

# MORTALITY TRENDS OF HIV-INFECTED PATIENTS AFTER THE INTRODUCTION OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY: ANALYSIS OF A COHORT OF 3,322 HIV-INFECTED PERSONS

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**Introduction:** The implementation of highly active antiretroviral therapies (HAART) has reduced the mortality attributed to the human immunodeficiency virus (HIV) infection. Variation in the specific causes of death has also changed since the implementation of these therapies.

**Methods:** A prospective study was performed in 3322 HIV-infected persons enrolled in Puerto Rico between 1992 and 2003. We measured the mortality rates and the causes of death as listed in the death certificate and analyzed the variation as a function of the antiretroviral therapy (ART) use. Statistical analyses were performed to evaluate differences.

**Results:** The study found that persons treated with HAART had significantly lower mortality risk than ART-naïve persons, regardless of gender and the use of injecting drugs. AIDS-defining conditions as a cause of demise were less frequently reported in patients with HAART. Gastrointestinal dysfunction, sepsis, metabolic abnormalities, and non-Kaposi neoplasms were more frequently reported as causes of death in patients treated with HAART. Hepatic failure as cause of death was also more frequent in these patients. The variation in the mortality trends was similar in both genders and according to the presence or absence of intravenous drug use.

**Conclusions:** Highly active antiretroviral therapies (HAART) is associated with significant reduction in mortality and an increment in gastrointestinal dysfunction, sepsis, non-Kaposi neoplasms, and metabolic disorders as listed causes of death. Adverse and toxic profile of ART, along with the potential synergy of concomitant conditions, may accelerate these trends. Continued mortality surveillance of HIV/AIDS is imperative to follow the epidemic changes. (*Ethn Dis.* 2005;15 [suppl 5]:S5-57-S5-62)

**Key Words:** HAART, HIV/AIDS, Mortality Trends, Puerto Rico

## INTRODUCTION

Patterns of morbidity and mortality among patients infected with human immunodeficiency virus (HIV) have significantly changed over the last two decades. With the introduction of highly active antiretroviral therapy (HAART), an increase in the life expectancy among subjects infected with HIV has been reported in developed countries.<sup>1-4</sup> The combination of drugs used in HAART suppresses the HIV viral load and improves immunological and clinical well-being.<sup>5-7</sup> As a consequence, AIDS-defining conditions, which in the past largely determined the morbidity and mortality profile of HIV infection, have declined substantially.<sup>3,4,8-10</sup>

With the introduction of HAART, HIV infection has evolved into a chronic condition in which fatality rates have dropped and the causes of demise have changed. Most published studies have reported that the causes of death in HIV-infected patients have changed to non-AIDS-defining conditions, mostly associated with a state of chronic disease along with the presence of toxicity from the antiretroviral therapies (ART).<sup>1,3,8,10</sup> The ART included in HAART are part of a broad category of medications which are combined into three or more treatment regimens with a profile of adverse effects and toxicities

that could increase the morbidity and mortality of HIV-infected persons. Nucleoside reverse transcriptase inhibitors cause mitochondrial toxicity, which can induce neuropathy, pancreatitis, hepatic steatosis, lactic acidosis, and anemia. Non-nucleoside reverse transcriptase inhibitors are associated with central nervous system disturbances. Protease inhibitors elicit gastrointestinal adverse effects and metabolic abnormalities that include hyperlipidemia, insulin resistance, and liver damage.<sup>11-13</sup> Protease inhibitors have also been associated with metabolic abnormalities and liver damage.<sup>14</sup> This scenario has introduced a number of issues, which changes the morbidity and may alter the mortality profile of HIV-infected patients.

Puerto Rico has a high prevalence of HIV/AIDS; in 2003, the Centers for Disease Control and Prevention reported that the metropolitan area of San Juan ranked fifth among US metropolitan areas.<sup>15</sup> In this study, we explored the changes in the mortality spectrum of HIV-infected patients followed by the Retrovirus Research Center (RRC) at Bayamón, Puerto Rico for the last 11 years. Particular attention was paid to the mortality changes after the introduction of HAART.

## MATERIALS AND METHODS

### Study Population

The study comprised 3322 HIV-infected patients of the RRC, a facility sponsored by the Research Centers for Minority Institutions (RCMI) program. The RRC has tracked the AIDS/HIV epidemic in our health region since 1992. The cohort was recruited and

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followed in the Ramón Ruíz Arnau University Hospital or in the specialized immunologic clinics of our medical facilities. Data were obtained from patients seen in our center between 1992 and 2003. Once an informed consent was obtained, data were collected using medical record abstraction and interviews with structured questionnaires. The questionnaire included variables related to sociodemographics, HIV risk factors, clinical manifestations, ART, laboratories, and mortality data. AIDS-defining illnesses such as *Pneumocystis carinii* pneumonia (PCP), cerebral toxoplasmosis, pulmonary tuberculosis, Kaposi sarcoma, and wasting syndrome were recorded. Appropriate laboratory tests were performed. The immunological status was evaluated with the help of CD4<sup>+</sup> T cell count. The HIV viral load was measured in patients after 1998. Highly active antiretroviral therapies (HAART) was defined as three or more ARTs used simultaneously at enrollment or any time during the followup.

The death status of the participants as of December 2003 was used to measure mortality trends in this study group. Mortality data were obtained from a review of our institutional medical records and from the Puerto Rican AIDS surveillance system. In addition, the Puerto Rico Health Department mortality registry was reviewed in order to confirm participant death status and to obtain the reported demise causes as listed in the death certificate. For purposes of evaluation, the reported causes of death were tabulated and organized into three categories. The first included the following AIDS-defining conditions: PCP, cerebral toxoplasmosis, wasting syndrome, pulmonary tuberculosis, and Kaposi sarcoma. The second classified the remaining death diagnoses according to a specific system or organ failure. The systems were cardiovascular, pulmonary, non-malignant hematologic, gastrointestinal, renal, metabolic, and

neurological. A separate category for patients with sepsis and non-Kaposi neoplasm was created. A sub-group of hepatic dysfunction, including liver failure (chronic and acute) and cirrhosis was made.

### Statistical Analysis

The Statistical Package of Social Sciences (SPSS; Chicago, Ill) program was used to perform univariate, bivariate, and multivariate analyses. Univariate analysis described the frequencies of antiviral drugs regimens used, mortality rates, and demise causes. Quality differences between patient groups were analyzed with the chi-square or the Fisher exact test. Risk ratios, ANOVA, and student *t* test were used to evaluate mean differences. The Mann Whitney test was used to evaluate median differences between groups. Group differences were also evaluated after stratifying by gender and by intravenous drug use (IDU).

Differences in mortality rates, causes of death, and disease duration were evaluated and analyzed in the cohort. Time of followup was defined as the time between the patient's enrollment and their death or the last time of contact. Human immunodeficiency virus (HIV) disease duration was defined as the time between the first documented positive HIV test and the last followup or death of the patient. Kaplan Meier analysis was performed to explore variation in survival time. The influence of covariate factors was studied with the help of Cox proportional-hazards analysis. The *P* value used to determine statistical significance was <.05. In addition a 95% confidence interval [CI] was used to evaluate significance.

## RESULTS

### General Cohort Data

Of the 3322 HIV/AIDS patients, 72.6% were men, 55.1% had IDU as a risk factor, 45.5% had not received

ART, 37.3% received HAART at some point in their followup, 17.2% received one or two ARTs, 52.5% died, and 26.0% were lost to follow up (Table 1). When compared with the HAART group, the ART-naïve group had a higher prevalence of men (75.5% vs 68.0%), IDU (65.9% vs 40.0%) and a higher mortality rate (70.4% vs 24.2%). No significant differences were found in the three groups that were lost to follow-up (24.5%, 29.2%, and 26.3%).

Of the 1744 cases who died, 1343 (77.0%) were men, 1102 (63.2%) reported IDU, 1064 (61.0%) did not receive any ART, 380 (22.0%) received less than three ARTs, and 300 (17.0%) received HAART. When compared with patients who were alive, patients who had died had a significantly higher prevalence of AIDS (61.3% vs 38.0%, *P*<.001), a lower median CD4<sup>+</sup> T cell count (106 vs 306, *P*<.01) and a higher median HIV viral load count ( $17.2 \times 10^4$  vs  $4.5 \times 10^4$  per ml) at study enrollment (data not shown).

In Table 2 we present a Cox proportional hazard analysis which shows that patients who were IDUs, had AIDS at enrollment and were infected with HIV at an older age, and had a significantly higher mortality risk. In addition, the presence of a history of having been on HAART at the time of study enrollment was associated with a significantly lower mortality risk.

### Mortality Trends

The number of deaths and mortality rates were analyzed and organized as to the absence or presence of ART and the presence of HAART at some point in the history of each patient (Table 1). As anticipated the highest number of deaths was seen in the ART-naïve group. The mortality rates were: 70.4%, 66.5%, 24.2%, respectively in each of the three groups. A lower mortality was seen in patients who received ART, with a relative risk (RR) of 0.39 (95% CI 0.36–0.43) in the

**Table 1. Demographic, risk factor, immunological status, HIV disease duration, and death rate of the RRC HIV patients, by ART regimen**

	No ART n=1512	1-2 ART n=571	HAART n=1239	All N=3322
General (%)	45.5	17.2	37.3	100.0
Gender (%)				
Male	75.5	74.8	68.0*	72.6
Female	24.5	15.8	32.0	27.4
IDU (%)				
Yes	65.9	59.5	40.0*	55.1
No	34.1	40.5	60.0	44.9
CD4 <200 at study entry (%) (n=2,410)				
Yes	49.7	52.3	46.4*	48.7
No	50.3	47.7	53.6	51.3
AIDS at study entry (%)				
Yes	50.1	51.3	49.9	50.2
No	49.9	48.7	50.1	49.8
Mean age				
HIV infection	35.2 ± 9.3	35.0 ± 8.9	37.4 ± 10.0*	35.7 ± 9.6
Study entry	37.3 ± 8.9	36.8 ± 8.8	38.9 ± 9.5*	37.8 ± 9.2
HIV disease duration	3.0 ± 3.0	4.0 ± 3.2	5.2 ± 4.7*	4.0 ± 4.0
Death cases (n)	1064	380	300	1744
Death rates (%)				
General	70.4	66.5	24.2*	52.5
Men	71.9	70.0	26.5†	55.7
Women	65.7	56.3	19.4†	44.0
IDUs	71.9	69.7	30.1†	60.2
No-IDUs	67.4	61.9	20.3†	43.1
AIDS at e.	86.3	82.3	28.3†	64.1
No AIDS at e.	54.4	50.0	20.1†	40.8
Lost of followed	24.5	29.2	26.3	26.0

\* P value<.05 between ART.

† P value<.01 between ART.

ART=antiretroviral therapy; HAART=highly active antiretroviral therapies; IDUs=injecting drug users; HIV=human immunodeficiency virus; at e.=at enrollment.

HAART group and 0.89 (95% CI 0.77–1.02) in the group who received one or two ARTs. Significant differences were only seen in the HAART group.

An analysis of trends in mortality according to gender yielded results similar to the entire group. The mortality risk in men (RR=0.38, 95% CI of 0.35–0.42) and women (RR=0.43, 95% CI of 0.37–0.49) who received HAART was significantly lower when compared with the ART-naïve group.

Variations in the mortality of patients with HAART were also seen when analyzed according to the presence or absence of IDU. In both groups the

mortality was more than 50% lower (RR=0.40, 95% CI≠1) in the persons with HAART as compared to the ART naive group. Furthermore, the positive trends in mortality seen in patients

treated with HAART were also detected in patients with AIDS at study entry. The mortality risk in patients with AIDS at study entry was 0.19 (95% CI 0.16–0.23) and in non-AIDS was 0.57 (95% CI .052–0.62). Thus, the presence of HAART was associated with a lower mortality irrespective of gender, risk scenario, and stage of HIV infection at the time of study enrollment.

The most prevalent recorded diagnosis was: pulmonary system failure in 44.2%, wasting syndrome in 29.2%; sepsis in 16.9%; cardiovascular system failure in 15.9%; non-malignant hematological conditions in 11.8%; and gastrointestinal conditions in 10.7%. In Table 3, we present the variations in these death certificate diagnoses by ART. One of the most prominent variations was seen in the set of gastrointestinal conditions. These disorders were listed more often in patients with HAART with 20%, followed by one or two ARTs with 16.3% and 10.7% for patients without ART. In a sub-analysis of this system, hepatic dysfunction was significantly higher in the HAART and ART groups, than in the ART-naïve group (10.3%, 8.4%, and 5.3%, *P*<.01). Other system dysfunctions more frequently reported in the HAART group as compared with the ART-naïve group included: sepsis (22.7% vs 16.1%), neoplasm (7.0% vs 3.5%), metabolic disorders (11.0% vs 8.4%), renal condition (7.3% vs 6.1%), and neurological disorders (8.0% vs 6.5%). Only the first two reached statistical significance.

**Table 2. Cox proportional hazard regression analysis: mortality in 3322 HIV infected patients**

Parameter	Mortality Risks	95% CI	P Value
Female	0.937	0.833–1.054	.277
Age of HIV infection	1.028	1.023–1.033	<.01
IDU	1.169	1.050–1.303	<.01
AIDS at enrollment	2.181	1.978–2.406	<.01
HAART at enrollment	0.587	0.540–0.639	<.01

CI=confidence interval; HIV=human immunodeficiency virus; IDU=intravenous drug use; HAART=highly active antiretroviral therapies.

Table 3. Death causes percentage by ART and gender

Death Causes	No ART			1 or 2 ART			HAART		
	Men n=827	Women n=243	All N=1064	Men n=299	Women n=82	All N=380	Men n=229	Women n=80	All N=300
Cardiovascular	16.2	14.8	15.9	14.0	14.8	14.2	13.9	11.7	13.3
Pulmonary	43.1	47.7	44.2	43.5	43.2	43.4	43.5	44.2	43.7
Hematologic	11.6	12.8	11.8	13.4	11.1	12.9	11.7	9.1	11.0
Gastrointestinal	11.3	8.6	10.7	14.4	23.5	16.3	22.0†	14.3†	20.0†
Hepatic	5.8	3.3	5.3	8.4	8.6	8.4	10.8*	9.1	10.3†
Renal	5.8	7.0	6.1	7.4	7.4	7.4	7.6	6.5	7.3
Metabolic	8.2	9.1	8.4	9.4	9.9	9.5	11.2	10.4	11.0
Neurological	5.5	9.9	6.5	5.7	7.4	6.1	8.1	7.8	8.0
Neoplasm	3.7	2.9	3.5	4.0	3.7	3.9	7.2	6.5	7.0*
Sepsis	15.6	17.7	16.1	14.0	14.8	14.2	21.1	27.3	22.7†
PCP	5.8	4.9	5.6	6.4	3.7	5.8	3.1	6.5	4.0
Brain toxoplasma	9.6	9.5	9.6	8.0	6.2	7.6	7.6	11.7	8.7
Wasting syndrome	5.4	7.4	5.8	4.7	3.7	4.5	3.6	2.6	3.3
Kaposi sarcoma	29.7	27.6	29.2	30.8	24.7	29.5	9.0†	6.5†	8.3†
Pulmonary TB	3.2	5.3	3.7	5.7	1.2	4.7	2.7	1.3	2.3
Poison/overdose	5.1	3.7	4.8	5.4	2.5	4.7	6.3	7.8	6.7
Trauma	2.2	2.1	2.2	2.7	0	2.1	1.8	0	1.3

\* P value<.05 between ART.

† P value <.01 between ART.

ART=antiretroviral therapy; HAART=highly active antiretroviral therapies. PCP=pneumocystis carinii pneumonia; TB=tuberculosis.

The prevalence of AIDS-defining illnesses in the death certificate was tabulated. When analyzed by “HAART vs ART-naïve” the following illnesses were consistently lower in the HAART group: PCP (4.0% vs 5.6%), brain toxoplasmosis (8.7% vs 9.6%), pulmonary tuberculosis (2.3% vs 3.7%), and Kaposi sarcoma (8.3% vs 29.2%). Variations in cause of death according to gender were minimal and similar to the entire group for most conditions (Table 3). Cause of death conditions related to gastrointestinal dysfunction, metabolic syndromes, neoplasm, and sepsis were listed more often for men and women who received HAART than the naïve group. When analyzed by gender, gastrointestinal dysfunction was the only non-AIDS condition that reached statistical significance. Hepatic damage as one of the causes of death was significantly higher in men treated with HAART than in women. The report of AIDS-defining illnesses in the death certificate decreased in both men and women who received HAART. With the exception of Kaposi sarcoma, all other

differences related to AIDS-defining illnesses were not statistically significant.

We also analyzed the relationship between intravenous drug use (IDU) and mortality diagnosis. When stratified according to the presence or absence of IDU, those who received HAART had a higher prevalence of gastrointestinal dysfunction, hepatic damage, metabolic disorders, and sepsis as compared with those who did not receive ART (Table 4).

## DISCUSSION

Implementation of HAART along with an increase in chronic co-morbid conditions in HIV-infected survivors is producing important changes in the natural history of the disease. These changes deserve additional study. In this paper we describe the mortality spectrum in an RRC cohort of HIV-infected individuals, one of the largest groups of HIV-infected individuals followed in Puerto Rico since the beginning of the 1990s. As reported by other authors, the

present study found a significant association between mortality reduction and use of three or more ARTs (also known as HAART), regardless of gender and intravenous drug use.<sup>1-5</sup> Patients treated with HAART experienced a decline in mortality by approximately 50% as compared with mortality rates for ART-naïve patients. Cox proportional hazard analysis performed on this cohort revealed a mortality risk reduction for individuals who were on HAART at the time of study entry. These findings confirmed the beneficial effect of HAART on the life expectancy of HIV-infected patients in Puerto Rico.

We were not able to find a significant mortality reduction in patients treated with only one or two ARTs. These findings concur with the study of Hogg et al in which they demonstrated that triple drug regimens produce a greater and more sustained suppression of the HIV replication than a regimen of two ARTs.<sup>16</sup> Additionally, they reported that a triple drug regimen was four times as likely to suppress HIV viral load as compared with a regimen of two

**Table 4. Death causes by ART and IDU**

Death causes	No ART (%) IDU/No-IDU n=721/n=349	1 or 2 ART (%) IDU/No-IDU n=237/n=144	HAART (%/%) IDU/No-IDU n=154/n=155
Cardiovascular	14.9/17.8	14.8/13.2	13.4/13.2
Pulmonary	41.8/49.3	41.8/46.2	39.6/47.7
Hematologic	11.9/11.5	13.1/12.6	10.7/11.3
Gastrointestinal	12.0/8.0	17.3/14.7	22.1†/17.9†
Hepatic	6.6/2.6	11.4/3.5	12.1†/8.6*
Renal	6.0/6.3	7.2/7.7	6.7/7.9
Metabolic	8.7/7.8	6.3/14.7	11.4/10.6
Neurological	5.3/8.9	5.1/7.7	8.1/7.9
Neoplasm	1.7/7.2	3.8/4.2	4.0/9.9
Sepsis	17.9/12.4	14.8/13.3	22.8/22.5*
PCP	5.7/5.5	5.5/6.3	4.0/4.0
Brain toxoplasma	9.8/9.2	8.0/7.0	11.4/6.0
Wasting syndrome	5.4/6.6	6.8/0.7	4.7/2.0†
Kaposi	24.6/38.8	27.4/32.9	8.7†/7.9†
Pulmonary TB	3.4/4.3	7.6/0	3.4*/1.3*
Poison/overdose	6.8/0.6	6.8/1.4	8.7/4.6
Trauma	2.8/0.9	2.1/2.1	2.7/0

\* P value<.05 between ART.

† P value<.01 between ART.

ART=antiretroviral therapy; HAART=highly active antiretroviral therapies; IDU=intravenous drug use; PCP=*pneumocystis carinii* pneumonia; TB=tuberculosis.

ARTs. The triple ART regimen (or HAART) produces a better therapeutic response (as judged by viral-count reduction) and consequently leads to improved life expectancy.

Our study also detected a lower prevalence of AIDS-related conditions as the cause of death in persons who had been treated with HAART. Similar trends were previously found by Louie et al in 5234 HIV-infected persons who died in San Francisco between 1994 and 1998.<sup>17</sup> These authors reported a significant reduction of AIDS-defining causes of demise in the post-HAART era as compared with the pre-HAART era.<sup>17</sup> Contrary to these authors, in our study, the reduction of Kaposi sarcoma in the HAART group was the only statistically significant difference. The Kaposi sarcoma reduction has been previously published and attributed to the use of combination ARTs.<sup>18,19</sup> Ives et al and Jones et al reported a reduction of more than 30% in this condition after triple ART implementation.<sup>18,19</sup> When compared with the finding of Louie et al, we found a low prevalence PCP reported as the cause of demise in our study,

particularly in the ART-naïve group. The limitations in the diagnosis procedures for PCP, especially in the pre-HAART era and the low number of autopsies performed in this population increase the possibility of underreporting of this condition.

Like other authors, we found an increase in non-AIDS-defining conditions and chronic diseases as causes of death in individuals treated with HAART.<sup>1,3,8,10,17</sup> The benefits of HAART in terms of survival are clear. Nevertheless, the potential for adverse and toxic effects influencing the morbidity and mortality of HIV-infected patients needs to be considered, particularly in patients receiving long-term HAART.<sup>11-13</sup> Antiretroviral therapies (ART) have been associated with side effects that include neuropathies, myopathy, gastrointestinal disorders, and metabolic abnormalities.<sup>11-14</sup> Increments in the causes of death attributed to these conditions in patients with HAART suggest that the toxic profile of ART may be playing a role in the mortality trends of this population. The high prevalence of IDU in our cohort

may introduce the synergistic toxic profile of viral co-infections, which may accelerate liver damage caused by ART. Hepatitis C (HCV) and hepatitis B (HCB) are two viral infections that are emerging as an important and frequent finding in the HIV epidemic in the HAART era.<sup>14,17</sup> Prevalence rates of HCB-induced cirrhosis are higher in the presence of HIV infection, and HIV-HCV co-infection has a more rapid progression to fibrosis, liver failure, and death.<sup>17</sup> It has been reported that between 30% and 50% of HIV-infected persons have a concurrent HCV co-infection.<sup>20,21</sup> The impact of this co-infection appears to be greater in IDUs, among whom the prevalence of HCV exceeds 80%.<sup>20</sup> This high co-infection rate correlates with the high percentage of hepatic dysfunctions, seen as a cause of death in patients who received HAART and who were IDUs. The increment of deaths associated with sepsis could be related to the high prevalence of IDU, a risky behavior that by itself increases the risk of demise. Both the increase of sepsis in non-IDUs and the increase of metabolic disorders and neoplasm as demise causes in patients who received HAART need further evaluation.

Our study had several limitations:

- (1) The cause of demise was obtained from death certificates completed by the responsible physician. The quality of our data depends on how accurately and thoroughly the causes of demise were reported. In very few cases autopsies were performed to confirm the clinical diagnosis. As a consequence underreporting or overreporting can occur.
- (2) The study measured and evaluated the presence of ART and HAART based on drug prescriptions without considering patient adherence.
- (3) The effects of disease-severity variation and the use of alcohol, cigarettes, and other medications or drugs were not taken into

account in this analysis. In spite of these limitations, this study enhances our understanding of the changing profile of our patients.

Our study found a significant mortality reduction in HIV-infected patients treated with HAART in Puerto Rico. The use of HAART was also associated with a significant variation in the causes of death. We detected fewer AIDS-defining conditions and more gastrointestinal disorders, sepsis, metabolic abnormalities, and neoplasm in patients treated with HAART. These mortality variations can be attributed to the adverse and toxic effects of HAART and perhaps to the presence of co-infection with other viruses. Additional efforts need to be made to detect, treat, and prevent hepatitis co-infection in this population, particularly among IDUs. Prevention strategies such as vaccination and risk-reduction education are vital components of the effort to reduce the co-infections that have the potential to amplify the adverse effects of HAART.

Mortality surveillance studies enable us to get a better picture of the changing face of the HIV/AIDS pandemic and are vital for evaluating the effectiveness of various therapeutic strategies. In light of the significant changes in the epidemic and the vulnerability of the population affected, we recommend continuing and enlarging mortality surveillance studies in Puerto Rico.

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