

Baseline Antiretroviral Resistance Profile and Correlation with Clinical Events in the OPTIMA Trial

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OPTIONS IN MANAGEMENT
WITH ANTIRETROVIRALS

MRC Medical
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**DEPARTMENT OF
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CIHR IRSC
Canadian Institutes of
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Abstract

Background: The OPTIMA trial is an ongoing strategy study for patients with virologic failure and multi-drug resistant (MDR) virus. The trial is a collaboration between the U.S. Department of Veterans Affairs, U.K. MRC and Canadian CIHR.

Methods: Patients (target N=504) with HIV RNA >2,500 copies/mL, CD4 < 300/mm³, on ARV therapy are randomized in a 2 x 2 factorial design to a 3-month antiretroviral (ARV) drug-free period (ARDFP) vs. no ARDFP followed by a new standard ART (≤ 4 ARVs) or MegaART (≥ 5 ARVs) regimen versus no ARDFP (immediate change to new ARV regimen of standard vs. MegaART). The primary endpoint is AIDS or death. Baseline resistance was assessed by virtual phenotype (vP). Cox proportional hazards models were derived to determine whether baseline variables (i.e. CD4 count, pVL, number of prior ARVs used, number of total and class specific resistant ARVs) were associated with clinical endpoints.

Results: 264 patients (98% male, mean age 48) have been enrolled thus far. Mean baseline HIV RNA = 4.79 log₁₀/ml and CD4 = 105 cells/mm³. Prior ARV utilization included > 2 PI (70%), > 2 NNRTI (90%) and > 2 NRTI (99%). Global vP resistance was highly correlated with the total ARV exposure. ARV class specific resistance was highly correlated with the number of prior ARV agents taken in that class. Broad vP resistance to all ARV classes was seen, except for tenofovir (< 10% vP resistance). Of the variables considered, only baseline CD4 count was significantly correlated with death or development of an AIDS event on study.

Conclusions: In this clinically advanced population, the prevalence of ARV resistance is significant and limited treatment options are available. Resistance was highly correlated with prior ARV exposure. However, neither the total number, nor class specific number of resistant ARVs correlated with clinical outcome. Only baseline CD4 count was a strong predictor of clinical events. We will continue to examine whether in the presence of such significant ARV resistance, benefit is derived from clinical response to standard or MegaART if preceded by ARDFP.

Introduction

Antiretroviral (ARV) resistance is found with increasing frequency among those patients with recently transmitted HIV-1 or in those patients exposed to one or several ARV regimens. The presence or quantity of baseline resistance has been correlated with virologic outcome in patients receiving highly active antiretroviral therapy (HAART) (1, 2). Older data suggests that the risk of developing an AIDS-defining illness or clinical progression to death is correlated with the presence of nucleoside reverse transcriptase inhibitor (NRTI) associated HIV-1 reverse transcriptase (RT) gene mutations at codons 41, 69, and 215 or phenotypic resistance to NRTIs in both adults and children (3-8). However, despite ARV resistance prevalence approaching 50-70% and multi-ARV class resistance approaching 25% in some surveys (9), little is known in the current HAART era regarding any correlation between the presence of ARV resistance and clinical (not virologic) outcome. There is some suggestion that resistance burden may be correlated with clinical outcome while receiving HAART (10), but this has not been conclusively demonstrated.

The OPTIMA trial is well-positioned to answer this question. The OPTIMA trial is an ongoing strategy study that is addressing questions about treatment interruption and Mega-HAART regimens for patients with virologic failure and multi-drug resistant (MDR) virus where the primary study endpoint is AIDS or death (11). In the current study, we analyzed the relationship between baseline resistance, determined by virtual phenotype, with primary endpoints, defined as a new AIDS-defining illness or death, adjusting for baseline CD4 and viral load.

Methods

In the OPTIMA trial, patients (target N=504) with HIV RNA >2,500 copies/mL, CD4 < 300/mm³, a history of 3-class ARV exposure in at least two different regimens that the patient could tolerate and/or 3 class ARV resistance, and who are on ARV therapy, are randomized in a 2 x 2 factorial design to a 3-month antiretroviral (ARV) drug-free period (ARDFP) vs. no ARDFP followed by a new standard ART (≤ 4 ARVs) or MegaART (≥ 5 ARVs) regimen versus no ARDFP (immediate change to new ARV regimen of standard vs. MegaART). The primary end points are new AIDS-defining illness or death. Baseline ARV resistance was measured by VirtualPhenotype™ (Virco, Mechelen, Belgium). Virtual phenotypic resistance was defined as any fold-change above the stated biological cutoff on the report.

The Cox proportional hazards model was used to assess both the univariate and multivariate contribution of the baseline predictors to the time to outcome of AIDS or death. Baseline variables considered in the model included CD4 count, HIV-1 viral load, ARV class and total ARV resistance. Categorical definitions (i.e., number of ARVs within a class) of resistance were also considered in the model.

Results

The study is still blinded to treatment strategy arm and correlation with primary outcomes. Two hundred eighty nine patients have been enrolled as of June 1, 2004 and 223 are included in this analysis. Table 1 lists some of the demographic and follow-up information. The cohort is almost all male and is relatively advanced with respect to HIV disease status. The average follow-up is now one year and 57 adjudicated primary endpoints were included in this analysis. Figure 1 illustrates the ARV exposure history, demonstrating that two-thirds of patients had been exposed to 9 or greater ARV agents. Table 2 details the VirtualPhenotype™ results, where reduced susceptibility is expressed as fold change in IC₅₀ above the biologic cutoff for the normal susceptible range. Except for a few NRTIs, baseline samples demonstrated reduced susceptibility to most ARVs. Figure 2 demonstrates the percentage of patients with virtual phenotypic resistance broken down by number of ARV agents and class. Over half of the patients had evidence of ARV resistance to 9 or more drugs.

In the univariate model, CD4 count, log₁₀ viral load/mL and NRTI resistance were significantly associated with time to AIDS or death (Table 3). NNRTI's demonstrated no significant predictive value in the univariate analysis and were therefore not considered for subsequent analysis. However, only CD4 count was a significant predictor of time to AIDS or death in the multivariate model. Further categorical analyses were performed to determine whether the number of ARV agents within classes demonstrating resistance was a significant predictor for endpoints. In a univariate analysis, having resistance to 6 or more NRTIs or 13 or more ARVs were significantly associated with time to AIDS or death (Table 4). However, in the multivariate analysis, CD4 count remained the strongest predictor, but having resistance to all PIs was also significantly associated with time to AIDS or death.

Table 1

Demographic and Follow-up Information

Number Randomized	289
Number Assessed	223
Number of Primary Endpoints	57
Male (%)	98%
Mean Age	48
Mean Baseline Viral Load	4.71 log ₁₀ /mL
Mean Baseline CD4 count	131/mm ³
AIDS (%)	96%
Follow-up (median)	1
Follow-up (range)	0 - 2.6 years

Figure 1

ARV Exposure History In The OPTIMA Cohort

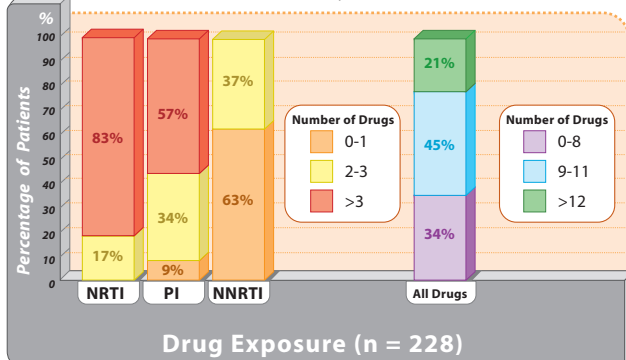


Figure 2

Percentage of Patients Demonstrating ARV Resistance by ARV Class

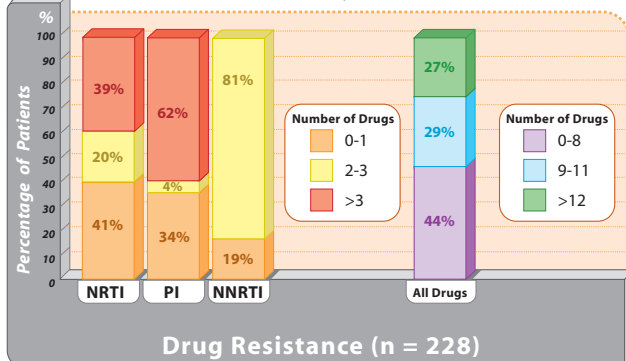


Table 3

Univariate and Multivariate Analyses Results

	Predictor	Relative Hazard	95% CI	p-value
Univariate Analysis	CD4 (per cell)	0.993	0.989-0.997	<0.001
	Log pVL	2	1.22-3.31	0.006
	NRTIs Resistant	1.139	1.004-1.291	0.043
	PI's Resistant	1.047	0.943-1.162	0.39
Multivariate Analysis	All Resistant	1.052	0.986-1.123	0.13
	CD4 (per cell)	0.993	0.990-0.997	<0.001
	Log pVL	1.45	0.81-2.38	0.23
	NRTIs resistant	1.11	0.98-1.26	0.11

Table 4

Univariate and Multivariate Results Analyzing the Number of ARVs within Each Class

	Predictor	Relative Hazard	95% CI	p-value
Univariate Analysis	NRTIs Resistant (0-5 vs. 6-7)	2.11	1.20-3.73	0.01
	PI's Resistant (0-5 vs. 6)	1.56	0.90-2.71	0.11
	All Resistant (≤12 vs. 13-16)	1.83	1.06-3.13	0.03
Multivariate Analysis	CD4 (per cell)	0.993	0.989-0.997	<0.001
	Log pVL	1.23	0.70-2.15	0.46
	PI (≤5 vs 6)	1.85	1.03-3.32	0.04

Categorical Definitions for ARV medication categories

Table 2

Virtual Phenotype Results

Drug	N	FC Cutoff	Mean FC	Median FC	Q1 FC	Q3 FC
ZDV	225	4	10.8	6	1.6	17.6
3TC	226	2.5	26.7	49	2.4	47.3
ddl	199	2	2.2	1.6	1.1	2.4
ddC	200	2	1.8	1.5	1.1	2
d4T	213	1.75	1.7	1.3	0.9	1.8
ABC	197	3	3	2.7	1.5	4.3
TDF	206	3	1.6	1.5	0.9	2
NVP	238	8	45	58	38	60
DLV	232	10	68	54	2.8	141
EFV	238	6	128	90	23	242
IDV	220	3	10	8.5	0.9	19.3
RTV	220	3.5	48	20	0.8	91
NFV	220	4	18	21	1.3	31
SQV	221	2.5	9.2	3.3	0.7	10.2
APV	215	2	4.6	2.2	0.7	4.8
LPV	202	2.5	18.2	3.9	0.8	37
ATV	0	2.5	-	-	-	-

Where Q1=25th percentile, Q3=75th percentile, N=number of observations.

Red square: Fold Change Indicating Reduced Susceptibility
Green square: Fold Change Indicating Susceptibility

Conclusions

The prevalence of ARV resistance is extremely high in our study population.

Only baseline CD4 was a consistently strong predictor of clinical events.

In this heavily pre-treated and clinically advanced population, there is some evidence to suggest that resistance is associated with clinical outcome.

The index of resistance was examined in many different ways, so these results must be interpreted with caution.

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