Clinical Case

Prof.ssa Cristina Mussini

Clinical history

- Male, born in Ivory Coast in 1968.
- HIV positive since dal 1998
- Risk factor: heterosexual contacts

- He started antiretroviral therapy in 2001 with Nelfinavir+ABC/DDI CD4 350 VL 7500 copies/mL

Antiretroviral therapy

14/09/2009	19/10/2012	ATV	RTV	TDF/FTC	
10/07/2009	14/09/2009	EFV	TDF/FTC		
26/03/2008	10/07/2009	NEV	TDF/FTC		
25/03/2008	26/03/2008	NEV			
27/04/2004	25/03/2008	3TC	AZT	NEV	
17/11/2001	27/04/2004	ABC	DDI	NFV	

He has always claimed to be adherent!!!

BUT.....

	Data	WBC	Hb	Plt	Linfo	CD4%	CD4Tot	CD8%	HIV-VL	HBsAg_Q	HCV_Q	Bili	GOT	GPT	yGT	FA	Trig	Col	C-HI
	29/11/2011	8260	12.7	492	1340	33.33	446.62	37.59	57			0.67	27	24	44	106	81	179	50
	20/07/2011	3720	14.7	310	1360	34.33	466.89	39.39	40			1.38	46	42	44	121	114	243	55
	02/02/2011	4600	15.5	283	2010	32.85	660.29	39.73	40			2.03	42	41	57	106	177	258	
	10/09/2010	5350	15.9	317	2640	23.12	610.37	34.37	147			1.11	42	44	56	108	403	307	48
	11/05/2010	5240	14.7	316	2430	35.93	873.10	40.04	40			1.53	39	35	48	127	82	227	52
	11/01/2010	4280	15.5	291	2100	30.64	643.44	38.84	40			1.50	30	29	63	140	183	252	
	11/09/2009	4490	14.8	324	2380	26.73	636.17	36.55	97			0.09	50	45	112	162	160	264	57
	23/06/2009	4110	14.2	306	2270	33.17	752.96	39.48	43			0.20	41	34	154	165	94	236	69
	27/02/2009	4190	15.0	268	2150	29.61	636.62	38.74	50			0.20	40	53	192	141	147	212	
	12/12/2008	4050	15.4	274	2170	32.16	697.87	40.11	65			0.18	50	57	141	141	184	201	60

- In January 2012 he received a diagnosis of non-Hodgkin Lymphoma stage IIIB on a lymph node. He underwent 6 cycles of chemotherapy R-CHOP (finished in August 2012)
- After the first cycle he developed seizures and he was admitted to hospital with a diagnosis of extended thrombosis of cavernous sinus, thus treatment with low molecular weight heparin was started.
- In September 2012 CT and PET scan showed a complete remission of NHL.

What is happening in the immuno-virological situation?

Data	WBC	Hb	Plt	Linfo	CD4%	CD4Tot	CD8%	HIV-VL
13/08/2012	7290	12.2	365					**838**
07/08/2012	2120	11.1	296					838

What would you do?

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Virologic Definitions

Virologic suppression: A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).

Virologic failure: The inability to achieve or maintain suppression of viral replication (to an HIV RNA level <200 copies/mL).

Incomplete virologic response: Two consecutive plasma HIV RNA levels >200 copies/mL after 24 weeks on an ARV regimen. Baseline HIV RNA may affect the time course of response, and some regimens will take longer than others to suppress HIV RNA levels.

EACS European AIDS Clinical Society

VIROLOGICAL FAILURE

Definition	Confirmed HIV-VL > 50 copies/mL 6 months after starting therapy (initiation or modification) in persons that remain on ART
General measures	Review expected potency of the regimen
	Evaluate adherence, compliance, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues
	Perform resistance testing on failing therapy (usually routinely available for HIV-VL levels > 350-500 copies/ mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations
	Tropism testing
	Consider TDM
	Review antiretroviral history
	Identify treatment options, active and potentially active drugs/combinations
Management of virological failure (VF)	If HIV-VL > 50 and < 500-1000 copies/mL
	Check for adherence
	Check HIV-VL 1 to 2 months later
	If genotype not possible, consider changing regimen based on past treatment and resistance history
	If HIV-VL confirmed > 500/1000 copies/mL, change regimen as soon as possible. What to change will depend on the resistance testing results:
	No resistance mutations found: re-check for adherence, perform TDM
	Resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary expert discussion advised
	Goal of new regimen: HIV-VL < 400 copies/mL after 3 months, HIV-VL < 50 copies/mL after 6 months

2.1.5 Managing virological failure (Section 7)

2.1.5.1 Blips, low-level viraemia and virological failure

7.2	In patients on ART:	
	A single VL 50–400 copies/mL preceded and followed by an undetectable VL is usually not a cause for clinical concern.	GPP
	We recommend a single VL >400 copies/mL is investigated further, as it is indicative of virological failure.	1C
	We recommend in the context of repeated viral blips, resistance testing is attempted.	1D

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

Novembre 2013

Tabella 1 - Definizione di fallimento terapeutico e relative azioni

	DEFINIZIONE	AZIONI	MODIFICA cART	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Fallimento virologico	Mancata soppressione dell'HIV-RNA plasmatico < 50 copie/mL dopo 24 settimane dall'inizio della stessa o dall'incremento della replicazione virale plasmatica, confermato in due determinazioni consecutive in pazienti che avevano precedentemente raggiunto una soppressione virale completa*.	• Rivalutare l'aderenza; • Rivalutare le interazioni farmacologiche; • Effettuare il test di resistenza per N(t)RTI, NNRTI, IP (per INI e IF se applicabile); • Effettuare la determinazione del tropismo virale**	Si	[AI]	[17, 24-36]

Clinical Infectious Diseases Advance Access published September 6, 2013

MAJOR ARTICLE HIV/AIDS

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

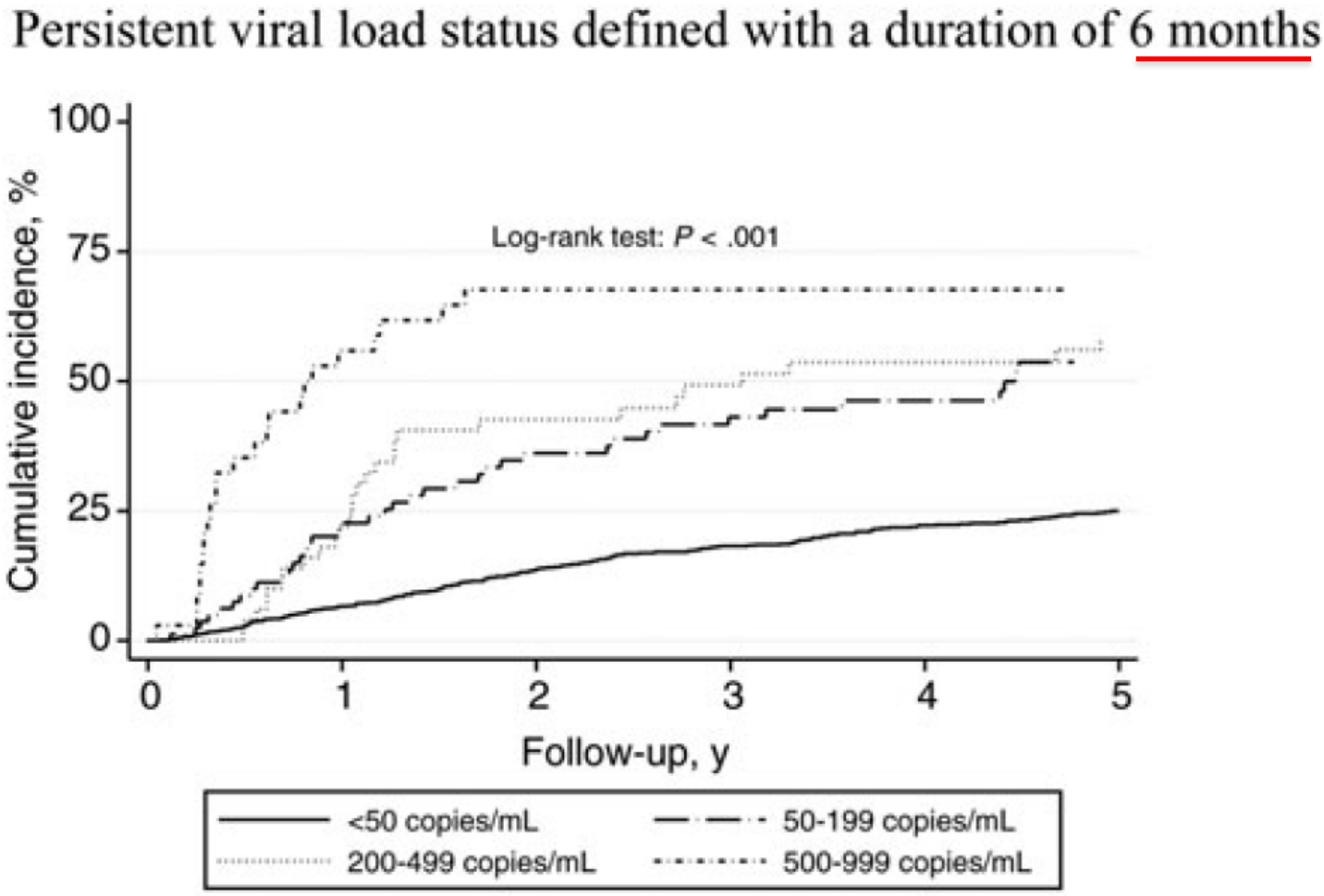
Background. The current goal of antiretroviral therapy (ART) is to maintain a suppressed human immunodeficiency virus (HIV) viral load below limits of assay detection. When viral loads remain in low-level viremia (LLV), especially between 50 and 200 copies/mL, the best management and clinical consequences 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.

The cumulative incidences of subsequent virologic failure (ie, > 1000 copies/mL) over 5 years, following persistence of LLV was significantly higher for all LLV strata compared to those who maintained undetectable HIV load.



Laprise et al, CID 2013

Data	WBC	Hb	Plt	Linfo	CD4%	CD4Tot	CD8%	HIV-VL
19/11/2012	3070	13.4	627	1680	23.02	386.74	45.01	40
14/11/2012	5130	12.4	344					
09/10/2012	3370	14.2	212	1670	23.33	389.61	47.36	**6431**
20/09/2012	3470	12.4	310	1250	27.24	340.50	52.83	
11/09/2012	3140	12.1	326					
04/09/2012	3020	12.4	338	1030	30.36	312.71	48.42	**3554**
29/08/2012	2240	11.4	219					
23/08/2012	2950	11.2	206					
13/08/2012	7290	12.2	365					**838**
07/08/2012	2120	11.1	296					838

- VL is confirmed not only detectable, but increasing despite the patients claims to be very adherent

What would you do?

Genotypic Test

DATA 07/08/2012 NUM

RT	RNA plasma	SUB CRF02	PRO	RNA plasma	SUB CRF02
ESITO	68G 74V 90I 184V		ESITO	13V 16E 20I 36I	
RTaltro	35T 60I 122E 123N 135V 162A 165I 173T 174K 177E 200A 207E 211K 245E		PROaltro	14R 37D 41K 69K 70R 89M	
Nulla	AZT D4T EFV ETV NVP TDF		Nulla	ATV ATV/rtv DRV/rtv FPV/rtv LPV/rtv N	
Trasc			Trasc		
Mod			Mod		
Cons	ABC DDI		Cons		
Elev	3TC FTC		Elev		
COM	Resistenza prevista - Elevata: 3TC FTC. Consistente: ABC DDI. Parziale: . Trascurabile: . Nessuna: AZT D4T EFV ETV NVP		COM	Resistenza prevista - Elevata: . Consistente: . Parziale: . Trascurabile: . Nessuna: ATV ATV/rtv DRV/rtv FPV/rtv LPV/rtv	
NOTE	Nella predizione sono computate le seguenti sensibilizzazioni: 74V/I (AZT, TDF), 184V/I (AZT, D4T,		NOTE		
DATA	06/09/2012		DATA	06/09/2012	

Tropisms

FPR 13.2%

No resistance associated mutation

What would you do?

- After the results of the genotypic test therapy was modified

with **DRV/R (800/100) + MVC 300 mg/die**.

WHY?

The decision was based on the presence of the mutation **74V**

Major HIV-1 Drug Resistance Mutations

Updated June 22, 2013

Updated summary from the HIV Drug Resistance Database. This document can be downloaded from the http://hivdb.stanford.edu home page. Detailed and referenced versions of each drug class summary can be found at http://hivdb.stanford.edu/pages/drugSummaries.html

Major Nucleoside RT Inhibitor (NRTI)-Resistance Mutations													
	Non-TAMs					TAMs						MDR	
	184	65	70	74	115	41	67	70	210	215	219	69	151
Cons	M	K	K	L	Y	M	D	K	L	T	K	T	Q
3TC	**VI**	**R**	E									**Ins**	**M**
FTC	**VI**	**R**	E									**Ins**	**M**
ABC	**VI**	**R**	E	**VI**	**F**	L			W	YF		**Ins**	**M**
ddI	**VI**	**R**	E	**VI**		L			W	YF		**Ins**	**M**
TDF	***	**R**	E		F	L		R	W	YF		**Ins**	**M**
d4T	***	**R**	E			**L**	**N**	**R**	**W**	**YF**	QE	**Ins**	**M**
ZDV	***	***	*	*		**L**	**N**	**R**	**W**	**YF**	QE	**Ins**	**M**

Table 1. Comparison of the percentage of patients who took the different drugs in the 74I vs. the 74V group, as a function of the two different inclusion criteria[a].

	Inclusion criteria L1 ($n=55$)			Inclusion criteria L2 ($n=74$)		
Drug	L74I ($n=26$) (%)	L74V ($n=29$) (%)	P^b	L74I ($n=32$) (%)	L74V ($n=42$) (%)	P^b
Zidovudine	**42**	**7**	**0.003**	**37**	**10**	**0.005**
Stavudine	23	10	0.281	34	17	0.103
Didanosine	27	55	0.055	**34**	**62**	**0.034**
Abacavir	62	69	0.584	56	64	0.631
Lamivudine	92	76	0.148	94	81	0.171
Tenofovir	**27**	**0**	**0.003**	**31**	**10**	**0.033**
Nevirapine	8	24	0.148	**9**	**29**	**0.047**
Efavirenz	23	34	0.389	25	29	0.796

[a]Two inclusion criterion levels, L1and L2, based on the number of antiretroviral drug combinations (1 only, 1 to 2, respectively), used between the two tests showing an L74 change.
[b]Fisher' exact tests; significant differences in bold.

Wirden et al. *AIDS* 2009, **23**:95–99

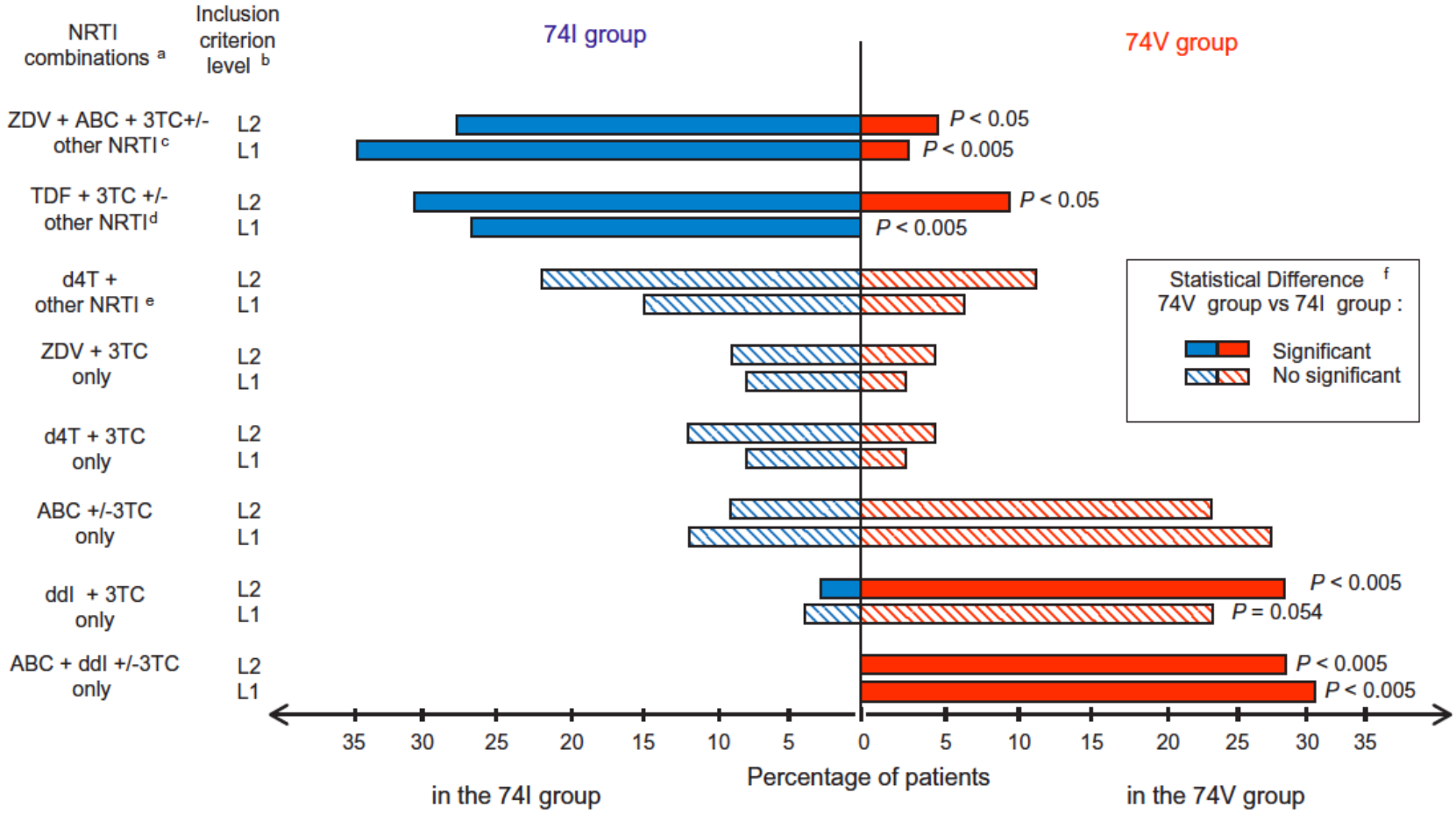


Fig. 1. Percentage distribution of patients who took the different nucleoside reverse transcriptase inhibitor combinations in the 74V and 74I groups, as a function of the two inclusion criterion levels. (a) 3TC, lamivudine; ABC, abacavir; d4T, stavudine; ddI,

Wirden et al. *AIDS* 2009, **23**:95–99

… Clinical evolution

Data	WBC	Hb	Plt	Linfo	CD4%	CD4Tot	CD8%	HIV-VL
14/06/2013	3890	13.8	305	1730	26.46	457.76	40.09	271
30/04/2013	5380	14.4	270	2140	28.00	599.20	45.93	135
29/03/2013	5090	13.8	279	2070	31.57	653.50	49.93	62
22/01/2013	3260	13.1	295	1570	26.49	415.89	46.88	40
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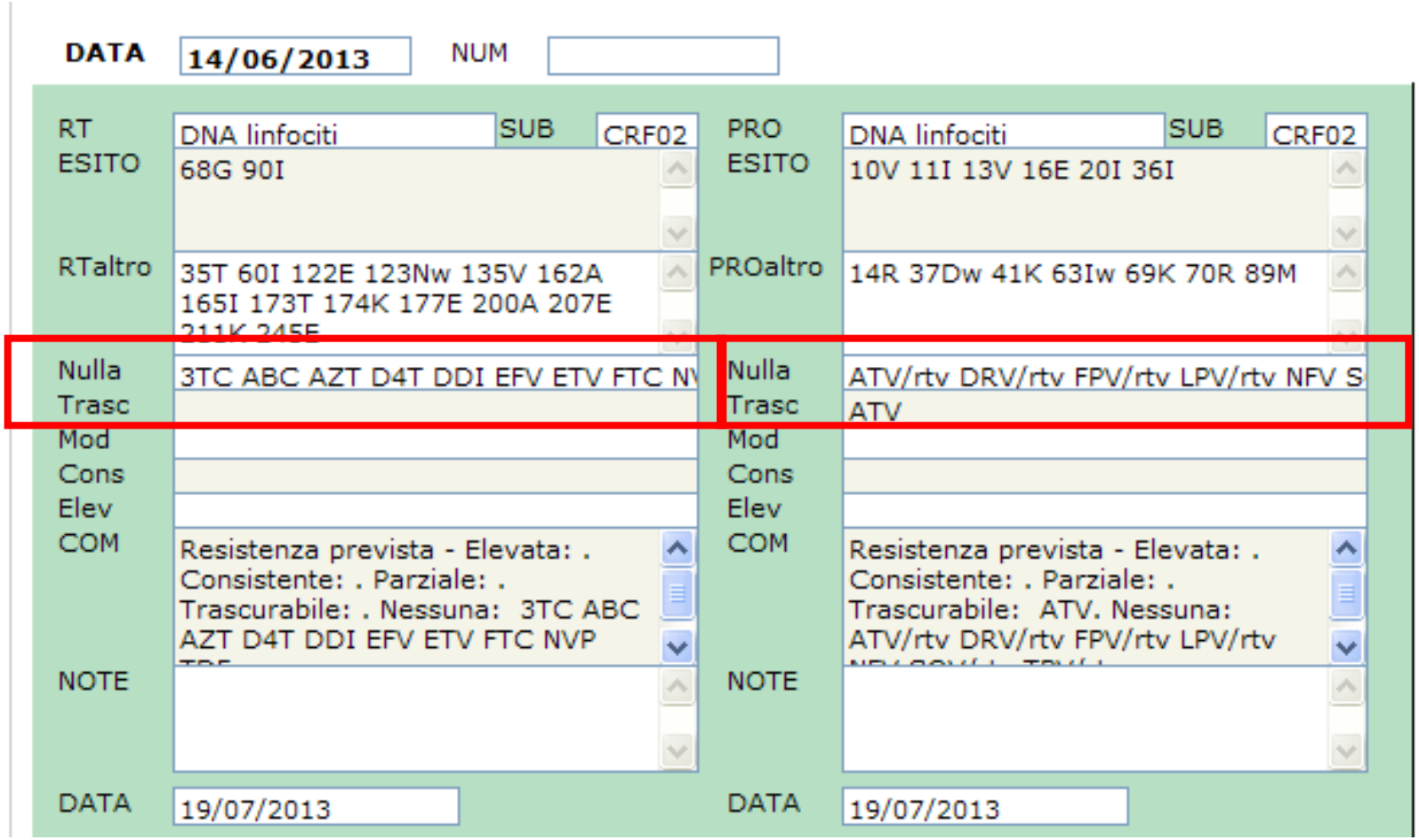
13/08/2012	7290	12.2	365					**838**
07/08/2012	2120	11.1	296					838

What would you do?

New genotypic test



DATA	14/06/2013	NUM			
RT	DNA linfociti	SUB	CRF02		
ESITO	68G 90I				
RTaltro	35T 60I 122E 123Nw 135V 162A 165I 173T 174K 177E 200A 207E 211K 245E				
Nulla	3TC ABC AZT D4T DDI EFV ETV FTC NV				
Trasc					
Mod					
Cons					
Elev					
COM	Resistenza prevista - Elevata: . Consistente: . Parziale: . Trascurabile: . Nessuna: 3TC ABC AZT D4T DDI EFV ETV FTC NVP				
NOTE					
DATA	19/07/2013				
				PRO	DNA linfociti
				SUB	CRF02
				ESITO	10V 11I 13V 16E 20I 36I
				PROaltro	14R 37Dw 41K 63Iw 69K 70R 89M
				Nulla	ATV/rtv DRV/rtv FPV/rtv LPV/rtv NFV S
				Trasc	ATV
				Mod	
				Cons	
				Elev	
				COM	Resistenza prevista - Elevata: . Consistente: . Parziale: . Trascurabile: ATV. Nessuna: ATV/rtv DRV/rtv FPV/rtv LPV/rtv
				NOTE	
				DATA	19/07/2013

Previous test: RT: 68G, 74V, 90I,184V **PRO: 13V,16E,20I,36I**

What would you do?

Therapy was modified to

ETV + DRV/r BID plus **MVC**

... Clinical evolution

Data	WBC	Hb	Plt	LInfo	CD4%	CD4Tot	CD8%	HIV-VL
23/01/2014	4370	13.8	307	2230	27.49	613.03	38.66	148
26/09/2013	3790	13.8	289	1710	29.52	504.79	40.76	116
13/08/2013	4620	12.7	258	1560	26.42	412.15	41.63	44
14/06/2013	3890	13.8	305	1730	26.46	457.76	40.09	271
30/04/2013	5380	14.4	270	2140	28.00	599.20	45.93	135
29/03/2013	5090	13.8	279	2070	31.57	653.50	49.93	62
22/01/2013	3260	13.1	295	1570	26.49	415.89	46.88	40
17/12/2012								
19/11/2012	3070	13.4	627	1680	23.02	386.74	45.01	40

What would you do?

GENOTIPO RT DNA linfociti

Data lettura 14/02/2014

ESITO 67Nw 68Gw 90Iw (Altre mutazioni:35T 60Iw 122E 123Nw 135Vw 158Sw 162Aw 165Iw 173T 174K 177E 200A 207E 211K 245E)

Resistenza prevista

Subtype **CRF02_AG**

NULLA	3TC ABC DDI EFV ETV FTC NVP TDF
TRASCURABIL	AZT D4T
PARZIALE	
CONSISTENTE	
ELEVATA	

NRTI: 3TC=lamivudina, AZT=zidovudina, D4T=stavudina, DDI=didanosina, DDC=zalcitabina, ABC=abacavir

NNRTI: DLV=delavirdina, EFV=efavirenz, NVP=nevirapina, ETV=etravirina NtRTI: TDF=tenofovir

GENOTIPO

DNA linfociti

Data lettura 14/02/2014

ESITO 10V 13V 16E 20I 36I (Altre mutazioni:14R 37Dw 41K 69K 70R 72Vw 89M)

Resistenza prevista

Subtype **CRF02_AG**

NULLA	ATV ATV/rtv DRV/rtv FPV/rtv LPV/rtv NFV SQV/rtv T
TRASCURABIL	
PARZIALE	
CONSISTENTE	
ELEVATA	

APV=amprenavir, ATV= atazanavir, IDV=indinavir, LPV=lopinavir/r, NFV=nelfinavir, SQV=saquinavir, RTV=ritonavir, TPV=tipranavir, DRV=Darunavir

Materiale: Plasma

Subtype C

V3 -CORECETTORE: **CXCR4** **FPR %: 1,3**

ESITO Maggiori: None Minori: E157Q (Altre mutazioni:K14R, S17NS, W19*W, S24NS, G47EG, V79IV, L101I, T112V, T124A, T125A, W131*W, G134N, I135V, K136T, G149EG, K160Q, R166KR, V201I, T206S, I208IL, R224QR, L234I, G245GS, R269K, S283G)

Resistenza prevista

Subtype CRF02_AG

Antiretroviral therapy

03/03/2014		DRV	ETR	RTV	
12/07/2013	03/03/2014	DRV	ETR	MVC	RTV
02/07/2013	12/07/2013	DRV	ETR	MVC	RTV
19/10/2012	02/07/2013	DRV	MVC	RTV	

Managing Persistent Low Level Viremia

Management of LLV/VLLV	**If HIV-VL > TND and < 50 copies/mL** Check for adherence Check for potency and genetic barrier of the regimen, Check time with viral load below 50 copies/ml, Check history of treatment Check inmune activation markers Check drug levels Before making clinical decisions aiming to bring them to the “No Signal” viral load