La compartimentalizzazione delle mutazioni di resistenza ai farmaci antiretrovirali

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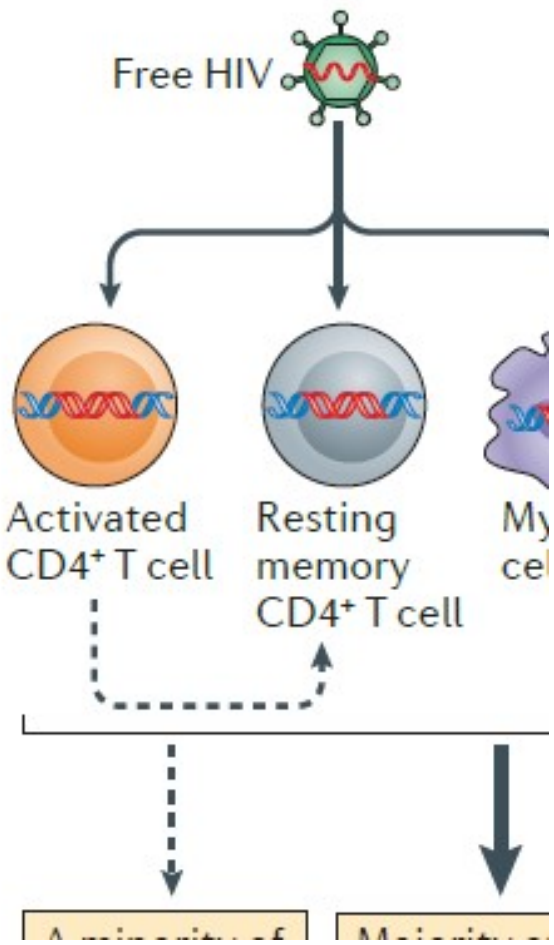
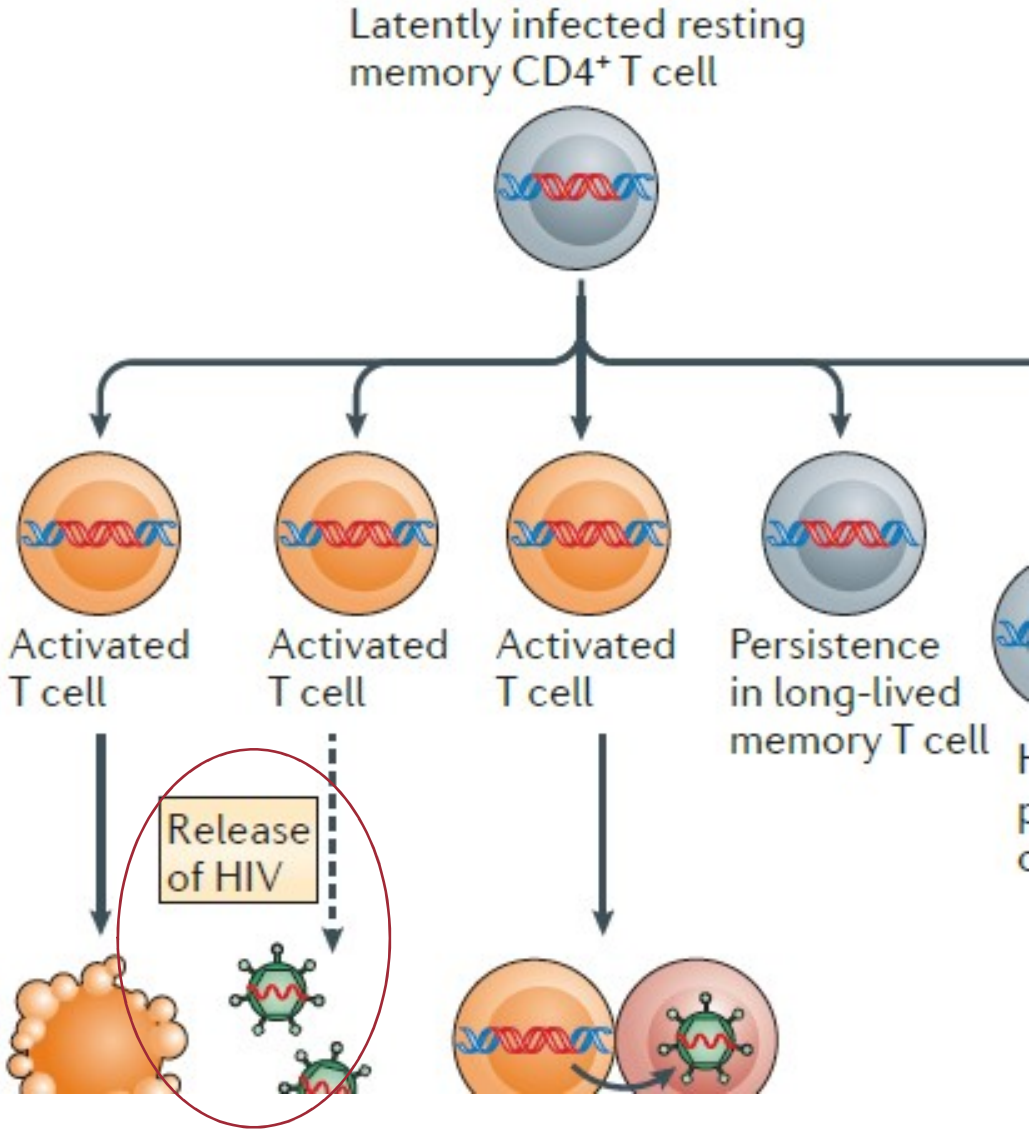
XLVI Congresso Nazionale
AMCLI
11 - 14 Novembre 2017

Fate of latently infected cells

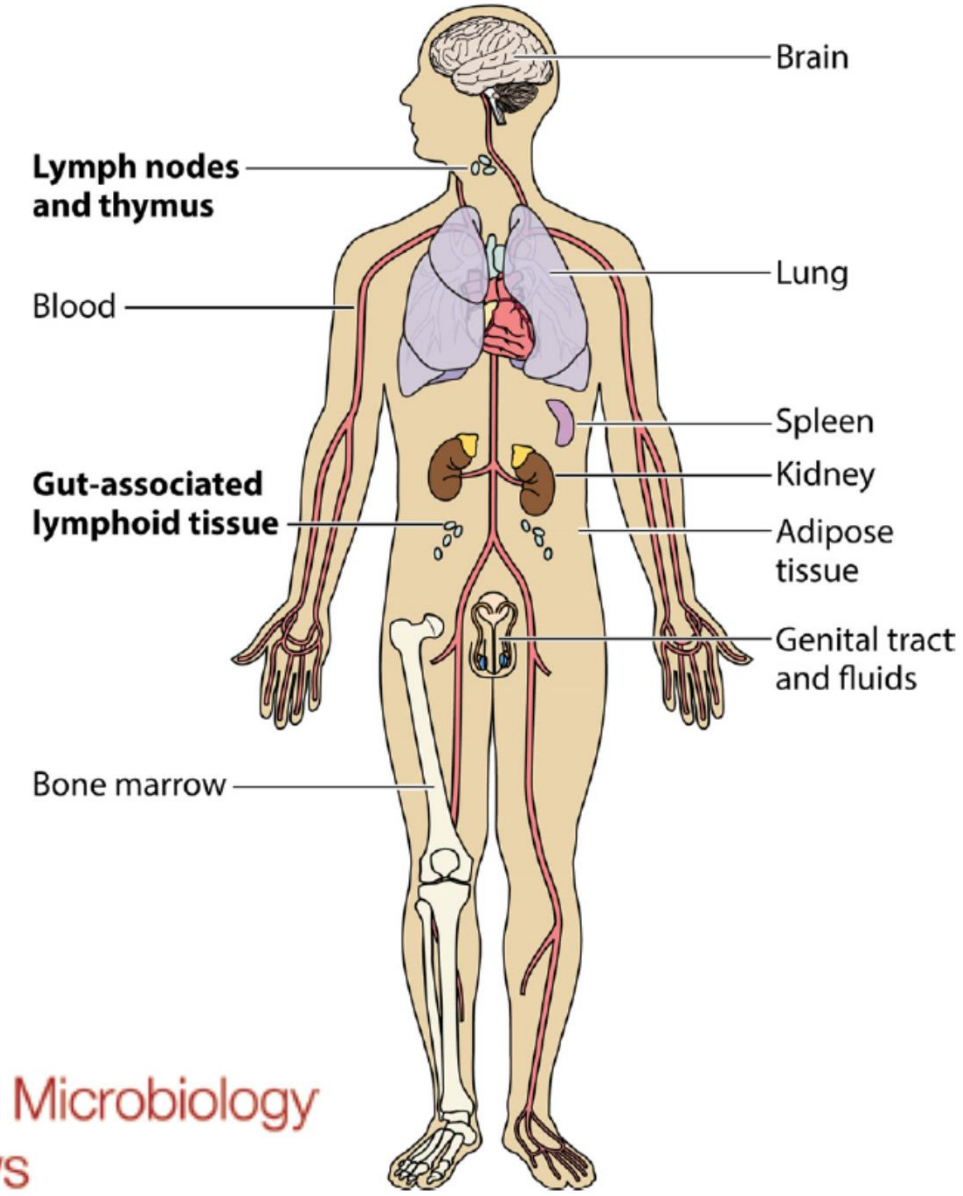


Fate of latently infected cells



NATURE REVIEWS | IMMUNOLOGY AUGUST 2012

Anatomical HIV reservoirs
Reservoir cells are highly disseminated



AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Avettand-Fenoel 2016

van Marle *et al. Retrovirology* 2010, **7**:74
http://www.retrovirology.com/content/7/1/74

RESEARCH

Higher levels of Zidovudine resistant HI
colon compared to blood and other

Drug resistance mutations by tissue source

Patient #7	PBL	Esophagus	Stomach	Duodenum
Visit 1				
ddI	None (100%)	None (20%) ***T215Y*** (20%) ***M41L, T215Y*** (40%) ***M41L***, T69N, ***T215Y*** (20%)	None (25% L74V (8.3%) ***T215Y*** (16.7%) L74V, ***T215Y*** (50%)	ND
Visit 2				
ddI	***M41L***, L74V, ***T215Y*** (100%)	***T215Y*** (100%)	None (45.5%) ***M41L***, L74V, ***T215Y*** (9.1%) ***T215Y*** (36.4%) L74V, ***T215Y*** (9.1%)	***M41L***, ***T215Y*** (54.5%) ***T215Y*** (27.3%) ***M41L***, L74V, ***T215Y*** (18.2%)
Visit 3				
AZT	None (87.5%) F77S (12.5%)	***M41L*** (42.9%) ***T215Y*** (57.1%)	***T215Y*** (93.8%) L210F, ***T215Y*** (6.25%)	***M41L*** (18.2%) None (81.8%)

van Marle et al Retrovirology 2010

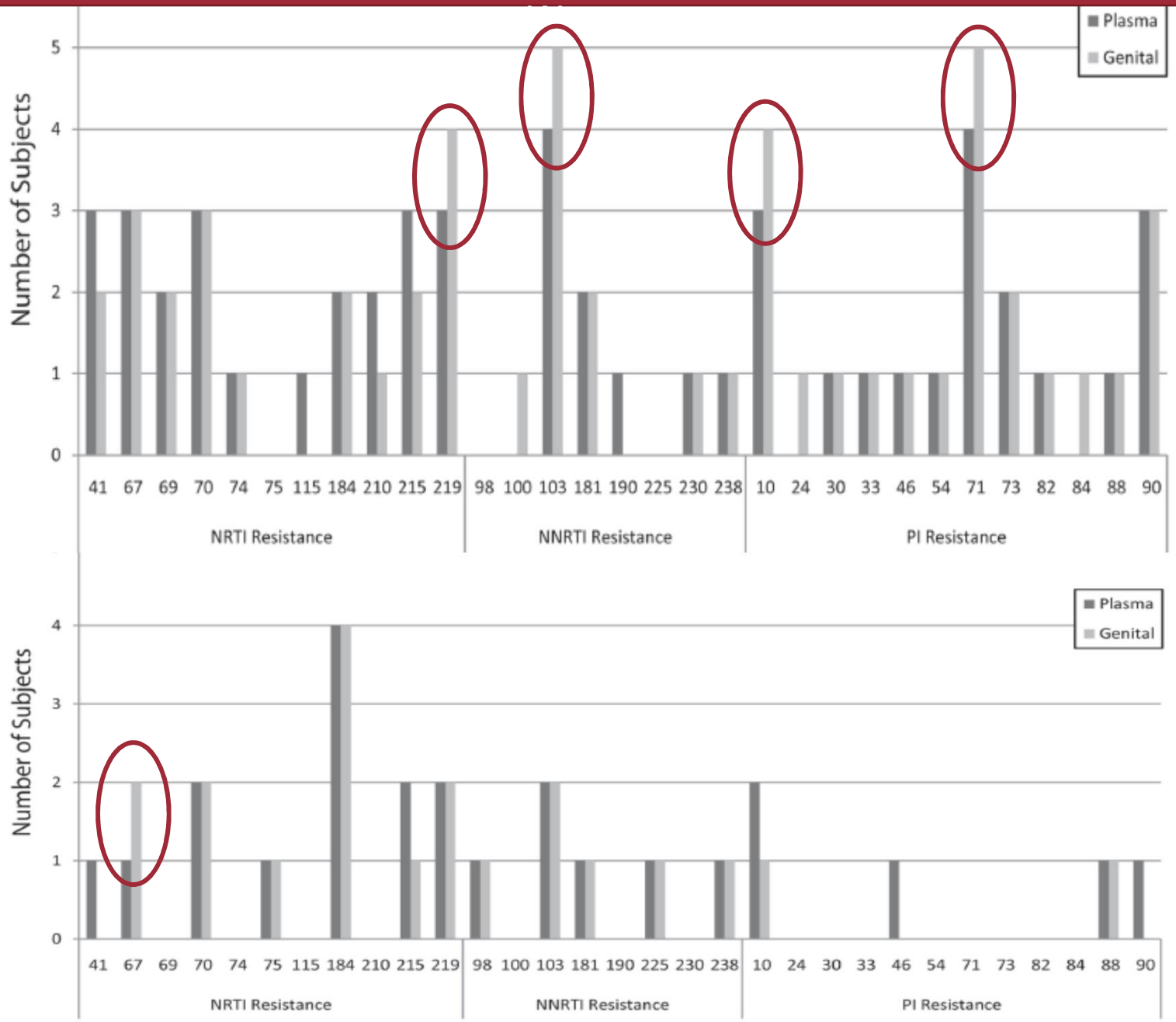
OPEN ACCESS Freely available online

PLOS | ONE

HIV-1 RNA Levels and Antiretroviral Drug Resistance in Blood and Non-Blood Compartments from HIV-1–Infected Men and Women enrolled in AIDS Clinical Trials Group Study A5077

Rami Kantor[1]*, Daniel Bettendorf[2], Ronald J. Bosch[2], Marita Mann[1], David Katzenstein[3], Susan Cu-Uvin[1], Richard D'Aquila[4], Lisa Frenkel[5], Susan Fiscus[6], Robert Coombs[7] for the ACTG A[5077] Study Team[¶]

Antiretroviral Drug Resistance in Plasma and Genital Tract Fluid in Enrolled Men and



Kantor et al PLOSONE 2014

J Antimicrob Chemother 2015; **70**: 566–572
doi:10.1093/jac/dku419 Advance Access publication 25 October 2014

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Antiretroviral-naive and -treated HIV-1 patients can ha resistant viruses in CSF than in plasma

Cathia Soulie[1–3]*, Diane Descamps[4,5], Maxime Grudé[1,2], Véronique Schneider[6], Mary-
Laurence Morand-Joubert[1,2,8], Constance Delaugerre[9,10], Brigitte Montes[11], Francis Barin
Stéphanie Raymond[14], Hélène Joulin[15,16], Chakib Alloui[17], Sabine Yerly[18], Coralie Pallier[19], S

Description of treated patients with discordant mutations between the CSF and plasma HIV-1 sequences

				CSF			Pl	
Patient	Treatment	CPE	Subtype	VL (log_{10} copies/mL)	RT	protease	VL (log_{10} copies/mL)	RT
1	f3TC, ddI, NVP	8.5	CRF01_AE	4.31112	V108I		4.15921	
2	f3TC, TDF, ETR	5.5	B	4.30103		K20R, L63P	5.63347	E138Q
3	f3TC, TDF, ETR	5.5	D	4.54845	M41L, L210W, T215Y	V82T		M230L
4	f3TC, ABC, TDF, NVP	10.5	B	3.61805	Y181C, M184V, T215Y, H221Y		5.71850	
5	f3TC, ABC, DRV	8.5	C	4.93952		K20R	3.55630	Y188L
6	f3TC, ABC, fAPV	8.5		3.64345		L10F, L10I	2.32428	
7	f3TC, TDF, fAPV	6.5	B	5.45618	M41L, L74V, Y181C, M184V, L210W, T215Y, K103N		2.90741	
8	f3TC, TDF, ATV	5.5	B	4.64640	K103N		4.22272	T69N
9	AZT, SQV, LPV	8	CRF02_AG	4.96480		L90M	3.75664	
10	AZT, f3TC, SQV	7.5	B	3.89209			3.98677	
11	f3TC, TDF, ATV	5.5	B	3.31492		A71V, L90M	5.13374	
12	f3TC, TDF, LPV	6.5	CRF02_AG	3.44592	M184V		2.21484	V90I
13	AZT, ABC, LPV	10	CRF06_CPX	5.14993		M46I	2.07555	
14	f3TC, d4T, ddI, ABC, SQV, NFV, LPV	14.5	B	3.21958			4.53842	D67N, K70R, Y L210W, K2
15	f3TC, ABC, LPV	8.5	CRF02_AG	3.41497			4.59356	M184I, M184
16	f3TC, TDF, LPV	6.5	B	3.20683		M36I	6.78056	
17	ddI, TDF, ATV	5	B	3.68422		A71L, A71V	2.27416	
18	f3TC, ABC, ATV	7.5	B	3.29667		M46I, I93M	3.58894	

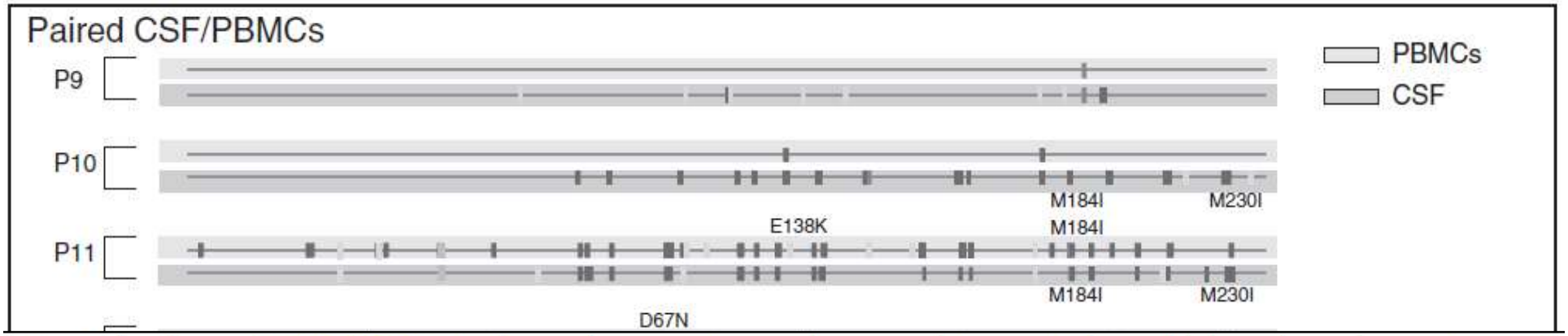
Soulie net al. JAC 2015

CONCISE COMMUNICATION

Differential impact of APOBEC3-driven mu on HIV evolution in diverse anatomical com

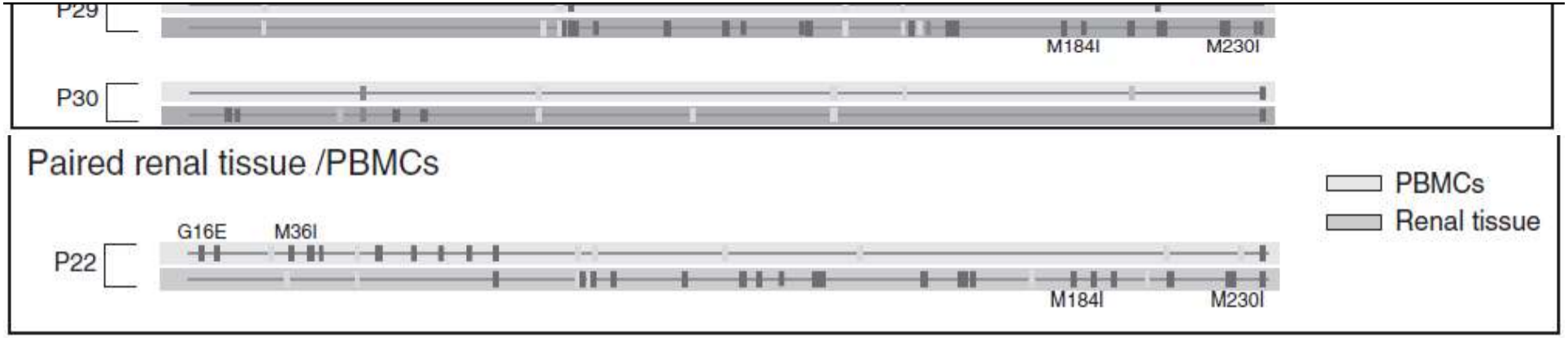
Slim Fourati[a,b], Sidonie Lambert-Niclot[a,b], Cathia S
Marc Wirden[a,b], Isabelle Malet[a,b], Marc A. Valan
Roland Tubiana[a,c], Anne Simon[a,d], Christine Katla

AIDS 2014, **28**:487–



Conclusion: APOBEC3-induced mutations observed in peripheral blood underestimate the overall proportion of hypermutated viruses in anatomical compartments. The resulting mutations may favor escape to antiretrovirals in these compartments in conjunction with a lower penetration of drugs in some sanctuaries. On the other side, because hypermutated sequences often harbor inactivating mutations, our results suggest that accumulation of defective viruses may be more dominant in sanctuaries than in peripheral blood of patients on effective HAART.

AIDS 2014, **28**:487–491



Saverio G. Parisi[a], *Romualdo Mazzi*[b], *Boldrin*[a], *Federico Dal Bello*[a], *Elisa* [illegible] *Massimo Andreoni*[c] *and Giorgio Palù*[a], [a]*Mi Department, Padua University, Padua, Ita tious Diseases Unit, Verona Hospital, Ver* [illegible]

Correspondence

AIDS 2006, **20**:1337–1357

J Acquir Immune Defic Syndr • Volume 44, Number 5, April 15, 2007

Genotypic Resistance of Archived and Circul Strains in the Blood of Treated HIV-Infected I

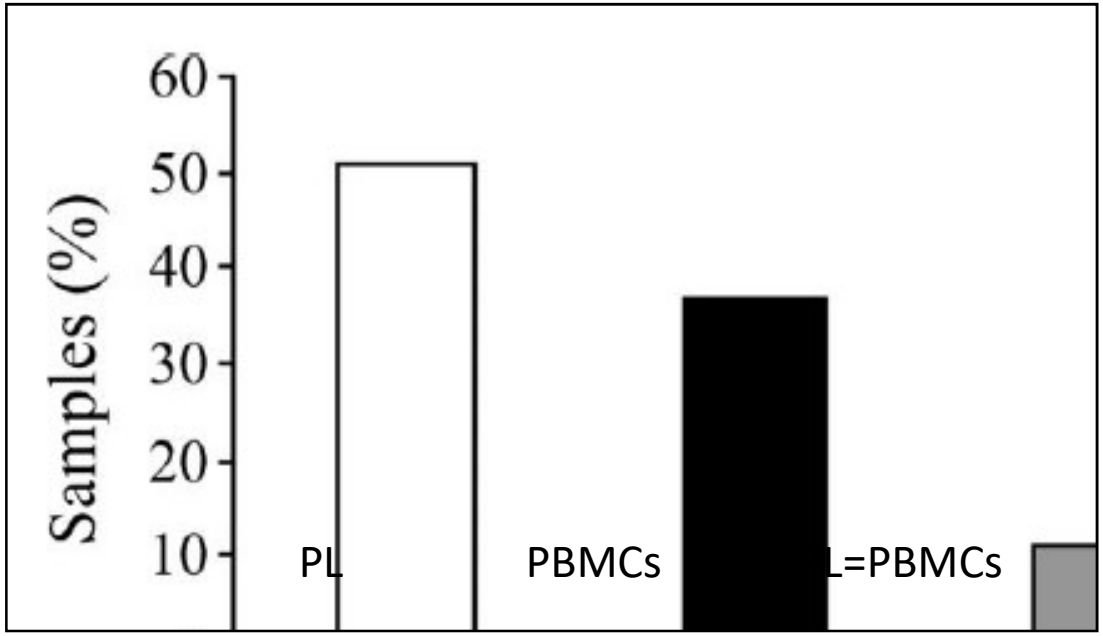
Ombretta Turriziani, PhD, Mauro Bucci, BSc,* Armando Stano, BSc,* Carolina* [illegible]

Journal of Clinical Virology 38 (2007) 3

Genotypic resistance in plasma and periphe lymphocytes in a group of naive HIV-1 p

Isabella Bon [a], Davide Gibellini [a], Marco Borderi [b], Federica

Percentage of samples with the highest number of mutations in plasma RNA or in PBMC DNA



Turriziani et al. JAIDS 2007

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 26, Number 6, 2010

DOI: 10.1089/aid.2009.0183

Mutational Resistance Pattern of HIV Type 1 Monocytes, CD4$^+$ T Cells, and Plasma Treated Patients

Abstract

It is necessary to understand the molecular nature of the virus population that persists in achieve this we planned to characterize the patterns of resistance of HIV-1 in CD14$^+$ mo and plasma. Blood samples were collected from 42 patients treated for HIV: 32 were in vir 10 viremia was undetectable. CD14$^+$ and CD4$^+$ T cells were isolated using magnetic bea reverse transcriptase and protease gene of HIV-1 was undertaken using the fluorescer method. Of the 32 patients in virological failure, 24 (75%) had resistance mutations in at le The numbers and types of mutations from monocytes were the same as those detected associated virus and plasma in only 8% whereas in 71% monocytes exhibited a differen 21% of patients, the profile of drug-resistant mutations in the virus from blood monocytes plasma but differed from that in CD4. In the 71% of patients with virological suppr

Reverse transcriptase mutations detectable at plasma and PBMC levels

Patient no.	Clinical category[a]	Viral load	Virus subtype	CD4	RT mutations detectable in plasma	RT mutations detectable in PBMCs
1	DII	89,700	CRF-AG	748	Wild type	Wild type
2	AI	502,000	B	119	D67N, K219Q, T69TT	D67N, K219Q, T69TT
3	DII	30,800	F	372	Wild type	Wild type
4	DII	302	B	1127	Not amplified	G190A
5	DII	95,900	B	705	Wild type	Wild type
6	BII	6,630	F	323	T215S	T215S
7	DII	675	C	585	M41L, T215D	M41L, T215D
8	DII	47,500	B	487	M41L, A62V, V75I, G190A	M41L, A62V, V75I, G190A
9	DII	900	B	669	Not amplified	M41L, T215D
10	AI	13,000	B	137	Wild type	T215S
11	DII	9,570	B	816	Wild type	Wild type
12	DII	17,500	B	393	Wild type	K101Q, V106A
13	DII	17,800	B	468	Wild type	Wild type
14	BII	15,700	B	341	D67N, T69N, K103N, G190A, T215S, K219Q	D67N, T69N, K103N, G190A, T215S, K219Q
15	DII	23,200	B	976	Wild type	Wild type
16	BII	83,100	B	283	Wild type	V106A
17	DII	18,700	B	491	Wild type	Wild type
18	DII	29,100	B	730	Wild type	Wild type
19	DII	63,600	B	412	Wild type	Wild type
20	DII	21,000	B	600	Wild type	Wild type
21	DII	77,400	B	451	Wild type	Wild type
22	DII	36,000	B	110	Wild type	T215S
23	CII	125,000	B	745	Wild type	Wild type
24	DII	3,930	B	915	Wild type	Wild type
25	DII	5,790	B	1000	Wild type	G190S
26	DII	17,600	B	806	Wild type	Wild type
27	DII	1,730	B	866	Wild type	M41L, T215F
28	BII	450,500	C	205	Wild type	K70R, V118I
29	DII	35,400	B	690	Wild type	Wild type
30	BII	29,000	B	228	Wild type	L100I
31	AI	500,000	B	89	Wild type	Wild type

[a] On the basis of the "guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents (www.aidsinfo.nih.gov/guidelines).

Bon I et al. J Clin Virol 2007

PLOS ONE

RESEARCH ARTICLE

High prevalence of HIV-1 transmitted drug-resistance mutations from proviral DNA massively parallel sequencing data of therapy-naïve chronically infected Brazilian blood donors

Rodrigo Pessôa[1], Sabri S. Sanabani[1,2]*

PLOS ONE | September 27, 2017

Sample ID	**Proteasegene coding region**		**Reverse transcriptase gene coding region (NRTI)**		**Reverse transcriptase gene coding region (NNRTI)**	
	PBMC (Deep sequencing)	PLASMA (Bulk sequencing)	**PBMC (Deep sequencing**)	PLASMA (Bulk sequencing)	**PBMC (Deep sequencing)**	PLASMA (Bulk sequencing)
10BR_MG006	M46I*, L63P, I93L	L63P, I93L	M184I*			
10BR_MG009	M36I, M46I*	M36I				
10BR_MG013	M46I*, I64V	I64V				
10BR_MG027	M36I*, I64V	I64V	M184I			
10BR_MG039	A71T, V77I, I93L	A71T, V77I, I93L	T69N	T69N		
10BR_MG045	M46L, I64V, I93L	M46L, I64V, I93L	D67E*		V108I	
10BR_PE004	M36I, M46I*, V77I, M89L	M36I, V77I, M89L				
10BR_PE009	L10V, M36I, L89M	L10V, M36I, L89M	F77L*, M184I*		M230I*	
10BR_PE014	K20R, D30N, M36I, I62V, A71V, N88D	K20R, D30N, M36I, I62V, A71V, N88D	M41L, L210W	M41L, L210W, T215E	L100I, K103N	L100I, K103N
10BR_PE019	M36I*, I62V, L63P, I93L	I62V, L63P, I93L	F77L*		K101E, V106I	V106I
10BR_PE021	G16E, M46I*, I64V	G16E, I64V	F77L*			
10BR_PE030	L10V, M36I, I62V, L63P	L10V, M36I, I62V, L63P			V179D	V179D
10BR_PE031	M36I, M46I*, I62V, L63P, V77I, I93L	M36I, I62V, L63P, V77I, I93L			Y181I, M230I*	
10BR_PE033	M36I*, V77I, I93L	G16E, V77I, I93L	F77L*, M184I*			
10BR_PE038	M36I, I93L	M36I, I93L			K101E, E138K	K101E, E138K
10BR_PE040	M36L, I62V, L63P	M36L, I62V, L63P	F77L*	T69N		

Usefulness of archived mutations detection

- To plan drug switches for toxicity, intolerance
- To Simplify therapy in suppressed HIV-1 infected patients
- In the case of lacking information about previous antiretrovirals treatment

J Antimicrob Chemother 2011; **66**: 709–712
doi:10.1093/jac/dkq544 Advance Access publication 26 January 2011

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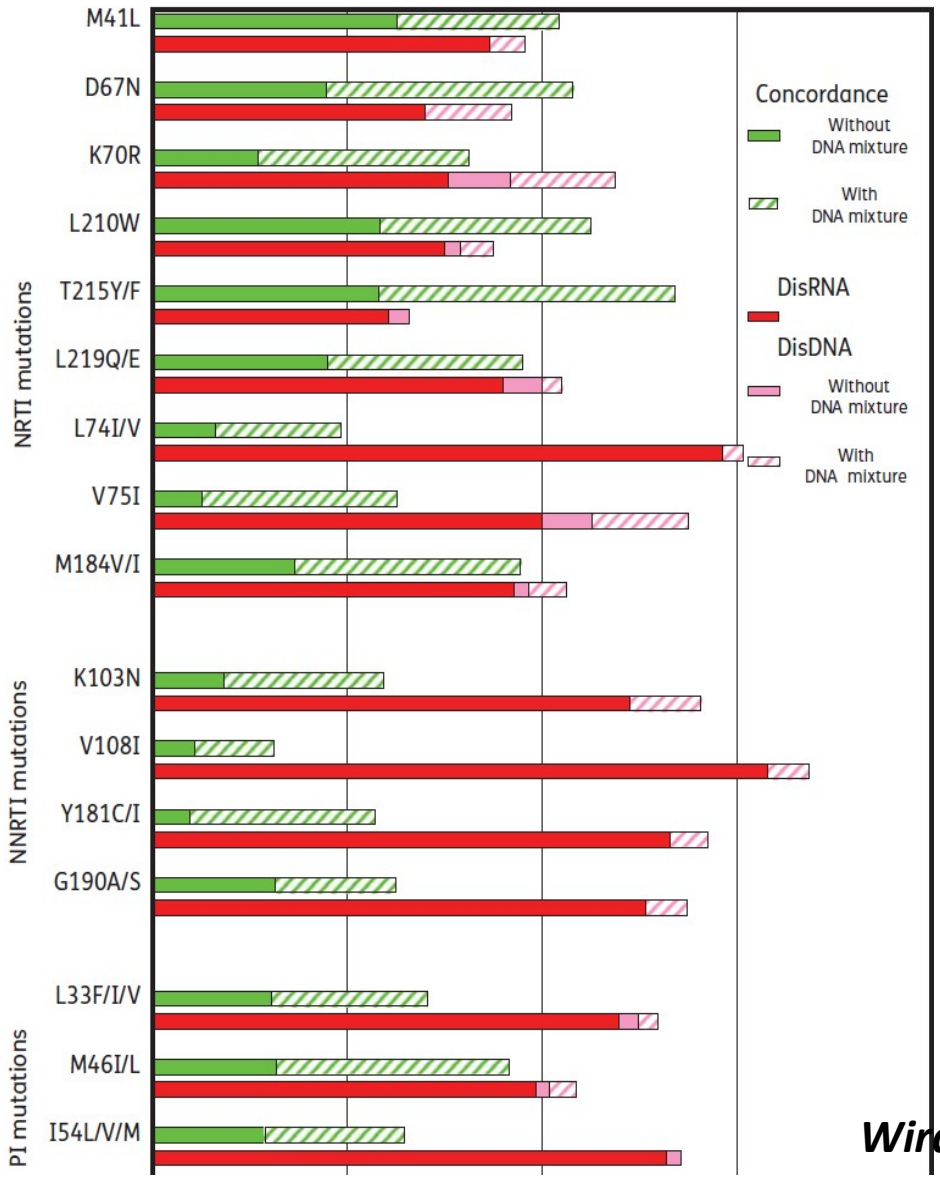
Historical HIV-RNA resistance test results are more inform proviral DNA genotyping in cases of suppressed or residu

Marc Wirden[1,2]*, Cathia Soulie[1,2], Marc-Antoine Valantin[2,3], Slim Fourati[1,2], Anne Simon[4], Sidoni
Manuela Bonmarchand[4], Cyril Clavel-Osorio[2,3], Anne-Genevieve Marcelin[1,2], Christine Ka
Vincent Calvez[1,2]

Percentage distribution of patients as function of the discordance or concordance between the DNA genotype and the entire history of plasma RNA results



Wirde M et al. JAC 2011

Journal of Clinical Virology 82 (2016) 94–100

Contents lists available at ScienceDirect

Journal of Clinical Virology

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

Genotypic resistance test in proviral DNA can identify resistance mutations never detected in historical genotypic test in patients w low level or undetectable HIV-RNA☆

Mauro Zaccarelli[a,1], Maria Mercedes Santoro[b,*,1], Daniele Armenia[b], Vanni Borghi[c]

J Antimicrob Chemother 2016; **71**: 2248–2251
doi:10.1093/jac/dkw146 Advance Access publication 26 May 2016

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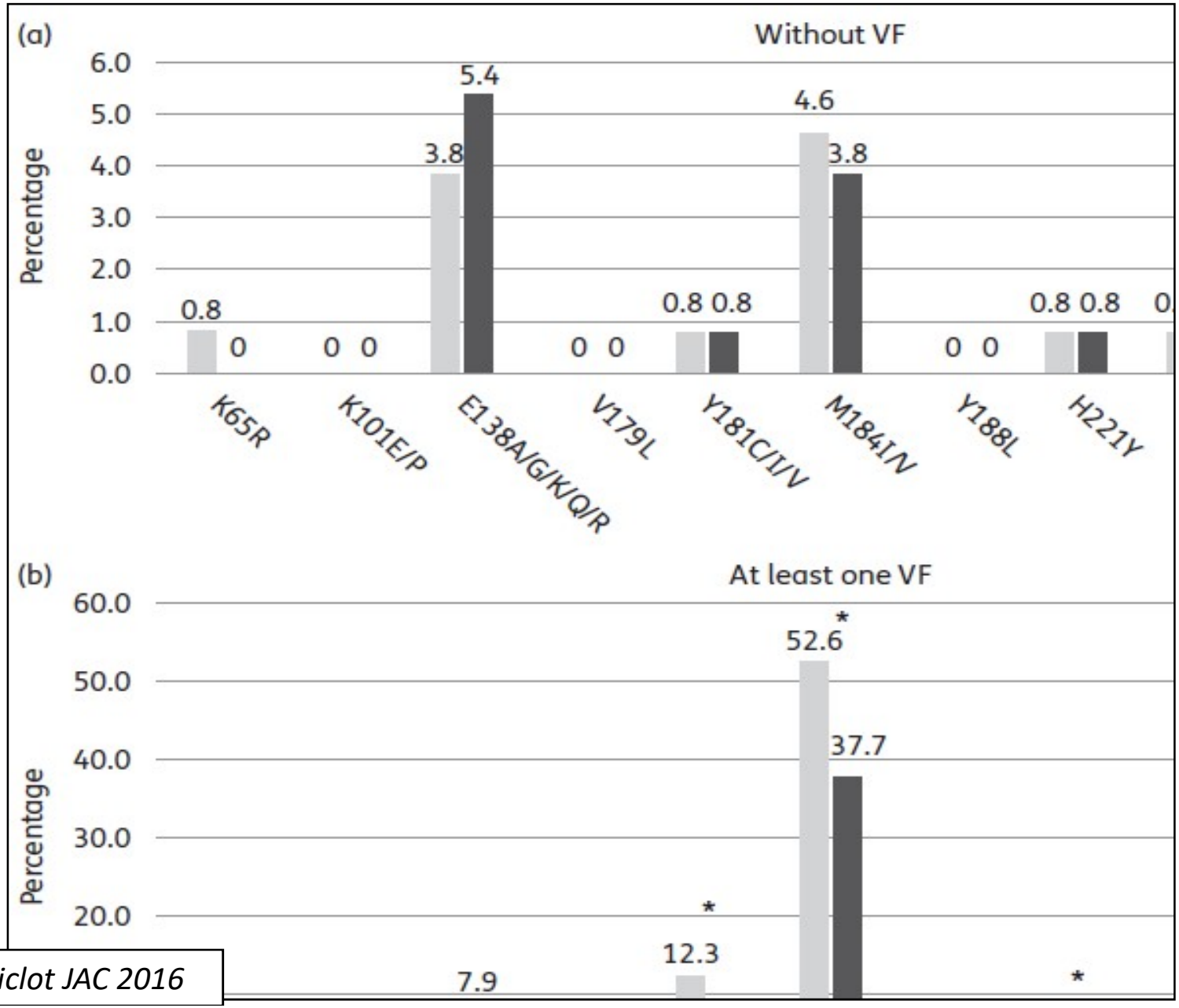
Usefulness of an HIV DNA resistance genotypic test in pat candidates for a switch to the rilpivirine/emtricitabine disoproxil fumarate combination

Prevalence of resistance mutations to rilpivirine/emtricitabine/tenofovir disoproxil fumarate in RNA and in DNA



Lambert-Niclot JAC 2016

Fernández-Caballero et al. BMC Infectious Diseases (2016) 16:197
DOI 10.1186/s12879-016-1545-8

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Usefulness of Integrase resistance testing in proviral HIV-1 DNA in patients with Raltegravir prior failure

Jose Ángel Fernández-Caballero[1,2*], Natalia Chueca[1], Marta Álvarez[1], María Dolores Mérida[1], Josefa López[1], José Antonio Sánchez[1], David Vinuesa[1], María Ángeles Martínez[1], José Hernández[1] and Federico García[1]

Primary and secondary resistance mutations in the Integrase by Sanger population sequencing

Patient	Major resistance mutation	Accesory mutation	Polymorphism mutation
1F	N155H	—	C56S, E85EG, L101I, S119P, T122I, H171Q, K173EK
1A	N155H	—	C56S, L101I, S119P, T122I, H171Q
2F	N155H	—	M50I, L68R, V71I, L101I, S119P, H171Q
2A	N155H	—	M50I, V71I, P90PS, L101I, S119P
3F	—	L74I	E96D, K111T, K160KT
3A	—	L74I	E96D, K111T, G123RS
4F	—	G163GR	L101I, I113V, G134E, V150AV
4A	—	G163GR	M50IM, L101I, I113V, V150A
5F	—	L74IM	M50V, V72I, K103R, K111T, A124T
5A	—	L74I	M50V, V72I, K103R, K111T
6F	N155H	T97A	D55Y, V72I, K111T, I113V, S119R, G123S, A124N, T125A
6A	—	—	V72I, K111T, I113V, S119R, G123S, A124N, T125A
6 UDS	N155H (9.77 %)	T97A (12.42 %)	V72I(37.44 %), Y99C(4.65 %), T122I(12.56 %), K156N(14.35 %), E157A(15.35 %), K111T(39.53 %), I113V(29.3 %), S119R(37.44 %), G123S(97.21 %), A124N (43.26 %), T125A(45.58 %)
7F	N155H	V151I	I113V, S119P, T122I, A124N, C130Y
7A	N155H	V151I	G52P, S119PR, T122I, I161X

Fernández-Caballero et al. BMC Infectious

….But

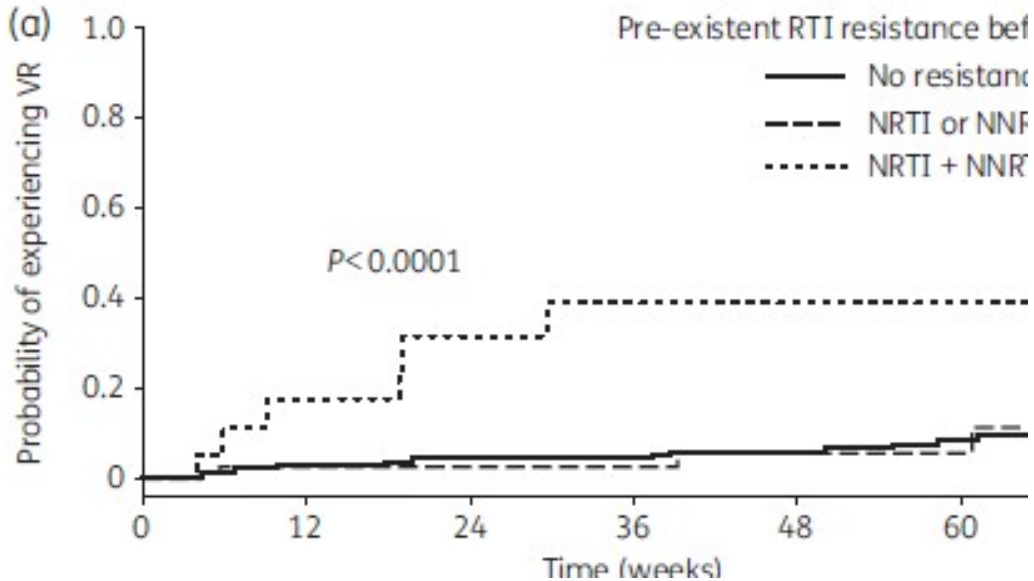
Which is the clinical significance of the archived mutations?

Which extent may the archived mutations influence the development of a clinically relevant antiretroviral resistance?

J Antimicrob Chemother 2017; **72**: 855–865

Pre-existent NRTI and NNRTI resistance impacts on ma virological suppression in HIV-1-infected patients who tenofovir/emtricitabine/rilpivirine single-tablet r

D. Armenia[1]†, D. Di Carlo[1]†, A. Calcagno[2], G. Vendemiati[2], F. Forbici[3], A. Bertoli[1], G. B
F. Continenza[3], V. Fedele[3], R. Bellagamba[4], S. Cicalini[4], A. Ammassari[4], R. Libertone[4]



Predictive Value of Provirus Load and I Human Immunodeficiency Virus Geno for Successful Abacavir-Based Simplifiec

JID 2003:187 (1 January) • Pelleg

Abilities of baseline virological parameters to predict virological outcome after switching from 2 NNRTI+s 1 PI to NRTI plus ABC

				Statistical ana		
				Univariate		
	Virologic outcome in ABC group (n = 49)			Success, failure, blip	Success vs. failure	Success vs. failure + blip
Parameters	Success (n = 22)	Failure (n = 17)	Blip (n = 10)	P[a]	P[a]	OR (95% CI)
Sex, M:F	3:19	3:14	1:9	1.00	1.00	0.99 (0.1–8.4)
Age in years[b]	40 [36, 46]	42 [39, 49]	45 [42, 54]	.42	.45	0.99 (0.1–8.4)
Baseline CD4$^+$ cell count, cells/μL[b]	522 [339, 740]	578 [331, 686]	393 [325, 616]	.42	.65	
Baseline DNA proviral load[b]	2.2 [2.0, 2.6]	2.8 [2.4, 3.2]	2.9 [2.3, 3.1]	.0012	.0023	0.1 (0.02–0.5)
Duration of virus suppression, months[b]	36 [29, 40]	38 [28, 44]		.88	.68	
Treatment history[c]						
1 Previous ART regimen	18 (82)	8 (47)	6 (60)	.06[d]	.04	3.25 (0.6–16.3)
≤3 Previous drugs	15 (68)	8 (47)	4 (40)	.28[e]	.21	
Previous monotherapy and/or dual therapy	1 (4.5)	6 (35.3)	2 (20)	.04	.03	
Baseline PBMC DNA sequences						
RT mutations/sequence[f]	0.21 (0–2)	1.2 (0–5)	0.5 (0–3)	.03	.0087	
ABC-resistance mutations[c]				.06[g]	.04	0.19 (0.0–1.1)
WT mutations	18 (82)	8 (47)	8 (80)			
1–3	4 (18)	7 (41)	2 (20)			

Pellegrin et Al JID 2003

Characteristics of patients experiencing virologic failure

ID	Age (yrs)	HAART Duration (mo)	HAART Regimen	CD4/µl	HIV-1 RNA Copies/mL	UUS HIV-1 RNA* Copies/mL	HIV-1 DNA Copies/10^6 PBMC	Mutations in Proviral DNA		Virologic Failure (Time)
								RT	PR	
M147	51	31	AZT/3TC/NFV	363	<50	2.8	10	M184V	—	month 18
M208	40	32	AZT/3TC/NVP	576	<50	ND	ND	M184V, V118I, K103N	—	month 3
M274	37	21	AZT/3TC/NVP	1098	<50	2.5	650	V108I	—	month 15
F186	33	19	AZT/3TC/NVP	392	<50	ND	ND	V108I	—	month 24
M133	36	33	AZT/3TC/EFV	399	<50	21	103	—	—	month 12

AZT, azidothymidine; 3TC, lamivudine; EFV, Efavirenz; NFV, Nelfinavir; NVP, Nevirapine; ND, not determined; PBMC, peripheral blood mononuclear cells; PR, protease; RT, reverse transcriptase; UUS, ultra-ultrasensitive assay.

*HIV-1 RNA by an ultra-ultrasensitive assay (limit of detection, 2.5 copies/mL).

Palmisano et al. J AIDS 2009

PLOS | ONE

RESEARCH ARTICLE

HIV Drug Resistance Mutations in Pr DNA from a Community Treatment

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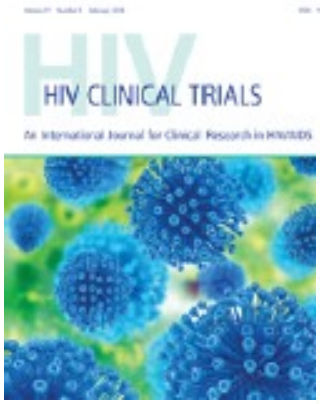
In assigning clinical significance to DRM in PBMC, the study is limited b modern suppressive regimens with relatively small numbers with virologic f follow-up of 46 weeks. However the frequency of DRM at entry among supp who developed virologic failure 4/11 (36%) was similar to DRM found amo mained suppressed, 17/68 (25%), suggesting that DRM in PBMC are not th



HIV Clinical Trials

Clinical Outcomes of Virologically-Suppre Patients with Pre-existing HIV-1 Drug Res Mutations Switching to Rilpivirine/Emtric Tenofovir Disoproxil Fumarate in the SPIR

Danielle P. Porter, Jonathan Toma, Yuping Tan, Owen Solberg,

Results: Drug resistance mutations in protease or reverse transcriptase were detected in historical RNA genotype and in 68.6% by proviral DNA genotyping at baseline. Proviral DNA 89% of occurrences of NRTI and NNRTI resistance-associated mutations reported by Mutations potentially affecting RPV activity, including E138A/G/K/Q, Y181C, and H22 isolates from 11 patients by one or both assays. None of the patients with single mutant through Week 48. One patient with pre-existing Y181Y/C and M184I by proviral DNA ge virologic failure. Nineteen patients with K103N present by historical genotype were confi sequencing and 18/19 remained virologically-suppressed.

Discussion: Virologic success rates were high among virologically-suppressed patients w and NNRTI resistance-associated mutations who switched to RPV/FTC/TDF in the SPIRI

Clin Microbiol Inf 2013

Analysis of intracellular human immunodeficiency virus (HIV)-1 dr resistance mutations in multi-failed infected patients treated with a sal

F. Falasca[1,†], C. Montagna[1,†], P. Maida[1], M. Bucc
Fantauzzi[2], L. Mezzaroma[2], G. Antonelli[1] and O.

Patients	Number of previous ARVs used	Number included
1	**5 PIs, 6 NRTIs, NNRTI, T20**	**0**
2	6 PIs, NNRTI, 7 NRTIs	1
3	6 PIs, 6 NRTIs, 2 NNRTIs, T-20	1
4	6 PIs, 6 NRTIs, 2 NNRTIs, T-20	0
5	3 PIs, 4 NRTIs	1
6	5 PIs, 6 NRTIs, NNRTI, T-20	1
7	4 PIs, NNRTI, 5 NRTIs, T-20	0
8	**4 PIs, 6 NRTIs, 2 NNRTIs, T-20**	**0**
9	6 PIs, 6 NRTIs, T-20	1
10	**6 PIs, 6 NRTIs, 2 NNRTIs**	**2**
11	6 PIs, 6 NRTIs, 2 NNRTIs, T-20	1
12	4 PIs, 2 NNRTIs, 6 NRTIs	1
13	**5 PIs, 2 NNRTIs, 6 NRTIs, T-20**	**1**
14	6 PIs, NNRTI, 7 NRTIs, T-20	1
15	**5 PIs, NNRTI, 6 NRTIs, T-20**	**0**
16	5 PIs, NNRTI, 4 NRTIs, T-20	0
17	**5 PIs, 2 NNRTIs, 6 NRTIs, T-20**	**1**
18	6 PIs, 6 NRTIs, 2 NNRTIs, T-20	0

Analysis of intracellular human immunodeficiency virus (HIV)-1 dr resistance mutations in multi-failec infected patients treated with a sal

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The human immunodeficiency virus (HIV) mutationa proviral DNA was monitored during a 72-week foll multidrug-experienced HIV-1-infected patients trea darunavir/ritonavir-based salvage therapy. At the begi study, all patients harboured a number of intrac resistance-associated mutations (RAMs) in peripl mononuclear cells. In some patients, a significant fl the number of RAMs was observed during the observa However, all patients, notwithstanding the prese fluctuation of intracellular RAMs, showed a persistent able viraemia. The data suggest that the archived re

Dolutegravir-based regimen maintains virological success in a patient with a to integrase inhibitors

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Falasca[a] *and Ombretta Turriziani*[a], [a]Depa
Molecular Medicine, and [b]Department c

AIDS 2017, Vol 31 N

B.A. HIV+ 1986

PLASMA 2013

T69N, K70R, L74V, Y115F, Y181I, M184V, H208Y, T215V, K219E, H221Y

ABC *ddI* *3TC/FTC* *D4t* *TDF* *AZT* *EFV* ETR NVP RPV

V32I, L33F, M36L, M46I, I47V, I54M, Q58E, A71V, G73S, L89V, L90M

ATV ATV/r DRV/r FPV FPV/r IDV IDV/r LPV LPV/r NFV SQV/r TPV

RAL

Feb 2015

VL 2651 cp/mL

PLASMA/PBMCs Feb2015

M41L, T69N, K70R, H208Y, T215V, K219E

ABC ddI 3TC/FTC D4t TDF AZT EFV ETR NVP RPV

V32I, L33F, M36L, M46I, I47V, I54M, Q58E, A71V, G73S, L89V, L90M

ATV ATV/r DRV/r FPV FPV/r IDV IDV/r LPV LPV/r NFV SQV/r TPV/r

E138A, G140S, Q148H

RAL EVG DTG

cART

Dic 2015

VL 2430 cp/mL

Dec 2015

PLASMA

T69N, K70R, L74V, Y115F, Y181I, M184V, H208Y, T215V, K219E, H221Y

ABC *ddI* *3TC/FTC* *D4t* *TDF* *AZT* *EFV* ETR NVP RPV

V32I, L33F, M36L, M46I, I47V, I54M, Q58E, A71V, G73S, L89V, L90M

ATV ATV/r DRV/r FPV FPV/r IDV IDV/r LPV LPV/r NFV SQV/r TPV/r

No mutations

RAL EVG DTG

DTG

Mar 2016
VL <37 cp/ml

Sept 2016
VL TND

Sep 2016

PBMCs

T69N, K70R, L74V, Y115F, Y181I, M184V, H208Y, T215V, K219E, H221Y

ABC *ddI* *3TC/FTC* *D4t* *TDF* *AZT* *EFV* ETR NVP RPV

V32I, L33F, M36L, M46I, I47V, I54M, Q58E, A71V, G73S, L89V, L90M

ATV ATV/r DRV/r FPV FPV/r IDV IDV/r LPV LPV/r NFV SQV/r TPV/r

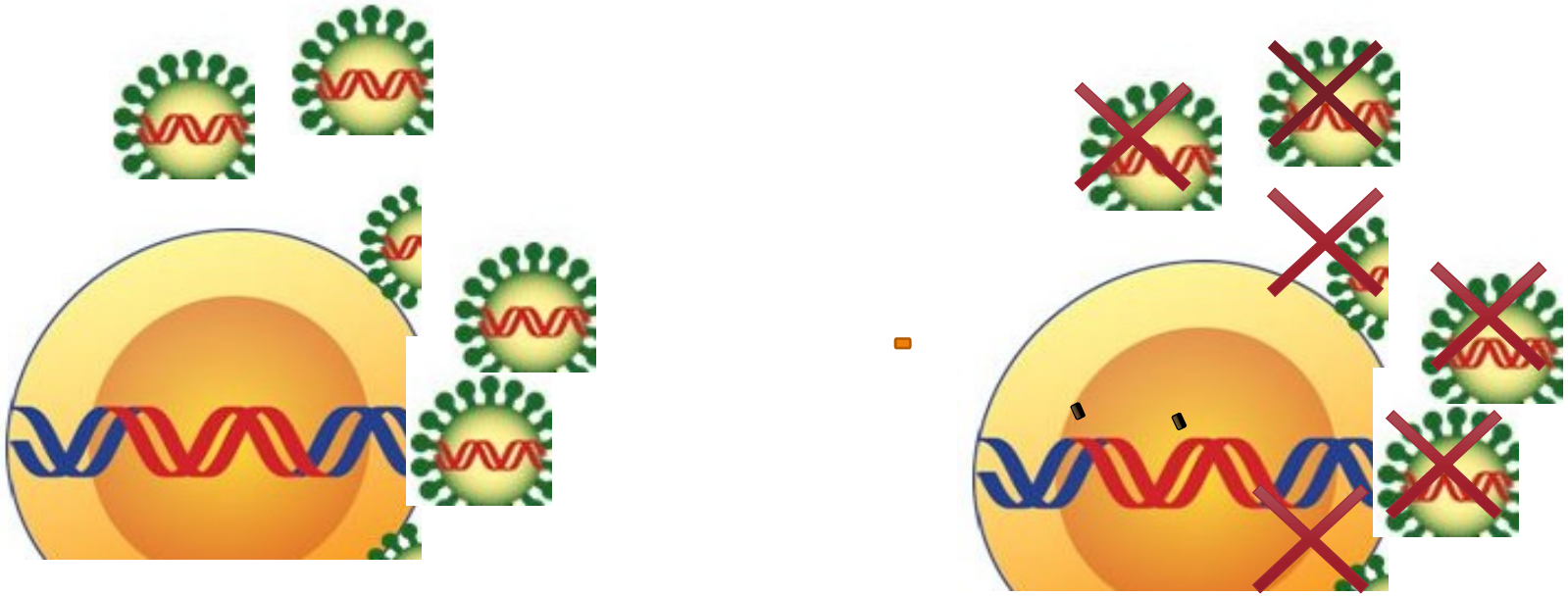
E138A, G140S, Q148H

RAL EVG DTG

June 2017
VL TND

Archived viral resistant variants

REPLICATION COMPETENT **or** **DEFECTIVE GENOME**



viral outgrowth assay should be performed to better characterized the archived resistant viral varints

CONCLUSIONS

- The clinical significance of proviral resistance is not fully defined

- Proviral DNA genotyping may provide value as an additional source of information on the total burden of drug resistance present in virologically- suppressed patients, particularly for those who lack a historical RNA genotype and/or have a complex treatment history.

- In 'difficult patients' archived DRMs in DNA should not limit the use of new generation drugs as a salvage-treatment option

- Further studies of proviral DNA sequences and sequences analysis in monitoring ART are warranted