Integrase strand-transfer inhibitors primary resistance in patients with acute/recent HIV infection

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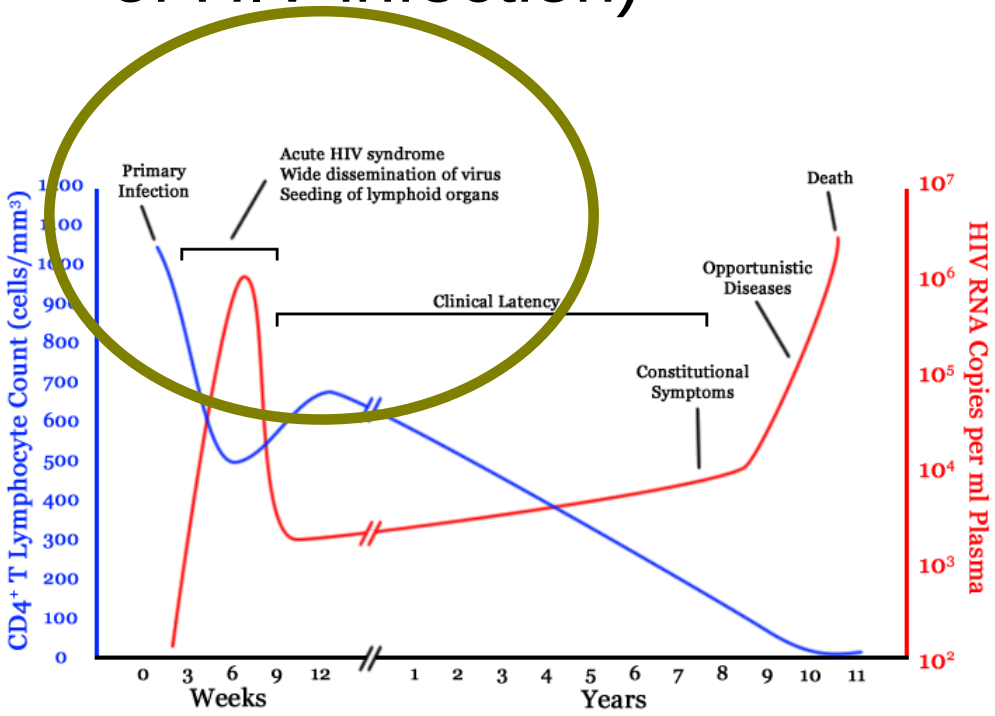
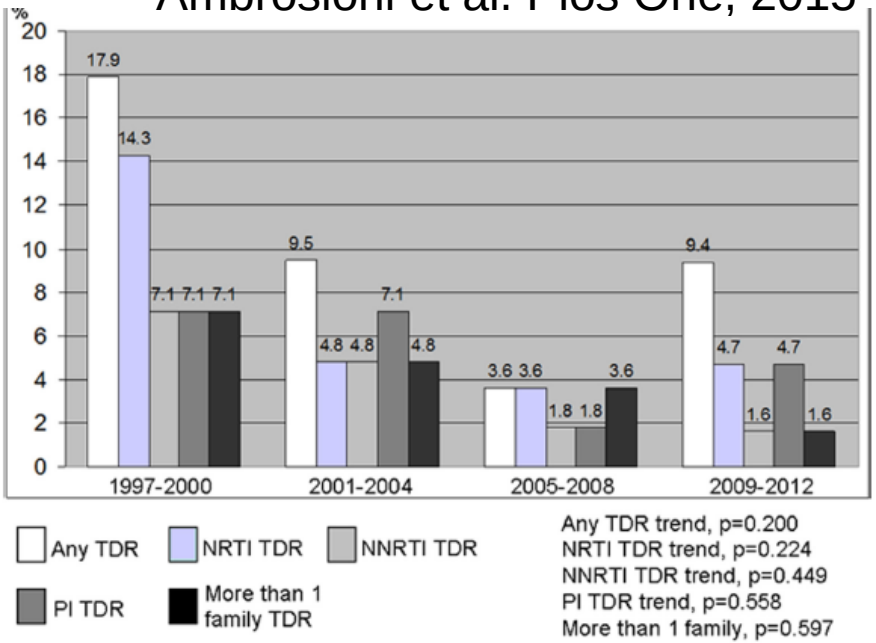
Background:

- Acute/recent HIV infection represents approximately 20 to 25% of new HIV-diagnosed patients in Europe
- However, these cases contribute disproportionately to HIV transmission (high VL, frequent unawareness of HIV infection)



Ambrosioni et al. Plos One, 2015



Background:

- Most recent international guidelines suggest integrase strand-transfer inhibitors (InSTIs) as preferred antiretroviral regimens for naïve HIV-infected individuals.
- However, primary resistance to InSTIs is still not monitored in many centers.

- Genotypic testing for reverse transcriptase and protease resistance mutations is recommended prior to treatment initiation (evidence rating AIIa).
- Routine screening for integrase resistance is currently not recommended prior to treatment initiation unless the source virus is suspected to have been from someone in whom treatment containing an integrase strand transfer inhibitor failed (evidence rating BIII).

IAS–USA
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GUIDELINES

JAMA, 12th July 2016

AIM:

To evaluate the prevalence of resistance mutations to InSTIs in newly-diagnosed patients with acute/recent HIV infection.

Methods:

- Genotypic drug resistance test were performed in all consecutive patients prospectively enrolled in the Acute/recent HIV infection cohort of Hospital Clinic (documented infection of less than 6 months), from May 12th 2015 to May 12th 2016
- Sequences were obtained by high-throughput sequencing. Mutations present in any proportion were reported; mutations present in more than 20% of sequences were considered as clinically relevant

Ambrosioni et al. Plos One, 2015

Methods:

- Cases with InSTIs mutations were described and compared with the rest of the patients included in the cohort in this 1-year period

- Categorical variables were expressed as a frequency (percentage), Fisher exact test; Continuous variables were expressed as median (IQR), Mann-Whitney test

- Data were analyzed with R software

Results:

- Five out of 36 consecutive patients (13.89%, IC95% [4.67-29.5]) with acute / recent HIV infection included in our cohort were detected to have strains carrying InSTIs polymorphisms or accesory mutations

- Four patients had the 157Q mutation and one patient the Q95K mutation (low level or potential low level resistance to raltegravir and elvitegravir)

- No patient had signature InSTI mutations (such Y143R/C, N155H or Q148K/R/H)

Results:

Patient	Risk Factor	Age	origin	VL (Copies/ mL)	CD4 cells/µl (%)	Fiebig Stage	InSTI mutation	%&	Other TDR	Subtype/ Tropism	Acute/recent HIV infection clinical presentation	ARV regimen	Clinical and virological outcomes
1	MSM	28	Venezuela	34960	528 (35%)	VI	157Q *	100%	no	B / R5	Asymptomatic seroconversion	TDF/ FTC/ RIL	VL<37 copies/mL at 12 weeks
2	MSM	44	Italy	8931000	383 (38%)	II	Q95K**	100%	138A	B / X4	Fever, myalgia, diarrhea, severe asthenia, rash and poly-adenopathies	TDF/ FTC/ DTG	Remission of symptoms in 10 days. VL<37 copies/mL at 12 weeks
3	MSM	42	Spain	703200	436 (12%)	V	157Q *	99%	no	B / ND	Fever, myalgia, asthenia, rash and poly-adenopathies	TDF/ FTC/ 3rd drug$	Remission of symptoms in 7 days. VL<37 copies/mL at 24 weeks
4	MSM	34	Spain	216000	351 (19%)	VI	157Q *	95%	no	B / X4	Poly-adenopathies	ABC/ 3TC/ DTG	VL<37 copies/mL at 12 weeks
5	MSM	37	Italy	839	470 (31%)	V	157Q *	100%	no	B / X4	Fever and myalgia	ABC/ 3TC/ DTG	Remission of symptoms in 7 days.

& Mutational load. Proportion of sequences carrying the detected InSTI mutation
$ Unknown 3rd drug (Blinded randomized clinical trial comparing efavirenz and a maturation inhibitor)
*Stanford HIV drug-resistance database interpretation: Low level resistance to raltegravir and elvitegravir (15 points). Dolutegravir full active.
**Stanford HIV drug-resistance database interpretation: Potential low level resistance to raltegravir and elvitegravir (10 points). Dolutegravir full active.
MSM: Men-who-have-sex-with-men, VL: Viral Load, ARV: Antiretroviral, TDF: Tenofovir, FTC: Emtricitabine, RIL: Rilpivirine, DTG: Dolutegravir, ABC: Abacavir, 3TC: Lamivudine
ND: Not done

All cases were MSM, median age of 37 y.o and infected with subtype B strains. All were HLA-B5701 negative. Mutational load >95% of viral load in all cases

Results:

	All patients	InSTI Resistance	No InSTI Resistance	p value
	N=36	N=5	N=31	
Gender (Male)	34 (94.44%)	5 (100%)	29 (93.55%)	1
Age Median (IQR)	34.5 (29.8-38)	37	34 (29.5-38)	0.492
Origin:				1
Western Europe	27 (75.0%)	4 (80.0%)	23 (74.2%)	
Latin America	8 (22.2%)	1 (20.0%)	7 (22.6%)*	
Other	1 (2.78%)	0 (0.00%)	1 (3.23%)	
Transmission:				1
MSM	34 (94.4%)	5 (100%)	29 (93.5%)	
HTSX	2 (5.56%)	0 (0.00%)	2 (6.45%)	
VL (log) Median (IQR)	4.50 (3.77;5.56)	5.33 (4.54-5.85)	4.43 (3.74-5.47)	0.478

	All patients	InSTI Resistance	No InSTI Resistance	p value
Fiebig Stage				0.735
II	4 (11.1%)	1 (20.0%)	3 (9.68%)	
III	1 (2.78%)	0 (0.00%)	1 (3.23%)	
IV	3 (8.33%)	0 (0.00%)	3 (9.68%)	
V	10 (27.8%)	2 (40.0%)	8 (25.8%)	
VI	18 (50.0%)	2 (40.0%)	16 (51.6%)	
Subtype				0.292
B	25 (71.4%)	5 (100%)	20 (66.7%)	
no-B	10 (28.6%)	0 (0.00%)	10 (33.3%)**	
TDR				
NRTI	1 (2.78%)	0 (0.00%)	1 (3.23%)[&]	1
NNRTI	4 (11.1%)	1 (20.0%)	3 (9.68%)[$]	0.466
PI	1 (2.78%)	0 (0.00%)	1 (3.23%)[#]	1
Any mut. (3 families)	5 (13.9%)	1 (20.0%)	4 (12.9%)	0.549
Any mut. (4 families)	9 (25.0%)	N/A	N/A	

Epidemiological, virological and immunological characteristics: **comparable**

Discussion:

- E157Q reduces RAL susceptibility by about five-fold and EVG susceptibility by about two-fold. E157Q has been reported to be rapidly selected during short-term low-level replication of RAL-based regimens
- Q95K is a nonpolymorphic accessory InSTI-resistance mutation selected in patients receiving RAL and *in vitro* by EVG
- Dolutegravir susceptibility is not affected by Q95K or E157Q
- New InSTIs? Cabotegravir? Bictegravir?
- Should the integrase be monitored in baseline genotype?

Ghosn et al, JAC 2009

Fun et al. JAC 2010

Conclusions:

- Signature InSTI mutations were not detected in patients with acute/recent HIV infection
- However, polymorphic and accessory substitutions conferring low level resistance to raltegravir and elvitegravir were frequently found in baseline genotypic test during this one-year study
- All cases were infected with subtype B, the most frequent in Europe, mutational load very high
- In the context of primary HIV infection (frequently very High VL), virological response to the different InSTI-based regimens should be carefully monitored to evaluate the impact of these InSTI substitutions

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Questions and discussion

- Open to questions…

- Thank you very much for your attention

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