

# Predictors of Virological Failure at 6 Months of Therapy in HIV-1 Infected Patients Starting Highly Active Antiretroviral Therapy in Porto Alegre, Brazil

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## ABSTRACT

**Background:** In therapy-naïve patients, immunological and virological responses at 6 months of highly active antiretroviral therapy (HAART) are important predictors of progression to AIDS(1). In this study, we assessed predictors of virological response 6 months after initiation of HAART in a cohort of HIV-infected patients in a developing country setting.

**Methods:** Treatment-naïve patients who started HAART in Porto Alegre, Brazil, between January 1996 and November 2003 and had information available on viral load at 6 months were included in this analysis. Demographic, antiretroviral regimen, adherence, prior AIDS diagnosis (according to CDC revised criteria), CD4 cell count and viral load at baseline and after 6 months on therapy were among the variables analyzed. Virological failure (VF) was defined as viral load  $\geq 10^4$  copies/mL. Univariate analyses were performed by using chi-square or Fisher's exact test for categorical and Student's t-test or Wilcoxon test for continuous variables. Variables with  $p < 0.10$  in univariate analysis were included in the multivariate analysis.

**Results:** 4545 patients included in this study, 127 (27.9%) had VF at 6 months. In the univariate analysis, VF was associated with younger age (median: 34 vs. 37,  $p < 0.001$ ), prior AIDS diagnosis (OR: 1.18, 95%CI: 1.03-1.36,  $p < 0.008$ ), higher baseline viral load (median: 5.24 vs. 5.00,  $p < 0.002$ ), lower baseline CD4 count (median: 66 vs. 62,  $p < 0.001$ ), non-adherence (OR: 1.28, 95% CI: 1.16-1.43,  $p < 0.001$ ), regimen containing a single protease inhibitor, as compared to ritonavir-based regimens (OR: 8.58, 95%CI: 3.53-20.82,  $p < 0.001$ ), and therapy started before 1999 ( $p < 0.001$ ). To minimize the systematic effect of therapy indication and year of initiation, we analyzed the subset of patients with CD4 count  $\geq 200$  cells/mm<sup>3</sup> who started therapy after 1999 (90/180). After adjusting for age, education, non-adherence, regimen and baseline viral load, non-adherence (OR: 6.78, 95%CI: 1.49-31.80,  $p < 0.016$ ) and  $\leq 5$  years of formal education (OR: 6.03, 95%CI: 1.09-35.86,  $p < 0.042$ ) remained independently associated with virological failure.

**Conclusions:** In this cohort, virological success was associated with year of therapy initiation, consistent with the introduction of non-nucleoside reverse transcriptase inhibitors and ritonavir-based regimens into clinical practice. With currently available therapy, adherence and education were shown to be predictors of virological response, particularly in patients with more advanced immune deficiency. Our results suggest a need for interventions that focus on improving adherence to HAART in persons with little formal education, particularly for those prescribed more complex regimens.

## MATERIAL AND METHODS

### Study design and patients

- Study setting: The Hospital de Clínicas de Porto Alegre, a government-owned facility, where treatment, including laboratory tests and antiretroviral of drugs, is provided free-of-charge.
- Study design: retrospective cohort.
- Inclusion criteria: treatment-naïve, HIV-1-infected individuals who attended the HIV/AIDS registration clinic at the Hospital de Clínicas de Porto Alegre, were prescribed HAART between January 1996 and November 2003, and for whom information was available on HIV plasma viral load 3 to 6 months after treatment was initiated.

### Variables and statistical analysis

- Demographic variables: sex, age, risk behavior, race and education.
- HAART: defined as any combination of two or more antiretroviral drugs including two nucleoside reverse-transcriptase inhibitors (NRTI) and at least one protease inhibitor (PI) or one non-nucleoside reverse-transcriptase inhibitor (NNRTI).
- Baseline CD4 count and HIV plasma viral load: These measures of disease activity are main of the antiretroviral regimen.
- Virological failure: defined as HIV plasma viral load greater than  $10^4$  copies/mL 3 to 6 months after initiation of HAART.
- Non-adherence to therapy: defined as being not filled on or more than five to the next prescribed refill visit.
- Christian analysis was performed by using Chi-Square or Fisher's exact test for categorical variables, and Student's t-test or Wilcoxon test for continuous variables. Variables found to be significant ( $p < 0.10$ ) in the univariate analysis were included in the multivariate analysis.

## RESULTS

### Baseline characteristics

- From 1996 to 2003, 1,976 patients started HAART, of whom 422 (21.3%) were antiretroviral naive. Of these, 454 (72.9%) had information available at 6 months and were included in the present study. The baseline characteristics are summarized in Table 1.
- The baseline characteristics of the patients by type of therapy are shown in Table 2.

**Table 1. Baseline characteristics of the 454 patients.**

Variable	median (IQR), n (%)	OR (95% CI)
Median age (years)	36 (31-40)	
Male	296/64 (65.2%)	
Race		
White vs Nonwhite	412/40 (90.7%)	
Risk behavior		
MSM	146/401 (35.7%)	
IDU	75/403 (19.7%)	
Transactional	5/403 (1.2%)	
Heterosexual	177/403 (43.9%)	
Education level (completed or incomplete)		
$\leq 5$ years vs $\geq 6$ years of formal education	109/388 (28.1%)	
CD4 count at baseline	66 (47-102)	
Median VL at baseline	156 (107-203)	
CD4 count at 6 months	156 (107-203)	
CD4 count at 6 months	156 (107-203)	
CD4 count at 6 months	156 (107-203)	
ADIS diagnosis	122/451 (27.1%)	
RNV RNA level at baseline (log <sub>10</sub> copies/mL)	5.0 (4.58-5.60)	
Year		
1996-1997	76/454 (16.7%)	
1998	68/454 (15.2%)	
1999	64/454 (14.3%)	
2000	58/454 (12.8%)	
2001	63/454 (13.9%)	
2002	58/454 (12.7%)	
2003-2004	49/454 (10.8%)	
Regimen		
1. 2 NRTI + 1 PI	266/451 (59.2%)	
2. 2 NRTI + 1 NNRTI	179/451 (39.7%)	
3. Regimen RNV boosted	57/451 (12.6%)	
4. Regimen with NNRTI + PI	5/403 (1.2%)	
5. 1 NRTI	3/403 (0.7%)	
6. Other	1/403 (0.2%)	

**Table 2. Baseline characteristics of the 454 patients stratified by regimen.**

Variable	NRTI + PI (n=296)	2NRTI+NNRTI (n=179)	RNV boosted (n=57)
Sex (male)	145/297 (49.1%)	116/179 (64.8%)	34/58 (58.6%)
Age*	34 (31-40)	37 (31-44)	39 (31-49)
Race: Nonwhite vs White	36/287 (12.5%)	28/179 (15.6%)	9/58 (15.5%)
Risk behavior			
MSM	79/167 (47.2%)	44/177 (28.2%)	19/50 (38.0%)
IDU	36/167 (21.5%)	28/177 (15.8%)	12/50 (24.0%)
Transactional	4/167 (2.4%)	0	1/50 (2.0%)
Heterosexual	46/167 (26.9%)	85/177 (48.0%)	18/50 (36.0%)
Immunity (non-estimated vs high)	43/178 (24.1%)	43/154 (28.1%)	19/51 (37.3%)
AIDS†	16/296 (5.4%)	11/179 (6.1%)	5/57 (8.8%)
Viral load at baseline*	5.11 (4.72-5.63)	4.80 (4.35-5.26)	5.60 (5.22-6.04)
CD4 count at baseline*	132 (99-209)	201 (102-256)	81 (37-109)

\*As-sign test for categorical variables and ANOVA for continuous variables. A Bonferroni correction was used to adjust the p value for multiple pair wise comparisons.

## RESULTS (cont)

### Factors associated with virological failure

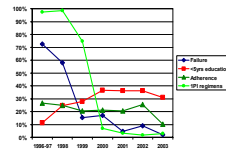
- After 6-9 months on HAART, 127 patients (27.9%) had undetectable HIV plasma viral load.
- Virological failure was associated with younger age (34 vs. 37 years of age) higher baseline HIV plasma viral load and lower baseline CD4 count; non-adherence, having received regimen containing a single PI, as compared to those prescribed ritonavir-based regimen, and having started therapy before 1999 (Table 3).
- Figure 1 shows changes in proportion of virological failure, adherence and patients receiving 1 PI regimen over time.

**Table 3. Factors associated with virological failure (n=454)**

Categorical variables	Univariate analysis		
	RR	95% CI	P
Sex (Male)	1.1	0.96-1.22	0.1151
Race Nonwhite vs White	0.91	0.76-1.07	0.324
Education			
$\leq 5$ years vs $\geq 6$ years	0.94	0.82-1.08	0.4267
Age group			
$\leq 30$	2.51	1.39-4.52	<b>0.0049</b>
30-40	2.36	1.41-3.96	<b>0.0586</b>
$\geq 40$ (ref)	1	-	-
Year			
1996-1997	125.6	16.29-969.42	<b>&lt;0.001</b>
1998	66.19	8.63-507.51	<b>&lt;0.001</b>
1999	8.78	1.11-69.38	0.7459
2000	9.99	1.23-81.15	0.9451
2001	2.39	0.24-23.80	<b>0.0091</b>
2002	4.79	0.54-42.58	0.1094
2003-2004 (ref)	1	-	-
Lack of adherence	1.39	1.16-1.68	<b>&lt;0.001</b>
ADIS	1.18	1.05-1.31	0.0089
Regimen			
2 NRTI + 1 PI	8.58	3.53-20.85	<b>&lt;0.001</b>
2 NRTI + 1 NNRTI	0.73	0.27-2.01	<b>0.0001</b>
Reg. RNV boosted(ref)	1	-	-

Continuous variables	Virological failure		Viral suppression	
	median (IQR)	OR (95% CI)	median (IQR)	OR (95% CI)
Viral load at baseline	5.34 (4.90-5.83)	5.00 (4.50-5.52)	<b>0.0002</b>	
CD4 count at baseline	86 (35-226)	182 (64-256)	0.0057	

**Figure 1. Proportion of virological failure, adherence and patients receiving 1 PI regimen over time.**



## RESULTS (cont)

### Factors associated with virological failure among immunosuppressed patients who started therapy after 1999

- In the subset of patients with baseline CD4 count  $\geq 200$  cells/mm<sup>3</sup> who started therapy after 1999, the year NNRTI and ritonavir boosted regimens became available independently associated with virological failure was lack of adherence, and less than 5 years of formal education (Table 4).

**Table 4. Factors associated with virological failure in a subset of patients who started HAART after 1999 and had CD4 count at baseline  $\geq 200$  cells/mm<sup>3</sup> (n=180).**

Factor (category of variable)	Univariate analysis			Multivariate analysis		
	RR	95% CI	P	OR	95% CI	P
Sex (Male)	0.96	0.86-1.09	0.515	-	-	-
Race: Nonwhite vs White	1.07	0.84-1.21	0.6049	-	-	-
Education						
$\leq 5$ years vs $\geq 6$ years	1.17	1.03-1.36	<b>0.0162</b>	0.85	1.02-	<b>0.0479</b>
Age group						
$\leq 30$	5.04	1.17-21.73	<b>0.07</b>			
30-40	3.28	0.84-12.63	0.47			
$\geq 40$ (ref)	1	-	-			
Lack of adherence	1.4	1.12-1.74	<b>&lt;0.001</b>	0.78	1.40-	<b>0.0164</b>
Regimen						
2 NRTI + 1 PI	4.92	0.95-25.57	<b>0.0256</b>			
2 NRTI + 1 NNRTI	1.73	0.34-8.71	0.6033			
CD4 count at baseline (ref)	1	-	-			

- In the multivariate analysis, the risk of virological failure was associated with lack of adherence (OR: 1.40, 95% CI: 1.12-1.74,  $p < 0.001$ ) and  $\leq 5$  years of formal education (OR: 1.17, 95% CI: 1.03-1.36,  $p < 0.016$ ).
- With currently available therapies, adherence and level of education were shown to be predictors of virological response, particularly in persons with more advanced immune deficiency.
- These results suggest a need for interventions that focus on improving adherence to HAART in persons with little formal education, particularly for those prescribed more complex regimens.

## LITERATURE CITED

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