Presence of drug resistance during the course of treatment in patients who developed virologic failure to the three original classes of antiretroviral drug

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Frank de Wolf (1,2), **on behalf of the PLATO II Project Team**
Collaboration of Observational HIV Epidemiological Research Europe (COHERE)
(1) HIV Monitoring Foundation, Amsterdam, NL and (2) Imperial College London, UK

Correspondence:
Professor Frank de Wolf,
Stichting HIV Monitoring
Academic Medical Centre of the University of Amsterdam,
Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
Email: f.dewolf@amc.uva.nl
Tel +31 20 5664172

Abstract

Objectives
To describe the extent to which resistance to the three main classes is present in patients who experience triple class virologic failure (TCVF).

Methods
Adult patients within the COHERE collaboration who developed TCVF were identified. Virologic failure of a drug was defined by a viral load >500 copies/ml despite four months of continuous use; TCVF was defined as virologic failure of two NRTIs, an NNRTI, and a ritonavir-boosted PI. Data were included from all resistance tests performed in routine patient care up to 4 months after TCVF.

Results
Of 2271 patients with TCVF, 1100 (48.4%) were from cohorts able to provide resistance data. Of these, mutation data was available for 722 (65.6%) patients (1514 tests). Pre-ART resistance data was available for 118 patients: 17 (14.4%) had an NRTI mutation, 13 (11.0%) had an NNRTI mutation, 11 (9.3%) had a PI mutation, and 5 (4.2%) had triple class resistance. Overall, 618 patients had a resistance test while on an NRTI after NRTI failure, of whom 444 (71.8%) had an NRTI mutation: 214 (34.6%) had a TAM, 303 (49.0%) had M184V, 52 (8.4%) had K65R, 58 (9.4%) had L74V. Of 240 patients with a resistance test while on a PI after failing a PI/r, 65 (27.1%) had a PI mutation. Of 427 patients with a resistance test while still on an NNRTI after NNRTI failure, 372 (87.1%) had an NNRTI mutation: 199 (46.6%) had K103N, 93 (21.8%) had Y181C, 66 (15.5%) had G190A. Of these 372 patients, 100 later had a resistance test while on a PI- and NRTI- (but not NNRTI-) containing regimen: 61 had an NNRTI mutation.

Conclusion
In this context of patients who subsequently virologically failed the original three classes, less than one third of patients who had virologically failed a protease inhibitor carried any protease inhibitor mutations.

Background

Current regimens of combination antiretroviral drugs (cART) tend to lead to sustained HIV suppression in the majority of patients but rates of virologic failure remain substantial. Virologic failure occurs as a result of an uncertain mixture of sub-optimal adherence and development of resistance. As most initial regimens used so far contain drugs from the original three ART classes, nucleos(t)ide reverse transcriptase inhibitors (NRTI) non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI), failure of the three original classes represents a key stage in the treatment of infected patients. We investigated the extent to which resistance to the three main classes is present in a large group of patients who experienced triple class failure (TCVF).

Methods

We analysed data of HIV- infected patients (aged >16 years at the time of starting cART) who developed TCVF. Data of these patients are collected through one of the xx cohorts that participate in the PLATO II project of COHERE.
Virologic failure of a drug was defined by a viral load >500 copies HIV-RNA per ml plasma, despite four months of continuous use. TCVF was defined as virologic failure of two NRTI's, an NNRTI and a ritonavir-boosted PI. Data were included from all resistance tests performed in routine patient care up to 4 months after TCVF.

Patients with resistance data

We evaluated 2,271 patients from 22 cohort studies across Europe with TCVF; 1,100 (48.4%) were from xx cohorts able to provide resistance data. Of these, mutation data were available for 722 (65.6%) patients, with in total 1514 resistance tests.

		No resistance data		Resistance data	
		n=1549	*100%*	n=722	*100%*
Gender	Female	476	*30.7*	219	*30.3*
	Male	1073	*69.3*	503	*69.7*
Risk group	Homosexual men	374	*24.1*	232	*32.1*
	Heterosexual	759	*49.0*	332	*46.0*
	IDU	287	*18.5*	93	*12.9*
	Other / unknown	129	*8.3*	65	*9.0*
Year of starting ART	1998	475	*30.7*	227	*31.4*
	1999	357	*23.0*	161	*22.3*
	2000-2001	450	*29.1*	187	*25.9*
	2002-2007	267	*17.2*	147	*20.4*
Year of TCVF	1998-2001	239	*15.4*	57	*7.9*
	2002-2003	409	*26.4*	184	*25.5*
	2004-2005	585	*37.8*	253	*35.0*
	2006-2008	316	*20.4*	228	*31.6*
Pre-ART AIDS	Yes	408	*26.3*	212	*29.4*
AIDS before TCVF	Yes	590	*38.1*	311	*43.1*
Age at start of ART	*years*	36 (31-41)*		35 (30-40)*	
Age at TCVF	*years*	40 (35-45)*		39 (34-45)*	
Pre-ART CD4 count	*cells mm^3*	185 (62-317)*		127 (40-252)*	
CD4 count at TCVF	*cells mm^3*	265 (136-414)*		267 (136-398)*	
Pre-ART viral load	*log$_{10}$ copies/ml*	4.9 (4.2-5.5)*		5.1 (4.6-5.5)*	
Viral load at TCVF	*log$_{10}$ copies/ml*	4.0 (3.3-4.8)*		4.0 (3.2-4.9)*	

* Median (IQR); Pre-ART CD4 count and viral load: within 6 months prior to the start of ART. CD4 count available for 1366 (88.2%) patients without resistance data and 580 (80.3%) patients with resistance data. Viral load available for 1290 (83.3%) patients without resistance data and 572 (79.2%) patients with resistance data.
CD4 count at TCVF: within 6 months prior to TCVF. Available for 1547 (99.9%) patients without resistance data and 722 (100%) patients with resistance data.

Pre-ART resistance tests

Pre-ART resistance data was available for 118 patients: 17 (14.4%) had an NRTI mutation, 13 (11.0%) had an NNRTI mutation, 11 (9.3%) had a PI mutation, and 5 (4.2%) had triple class resistance.

"On treatment" resistance tests

NRTI

Overall, 618 patients had a resistance test while on an NRTI after NRTI failure, of whom 444 (71.8%) had an NRTI mutation: 214 (34.6%) had a TAM, 303 (49.0%) had M184V, 52 (8.4%) had K65R, 58 (9.4%) had L74V.

NRTI mutations (618 patients):

Mutation	n	%	Mutation	n	%
69 ins	4	0.6	115F	14	2.3
41L	114	18.4	116Y	13	2.1
62V	32	5.2	151M	19	3.1
65R	52	8.4	184I	25	4.0
67N	109	17.6	184V	303	49.0
70E	11	1.8	210W	50	8.1
70R	84	13.6	215Y	89	14.4
74V	58	9.4	215F	43	7.0
75I	24	3.9	219Q	34	5.5
77L	12	1.9	219E	39	6.3
TAM	214	34.6			
41L, 67N, 70E, 70R, 210W, 215Y, 215F, 219Q, 219E					

PI

Of 240 patients with a resistance test while on a PI after failing a PI/r, 65 (27.1%) had a PI mutation.

PI mutations (240 patients):

Mutation	n	%	Mutation	n	%
30N	7	2.9	54M	5	2.1
32I	8	3.3	58E	2	0.8
33F	11	4.6	74P	1	0.4
46I	24	10.0	76V	4	1.7
46L	7	2.9	82F	6	2.5
47V	7	2.9	82A	18	7.5
47A	0	0.0	82T	5	2.1
48V	7	2.9	82S	3	1.3
50V	4	1.7	82L	0	0.0
50L	3	1.3	84V	16	6.7
50M	1	0.4	88S	5	2.1
54L	5	2.1	90M	40	16.7

"On treatment" resistance tests (cont'd)

NNRTI

Of 427 patients with a resistance test while still on an NNRTI after NNRTI failure, 372 (87.1%) had an NNRTI mutation: 199 (46.6%) had K103N, 93 (21.8%) had Y181C, 66 (15.5%) had G190A. Of the 372 patients with an NNRTI mutation when on treatment, 100 later had a resistance test while on a PI- and NRTI- (but not NNRTI-) containing regimen; 61 patients still had an NNRTI mutation.

NNRTI mutations (427 patients):

Mutation	n	%
100I	20	4.7
101E	37	8.7
101H	0	0.0
101P	6	1.4
103N	199	46.6
106A	24	5.6
106M	14	3.3
108I	34	8.0
181I	8	1.9
181C	93	21.8
181V	2	0.5
188C	5	1.2
188L	66	15.5
188H	8	1.9
190S	20	4.7
190A	66	15.5
225H	33	7.7

Conclusion

Pre-cART resistance amongst patients who subsequently failed the original three classes of NRTI, NNRTI and PI with triple class virological failure seems to be limited, although pre-cART triple class resistance is found in 4%. In addition, selection of patients who were tested pre-cART might bias the proportion with resistance.
Whilst on NRTI and NNRTI containing cART, the prevalence of NRTI and NNRTI resistance associated mutations found in patients with triple class virological failure is high. In contrast, less than one third of patients who had virologically failed a boosted protease inhibitor carried any protease inhibitor mutations.

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COHERE Steering Committee
Executive Committee: Ian Weller (Chair, University College London), Dominique Costagliola (Vice-chair, FHDH), Bruno Ledergerber (Vice-chair, SHCS), Jens Lundgren (Head, Copenhagen Regional Co-ordinating Centre), Genevieve Chene (Head, Bordeaux Regional Co-ordinating Centre).
Cohort representatives: Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Cecile Goujard (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Frank de Wolf (ATHENA), Peter Reiss (ATHENA), Knolsud Porter (CASCADE), Maria Dorrucci (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne Bonn), Julia Del Amo (Co-RIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Schlomo Staszewski (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Jesus Almeda (HIV-MIP), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA, IMIT), Pier-Angelo Tovo (ITLR), Maurizio de Martino (ITLR), Bernd Salzberger (KOMPNET), José Ramos (Madrid Cohort), Manuel Battegay (MoCHIV, SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Stephane de Wit (St. Pierre Cohort), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH),Myriam Garrido (VACH).
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