

Background

The negative impacts of HIV-1 antiretroviral (ARV) resistance on the effectiveness of HAART have been well-established. Drug-resistant HIV-1 variants are a major barrier to long-term ARV efficacy and a major cause of treatment failure.

Previous studies have indicated that treatment failure resulting from the exhaustion of available and effective treatment options, due to multi-drug resistance, does not significantly drive mortality. This was shown for a subset of the HOMER cohort of drug-naïve individuals initiating HAART in British Columbia, Canada between August 1, 1996 and September 30, 1999 in a study by Recsky et al. (JID 2004). Insufficient and/or intermittent exposure to antiretroviral agents, comorbidity and other factors, likely play a larger role for most individuals in this cohort. However, the exact associations between the accumulation of HIV-1 drug resistance mutations and HIV-related mortality remains controversial.

We wish to re-examine this association in the context of modern HAART and update this study having followed this cohort for a longer period of time from August 1, 1996 until November 30, 2005 with a median follow up of approximately 2037 days (approximately 5.6 years; maximum 9.25 years) over this period.

Objective

The goal of this analysis is to examine the impact of accumulated HIV-1 ARV resistance mutations on non-accidental HIV-related mortality, and to describe the causes of death associated with drug resistance, in a large antiretroviral-naïve cohort initiating HAART between August 1, 1996 and November 30, 2004 in British Columbia Canada.

Methods

Study Population
• Participants were members of the well-characterized HAART Observational Medical Evaluation and Research (HOMER) cohort (JID 2004).

• The study population consisted of 2506 individuals beginning HAART in British Columbia, Canada.
• Eligible study participants were ≥ 18 years old, and antiretroviral naïve when they initiated HAART. Participants started treatment between August 1, 1996 and November 30, 2004 and were followed until November 30, 2005.

Data Collection
• Of the 2506 people initiating HAART, HIV-1 drug resistance genotypes were available for 1472 (58.7%) individuals.

• HIV-1 drug resistance mutations were determined via 'bulk' genotyping of patient-derived plasma samples and interpreted using a modified IAS-USA list. Drug resistance categories are defined as 3TC, Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (except 3TC), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors (PIs).
• The accumulation of resistance to drug categories was described for 3 adherence strata (defined as: <50%, 50-95%, and ≥95%) based on prescription refill percentages, using a mean cumulative function analysis (MCF) over a median of 2037 days (~5.6 years; maximum 9.25 years) of follow-up.

Outcome Measures and Predictor Variables

The primary outcome was emergence of drug resistance in any of the four resistance categories (yes vs. no). The following baseline predictor variables were investigated: age, gender, CD4 cell count, pVL (log₁₀ transformed), first regimen, AIDS diagnosis, history of injection drug use, year of first therapy and adherence. Estimates of adherence were based on medications actually dispensed, not just prescribed, in the first year of therapy, estimated by dividing the number of months of medications dispensed by the number of months of follow-up.

ICD Groupings for Causes of Death

A total of 280 people who initiated therapy from August 1, 1996 to November 30, 2004 had died by November 30, 2005 and had available on-therapy plasma viral loads and CD4 counts within the two years prior to death. Causes of death, where available, were coded according to the standards of the International Classification of Diseases, 9th and 10th Revision (ICD-9 and ICD-10). ICD codes were grouped by letter, which is the broadest categorization. According to ICD classifications, causes of death directly attributable to HIV are coded in groups B20-B24, which are also the categories that most of the causes of death in our cohort are coded. Therefore, during analysis, deaths coded as "B" were highlighted. Deaths coded as "I", which covers diseases of the circulatory system, were also highlighted due to their relatively high number in comparison to other causes. All other causes of death were grouped together in an "Other" category, which included deaths coded as A, C, D, E, G, J, K, N, O, and R. Individuals were considered to have died with resistance if they had a genotype that showed any resistance to the four drug categories previously defined from a sample collected within the two years before their death. For definitions of ICD categories, please consult: <http://www.who.int/classifications/apps/icd/icd00/nl/en/>

Statistical Analyses

A method was needed that could handle recurrent events, since accumulated resistance mutations are recurrent. The Mean Cumulative Function is a method that has been used in the automotive industry to summarize the number of repairs that a population of repairable systems need over time. For example, if a particular type of diesel engine contains 16 valves, the mean cumulative function could be used to summarize the mean number of valves that have worn out by a particular time. Here, MCF was used to represent the average (mean) number of HIV-1 drug resistance categories which accumulated in the population over time. The follow-up time for each patient was calculated as the difference in the number of days from the time of the last contact date of the patient and the date that the patient started their first ever antiretroviral regimen. The time to a person developing a resistance was carried out for the first resistance shown to a particular drug category. If patients did not develop resistance to a particular drug category by the end of the study period, then they were censored at the end of the study period. Nonparametric estimates of population MCF and 95% confidence intervals for the number of drug category resistances are shown. MCF analysis was carried out in SAS 9.1 using SAS RELIABILITY Procedure (SAS Institute, Inc., Cary, NC).

Results

Data from all patients in HOMER who had resistance testing done was used; 'HIV-related' mortality was considered.

- Total number of patients with resistance (R) tests done = 1472
- Number of patients with resistance to at least 1 drug category (1R) = 635
- Number with just 1R = 262(41.3%)
- Number with 2R = 227 (35.7%)
- Number with 3R = 114 (18.0%)
- Number with 4R = 32 (5.0%)

Within the median follow up period (2037 days) of initiating HAART:

- 247 of the 1472 participants (16.8%) died
- 1114 survived (75.7%)
- 111 (7%) were lost to follow-up or were not on therapy for at least 2037 days.

Results Continued...

Baseline Characteristics

Table 1. Baseline characteristics of the 1472 people genotypes were available for, stratified as non-survivors (N=284) and survivors (N=1188). Significant differences are highlighted in red.

Variable	Non-survivors (N=284)	Survivors (N=1188)	P-Value
Gender, no (%)			
Female	55 (19.4)	244 (20.5)	0.7
Male	229 (80.6)	944 (79.5)	
CD4+ cell count (cells/mm³), no (%)			
<200	188 (66.2)	500 (42.1)	<0.001
200-350	45 (15.9)	331 (27.9)	
≥350	51 (18.0)	357 (30.0)	
Plasma HIV-1 RNA level (log₁₀ copies/mL), no (%)			
<-4	12 (4.23)	90 (7.6)	<0.001
4.4-9.9	70 (24.7)	407 (34.3)	
≥5	202 (71.1)	691 (58.2)	
AIDS diagnosis, no (%)			
No	231 (81.3)	1030 (86.7)	0.02
Yes	53 (18.7)	158 (13.3)	
History of injection drug use, no (%)			
No	192 (67.6)	791 (66.6)	0.7
Yes	92 (32.4)	397 (33.4)	
Regimen, no (%)			
PI-single	91 (32.0)	412 (34.7)	0.3
PI-boosted	36 (12.7)	174 (14.7)	
NNRTI	157 (55.3)	602 (50.7)	
Year of first therapy, no (%)			
Before June 1999	162 (57.0)	609 (51.3)	0.08
After June 1999	122 (43.0)	579 (48.7)	
Age			
Median	37.3	40.0	<0.001
Interquartile range	31.8 - 43.9	34.0 - 46.7	

Mean Cumulative Function as a Function of Mortality and Adherence

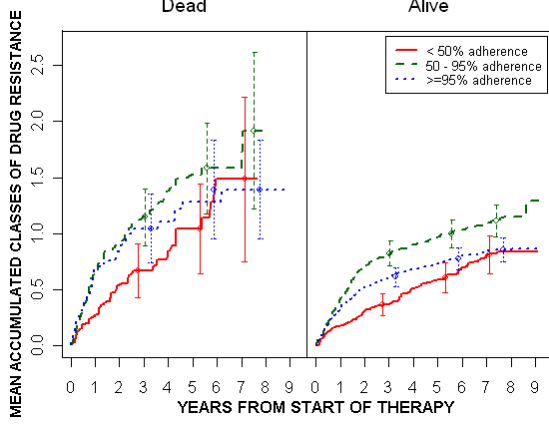


Figure 1. HOMER cohort showing cumulative resistance events broken down by death and adherence category. N=1472, which is the number of people with HIV-1 drug resistance genotyping performed. 95% CI's are shown at the first quartile, median, and third quartile follow-up periods, which correspond to 1111, 2037, and 2701 days respectively

At the time of median follow up (~5.6 years), patients were, on average, resistant to only one drug category. The mean accumulated HIV-1 drug-category resistance is greater in non-survivors than survivors across all adherence strata (Figure 1).

Across all adherence strata, the mean accumulation of HIV drug-category resistance mutations is fastest at the start of therapy and slows over time. Mean accumulation of HIV drug-category resistance is fastest in those within the 50-95% adherence stratum. The 50-95% strata has the highest MCF scores for both survivor and non-survivor populations and resistance mutations accumulate fastest in this group suggesting that imperfect adherence is a risk factor for developing antiretroviral resistance mutations.

The greatest difference between the survivor and non-survivor populations is observed in the intermediate 50-95% strata. Within the 95% confidence intervals, the amount of accumulated resistance is quite low even among the non-survivors. The maximum MCF value is 1.92, meaning that the mean number of resistance categories for patients in this strata is less than 2.

Results Continued...

Mean cumulative resistance is highest in non-survivors with 50-95% adherence

• When stratified by mortality alone, non-survivors had a higher mean number of drug classes for which they showed resistance (MCF score) [1.33, 95% confidence interval (CI) = (1.09, 1.56)] than survivors (0.81, CI = 0.75, 0.88) by the mean follow-up date of 2037 days.

• When stratified by adherence alone, individuals who were in the 50-95% adherence stratum had a higher MCF score (1.09, CI = 0.98, 1.21) than people in the ≥95% stratum (0.82, CI = 0.73, 0.91) and the <50% stratum (0.72, CI = 0.59, 0.85) by the mean follow-up date.

• After stratifying by both adherence and mortality, non-survivors in the 50-95% adherent group had the highest MCF score across all stratifications (1.58, CI = 1.18, 1.98) by the mean follow-up date. Non-survivors had higher MCF scores than their survivor counterparts in each individual adherence category.

• It is important to note that fewer people were followed at the mean follow-up date than at the end of follow-up for both survivors and non-survivors.

Causes of Death and Mortality

Table 3. Causes of death for individuals who initiated HAART between August 1, 1996 to November 30, 2004 and died by November 30, 2005. ICD-9 and ICD-10 codes were grouped together by first letter for categories "I" and "B", and "Other" for all other causes. Deaths with unspecified causes are also shown. Individuals were stratified as either showing resistance at the time of death or not and by prescription-refill adherence percentage within the first year of therapy (<50%, 50-95%, and ≥95%).

ICD Category	Without Resistance			With Resistance			Totals		
	<50%	50-95%	≥95%	<50%	50-95%	≥95%			
B (HIV-related)	54	34	31	119	26	44	23	93	212
I (Circulatory-related)	4	1	3	8	2	5	3	10	18
Unknown	2	2	1	5	0	7	3	10	15
Other	6	7	10	21	5	4	7	16	39
Totals	66	44	45	155	33	60	36	129	284

• Direct HIV-related causes of death are coded as B20-B24, which accounts for the majority of deaths coded as B.

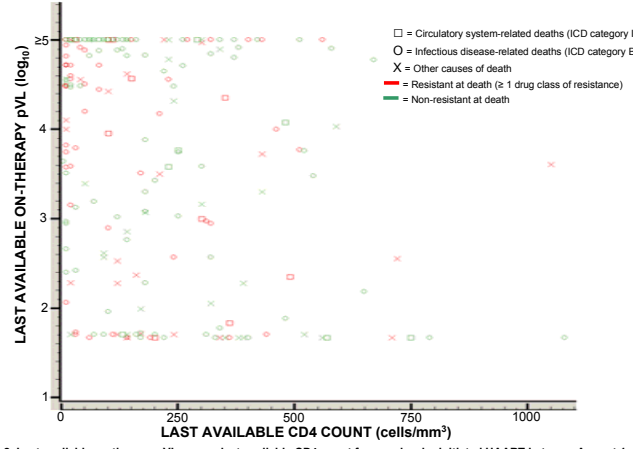


Figure 2. Last available on-therapy pVL versus last available CD4 count for people who initiated HAART between August 1, 1996 to November 30, 2004 and who died by November 30, 2005. ICD categories for cause of death are indicated by shapes (□ = circulatory system-related deaths, ○ = infectious disease-related deaths (almost entirely HIV-related), X = all other causes of death). Resistance to ≥1 ARV-class at time of disease is indicated by the color red, and lack of resistance is indicated by green.

• A cluster of HIV-related deaths appears for individuals who had a low last CD4 count and high last on-therapy pVL, including both resistant and non-resistant individuals.

• HIV-related deaths that are associated with ARV-resistance appear especially more frequently at low CD4 counts.

• No clear relationship between pVL and CD4 is seen with all other causes of death than those categorized as "B"

Conclusion

• Even after 9 years of HAART exposure, there is very little accumulated resistance to the four drug categories across all adherence strata and in both survivors and non-survivors in the HOMER cohort of drug-naïve individuals initiating HAART in British Columbia, Canada.

• Mean accumulated HIV-1 drug-category resistance was highest between the 50-95% adherence stratum.

• Although most individuals did not have resistance to many categories of drugs even after years of exposure, mean accumulated HIV drug-category resistance was greater in non-survivors than survivors across all adherence strata, suggesting that resistance remains a risk factor for mortality.