associazione NADIR onlus

Giovedì 24 Settembre 2015

PROGRAMMA SEMINARIO 2015

Presso Hotel Michelangelo, Piazza Luigi di Savoia 6 - Milano

INNOVAZIONE NELLA TERAPIA ANTIRETROVIRALE
GLI INIBITORI DELLE INTEGRASI: I PROTAGONISTI DI UNA NUOVA ERA
Sfide e opportunità per le persone con HIV

Eliminare il fallimento

Antonella Castagna

IRCCS San Raffaele

Significant Reduction in HIV Virologic Failure During a 15-Year Period in a Setting With Free Healthcare Access

Constance Delaugerre,[1,2,3,a] Jade Ghosn,[4,5,a] Jean-Marc Lacombe,[6,7] Gilles Pialoux,[8] Lise Cuzin,[9] Odile Launay,[10] Amélie Menard,[11] Pierre de Truchis,[12] and Dominique Costagliola[6,7]; for the FHDH-ANRS CO4[b]

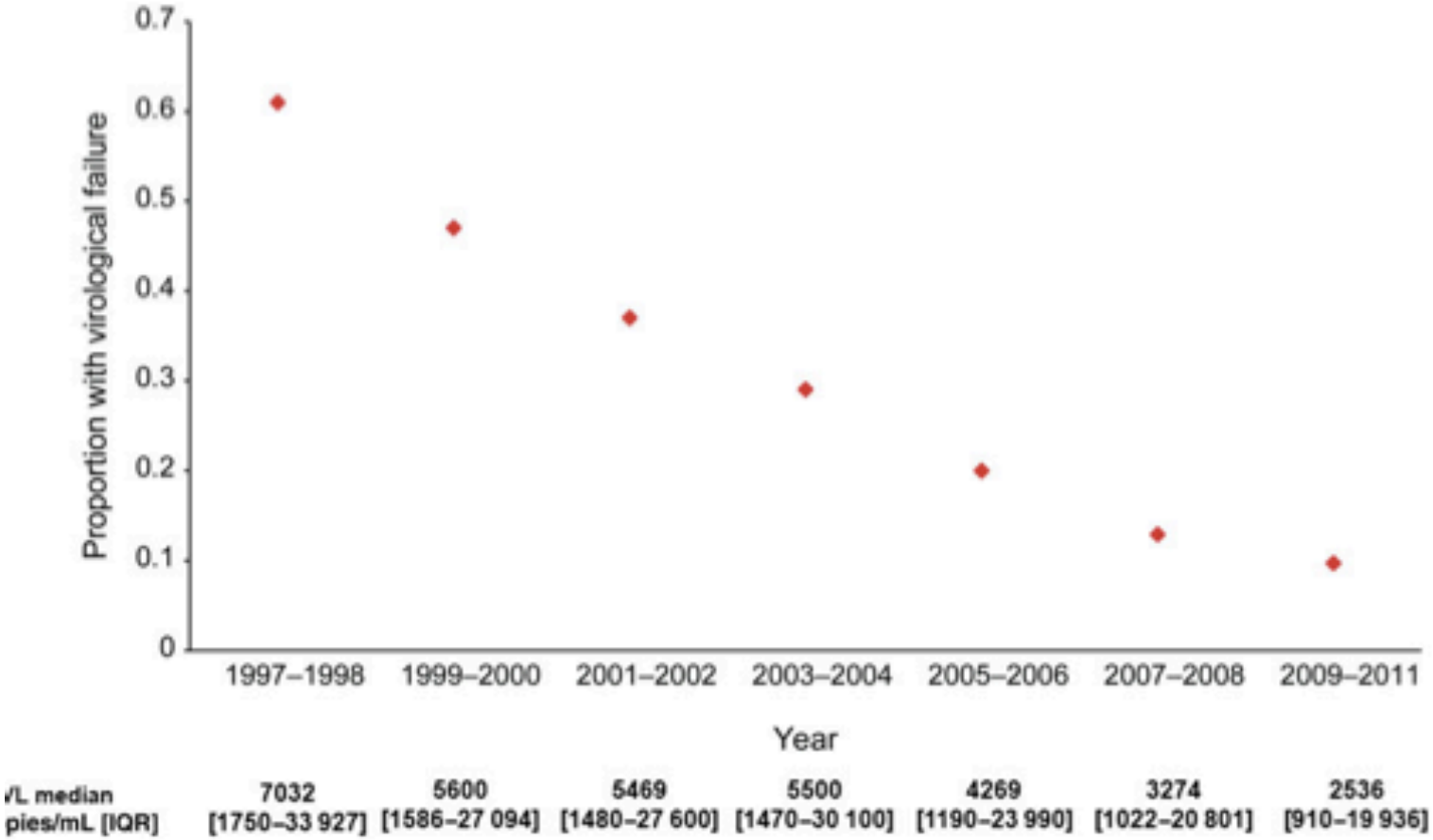
Patients followed up between 1997 and 2011, who received ART for at least 6 months. In case of treatment interruption, viremia follow-up was censored at the time of treatment discontinuation and resumed 6 months after treatment resumption.

VF was defined as 2 consecutive plasma HIV-RNA values (pVL) >500 copies/mL at least 6 months after treatment initiation; or as 1 value >500 copies/mL >6 months after treatment initiation, followed by a treatment switch (ie, addition or re- placement of at least 1 drug).

CID 2015

Proportion with virological failure

81738 pts, FU 9.4 years



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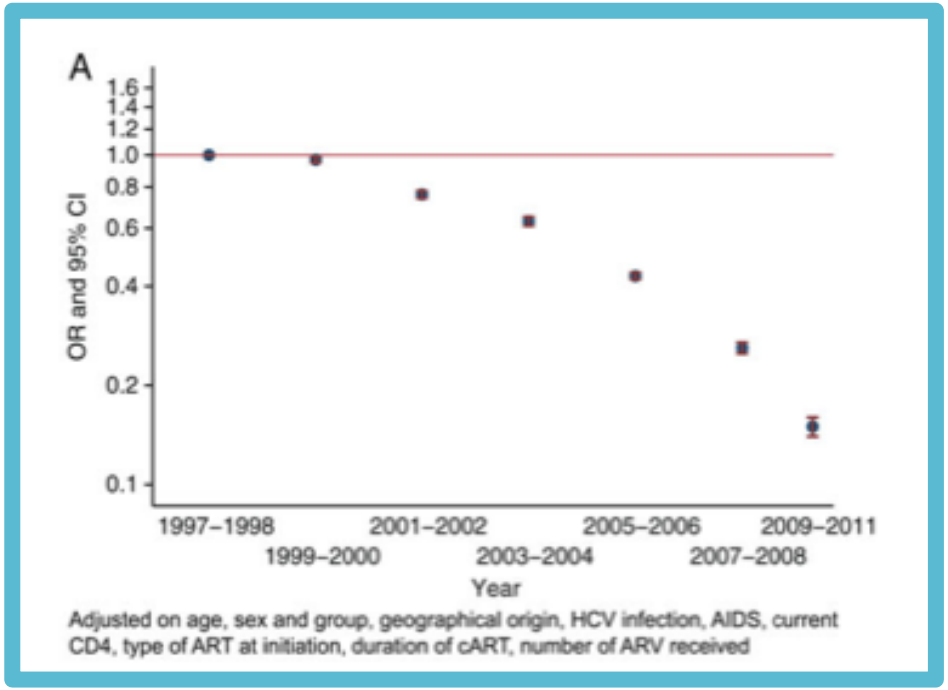

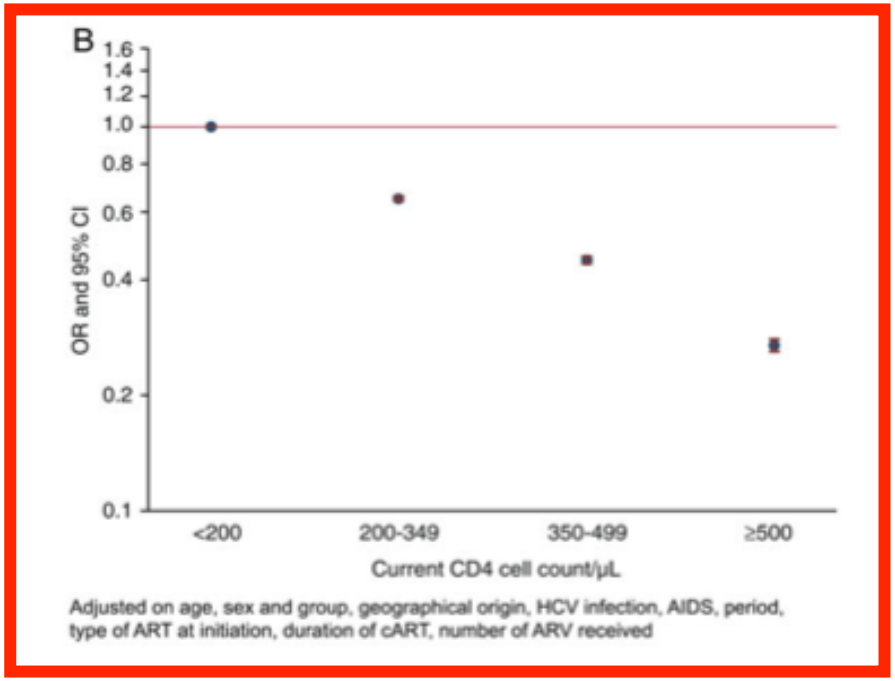

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Proportion with virological failure

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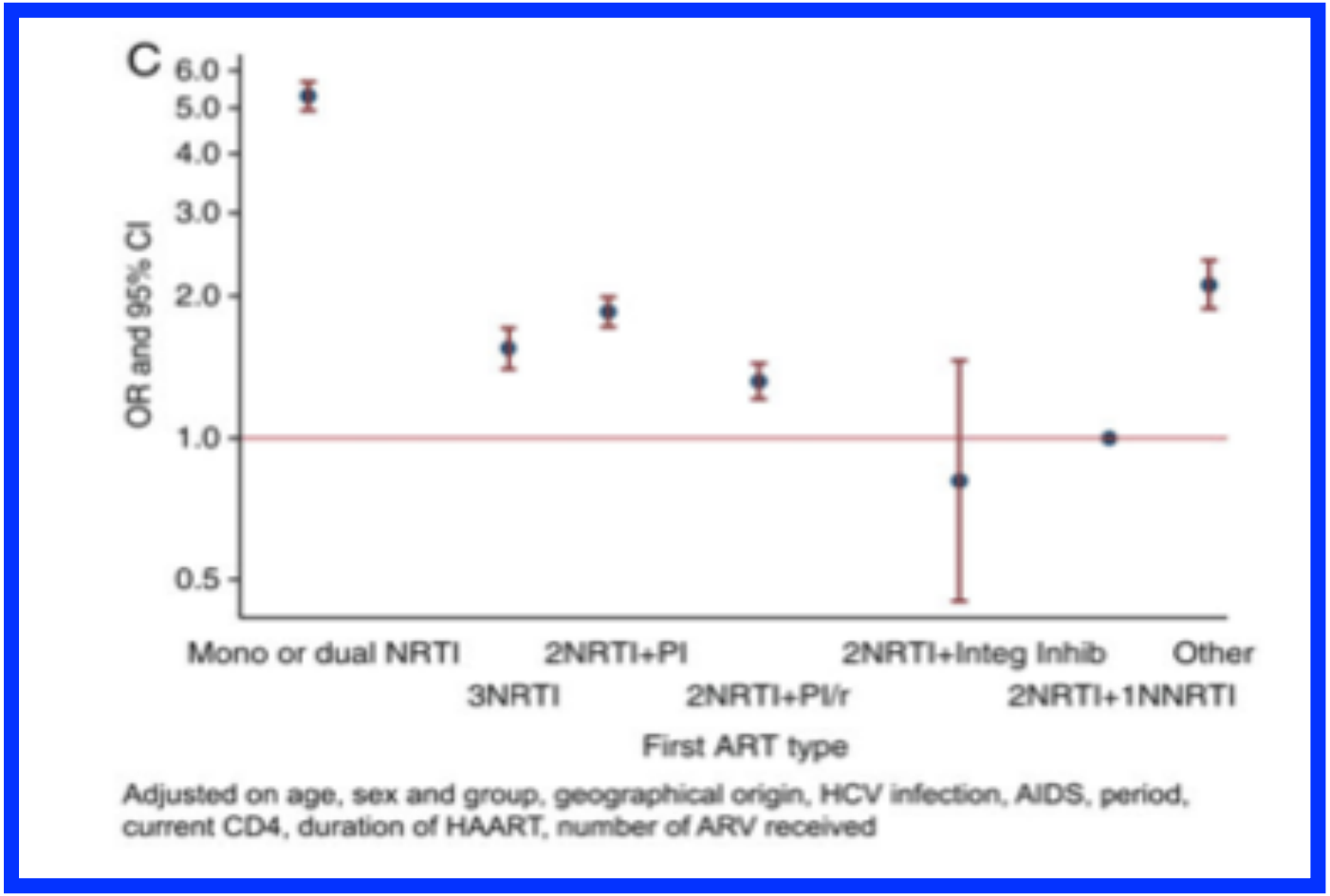

BRIEF REPORT

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

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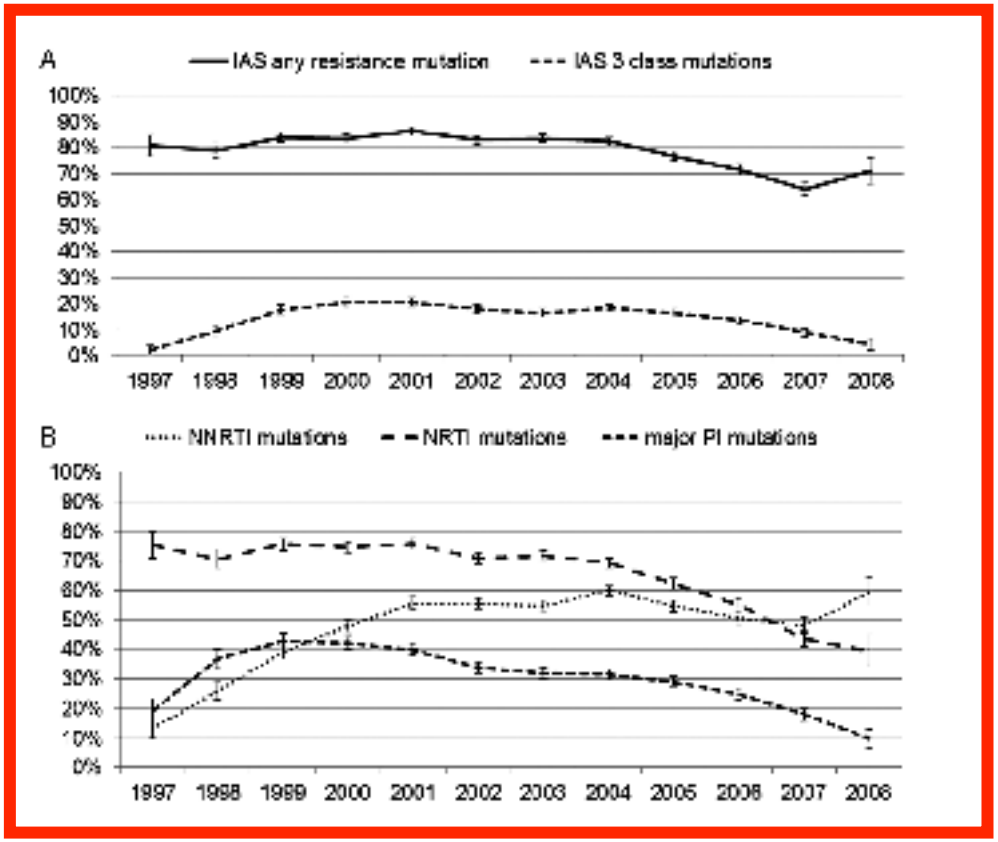
HIV-1 drug resistance represents a major obstacle to infection and disease control. This retrospective study analyzes trends and determinants of resistance in antiretroviral treatment (ART)-exposed individuals across 7 countries in Europe. Of 20 323 cases, 80% carried at least one resistance mutation: 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.



Gestire il fallimento

- Paziente di 42 anni, infezione da HIV nota dal 1998
- Prima visita OSR, luglio 2015: CD4 502 (16%) cell/$mm^{3;}$ HIV-RNA 2357 copie/ml
- Terapia attuale con ABC/3TC,DRV/r, ETV
- Prima linea di trattamento introdotta 17 anni fa.
- Multipli cambi di terapia, ripetuti **fallimenti virologici**, aderenza subottimale.
- **Precedente utilizzo RAL**

Ulteriori esami:

G2P FPR **57%**
Genotipo: **?**

PI Major Resistance Mutations: V32I, M46L,I54L, L76V, I84V
PI Minor Resistance Mutations: L10F, L33F, A71V

atazanavir (ATV)	High-level resistance
darunavir (DRV)	High-level resistance
fosamprenavir (FPV)	High-level resistance
indinavir (IDV)	High-level resistance
lopinavir (LPV)	High-level resistance
nelfinavir (NFV)	High-level resistance
saquinavir (SQV)	High-level resistance
tipranavir (TPV)	Intermediate resistance

Integrase Inhibitors Mutations = Y143C, T97A

raltegravir (RAL)	High-level resistance
elvitegravir (ELV)	Low-level resistance

NRTI Resistance Mutations: M41L, L74V, M184V, L210W, T215Y

NNRTI Resistance Mutations: L100I, E138R

Nucleoside RTI

lamivudine (3TC)	High-level resistance
abacavir (ABC)	High-level resistance
zidovudine (AZT)	High-level resistance
stavudine (D4T)	High-level resistance
didanosine (DDI)	High-level resistance
emtricitabine (FTC)	High-level resistance
tenofovir (TDF)	Intermediate resistance

Non-Nucleoside RTI

efavirenz (EFV)	Intermediate Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	Intermediate Resistance
rilpivirine (RPV)	High-level resistance

Dolutegravir in patients with RAL/EVG resistance: VIKING-3 results

Primary INI mutations at BL	N	Mean HIV-1 RNA (log10) change from BL (SD) at Day 8	% with < 50c/mL HIV-1 RNA at Week 24
Total	183	-1.4 (0.61)	69%
No primary mutations	60	-1.6 (0.55)	78%
T66	1	-1.9	100%
Y143	28	-1.7 (0.42)	75%
N155	33	-1.4 (0.51)	88%
≥ 2 Primary mutations	8	-1.4 (0.76)	50%
Q148 + 1 secondary mutation	32	-1.1 (0.51)	59%
Q148 + ≥2 secondary mutations	21	-1.0 (0.81)	24%

In multivariate analysis, Q148 + ≥ 2 mutations and increasing DTG FC were each highly correlated with smaller reductions in HIV-RNA ($p<0.001$)

Vavro CL, et al. IWDR 2013 Toronto: Abstract 29
Castagna A et al. JID 2014

Linee Guida Italiane

	Modifica ART	Forza/Evidenza
HIV-RNA 1-49 copie/mL	Non indicata	
HIV-RNA ≥50 ≤ 200 copie/mL, blip viremici isolati, intervallati da determinazioni a viremia negativa, GND, AMAR **HIV-RNA > 200 copie /mL, isolata, seguita da determinazioni a viremia negativa, GND, AMAR**	Non indicata	
HIV-RNA > 200 copie/mL, saltuariamente, alternata a viremie negative, GND, AMAR	Opzionale	**CII**
HIV-RNA > 200 copie/mL stabilmente (almeno 2 determinazioni consecutive) GND, AMAR	Moderatamente raccomandata	**BII**
HIV-RNA > 200 copie/mL stabilmente (almeno 2 determinazioni consecutive) o PMAR con viremia ≥50 ≤ 200 copie/mL	Fortemente raccomandata	**AII**

GND: genotipo non determinabile
AMAR: assenza di mutazioni associate a resistenza
PMAR: presenza di mutazioni associate a resistenza

Virologic Failure Following Persistent Low-level Viremia in a Cohort of HIV-Positive Patients: Results From 12 Years of Observation

Claudie Laprise,[1] Alexandra de Pokomandy,[2,3] Jean-Guy Baril,[4] Serge Dufresne,[4] and Helen Trottier[1]

[1]Department of Social and Preventive Medicine, University of Montreal, Sainte-Justine Hospital Research Center, [2]Department of Family Medicine, McGill University, [3]Chronic Viral Illnesses Service, McGill University Health Center, and [4]Clinique Médicale du Quartier Latin, Montreal, Canada

Background. The current goal of antiretroviral therapy (ART) is to maintain a suppressed human immunodeficiency virus (HIV) viral load below limits of assay detection. When viral loads remain in low-level viremia (LLV), especially between 50 and 200 copies/mL, the best management and clinical consequences remain unknown. Our objective was to study the long-term impact of persistent LLV on the subsequent risk of virologic failure in a cohort of people living with HIV in Montreal, Canada.

Methods. We compared the cumulative incidence of subsequent virologic failure (defined as an HIV RNA viral load of >1000 copies/mL) in patients receiving ART for at least 12 months by following 4 persistence categories (<50, 50–199, 200–499, and 500–999 copies/mL) for 6, 9, or 12 months, using Kaplan-Meier analysis. The association between subsequent virologic failure and persistence status were estimated using a Cox proportional hazards model.

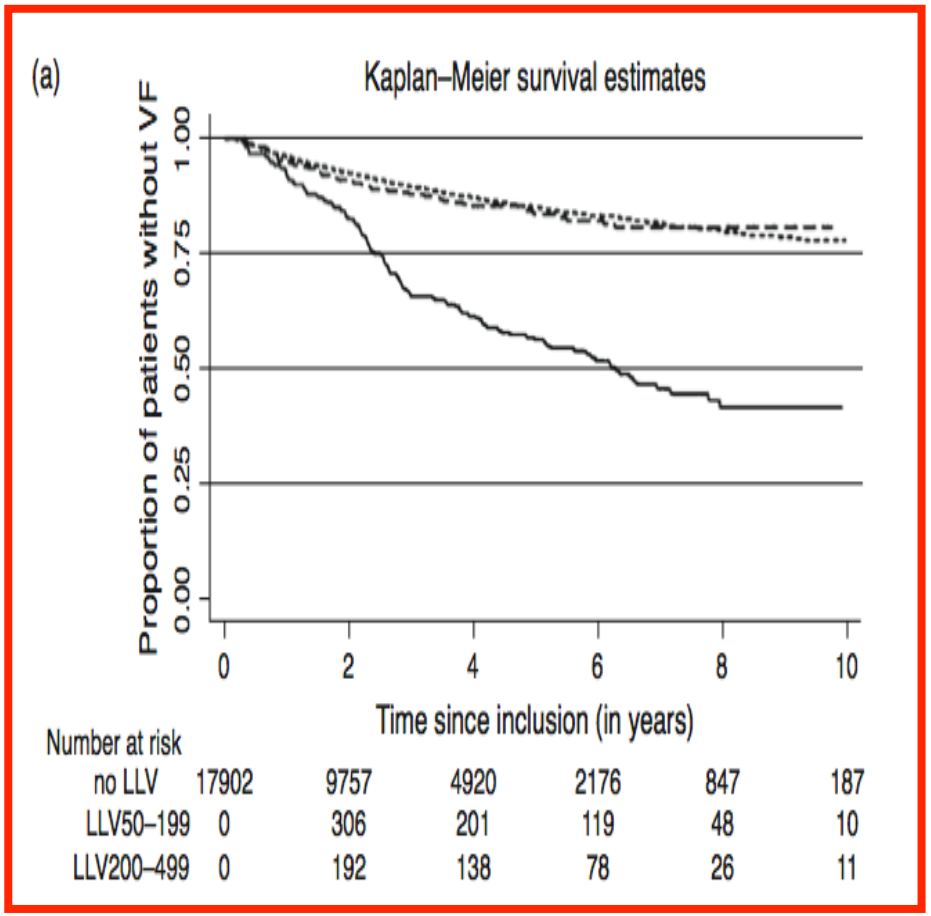
Results. The cumulative incidence of virologic failure 1 year after having maintained a LLV for 6 months was 22.7% (95% confidence interval [CI], 14.9–33.6) for 50–199 copies/mL, 24.2% (95% CI, 14.5–38.6) for 200–499 copies/mL, and 58.9% (95% CI, 43.1–75.2) for 500–999 copies/mL, compared with 6.6% (95% CI, 5.3–8.2) for an undetectable HIV RNA viral load. Even after adjustment for potential confounders, a persistent LLV of 50–199 copies/mL for 6 months doubled the risk of virologic failure (hazard ratio, 2.22; 95% CI, 1.60–3.09), compared with undetectable viral loads for the same duration. Similar results have been found for persistent LLV of 9 or 12 months.

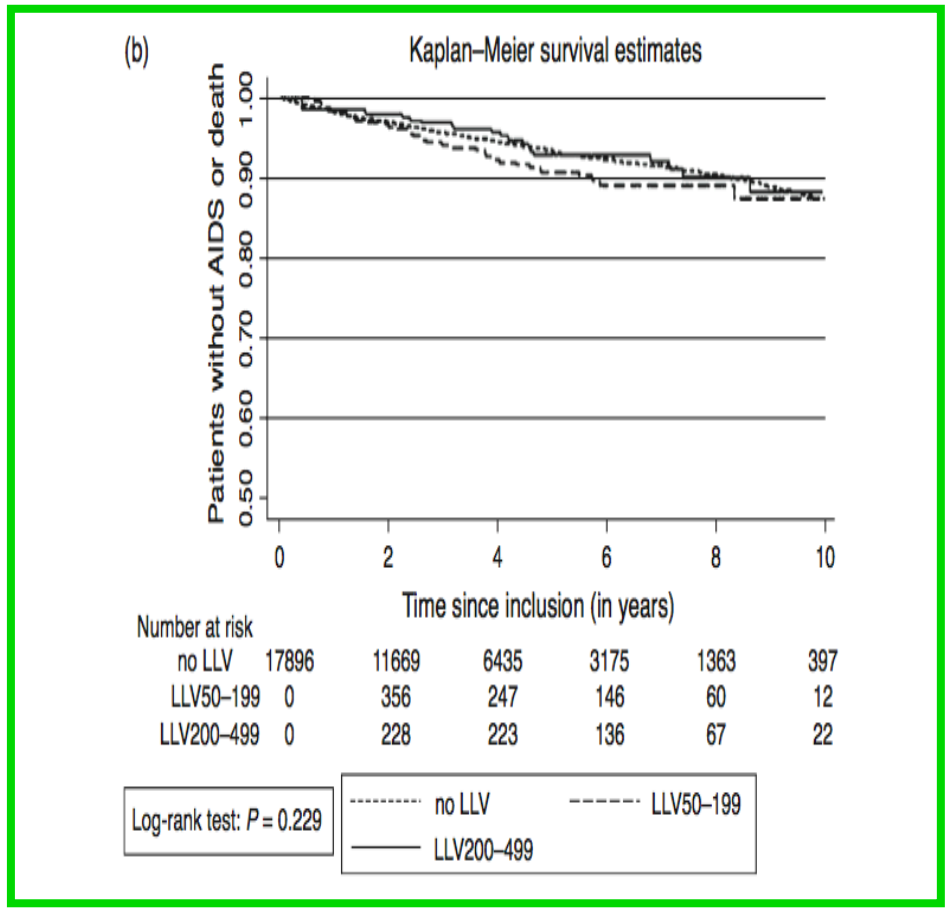
Conclusions. In this cohort, all categories of persistent LLV between 50 and 999 copies/mL were associated with an increased risk of virologic failure. The results shed new light for the management of patients with LLV, especially with regard to LLV of 50–199 copies/mL.

Keywords. cohort study; HIV; viral load; virological failure; low-level viremia.

Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients

The Antiretroviral Therapy Cohort Collaboration (ART-CC)*





Esami CD4

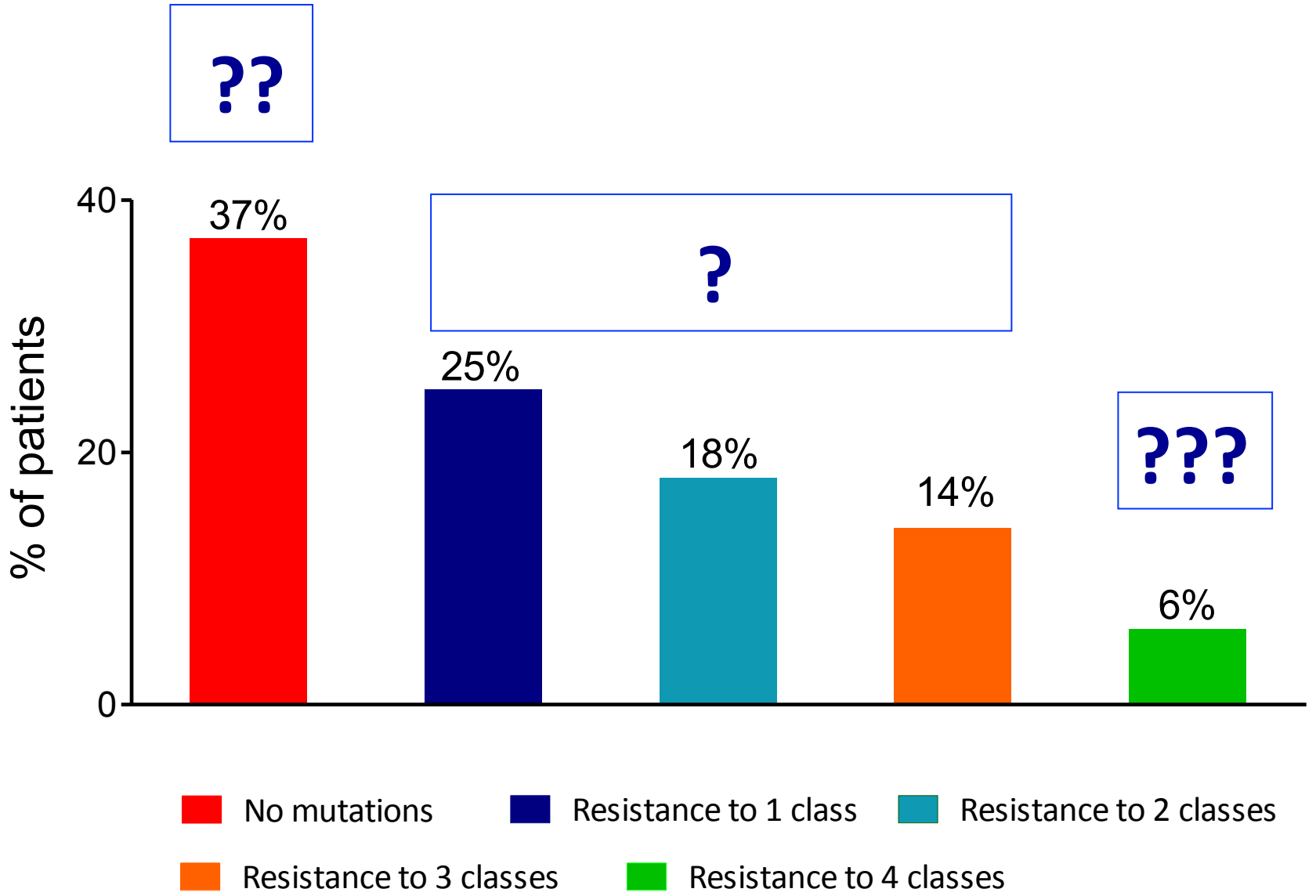
Date	Valori	Terapia
2014		
20/01/2014	**316** Cell./?L [493 -1666]	ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG PREZISTA*400MG 60 CPR
2013		
19/11/2013	**257** Cell./?L [493 -1666]	PREZISTA*600MG 60 CPR ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG
26/08/2013	**227** Cell./?L [493 -1666]	PREZISTA*600MG 60 CPR ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG
24/06/2013	**148** Cell./?L [493 -1666]	PREZISTA*600MG 60 CPR ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG
03/06/2013	**50** Cell./?L [493 -1666]	PREZISTA*600MG 60 CPR ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG
23/04/2013	**32** Cell./?L [493 -1666]	naive*

Cosimo 27.4.1988

Esami VIREMIA HIV

Date	Valori	Terapia
2014		
20/01/2014	**72** Copie/mL [-]	ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG PREZISTA*400MG 60 CPR
2013		
19/11/2013	**36** Valore compreso tra 1-37 Copie/mL [-]	PREZISTA*600MG 60 CPR ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG
26/08/2013	**92** Copie/mL [-]	PREZISTA*600MG 60 CPR ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG
24/06/2013	**291** Copie/mL [-]	PREZISTA*600MG 60 CPR ISENTRESS*400MG 60CPR NORVIR*100MG 30CPR RIV. TRUVADA*30CPR 200/245MG
23/04/2013	**586600** Copie/mL [-]	naive*

October 2014 - April 2015 – GRTs from 52 HIV-1 failing subjects



OSR Database, data on file May 2015

GA Sandra

Date	Valori	Terapia
2014		
01/02/2014	**368** Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
11/01/2014	**1009** Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
2013		
14/09/2013	**2069** Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
23/03/2013	**0.9** Negativo [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
2012		
06/11/2012	**0.9** Negativo [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
23/06/2012	**0.9** Negativo [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
25/02/2012	**0.9** Negativo [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
2011		
01/10/2011	**0.9** Negativo [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
07/05/2011	**0.9** Negativo [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
15/01/2011	**36** Valore compreso tra 1-37 Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV
2010		
17/08/2010	**36** Valore compreso tra 1-37 Copie/mL [-]	TRUVADA*30CPR 200/245MG CELSENTRI*300MG 60CPR RIV

FPR 38.7, no RTI major mutations

MAJOR ARTICLE HIV/AIDS

Resistance to HIV Integrase Strand Transfer Inhibitors Among Clinical Specimens in the United States, 2009–2012

Christopher B. Hurt,[1] Joseph Sebastian,[2] Charles B. Hicks,[3] and Joseph J. Eron[1]

[1]Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, [2]Laboratory Corporation of America, Research Triangle Park, and [3]Division of Infectious Diseases, Duke University, Durham, North Carolina

Background. Data on integrase inhibitor resistance come primarily from clinical trials and in vitro studies. We examined results of all clinically indicated integrase genotypic resistance tests (GRTs) performed at a US national referral lab from 2009 through 2012.

Methods. Integrase sequences and demographic data were compiled with paired protease–reverse transcriptase (PR-RT) GRT results, when available. Analyses utilized the Stanford HIV Drug Resistance Database. "Major" integrase mutations included T66AIK, E92QV, F121Y, Y143CHR, S147G, Q148HKR, and N155H; multiple accessory mutations were also assessed.

Results. Among 3294 sequences from 3012 patients, 471 patients had viruses with ≥1 raltegravir or elvitegravir resistance mutation (15.6%). Q148 and N155 pathways were equally represented (both n = 197); 84 had Y143 mutations. Q148 rarely occurred without accessory mutations (n = 3). Among 224 patients with serial integrase GRTs, 22 with baseline wild-type acquired a major mutation, after a median 224 days between tests (interquartile range, 148–335 days). Major mutations were observed to persist up to 462 days. Most (62%) had paired PR-RT results. Patients with integrase-resistant viruses were older and more likely to have PR-RT mutations (both $P < .001$). Among those with PR-RT data, 42 patients had 4-class resistance (2.3%). Sex, geographic region, and test year were not associated with integrase resistance. High-level dolutegravir resistance was predicted in 12% of patients with raltegravir- or elvitegravir-resistant viruses (2% of all patients).

Conclusions. Approximately 1 in 6 US patients undergoing integrase GRT for clinical decision making harbors significant resistance, with Q148 and N155 pathways equally common. Dolutegravir is likely to have full or partial activity against most variants observed.

Keywords. human immunodeficiency virus; antiretroviral resistance; raltegravir; elvitegravir; dolutegravir.

Caso Clinico 1

- Paziente di 37 anni,MSM
- Prima linea di trattamento con **TDF/FTC + RAL** introdotta 2 anni fa.
- Assenza di mutazioni di farmacoresistenza al genotipo pre HAART
- All'impostazione della terapia: CD4 435 (21%), HIV-RNA 107.300 copie/ml
- Viremia sempre soppressa durante la terapia**, aderenza buona** ma non ottima.
- All'ultimo controllo: HIV-RNA 1400cp/ml

Genotipo virale:

RT: **M184V**
Integrasi: **N155H**
PRO: nessuna mutazione

Caso Clinico 2

- Paziente di 31 anni.
- Prima linea di trattamento con **TDF/FTC/EVG/cobi** introdotta 8 mesi fa
- Assenza di mutazioni di farmacoresistenza al genotipo pre HAART
- All'impostazione della terapia: CD4 339 (18%), HIV-RNA 207.300 copie/ml
- Viremia sempre soppressa a partire dalla settimana 8**, aderenza buona**.
- All'ultimo controllo: HIV-RNA 1156 cp/ml

- M184V, Y143R
- M184V, E92Q
- K65R, N155H
- K65R, R263K

DHHS Guidelines 2012: Preferred Regimens for ARV naive patients

Class	Regimen
INSTI-based	Raltegravir + Tenofovir-Emtricitabine (**AI)**
NNRTI-based	Efavirenz-Tenofovir-Emtricitabine (**AI)**
PI-based	Atazanavir + Ritonavir + Tenofovir-Emtricitabine (**AI)** Darunavir (qd) + Ritonavir + Tenofovir-Emtricitabine (**AI)**

DHHS Guidelines 2015: Preferred Regimens for ARV naive patients

Class	Regimen
INSTI-based	Raltegravir + Tenofovir-Emtricitabine (**AI)** Dolutegravir/Abacavir/Lamivudine[a] **(AI)** Dolutegravir + Tenofovir-Emtricitabine **(AI)** Elvitegravir/cobi/Tenofovir/Emtricitabine[b] **(AI)**
PI-based	Darunavir (qd) + Ritonavir + Tenofovir-Emtricitabine (**AI)**

a. only for patients who are HLA-B*5701 negative
b. only for patients with pre-treatment estimated CrCl ≥70 mL/min

A Multicenter Study of Initiation of Antiretroviral Therapy and Transmitted Drug Resistance in Antiretroviral-Naive Adolescents and Young Adults With HIV in New York City

Christina Gagliardo,[1] Ava Brozovich,[1] Jeffrey Birnbaum,[2] Anita Radix,[3] Marc Foca,[1] John Nelson,[1] Lisa Saiman,[1,4] Michael Yin,[1] Elektra Carras-Terzian,[1] Emily West,[1] and Natalie Neu[1]

[1]Columbia University Medical Center, New York, [2]SUNY Downstate Medical Center, Brooklyn, [3]Callen-Lorde Community Health Center, New York, and [4]Department of Infection Prevention and Control, NewYork–Presbyterian Hospital, New York, New York

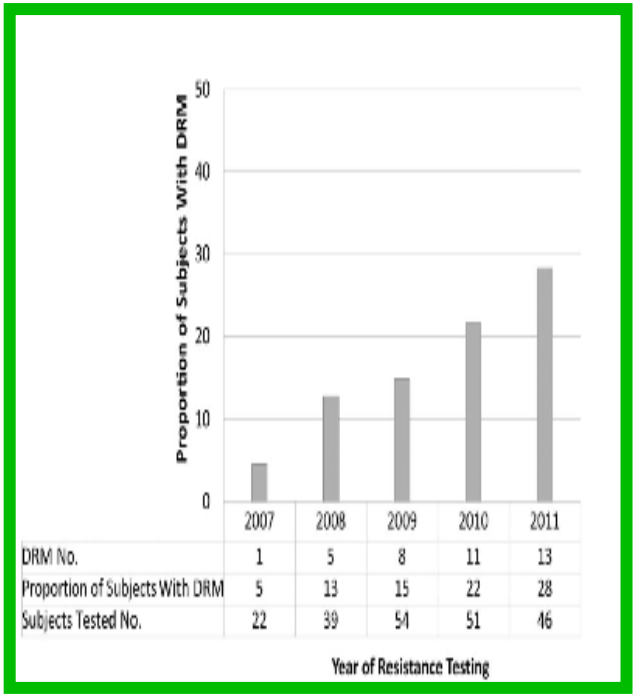
Background. In December 2009, the Department of Health and Human Services guidelines for initiation of antiretroviral therapy (ART) changed to include patients with CD4 counts between 350 and 500 cells/μL. The aims of this study were to assess uptake of this recommendation in ART-naive youth with human immunodeficiency virus (HIV) and to describe the epidemiology of transmitted genotypic drug resistance mutations (DRMs) in this population.

Methods. A multicenter, retrospective cohort study of ART initiation in ART-naive youth was performed. Eligible subjects were 13–25 years of age, were diagnosed with HIV within 1 year of presentation to care at the study sites, and presented to care from January 2007 to June 2011.

Results. Of 685 potential subjects identified, 331 (49%) fulfilled inclusion criteria. Mean CD4 count at presentation to care was 452 cells/μL. Overall, 191 (58%) subjects started ART. The mean CD4 count at ART initiation was 261 cells/μL before and 363 cells/μL after the 2009 guideline change ($P < .0001$). Of 212 (64%) subjects with resistance testing available prior to ART initiation, 38 (18%) subjects had a major DRM and an increased proportion of resistance was seen in later study years.

Conclusions. Our study demonstrated an uptake in recently changed guideline recommendations to treat HIV-infected individuals at higher CD4 counts and reinforces the importance of performing resistance testing at entry into care, as 18% of our population had major DRMs prior to initiation of ART.

Keywords. HIV; adolescents; youth; genotypic resistance; antiretroviral therapy.



	2007	2008	2009	2010	2011
DRM No.	1	5	8	11	13
Proportion of Subjects With DRM	5	13	15	22	28
Subjects Tested No.	22	39	54	51	46

Global HIV-1 transmitted drug resistance in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial

Table 2 Prevalence of transmitted drug resistance (TDR) by geographical region

(a)

Region	No. of participants	Transmitted drug resistance							
		Any		NRTI		NNRTI		PI	
		n	% (95% CI)†	*n*	% (95% CI)†	*n*	% (95% CI)†	*n*	% (95% CI)†
Total	1869	188	10.1 (8.7, 11.5)	75	4.0 (3.2, 5.0)	85	4.5 (3.6, 5.6)	52	2.8 (2.1, 3.6)
USA	405	51	12.6 (9.5, 16.2)	15	3.7 (2.1, 6.0)	34	8.4 (5.9, 11.5)	8	2.0 (0.9, 3.9)
Australia	97	17	17.5 (10.6, 26.6)	9	9.3 (4.3, 16.9)	4	4.1 (1.1, 10.2)	5	5.2 (1.7, 11.6)
Asia	75	6	8.0 (3.0, 16.6)	2	2.7 (0.3, 9.3)	3	4.0 (0.8, 11.2)	2	2.7 (0.3, 9.3)
Europe	1292	114	8.8 (7.3, 10.5)	49	3.8 (2.8, 5.0)	44	3.4 (2.5, 4.5)	37	2.9 (2.0, 3.9)
UK	320	15	4.7 (2.6, 7.6)	6	1.9 (0.7, 4.0)	3	0.9 (0.2, 2.7)	6	1.9 (0.7, 4.0)
Germany	271	29	10.7 (7.3, 15.0)	12	4.4 (2.3, 7.6)	10	3.7 (1.8, 6.7)	11	4.1 (2.0, 7.1)
Spain	191	24	12.6 (8.2, 18.1)	6	3.1 (1.1, 6.7)	11	5.8 (2.9, 10.1)	10	5.2 (2.5, 9.4)
France	96	16	16.7 (9.8, 25.7)	12	12.5 (6.6, 20.8)	4	4.2 (1.1, 10.3)	3	3.1 (0.6, 8.9)
Belgium	88	5	5.7 (1.9, 12.8)	3	3.4 (0.7, 9.6)	2	2.3 (0.3, 8.0)	0	0 (0, 4.1)
Greece	92	8	8.7 (3.8, 16.4)	3	3.3 (0.7, 9.2)	8	8.7 (3.8, 16.4)	0	0 (0, 3.9)
Other	234	17	7.3 (4.3, 11.4)	7	3.0 (1.2, 6.1)	6	2.6 (0.9, 5.5)	7	3.0 (1.2, 6.1)

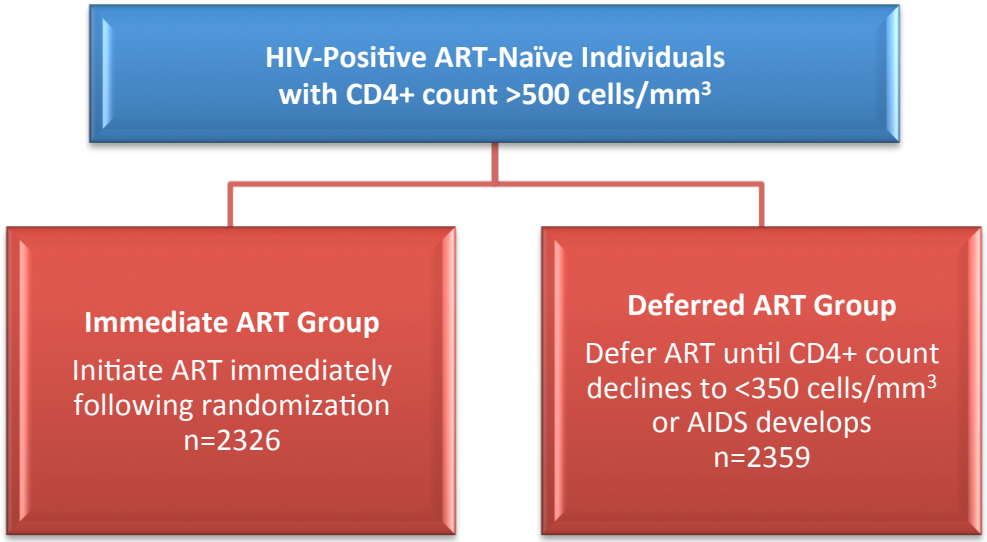
Baxter , HIV medicine 2015

START: **S**trategic **T**iming of **A**nti**R**etroviral **T**reatment Trial

Study Design and Baseline Characteristics

START is an international randomized trial comparing immediate ART (CD4 >500cells/µL) versus deferred ART (CD4 <350 cells/µL)

- Primary endpoint is the development of a serious AIDS event, a serious non-AIDS event, or death from any cause



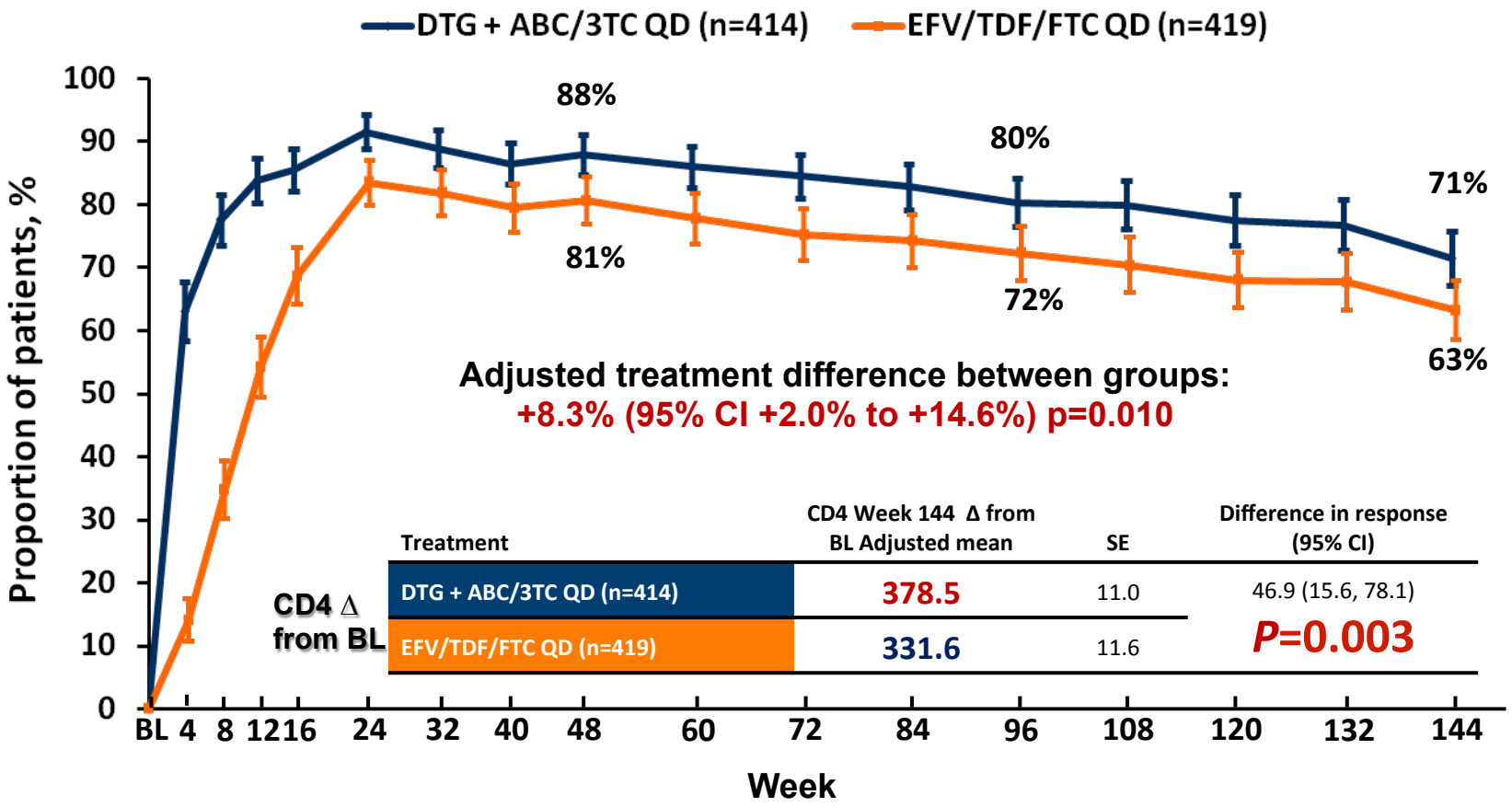
Characteristic	N=4685
Age (yr)*	36 (29, 44)
Female, n (%)	1257 (27)
Race, n (%)	
White	2086 (45)
Black	1410 (30)
Time since HIV diagnosis (yr)*	1.0 (0.4, 3.1)
CD4 cell count (cells/mm³)*	651 (584-765)
Baseline HIV-RNA (copies/mL)*	12,759 (3019-43,391)
TDF Usage	89% in both groups

* Median (IQR)

- On May 15, 2015 at a planned interim review, the international Data & Safety Monitoring Board recommended that participants in the deferred arm who were not already on ART should be offered ART and follow-up should continue with all subjects on therapy

Lundgren D, et al. IAS 2015. Vancouver, CAN. Oral # MOSY03

144 WEEKS: PROPORTION <50 C/ML (95% CI) AND CD4 CHANGE FROM BASELINE



Pappa et al. ICAAC 2014; Washington, DC. H-647a.

WEEK 144: TREATMENT-EMERGENT RESISTANCE

		DTG + ABC/3TC QD (N=414)	EFV/TDF/FTC QD (N=419)
Subjects with PDVF		39 (9%)	33 (8%)
Primary INI-r		0	0
Primary NRTI	K65R	0	1
Primary NNRTI	Any	0	6
	K101E	0	1
	K103N	0	2
	K103K/N	0	2
	G190G/A	0	2

PDVF definition:

- Confirmed HIV-1 RNA ≥50 c/mL at or after Week 24
- PDVF triggered resistance testing for all subjects
- PDVF before week 48 required withdrawal from study
- After week 48, subjects with HIV RNA 50-200 c/mL could remain on study

PDVF: protocol defined virologic failure

Pappa et al. ICAAC 2014; Washington, DC. H-647a.

Emergent Resistance

	EVG/COBI/FTC/TDF n=289	ATV+RTV+FTC/TDF n=286
RAP	19	21
Final RAP*	7	12
Developed resistance mutations to study drugs	0	3
Any NRTI-R	1†	3
M184V/I	0	3
K65R	0	0
Any INSTI-R	0	0
Any primary PI-R	0	0
Developed primary NNRTI-R	0	0

*Patients included in resistance-analysis population (RAP): a) suboptimal virologic response (HIV-1 RNA ≥50 copies/mL and <1-log10 reduction from baseline by Week 8, confirmed); b) virologic rebound (>400 copies/mL after achieving HIV-1 RNA <50 copies/mL, or 2 consecutive visits with >1-log10 increase in HIV-1 RNA from nadir); and c) HIV-1 RNA >400 copies/mL at Week 48; RAP excludes patients with HIV-1 RNA <50 copies/mL at subsequent visits.
†Emergent D67D/N with no phenotypic change to any drug. INSTI-R, integrase strand transfer inhibitor resistance; NNRTI-R, non-nucleoside reverse transcriptase inhibitor resistance; NRTI-R, nucleoside reverse transcriptase inhibitor resistance; PI-R, protease inhibitor resistance.

Squires K, et al. IAS 2015, #MOLBPE08.

Dolutegravir virological failures in naive patients

SINGLE

Subjects with emergent resistance mutations at VF:

- TDF/FTC/EFV arm: 1 NRTI, 6 NNRTI
- ABC/3TC/DTG arm: 0 NRTI, 0 INSTI

SPRING-2

Subjects with emergent resistance mutations at VF:

- RAL arm: 4 NRTI, 1 INSTI
- DTG arm: 0 NRTI, 0 INSTI

FLAMINGO

Subjects with emergent resistance mutations at VF:

- DRV/r arm: 0 NRTI, 0 PRO
- DTG arm: 0 NRTI, 0 INSTI

Walmsley SL, et al. NEJM 2013; 369: 1807-1818
Raffi F, et al. Lancet 2013; 381: 735-43
Clotet B et al. Lancet 2014; 383: 2222-31

J Antimicrob Chemother 2013; **68**: 2339–2343
doi:10.1093/jac/dkt199 Advance Access publication 27 May 2013

Journal of Antimicrobial Chemotherapy

Low frequency of genotypic resistance in HIV-1-infected patients failing an atazanavir-containing regimen: a clinical cohort study

David I. Dolling[1]*, David T. Dunn[1], Katherine A. Sutherland[2], Deenan Pillay[3], Jean L. Mbisa[2], Chris M. Parry[4], Frank A. Post[5], Caroline A. Sabin[3] and Patricia A. Cane[2] on behalf of the UK HIV Drug Resistance Database (UKHDRD) and the UK Collaborative HIV Cohort Study (UK CHIC)†

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†For further details please see the Acknowledgements section.

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Objectives: To determine protease mutations that develop at viral failure for protease inhibitor (PI)-naive patients on a regimen containing the PI atazanavir.

Methods: Resistance tests on patients failing atazanavir, conducted as part of routine clinical care in a multicentre observational study, were randomly matched by subtype to resistance tests from PI-naive controls to account for natural polymorphisms. Mutations from the consensus B sequence across the protease region were analysed for association and defined using the IAS-USA 2011 classification list.

Results: Four hundred and five of 2528 (16%) patients failed therapy containing atazanavir as a first PI over a median (IQR) follow-up of 1.76 (0.84–3.15) years and 322 resistance tests were available for analysis. Recognized major atazanavir mutations were found in six atazanavir-experienced patients ($P<0.001$), including I50L and N88S. The minor mutations most strongly associated with atazanavir experience were M36I, M46I, F53L, A71V, V82T and I85V ($P<0.05$). Multiple novel mutations, I15S, L19T, K43T, L63P/V, K70Q, V77I and L89I/T/V, were also associated with atazanavir experience.

Conclusions: Viral failure on atazanavir-containing regimens was not common and major resistance mutations were rare, suggesting that adherence may be a major contributor to viral failure. Novel mutations were described that have not been previously documented.

OSPEDALE SAN RAFFAELE

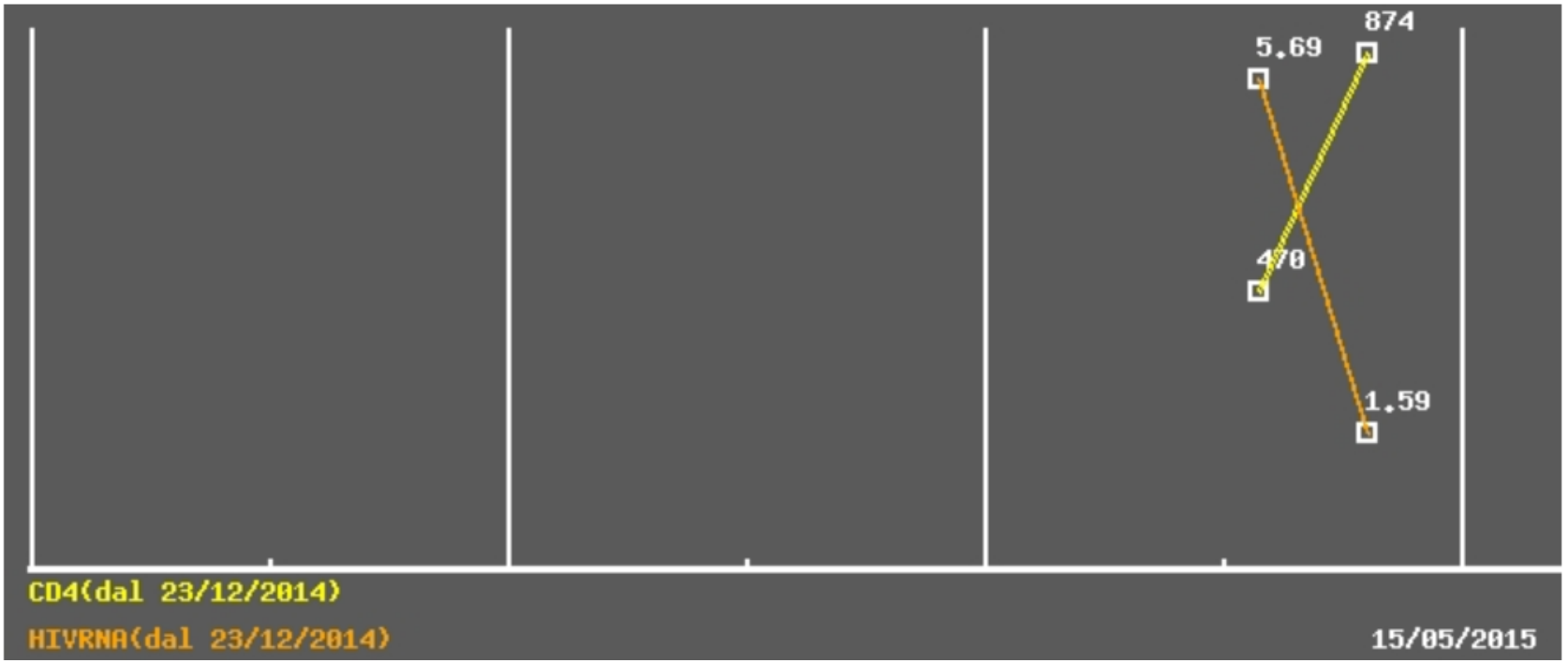
Phase IIb, pilot study
40 HIV-1 treated failing subjects
Susceptible to DTG and ATV
HBs Ag negative
Any CD4 level

DTG 50 mg QD + ATV/r 300/100 mg QD

Removal of ritonavir allowed

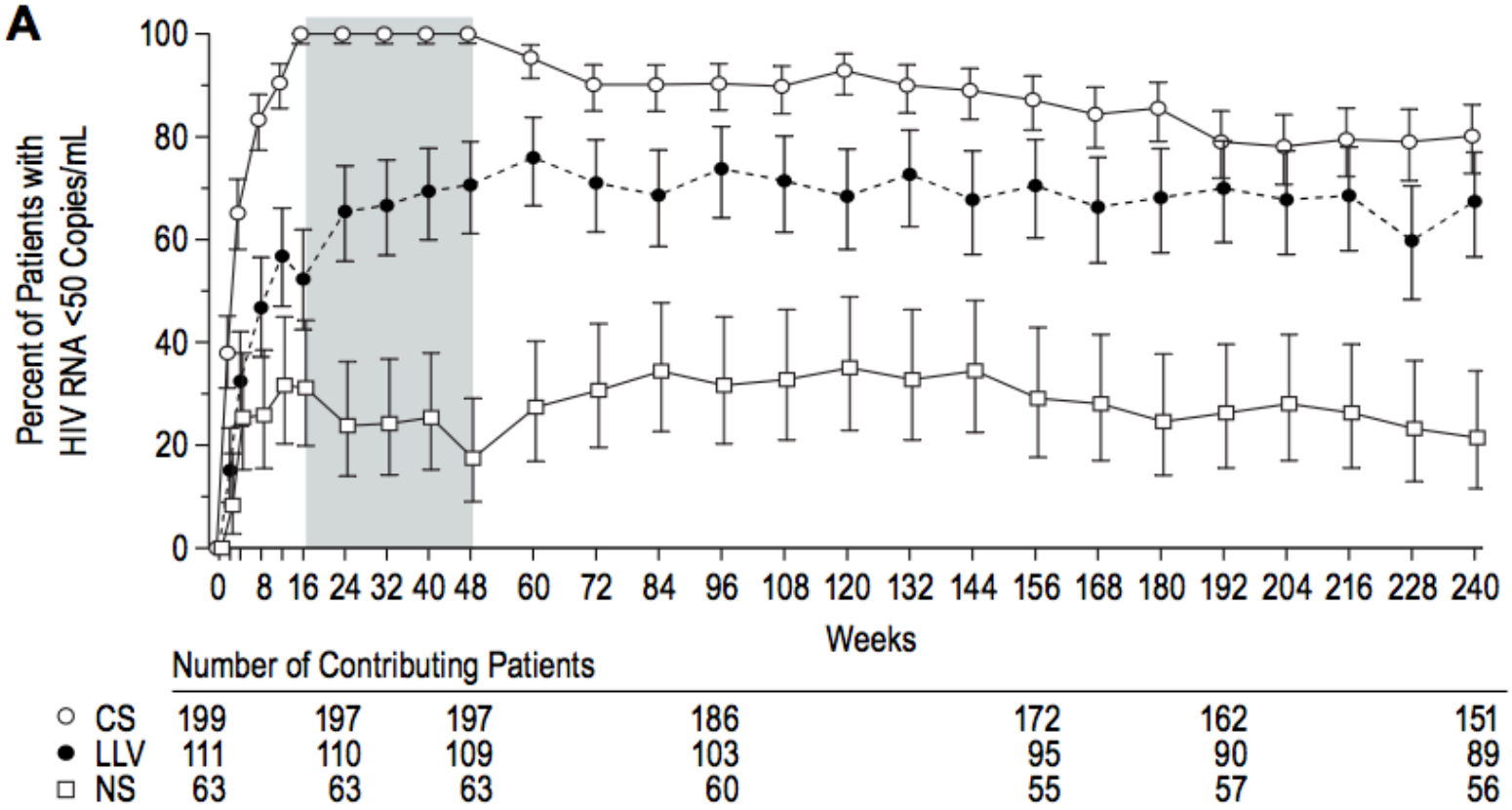
Proportion of HIV-RNA <50 copies at 24 weeks

Andamento CD4/HIVRNA



Date	Viremia	Terapia
16/03/2015	**39** Copie/mL	TIVICAY*50MG 30 CPR - TRUVADA*30CPR 200/245MG
19/12/2014	**489662** Copie/mL	NAIVE

Learning from BENCHMRK



Linear Regression Modeling – Week 240

	Change in CD4 count	Change in CD4 %
Covariate	P-value	P-value
Treatment group (RAL vs. EFV)	0.009*	0.539
Week 8 log vRNA decline	<0.001*	0.032*

p-values were calculated using a multiple linear regression model adjusted for: week 8 log vRNA decline, treatment, and interactions between treatment and week 8 log vRNA decline. However, in both models, interaction terms are not significant and are dropped from the model.

*Significant at nominal critical level of 0.05

Seminario Nadir 2015 - Iniziativa resa possibile grazie al supporto di ViiV Healthcare

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