

Poster # 659

14th Conference on Retroviruses and Opportunistic Infections, 2007, Los Angeles, USA



Resistance Mutations Predict Mortality in HIV Patients with Triple-class Antiretroviral Drug Failure



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Abstract

Objective: To examine the prevalence of mutations in HIV patients with triple-drug class virological failure (TCF) and their association with long-term mortality.
Design: Population-based study from the Danish HIV Cohort Study (DHCS).
Methods: We included all patients in the DHCS who experienced TCF between January 1995 and November 2004, and we performed genotypic resistance testing for IAS-USA primary mutations on virus from plasma samples taken around the date of TCF. We computed time to all-cause death from date of TCF. The relative risk of death according to the number of mutations and individual mutations was estimated by Cox regression analysis and adjusted for potential confounders.
Results: Resistance tests were done for 133 of the 179 patients who experienced TCF. The median number of resistance mutations was eight (interquartile range, 2-10), and 81 (61%) patients had mutations towards all three major drug classes. In a regression model adjusted for CD4 count, HIV RNA, year of TCF, age, gender, and previous inferior antiretroviral therapy, harboring ≥9 vs. ≤8 mutations was associated with increased mortality (mortality rate ratio (MRR)=2.3 (95% confidence interval: 1.1-4.8)), as were the individual mutations T215Y (MRR=3.4 (1.6-7.0)), G190A/S (MRR=3.2 (1.6-6.5)), and V82F/A/T/S (MRR=2.5 (1.2-5.3)). When adjusting for the latest (time-updated) CD4 count, only the T215Y mutation remained a prognostic factor for death (MRR=3.0 (1.3-7.0)), along with the latest CD4 count.
Conclusions: In HIV patients with TCF, the total number of genotypic resistance mutations and specific single mutations predicted mortality and were associated with a further decline in CD4 count.

Patient characteristics	Patients with resistance test		Comparison of patients with and without resistance test
	Number (%)	Number (%)	
Total	133 (76)	146 (82)	
Male gender	101 (76)	104 (72)	0.783
ART-naïve at initiation of HAART	24 (18)	14 (10)	0.077
Risk exposure			
MSM	71 (53)	22 (16)	0.573
heterosexual contact	46 (34)	15 (11)	
Other	4 (3)	4 (3)	
Other	12 (9)	5 (4)	
AIDS before initiation of HAART	65 (49)	17 (12)	0.162
Race			
Caucasian	109 (82)	35 (25)	0.510
Black African	20 (15)	8 (6)	
Other	4 (3)	3 (2)	
Year of TCF			0.241
1987	24 (18)	5 (4)	
1989	37 (28)	16 (12)	
2000	29 (22)	8 (6)	
2001	15 (11)	2 (2)	
2002	1 (1)	1 (1)	
2003	0 (0)	1 (1)	
Median (IQR) CD4 count at initiation of HAART	80 (30-170)	100 (22-220)	0.363
Median (IQR) CD4 count at time of TCF	194 (88-340)	180 (80-310)	0.643
Median (IQR) log ₁₀ VL at initiation of HAART	5.2 (4.5-6.0)	5.1 (4.5-6.0)	0.863
Median (IQR) log ₁₀ VL at time of TCF	4.3 (3.7-4.9)	3.9 (3.5-5.0)	0.376
Median (IQR) age at initiation of HAART	38.8 (30.1-48.4)	38.9 (34.1-48.3)	0.734
Median (IQR) age at time of TCF	40.0 (33.2-49.3)	42.8 (37.4-46.5)	0.609
Mean number of days with failure			
NARTI	754	696	0.373
NNRTI	167	192	0.510
PI	686	610	0.230
† Chi-square test			
†† Student's t-test			

Introduction

Virological failure to all three major drug classes (nucleoside reverse transcriptase inhibitors (NRTI), non-NRTI (NNRTI), and protease inhibitors (PI)), (i.e., triple-class failure (TCF)) in HIV patients is an important clinical problem and is associated with a poor prognosis. The goals of the present study were 1) to examine the prevalence of mutations in patients with TCF, and 2) to examine how resistance mutations influence long-term mortality in TCF patients, while controlling for other prognostic factors.

Methods

Virological failure
 Virological failure was defined as a VL of more than 1000 copies/mL for a total of 120 days (not necessarily successive) while receiving treatment with a given class of drug. The time that TCF occurred was the date the patient met the failure requirements for three drug classes. All DHCS patients that experienced TCF up to 1 Nov 2004 were eligible for the study.

Mutations present at time of TCF and their association with mortality	Number of patients with a mutation at that position	Cox regression analysis of time to all-cause death after TCF	
		Unadjusted	Adjusted †
None	1	1.0	1.0
1-2	1	1.0	1.0
3-4	1	1.0	1.0
5-6	1	1.0	1.0
7-8	1	1.0	1.0
9-10	1	1.0	1.0
11-12	1	1.0	1.0
13-14	1	1.0	1.0
15-16	1	1.0	1.0
17-18	1	1.0	1.0
19-20	1	1.0	1.0
21-22	1	1.0	1.0
23-24	1	1.0	1.0
25-26	1	1.0	1.0
27-28	1	1.0	1.0
29-30	1	1.0	1.0
31-32	1	1.0	1.0
33-34	1	1.0	1.0
35-36	1	1.0	1.0
37-38	1	1.0	1.0
39-40	1	1.0	1.0
41-42	1	1.0	1.0
43-44	1	1.0	1.0
45-46	1	1.0	1.0
47-48	1	1.0	1.0
49-50	1	1.0	1.0
51-52	1	1.0	1.0
53-54	1	1.0	1.0
55-56	1	1.0	1.0
57-58	1	1.0	1.0
59-60	1	1.0	1.0
61-62	1	1.0	1.0
63-64	1	1.0	1.0
65-66	1	1.0	1.0
67-68	1	1.0	1.0
69-70	1	1.0	1.0
71-72	1	1.0	1.0
73-74	1	1.0	1.0
75-76	1	1.0	1.0
77-78	1	1.0	1.0
79-80	1	1.0	1.0
81-82	1	1.0	1.0
83-84	1	1.0	1.0
85-86	1	1.0	1.0
87-88	1	1.0	1.0
89-90	1	1.0	1.0
91-92	1	1.0	1.0
93-94	1	1.0	1.0
95-96	1	1.0	1.0
97-98	1	1.0	1.0
99-100	1	1.0	1.0
101-102	1	1.0	1.0
103-104	1	1.0	1.0
105-106	1	1.0	1.0
107-108	1	1.0	1.0
109-110	1	1.0	1.0
111-112	1	1.0	1.0
113-114	1	1.0	1.0
115-116	1	1.0	1.0
117-118	1	1.0	1.0
119-120	1	1.0	1.0
121-122	1	1.0	1.0
123-124	1	1.0	1.0
125-126	1	1.0	1.0
127-128	1	1.0	1.0
129-130	1	1.0	1.0
131-132	1	1.0	1.0
133-134	1	1.0	1.0
135-136	1	1.0	1.0
137-138	1	1.0	1.0
139-140	1	1.0	1.0
141-142	1	1.0	1.0
143-144	1	1.0	1.0
145-146	1	1.0	1.0
147-148	1	1.0	1.0
149-150	1	1.0	1.0
151-152	1	1.0	1.0
153-154	1	1.0	1.0
155-156	1	1.0	1.0
157-158	1	1.0	1.0
159-160	1	1.0	1.0
161-162	1	1.0	1.0
163-164	1	1.0	1.0
165-166	1	1.0	1.0
167-168	1	1.0	1.0
169-170	1	1.0	1.0
171-172	1	1.0	1.0
173-174	1	1.0	1.0
175-176	1	1.0	1.0
177-178	1	1.0	1.0
179-180	1	1.0	1.0
181-182	1	1.0	1.0
183-184	1	1.0	1.0
185-186	1	1.0	1.0
187-188	1	1.0	1.0
189-190	1	1.0	1.0
191-192	1	1.0	1.0
193-194	1	1.0	1.0
195-196	1	1.0	1.0
197-198	1	1.0	1.0
199-200	1	1.0	1.0
201-202	1	1.0	1.0
203-204	1	1.0	1.0
205-206	1	1.0	1.0
207-208	1	1.0	1.0
209-210	1	1.0	1.0
211-212	1	1.0	1.0
213-214	1	1.0	1.0
215-216	1	1.0	1.0
217-218	1	1.0	1.0
219-220	1	1.0	1.0
221-222	1	1.0	1.0
223-224	1	1.0	1.0
225-226	1	1.0	1.0
227-228	1	1.0	1.0
229-230	1	1.0	1.0
231-232	1	1.0	1.0
233-234	1	1.0	1.0
235-236	1	1.0	1.0
237-238	1	1.0	1.0
239-240	1	1.0	1.0
241-242	1	1.0	1.0
243-244	1	1.0	1.0
245-246	1	1.0	1.0
247-248	1	1.0	1.0
249-250	1	1.0	1.0
251-252	1	1.0	1.0
253-254	1	1.0	1.0
255-256	1	1.0	1.0
257-258	1	1.0	1.0
259-260	1	1.0	1.0
261-262	1	1.0	1.0
263-264	1	1.0	1.0
265-266	1	1.0	1.0
267-268	1	1.0	1.0
269-270	1	1.0	1.0
271-272	1	1.0	1.0
273-274	1	1.0	1.0
275-276	1	1.0	1.0
277-278	1	1.0	1.0
279-280	1	1.0	1.0
281-282	1	1.0	1.0
283-284	1	1.0	1.0
285-286	1	1.0	1.0
287-288	1	1.0	1.0
289-290	1	1.0	1.0
291-292	1	1.0	1.0
293-294	1	1.0	1.0
295-296	1	1.0	1.0
297-298	1	1.0	1.0
299-300	1	1.0	1.0
301-302	1	1.0	1.0
303-304	1	1.0	1.0
305-306	1	1.0	1.0
307-308	1	1.0	1.0
309-310	1	1.0	1.0
311-312	1	1.0	1.0
313-314	1	1.0	1.0
315-316	1	1.0	1.0
317-318	1	1.0	1.0
319-320	1	1.0	1.0
321-322	1	1.0	1.0
323-324	1	1.0	1.0
325-326	1	1.0	1.0
327-328	1	1.0	1.0
329-330	1	1.0	1.0
331-332	1	1.0	1.0
333-334	1	1.0	1.0
335-336	1	1.0	1.0
337-338	1	1.0	1.0
339-340	1	1.0	1.0
341-342	1	1.0	1.0
343-344	1	1.0	1.0
345-346	1	1.0	1.0
347-348	1	1.0	1.0
349-350	1	1.0	1.0
351-352	1	1.0	1.0
353-354	1	1.0	1.0
355-356	1	1.0	1.0
357-358	1	1.0	1.0
359-360	1	1.0	1.0
361-362	1	1.0	1.0
363-364	1	1.0	1.0
365-366	1	1.0	1.0
367-368	1	1.0	1.0
369-370	1	1.0	1.0
371-372	1	1.0	1.0
373-374	1	1.0	1.0
375-376	1	1.0	1.0
377-378	1	1.0	1.0
379-380	1	1.0	1.0
381-382	1	1.0	1.0
383-384	1	1.0	1.0
385-386	1	1.0	1.0
387-388	1	1.0	1.0
389-390	1	1.0	1.0
391-392	1	1.0	1.0
393-394	1	1.0	1.0
395-396	1	1.0	1.0
397-398	1	1.0	1.0
399-400	1	1.0	1.0
401-402	1	1.0	1.0
403-404	1	1.0	1.0
405-406	1	1.0	1.0
407-408	1	1.0	1.0
409-410	1	1.0	1.0
411-412	1	1.0	1.0
413-414			