, Descamps et al, Assoumou L et al.

NRTIs

Comparative Activity of TAF vs. Major Nucleoside Reverse Transcriptase Inhibitors against HIV-1 Harboring K65R or Thymidine Analog Mutations, with or without M184V

Poster 16

GILEAD

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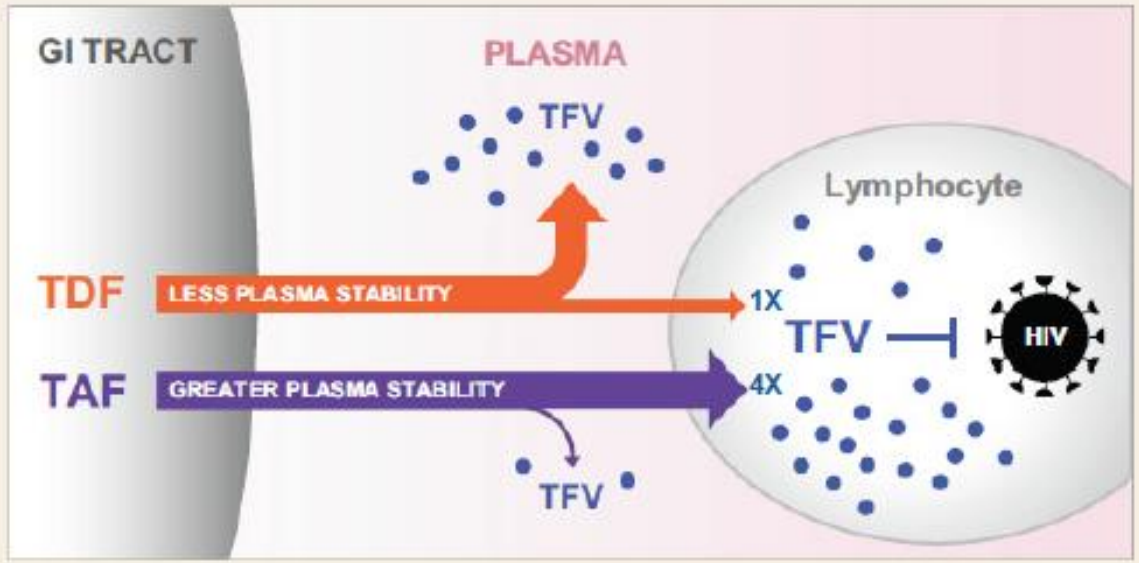
Figure 1. Tenofovir Prodrugs



- Upon treatment with TDF, cells are loaded with TFV-DP
- Upon treatment with TAF:
  - 4-fold improved delivery of intracellular TFV-DP (vs. TDF)
  - reduction of plasma [TFV] by ~90% (vs. TDF)
  - 10-fold lower dose for same or higher efficacy (vs. TDF)

Margot N, CROI 2018 & EHDRW 2018

Results

Table 1. NRTIs Susceptibility of TAM-Containing Mutants in the Presence or Absence of M184V

Site-Directed Mutants

Mutant Class (n per class)	Mean EC_{60} Fold Change (FC) Compared to Wild-Type[a]							
	TAF		AZT		ABC		FTC	
	No M184V	With M184V	No M184V	With M184V	No M184V	With M184V	No M184V	With M184V
No TAMs (n=2)	1.0	0.4	1.0	0.2	1.0	5.3	1.0	>118.7
1 TAMs (n=12)	0.5	0.5	0.7	0.4	1.3	5.0	0.6	>116.1
2 TAMs (n=30)	1.3	0.8	7.1	1.3	1.5	4.6	1.8	>94.4
3 TAMs (n=24)	1.3	0.9	16.1	2.2	1.9	5.7	1.5	>76.1
4 TAMs (n=14)	2.3	1.6	39.8	4.4	3.5	7.4	3.8	>82.4
5 TAMs (n=12)	2.7	1.8	45.5	3.6	3.1	5.5	1.9	>110.2
6 TAMs (n=2)	4.0	2.1	66.1	13.4	2.3	5.6	2.6	>118.7
All Mutants (n=96)	1.6	1.0	19.6	2.4	2.1	5.5	1.9	>93.3

a. Mean values calculated from ≥3 independent triplicate experiments for each mutant
Wild-type EC_{50}s were 15 nM, 162 nM, 774 nM, and 421 nM, for TAF, AZT, ABC, and FTC, respectively.

- Gradual increase in resistance to NRTIs observed with increasing # of TAMs
- Significant M184V effect ($p<0.05$, not shown)

Margot N, CROI 2018 & EHDRW 2018

Results

Table 2. NRTIs Susceptibility of K65R-Containing Mutants in the Absence or Presence of M184V

Site-Directed Mutants

Mutant Class (n per class)	Mean EC_{50} Fold Change (FC) Compared to Wild-Type[a]							
	TAF		AZT		ABC		FTC	
	No M184V	With M184V	No M184V	With M184V	No M184V	With M184V	No M184V	With M184V
No K65R (n=2)	1.0	0.4	1.0	0.2	1.0	5.3	1.0	>118.7
K65R (n=2)	3.3	2.5	1.9	0.6	15.9	>19.4	9.2	>118.7

a. Mean values calculated from ≥3 independent triplicate experiments for each mutant
Wild-type EC_{50}s were 15 nM, 162 nM, 774 nM, and 421 nM, for TAF, AZT, ABC, and FTC, respectively.

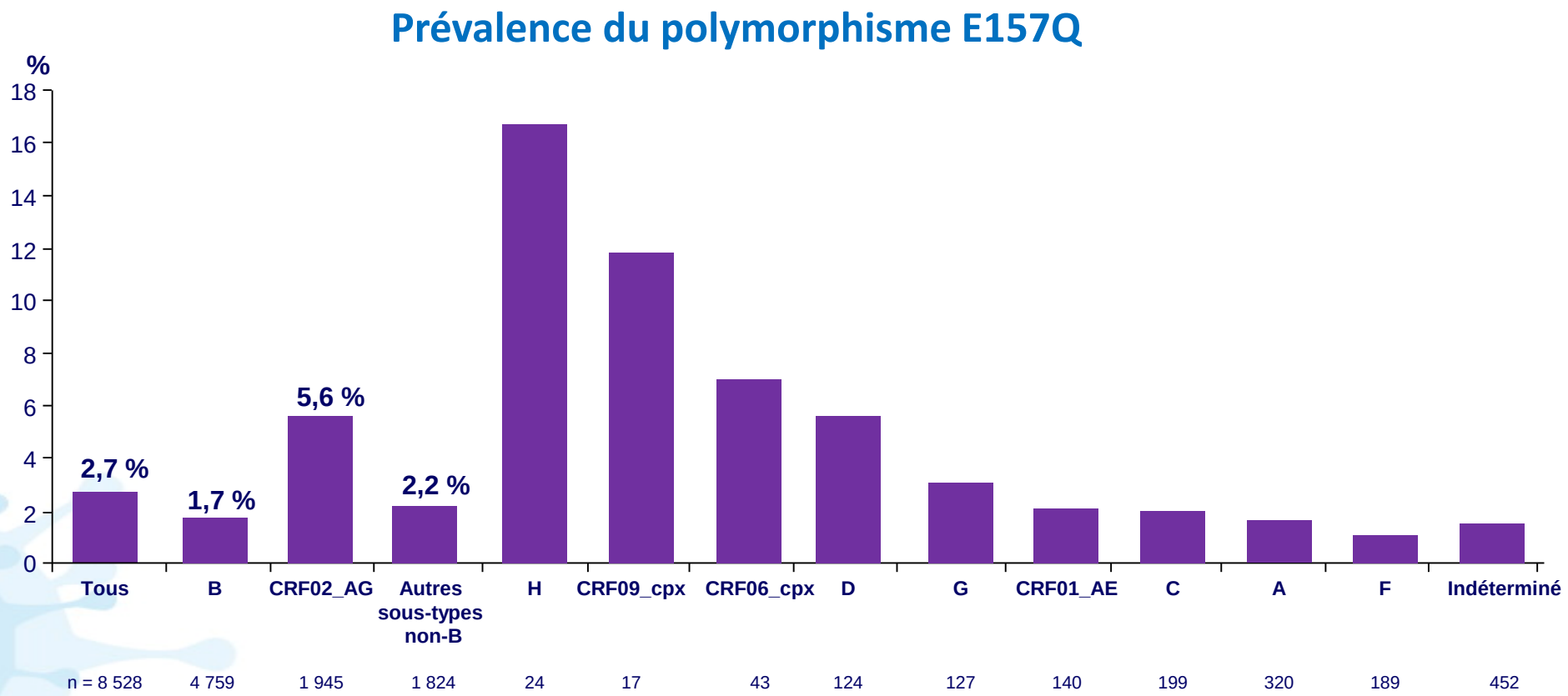
- Re-sensitizing effect of M184V when added to K65R for TAF and AZT

Margot N, CROI 2018 & EHDRW 2018

INIs

Polymorphisme E157Q dans l'intégrase : phénotype et réponse au traitement (1)

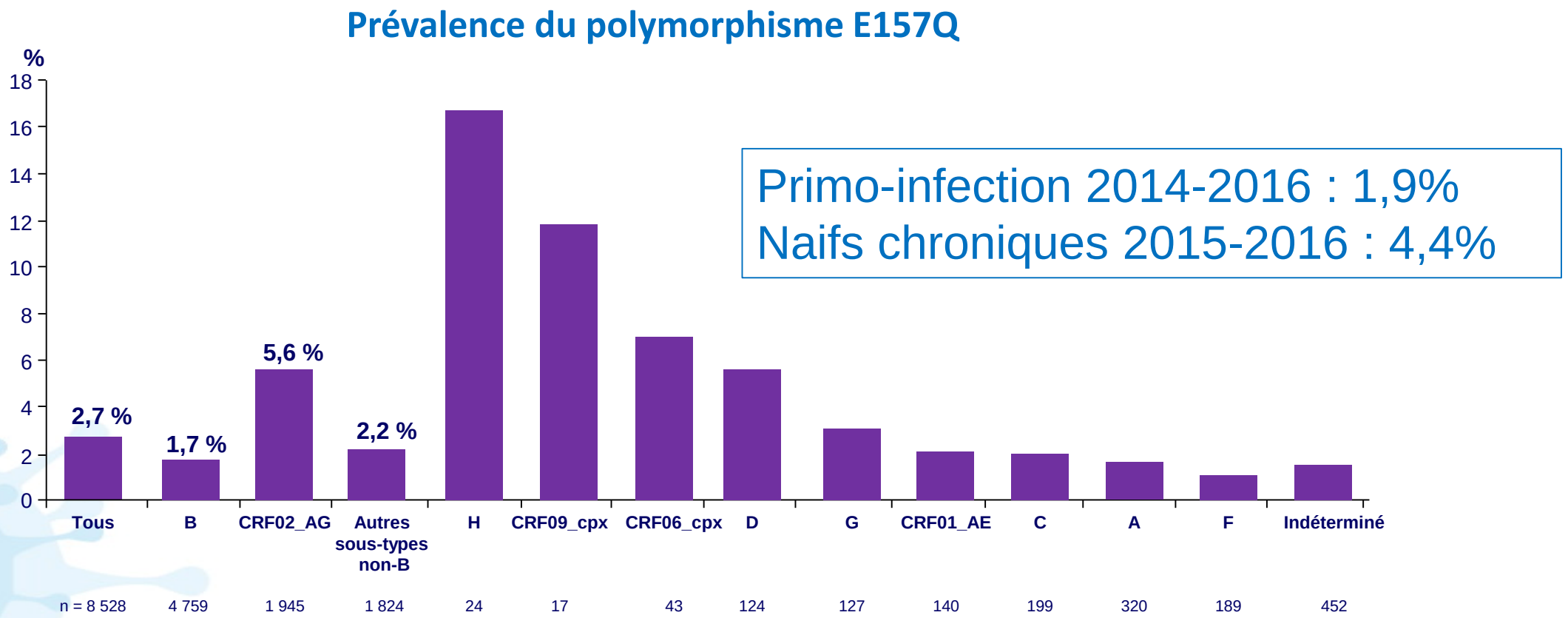
- Etude multicentrique ANRS : analyse de 8 528 séquences d'intégrase issues de patients naïfs d'INI (56 % B, 23 % CRF02_AG et 21 % autres non-B)



Charpentier C, J. Antimicrob Chemother 2018 ; EACS 2017, Abs. PE 6/11 ; CROI 2018, Abs. 547

Polymorphisme E157Q dans l'intégrase : phénotype et réponse au traitement (1)

- Etude multicentrique ANRS : analyse de 8 528 séquences d'intégrase issues de patients naïfs d'INI (56 % B, 23 % CRF02_AG et 21 % autres non-B)



Primo-infection 2014-2016 : 1,9%
Naifs chroniques 2015-2016 : 4,4%

Charpentier C, J. Antimicrob Chemother 2018 ; EACS 2017, Abs. PE 6/11 ; CROI 2018, Abs. 547

Polymorphisme E157Q dans l'intégrase : phénotype et réponse au traitement (2)

Tests phénotypiques recombinants avec des mutants E157Q, CE_{50} moyenne ± ET

		RAL		EVG		DTG	
		CE_{50} (nM) ± ET	FC	CE_{50} (nM) ± ET	FC	CE_{50} (nM) ± ET	FC
pNL43 (sous-type B)	WT	20,3 ± 7,8	-	20,1 ± 5,5	-	7,7 ± 2,1	-
	E157Q	12,2 ± 5,2	0,6	39,1 ± 2,4	1,9	6,9 ± 1,5	0,9
CRF02_AG	WT	26 ± 7,1	-	39,8 ± 15,6	-	7,1 ± 3,4	-
	E157Q	29,3 ± 0,9	1,1	95,5 ± 31	**2,4**	13,5 ± 1,0	1,9

En triplicate

- **Conclusions :** en présence d'une mutation E157Q :
  - EVG ne devrait pas être proposé en raison de l'augmentation modérée du FC dans le contexte CRF02_AG
  - DTG et RAL semblent envisageables ?? au vu des résultats phénotypiques
    - Toutefois 2 cas décrits de sélection *in vivo* de la mutation E157Q en cas d'échec sous RAL

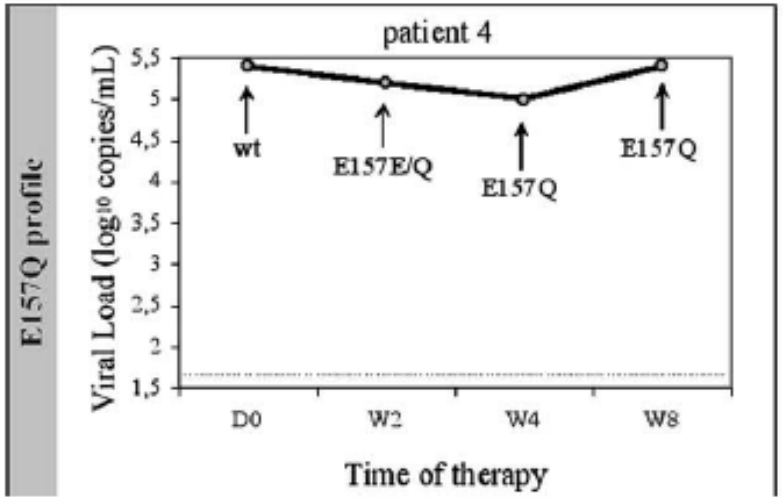
Charpentier C, J. Antimicrob Chemother 2018 ; CROI 2018, Abs. 547

Mutation E157Q sélectionnée *in vivo* sous RAL

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1351–1358 Vol. 52, No. 4
0066-4804/08/$08.00+0 doi:10.1128/AAC.01228-07

Mutations Associated with Failure of Raltegravir Treatment Affect Integrase Sensitivity to the Inhibitor In Vitro▽

Isabelle Malet,[1]* Olivier Delelis,[2] Marc-Antoine Valantin,[3,4] Brigitte Montes,[5] Cathia Soulie,[1] Marc Wirden,[1] Luba Tchertanov,[2] Gilles Peytavin,[6] Jacques Reynes,[5] Jean-François Mouscadet,[2] Christine Katlama,[3,4] Vincent Calvez,[1] and Anne-Geneviève Marcelin[1]



Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkp182
Advance Access publication 20 May 2009

Rapid selection and archiving of mutation E157Q in HIV-1 DNA during short-term low-level replication on a raltegravir-containing regimen

Jade Ghosn[1,2]*, Anne-Aurélie Mazet[3],
Véronique Avettand-Fenoel[1], Gilles Peytavin[4], Marc Wirden[5],
Jean-François Delfraissy[2] and Marie-Laure Chaix[1]

Polymorphisme E157Q dans l'intégrase : phénotype et réponse au traitement (3)

39 patients avec un virus E157Q initiant un traitement ARV à base d'INI

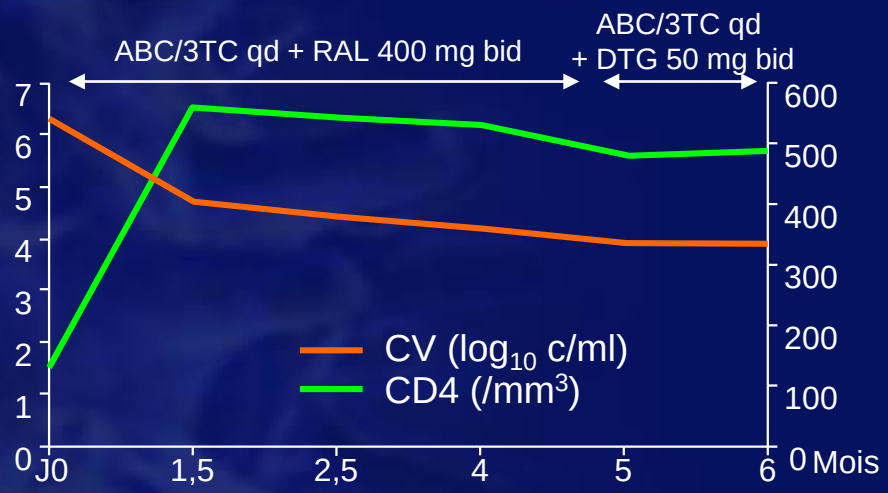
- **15 patients avec CV < 50 c/ml**
  - Maintien de la CV < 50 c/ml : n = 13
  - Blip : n = 2 (à S48 dans les 2 cas)
- **8 patients en 1ère ligne de traitement ARV (EVG, n = 5 ; RAL, n = 2 ; DTG, n = 1)**
  - CV < 50 c/ml à S24 et à S48 (n = 6)
  - 2/5 patients recevant un traitement à base d'EVG n'atteignent pas une CV < 50 c/ml à S24 (151 c/ml et 236 c/ml), changement de traitement ARV entre S24 et S48 dans les 2 cas
- **16 patients traités par ARV en échec avec CV > 50 c/ml (RAL, n = 11 ; EVG, n = 2 ; DTG, n = 3)**
  - CV < 50 c/ml à S24 : n = 8 (devenir à S48 : CV < 50 c/ml : n = 4 ; arrêt du traitement INI : n = 2 ; blip : n = 2)
  - ↘ initiale de la CV > 2,5 $\log_{10}$ c/ml à S24 mais sans atteindre < 50 c/ml (n = 4)
  - Non réponse virologique avec une ↘ de la CV < 2 $\log_{10}$ c/ml à S24 (n = 4)
  - Pas d'association entre le GSS du traitement INI et la réponse virologique

Charpentier C, J. Antimicrob Chemother 2018 ; EACS 2017, Abs. PE 6/11 ; CROI 2018, Abs. 547

Mutation intégrase E157Q et non réponse à un traitement à base de DTG

- Patient en primo-infection : virus sous-type B avec polymorphisme E157Q dans l'intégrase à J0

Suivi immuno-virologique

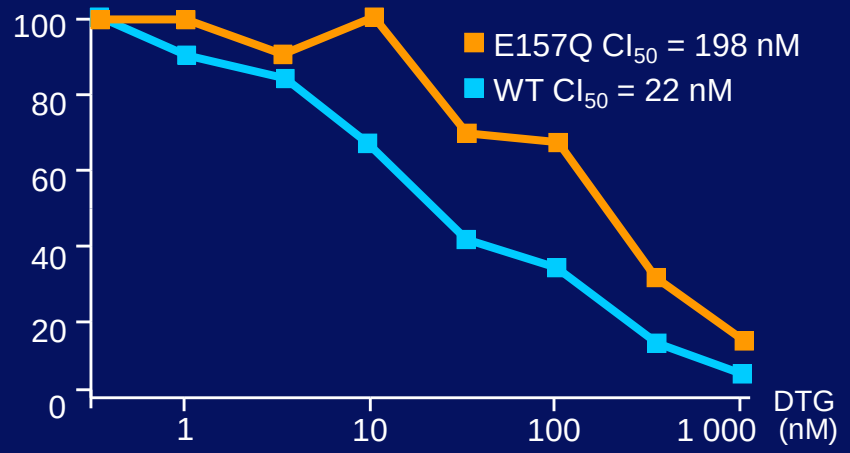


RAL C_{12h}*	1 404	-	1 635	524	-
DTG C_{12h}	-	-	-	-	3 004
ABC C_{24h}	< 10	-	18	11	< 10
3TC C_{24h}	362	-	313	225	261

*(ng/ml)

- Non réponse à un traitement à base de RAL puis de DTG malgré une bonne observance
- Pas de sélection de nouvelles mutations de résistance dans l'intégrase
- Relais ultérieur avec DRV/r : CV reste détectable à M4 (500 c/ml)

Activité de transfert de brin (% par rapport au contrôle sans DTG)



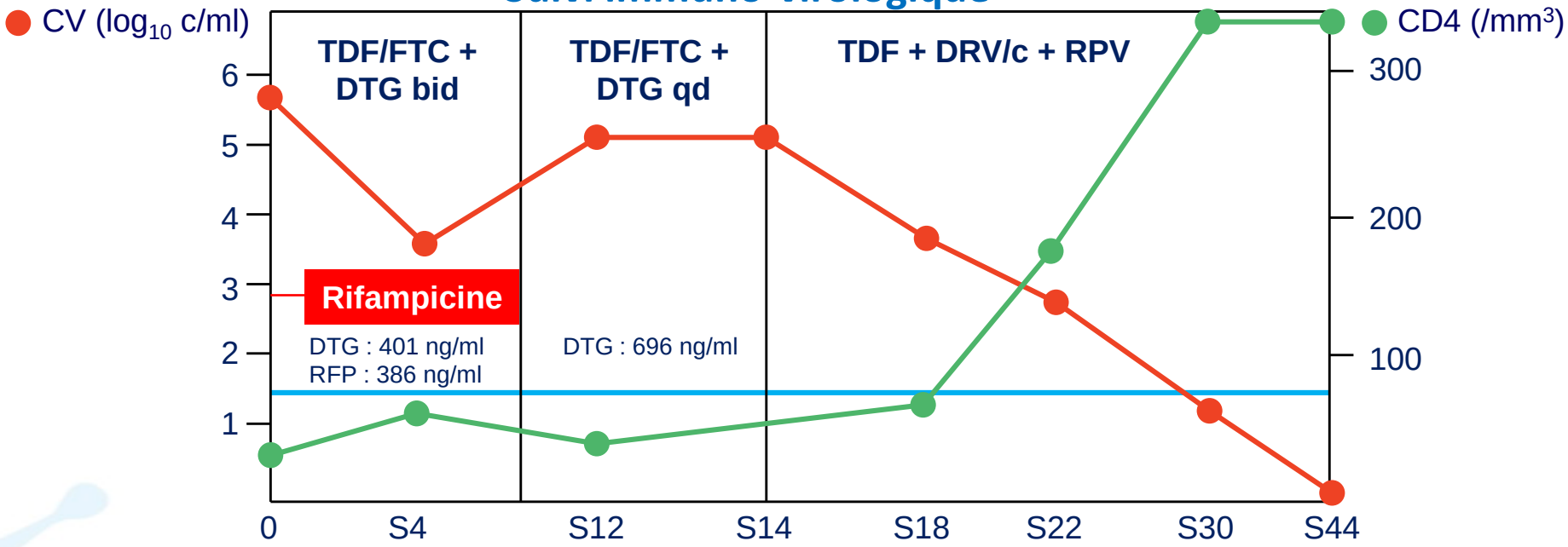
- Activité de transfert de brin du virus E157Q >> celle du virus WT
- ↗ résistance du virus E157Q à DTG avec un Fold-change = 9
- Quotient inhibiteur phénotypique du virus E157Q = 38

Danion F, IHDRW 2015, Abs. 43

Emergence des mutations E157Q et R263K à l'échec d'une 1ère ligne à base de DTG

- Femme de 49 ans, diagnostiquée VIH en 2017 lors d'une intervention chirurgicale
- CV = 457 000 c/ml, CD4 = 39/mm^3
- Rifampicine pour infection à staphylocoque de la plaie chirurgicale (arrêt à S8 pour EI)
- Séquençage haut débit TI et intégrase

Suivi immuno-virologique



	0	S4	S12	S14	S18	S22	S30	S44
Sanger	WT	Non fait	Non fait	M184V R263K	M184V R263K	Non amplifiable	Non fait	Non fait
Séquençage haut débit	WT	M184I (40 %)	M184I (42 %) M184V (57 %) E157Q (4 %) R263K (97 %)	M184I (14 %) M184V (85 %) E157Q (8 %) R263K (98 %)	K70E (8 %) M184I (6 %) M184V (45 %) E157Q (20 %) R263K (98 %)	Non amplifiable	Non fait	Non fait

Pena Lopez MJ, IAC 2018, Abs. THPEB041

Dolutegravir (DTG; S/GSK1349572) + Abacavir/Lamivudine Once Daily Statistically Superior to Tenofovir/Emtricitabine/Efavirenz: 48-Week Results - SINGLE (ING114467)

S. Walmsley[1], A. Antela[2], N. Clumeck[3], D. Duiculescu[4], A. Eberhard[5], F. Gutiérrez[6], L. Hocqueloux[7], F. Maggiolo[8], U. Sandkovsky[9], C. Granier[10], B. Wynne[10], K. Pappa[10]

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SHIONOGI ViiV Healthcare

Shionogi–ViiV Healthcare LLC

52nd Interscience Conference on Antimicrobial Agents and Chemotherapy
September 9-12, 2012; San Francisco, CA

Virology: Resistance

	DTG 50mg +ABC/3TC QD (N=414)	Atripla QD (N=419)
Subjects with PDVF	**18 (4%)**	**17 (4%)**
PDVF genotypic population	**11**	**9**
PDVF Genotypic (RT Results at Baseline and PDVF)	**9**	**9**
NRTI tmt-emergent major mutations	0	1(K65R)
NNRTI tmt-emergent major mutations	0	4 (K101E, K103N, G190A)*
PDVF Genotypic (IN Results at Baseline and PDVF)	**7**	**7**
INI-r tmt-emergent major substitution	0**	0

* n=1 with K101E, n=1 with K103N, n=1 with G190A and n=1 with K103N+G190A
**E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

INTEGRASE INHIBITORS & MUTATIONS : Index de résistance *in vitro*

Single Primary Mutations				
IN Genotype	Fold Change vs WT			
	BIC	DTG	EVG	RAL
T66I	0.3	0.4	15	1.1
T66A	0.4	0.4	11	1.2
T66K	1.4	2.1	50	9.8
E92Q	1.2	1.4	29	4.9
E92G	1.3	1.7	16	2.1
T97A	0.6	0.6	3.8	1.6
F121Y	0.4	0.6	16	5.3

Single Primary Mutations				
IN Genotype	Fold Change vs WT			
	BIC	DTG	EVG	RAL
Y143R	1.3	1.2	3.4	16.0
Y143H	0.9	1.1	1.6	2.5
Y143C	0.9	0.9	2.2	4.3
S147G	1.0	1.0	5.8	1.3
Q148R	0.7	0.6	109	28
Q148H	0.7	0.8	8.7	4.3
Q148K	0.9	0.6	119	41
N155H	1.3	1.4	44	13
R263K	1.7	1.7	4.5	1.2

EC_{50} Fold Change (FC) vs Reference Wild Type

- < 2.5 BIC
  < 4.0 DTG
  < 2.5 EVG
  < 1.5 RAL
- 2.5 to < 10 BIC
  4.0 to < 13 DTG
- ≥ 10 BIC
  ≥ 13 DTG
  ≥ 2.5 EVG
  ≥ 1.5 RAL

Margot et al.; Submitted

INTEGRASE INHIBITORS & MUTATIONS : Index de résistance *in vitro*

G140A/C/S + Q148H/R/K +/- other		
IN Genotype	Fold Change vs WT	
	DTG	BIC
G140S,Q148H	3.44	2.12
G140S,Q148H	3.52	2.03
G140S,Q148H	3.59	2.42
G140S,Q148H	3.60	1.99
G140S,Q148H	4.00	2.17
E138K,G140S,Q148H	4.73	2.46
G140S,Q148H	5.56	2.49

G140A/C/S + Q148H/R/K +/- other		
IN Genotype	Fold Change vs WT	
	DTG	BIC
E138K,G140S,Q148H	5.34	2.52
G140S,Q148H	5.46	2.92
G140S,Q148R	6.15	3.01
E138K,G140C,Q148R	8.58	5.32
L74L/M,G140A,Q148R	8.81	5.38
L74M,G140C,Q148R	9.06	8.36
L74L/M,G140A,Q148R	8.81	5.38
L74M,G140C,Q148R	9.06	8.36
E138A, G140S,Q148H	10	7.23
G140S,Q148H	11	3.81

G140A/C/S + Q148H/R/K +/- other		
IN Genotype	Fold Change vs WT	
	DTG	BIC
E138K,G140S,Q148H	13	2.62
G140S,Q148H	13	4.37
T97A,G140S,Q148H	14	7.62
T97A,G140S,Q148H	15	4.39
G140S,Q148R	17	7.05
E138K,G140A,Q148K	63	19

- **BIC has an improved resistance profile compared to DTG (p=0.037)**

EC_{50} Fold Change (FC) vs Reference Wild Type

< 2.5 BIC < 4.0 DTG < 2.5 EVG < 1.5 RAL	2.5 to < 10 BIC 4.0 to < 13 DTG	≥ 10 BIC ≥ 13 DTG ≥ 2.5 EVG ≥ 1.5 RAL

White K, et al., European Workshop HIV & Hep 2016. Rome, Italy. Poster O-01. Tsiang M, et al., AAC 2016;60:7086-7097.

B/F/TAF Phase 3 Efficacy through Week 48

Study	Population	Comparator	Efficacy	Resistance
1489[1]	Naïve	DTG/ABC/3TC	Non-inferior*	0
1490[2]	Naïve	DTG+FTC/TAF	Non-inferior*	0
1844[3]	Suppressed	DTG/ABC/3TC	Non-inferior†	0
1878[4]	Suppressed	Boosted PI + 2 NRTIs	Non-inferior†	0‡
1961[5]	Women, Suppressed	E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF	Non-inferior†	0**

In five Phase 3 trials of 1,440 patients through Week 48 B/F/TAF had non-inferior efficacy with zero emergent resistance

* For ART-naïve studies: Treatment outcomes [between treatment groups] were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.[6]
† For virologically suppressed studies: Treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region.[5,6]
‡ One boosted PI regimen participant on DRV+RTV+ABC/3TC developed ABC mutation L74V
** One E/C/F/TAF participant developed FTC mutation M184M/I/V

1. Gallant J, et al. Lancet 2017;390:2063-72.
2. Sax P, et al. Lancet 2017;390:2073-82.
3. Molina JM, et al. CROI 2018. Boston, MA. Oral 22
4. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4
5. Kityo C, et al. CROI 2018. Boston, MA. Poster 500.
6. Gilead Sciences. Biktarvy US Prescribing Information. February 2018.

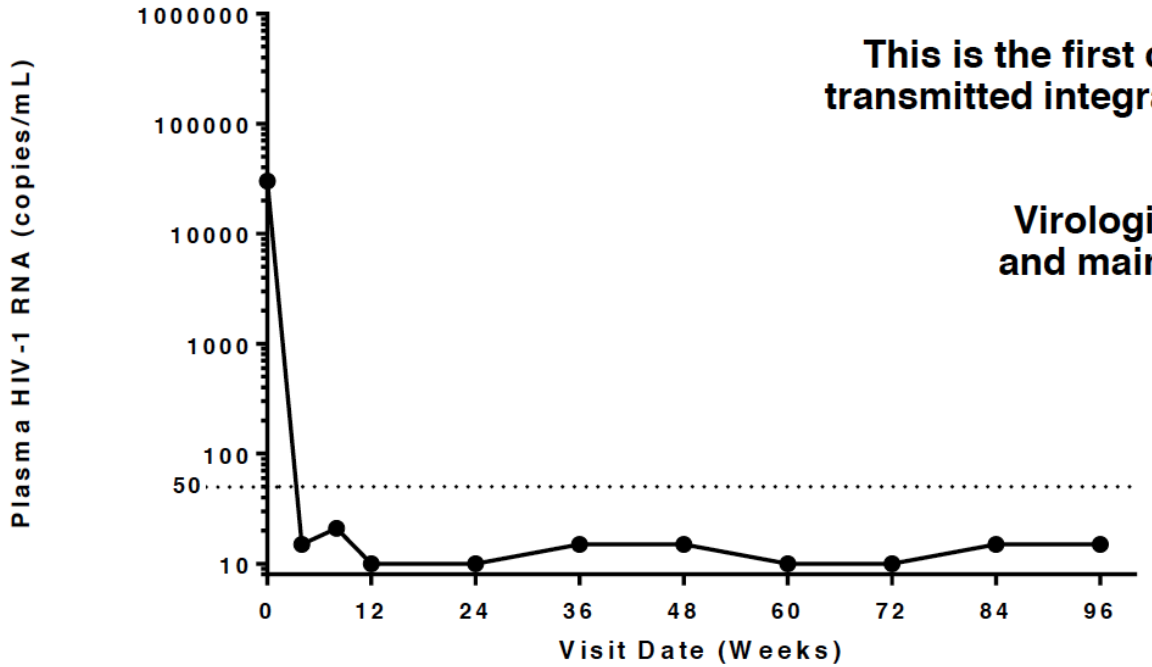
Baseline Resistance-Associated Substitutions & FDA Snapshot Outcome

	Number of Participants, n (%)	
Resistance Class	**B/F/TAF n=634**	**Week 48 HIV-1 RNA <50 c/mL**
With Data	**634 (100%)**	**576/634 (91%)**
Primary INSTI-R	6 (1.0%)	6/6 (100%)
T97A	5 (0.8%)	5/5 (100%)
Q148H (+G140S)	1 (0.2%)	1/1 (100%)
Primary NRTI-R	16 (2.5%)	14/16 (88%)
Any TAM	16 (2.2%)	14/16 (88%)
Primary NNRTI-R	76 (12%)	68/76 (90%)
K103N/S	41 (6.5%)	38/41 (93%)
E138A/G/K/Q	24 (3.8%)	21/24 (88%)
Primary PI-R	16 (2.5%)	15/16 (94%)

B/F/TAF Patient with Transmitted Resistance: Baseline

	DRUG			PHENOSENSE® SUSCEPTIBILITY		ASSESSMENT	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing ← Drug Susceptibility → Decreasing (.1 / 1 / 10 / 100)	Drug	
INI	Bictegravir	Bictegravir	*(2.5 – 10)*	2.14		BIC	Sensitive
INI	Dolutegravir	Tivicay	*(4 - 13)*	4.45		DTG	Partially Sensitive
INI	Elvitegravir	Vitekta	*(2.5)*	>MAX		EVG	Resistant
INI	Raltegravir	Isentress	*(1.5)*	>MAX		RAL	Resistant

Lower Clinical Cutoff (in bold)
Upper Clinical Cutoff (in bold)
Biological Cutoff
Hypersusceptibility Cutoff
Sensitive
Partial Sensitivity
Resistance



This is the first case of an ART-naïve patient with transmitted integrase resistance (G140S + Q148H) on B/F/TAF

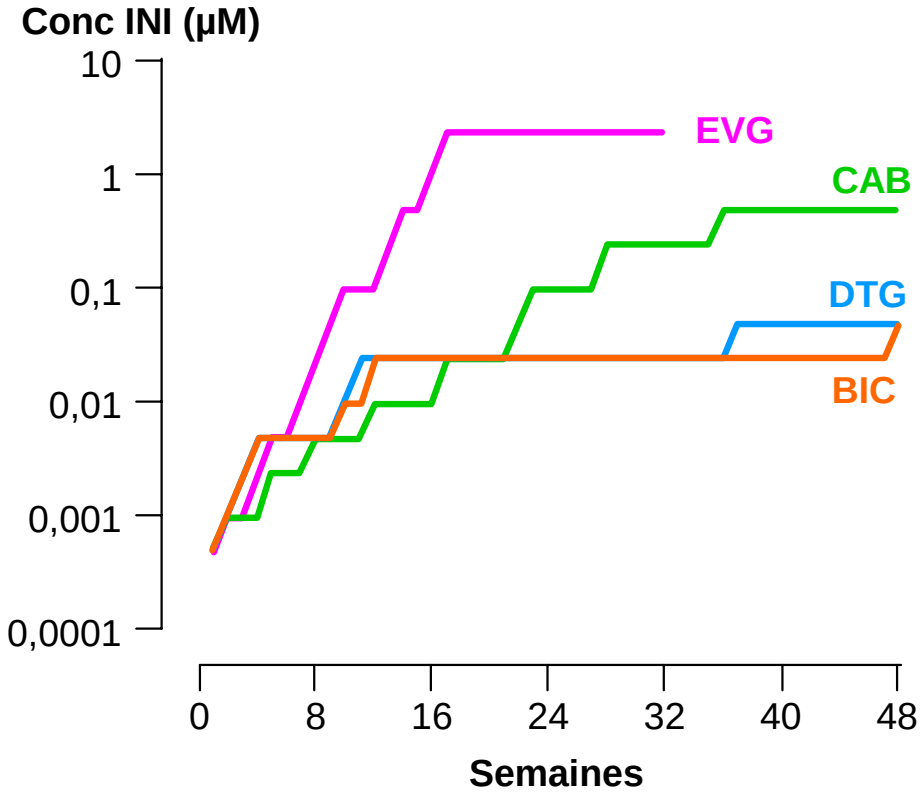
Virologic suppression was rapid and maintained from Week 4 to 96

Baseline Genotype:
NRTI: K70R
NNRTI: K103N
PI: *none*
INSTI: G140S, Q148H

Sélection de résistance in vitro avec les INI selon le sous-type de VIH (1)

- Expériences de **sélections de résistance in vitro à EVG, CAB, BIC et DTG**

Délai dans l'acquisition de mutations de résistance aux INI (à partir d'un sous-type B)



Brenner B, CROI 2018, Abs. 549

Protocol-Defined Virologic Failure

	744 total n=181	EFV n=62
Subjects with PDVF during Induction	**3* (2%)**	**3 (5%)**

*1 subject per 744 dose
No NRTI, NNRTI or INI treatment-emergent mutations

	744 total n=160	EFV n=47
Subjects with PDVF during Maintenance	**2** (1%)**	**1 (2%)**
IN genotypic results at BL and time of PDVF	1	1
INI-r mutations	**1**	**0**
PR/RT genotypic results at BL and time of PDVF	2	1
NRTI-r mutations	**0**	**0**
NNRTI-r mutations	**1**	**0**

**744 10 mg – treatment emergent INI (Q148R) and NNRTI (E138Q) at W48; 744 FC = 3; RPV FC = 2
- 744 and RPV concentrations <50% of expected; extreme calorie restricted diet W40-W48

**744 30 mg – PDVF at W36; no treatment-emergent mutations

PDVF: <1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4 **OR** confirmed HIV-1 RNA ≥200 c/mL at or after Week 16 or after prior suppression to <200 c/mL

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Conclusions

- Résistance primaire (TDR) suit l'évolution des traitements ARV
  - Plus faible prévalence de TDR en Europe versus US : utilisation plus large des IPs probable
  - Apparition (rare) de la R primaire aux INIs après 10 ans d'utilisation
- Augmentation des sous types Non-B
  - Impact des polymorphismes pour les INIs ??? Ex mutation 157, 263 ....
- Test & Treat
  - NNRTI : pas envisageable au vu des chiffres de TDR
  - IP: pas de problème virologique trithérapie, bithérapie
  - INI : ?
    - RAL , EVG & CAB : non
    - DTG & BIC : à évaluer
      - Fast Start : BIC/TAF/FTC (15 centres 2019) IP Dr J Ghosn Bichat-Claude Bernard
      - DTG/3TC?
      - DTG/RPV non

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Gilles Peytavin

Agence autonome de l'Inserm

Sélection de résistance in vitro avec les INI : BIC vs DTG

- **Expériences de pression de sélection à partir de virus porteurs de mutations aux INI :** E92Q, Q148R, R263K, N155H

Profils génotypiques et phénotypiques des virus sélectionnés in vitro après passages multiples

Virus J0	Mutations intégrase sélectionnées par BIC	FC BIC	FC DTG	CR	Mutations intégrase sélectionnées par DTG	FC BIC	FC DTG	CR
E92Q	E92Q-G140G/E-M154M/I	0,9	1,7	2 %	E92Q	1,1	1,4	13 %
Q148R	Q148R	0,6	0,6	4,9 %	G52G/E-E138K-Q148R-H171H/Y	1,4	1,4	3,5 %
R263K	R263K	1,7	1,6	NR	R263K	1,6	1,8	7,5 %
N155H	L45Q-N155H	1,5	1,5	59 %	S147N-N155H	NR	NR	NR

CR : capacité réplicative virale, NR : non réalisé

  - Mutant E92Q-G140E : FC BIC > 100, FC DTG > 200 et CR < 1 %

- **Conclusions**
  - Identification de 2 profils de résistance à BIC : S153F/Y (FC < 2) et E92Q-G140E (FC > 100 mais CR < 1 % → non présent in vivo ?)
  - L'ensemble des virus sélectionnés sous pression d'INI reste sensible à BIC ou avec une faible ↗ du FC

Andreatta K, CROI 2018, Abs. 546

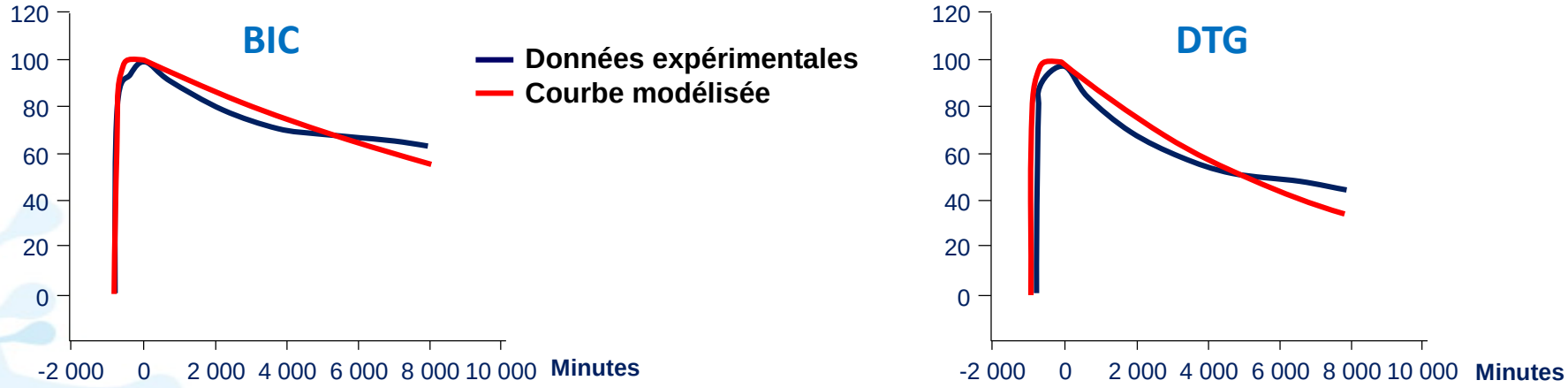
Constante de dissociation du bictégravir (BIC)

- **Objectif :** décrire la cinétique de dissociation in vitro du BIC et des autres II à partir des complexes intégrase VIH-1/ADN

Demi-vie apparente de dissociation des II à partir des complexes intégrase VIH-1/ADN

II	Demi-vie (h)
BIC	135 ± 20
DTG	79 ± 13
RAL	14 ± 3
EVG	3,6 ± 0,7

Suivi de la dissociation de l'II des complexes intégrase VIH-1/ADN (% liaison)



- Parmi les 4 II testés, BIC présente la plus longue demi-vie de dissociation à partir des complexes intégrase VIH-1/ADN

White K, HIV Glasgow 2016, Abs. P025

Switch pour BIC/FTC/TAF : analyse de la résistance

- Essais GS-US-380-1878 et 1844 : switch chez des patients avec CV < 50 c/ml pour BIC/FTC/TAF
  - Echec virologique (CV ≥ 50 c/ml, ITT snapshot) à S48 = 1,4 %
  - Aucune émergence de résistance
  - Maintien du succès virologique (CV < 50 c/ml) à S48 chez les patients avec mutations de résistance archivées (génotype ADN VIH PBMC au switch)

Mutation de résistance à FTC/TAF	35/36 (97 %)
K65K/N	5/5
M184V/I/T	18/18
M184 + autre(s) mutation(s) INTI	12/13
≥ 2 TAM sans M184V	4/4

  - Parmi les 170 patients avec génotype ADN sur l'intégrase au switch, présence de polymorphisme aux INI chez 87 patients (T97A, n = 1, M50I = 30 et S119P/R/T = 54, E157K/Q = 8)
    - Echec virologique à S48 = 4/87 patients avec polymorphisme à J0 dont 2 avec S119P/T et 1 avec M50I

Andreatta K, CROI 2018, Abs. 506