

Drug Resistance Monitoring Practices Are Strongly Associated With Mortality

Viviane D. Lima*, Oghenowede Eyawo, Luke Swenson, Robert Hogg, Julio S.G. Montaner, P. Richard Harrigan
British Columbia Centre for Excellence in HIV/AIDS

PRESENTING AUTHOR:
Dr. Viviane Dias Lima
BC Centre for Excellence in HIV/AIDS
608-1081 Burrard Street
Vancouver, Canada, V6Z 1Y6
vlima@cfe.net.ubc.ca

Abstract

Background: HIV-treatment guidelines recommend HIV drug resistance testing for all patients before therapy initiation. If the patient is experiencing treatment failure, resistance testing should be performed before therapy modification. Here we aim to determine clinical and demographic factors associated with failing to receive HIV drug resistance testing when indicated in a cohort of HAART-naïve patients in an environment with universal free access to health services. Additionally, we investigate whether accessing resistance testing at baseline and/or after starting therapy are associated with mortality.

Methods: Eligible participants initiated HAART between January 2000 and June 2006 and were followed until June 2007 (N=1820). The first two outcomes in this analysis were whether the patient underwent physician-ordered genotypic resistance testing before starting HAART (yes/no) and the number of physician-ordered genotypic resistance tests while on HAART. Lastly, we modeled the effect of these previous outcomes on survival.

Results: Pre-therapy HIV drug resistance testing was more likely to be ordered for those with CD4 cell count <350 cells/mm³ (odds ratio [OR]: 1.64; 95% confidence interval [CI]: 1.26-2.15) and more likely to have been performed for those initiating therapy in the past 3 years (OR: 3.65; 95%CI: 2.81-4.73). Once on HAART, females, injection drug users, those with high viral load and those with adherence <95% were more likely to have physician-ordered genotypic resistance testing with detectable viral load (p<0.02). In terms of mortality, individuals with no resistance test done before therapy initiation had a 1.7-fold higher risk of mortality, while those with fewer resistance tests performed while on therapy had a 2.7-fold higher risk of mortality than those with resistance tests, after adjusting for clinical and demographic factors.

Conclusion: Even in a setting where care for HIV-positive patients is free of charge, a significant number of individuals are not monitored according to accepted programme guidelines; this lack of monitoring is associated with an increased risk of mortality. While these results do not allow us to establish a causal relationship regarding the association between physician-ordered genotypic resistance testing and survival (this could be a surrogate for higher physician's experience/expertise), these findings suggest a close monitoring of physicians' practices to ensure all patients receive appropriate care.

Background

- The availability of a multitude of antiretroviral drugs to treat HIV/AIDS antiretroviral-naïve and -experienced patients makes the treatment of these patients a complex endeavour.
- In British Columbia (BC), Canada, despite universal access to health services, resistance testing and antiretroviral therapy to all eligible HIV/AIDS patients, there is still a high proportion of patients who have sub-optimal access to these recommended tests as part of their routine HIV/AIDS care. The reasons for this lack of testing are still unknown

Objectives

- To determine clinical and demographic factors associated with failing to receive HIV drug resistance testing when indicated in a cohort of HAART-naïve patients in an environment with universal free access to health services
- To investigate whether accessing resistance testing at baseline and/or after starting therapy are associated with mortality

Methods

Participants were ...

- Enrolled in large population-based cohort of HIV-1 infected antiretroviral-naïve adults initiating HAART in British Columbia, Canada, between January 1, 2000 and June 30, 2006 and were followed until June 30, 2007
- Naïve to antiretroviral therapy when they started HAART consisting of: two nucleosides [nRTI], or a nRTI and a nucleotide reverse transcriptase inhibitor [NtRTI] as backbone, plus either (1) the non-nucleoside reverse transcriptase inhibitors [NNRTIs] efavirenz or nevirapine, or (2) the protease inhibitors atazanavir or lopinavir, each boosted with ≤400mg/day ritonavir [boosted PI].

Analyses

- (1) Using exploratory logistic regression models to find the factors associated with having a genotypic resistance testing done requested by the family/consulting physician at baseline and during follow-up.
- (2) We built exploratory models using Cox proportional hazards survival regression to estimate the effect of the previous outcomes on survival.

Results

- A total of 1820 antiretroviral naïve adults were eligible to participate in this study. At baseline, the median age was 41 years (interquartile range [IQR]: 35 - 48 years), CD4 cell count was 160 cells/mm³ (IQR: 70-240 cells/mm³), pVL was 5.0 log₁₀ copies/mL (IQR: 4.7-5.0 log₁₀ copies/mL) and the median number of patients for whom physicians had written HAART prescriptions was 80 patients (IQR: 14-206 patients). Of these, 26% had a history of IDU, 16% had AIDS at baseline, 47% were first prescribed therapies containing boosted PIs and 45% NNRTIs, and 61% of participants were more than 95% adherent during the first year of follow-up.
- At baseline, 36% of patients were offered a resistance test before therapy initiation. During a median of 38 months of follow-up (IQR: 21-59 months), 68% of patients had no resistance test done as part of their routine care, and 15% of patients were deceased at the end of follow-up.
- Results for the logistic and survival analyses are presented in Table 1.

Conclusions

- Even in a setting where care for HIV-positive patients is free of charge, a significant number of individuals are not monitored according to accepted programme guidelines; this lack of monitoring is associated with an increased risk of mortality.
- While these results do not allow us to establish a causal relationship regarding the association between physician-ordered genotypic resistance testing and survival, these findings suggest a close monitoring of physicians' practices to ensure all patients receive appropriate care.

Table 1. Factors associated with having a resistance test performed at baseline and during follow-up (columns 2-3), and the impact of having these tests on survival (all causes) (columns 4-5).

Variable	Odds Ratio (95% Confidence Interval)		Hazard Ratio (95% Confidence Interval)	
	Resistance tests performed		Resistance tests performed	
	Baseline	Follow-up	Baseline	Follow-up
Resistance tests performed				
No	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
Yes	0.58 (0.44 - 0.77)	—	—	—
Resistance tests performed				
0 tests	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
1 test	—	0.53 (0.36 - 0.78)	—	0.50 (0.32 - 0.77)
2 tests	—	—	—	0.50 (0.32 - 0.77)
≥3 tests	—	—	—	0.37 (0.25 - 0.56)
Gender				
Male	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
Female	0.79 (0.61 - 1.01)	1.36 (1.06 - 1.73)	1.28 (0.95 - 1.73)	—
Age (years)	—	0.99 (0.98 - 1.00)	1.02 (1.01 - 1.03)	1.03 (1.02 - 1.04)
Injection drug use history				
No	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
Yes	—	2.16 (1.74 - 2.69)	—	—
AIDS diagnosis				
No	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
Yes	—	—	0.64 (0.46 - 0.90)	0.69 (0.49 - 0.96)
Year of first ARV				
2000 - 2001	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
2002 - 2004	1.93 (1.45 - 2.56)	0.88 (0.69 - 1.13)	—	—
2005 - 2006	3.65 (2.81 - 4.73)	0.42 (0.33 - 0.54)	—	—
Initial Regimen				
Non-boosted PI	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
Boosted PI	—	—	—	—
NNRTI	—	—	—	—
Adherence (1 st year)				
≥ 95%	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
80% - <95%	—	1.77 (1.31 - 2.41)	—	1.77 (1.20 - 2.61)
40% - <80%	—	2.83 (2.17 - 3.69)	—	3.85 (2.81 - 5.26)
<40%	—	1.91 (1.41 - 2.61)	—	5.61 (4.00 - 7.87)
CD4 cell count (cells/mm ³)				
<50	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
50 - 199	1.64 (1.23 - 2.18)	—	0.46 (0.34 - 0.62)	0.45 (0.34 - 0.60)
200 - 349	1.66 (1.22 - 2.25)	—	0.34 (0.24 - 0.49)	0.31 (0.22 - 0.45)
≥ 350	1.18 (0.78 - 1.80)	—	0.23 (0.13 - 0.40)	0.19 (0.11 - 0.34)
Plasma HIV-1 RNA level (log ₁₀ c/mL)	1.30 (1.09 - 1.56)	1.44 (1.19 - 1.75)	1.41 (1.03 - 1.92)	1.62 (1.17 - 2.24)
Physician experience (per 100 patients)	—	—	0.82 (0.74 - 0.91)	0.84 (0.75 - 0.94)