ANTIRETROVIRAL THERAPY AND DECLINING AIDS MORTALITY IN NEW YORK CITY

T. WONG, MD, M. A. CHIASSON, DrPH, A. REGGY, MD, R. J. SIMONDS, MD, J. HEFFESS, MPH, AND V. LOO, BA

ABSTRACT The objective was to evaluate the association between antiretroviral therapy and AIDS mortality in New York City (NYC). Design was a population-based case-control study. We randomly selected 150 case patients and 150 control patients whose AIDS diagnosis was made during 1994 to 1996 (male : female, 2 : 1) from among 19,238 persons reported to the NYC Health Department HIV/AIDS Reporting System (HARS). Case patients had died of AIDS-related causes in 1996. Control patients, category matched with case patients on gender, were not known to have died by the end of 1996. Analysis was performed on 279 patients (142 cases and 137 controls). Cases and controls were similar in age, gender, race, HIV transmission category, and health insurance coverage. The median baseline CD4 count was 30 cells/μL for those who died and 103 cells/μL for survivors ($p < .0.001$). The prescription of HAART (antiretroviral combination that includes at least one protease inhibitor) in 1996 was strongly associated with survival in univariate analysis (OR = 5.1, 95%CI = 2.5–10.2). This association remained in a logistic regression analysis after adjusting for sex, age, race, health insurance status, HIV transmission categories, year of AIDS diagnosis, baseline CD4 count, and other antiretroviral therapy (AOR = 8.6, 95%CI = 3.5–20.7). Prescription of combination therapy other than HAART in 1996 and baseline CD4 count were also associated with survival, but less strongly so. The survival benefit of HAART extends beyond the confines of a few highly selected patients into the "real world," reducing AIDS deaths at the population level. This population-based study sup-

At the time of the study, Drs. Wong and Chiasson and Ms. Heffess were affiliated with Columbia University and the New York City Department of Health; Drs. Reggy and Simonds were affiliated with the Centers for Disease Control and Prevention, Atlanta, Georgia; and Ms. Loo was affiliated with the New York City Department of Health.

Dr. Wong is currently with Laboratory Centre for Disease Control, Health Canada; Dr. Chiasson is currently with Medical and Health Research Association of NYC, Incorporated; Ms. Loo is currently with the California Department of Health Services—STD Control Branch.

Correspondence and reprints: Thomas Wong, MD, MPH, Bureau of HIV/AIDS, STD, and TB, Laboratory Centre for Disease Control, Health Canada, Brooke Claxton Building, Room 0108B, Postal Locator 0900B1, Tunney's Pasture, Ottawa, ON, Canada K1A 0L2. (E-mail: tom_wong@hc-sc.gc.ca)

ports the likelihood that the introduction of HAART in 1996 played a primary role in the decline in NYC AIDS mortality.

KEY WORDS Antiretroviral Therapy, HAART, Mortality, Protease Inhibitors.

INTRODUCTION

Since the beginning of the acquired immunodeficiency syndrome (AIDS) epidemic, over 700,000 cases have been reported nationally. New York City suffered a heavy toll by having the largest number of cases of any single American city, with over 110,000 cases reported to date.[1] The transmission risk categories in New York City are diverse, including men having sex with men (MSM), injecting drug users (IDUs), and heterosexuals. Of all reported AIDS cases in the city, females account for 22%, IDUs account for 42%, and more than 75% are people of color.[2]

Beginning in 1996, the number of AIDS deaths declined in New York City,[3] from an average of 20 per day in 1995 to 6 per day in 1998. Because this reduction in deaths coincided with the introduction of protease inhibitors, it has been hypothesized that highly active antiretroviral therapy (HAART) combinations that include at least one protease inhibitor might have played a role in this decline.[4–6] Clinical trials have shown that HAART reduces mortality in highly selected and rigorously monitored patients.[7,8] To assess the public health impact at the population level, we evaluated the association between antiretroviral therapy and mortality among persons with AIDS in New York City in 1996, the year when HAART was first available widely.

METHODS

Study Design and Population

We conducted a case-control study among all persons with AIDS diagnosed in New York City between 1994 and 1996, aged 25–59 years, who were reported to the New York City Health Department HIV/AIDS Reporting System (HARS). By law, individuals meeting the CDC definition of having AIDS are reportable to the New York City Department of Health. From this population of 19,238, we randomly selected 150 cases and 150 controls using computer-generated random numbers.

Case patients were those who died of AIDS-related causes in 1996, with information obtained in any of the following ways. All deaths occurring within New York City must have been filed with the New York City Department of Health within 72 hours of death. Underlying cause of death was determined by a health department nosologist using the coding algorithm established by the

National Center for Health Statistics and International Classification of Diseases, Ninth Revision (ICD-9) codes.[9] Biannual matches between the AIDS case registry and the New York City death file were conducted. A match between the New York City AIDS case registry and the National Death Index documented that only a small proportion (~6%) of New York City AIDS cases died elsewhere.[3] Second, medical personnel must have reported deaths directly to the Department of Health Office of AIDS Surveillance. Finally, we reviewed medical records from the primary treatment facility of all sampled patients, as well as other inpatient and outpatient health care facilities that the patients visited during the study period, to abstract survival data and demographic, behavioral, medical, and treatment information. Using the above methods, control patients were determined not to have died from any cause by December 31, 1996. Women were oversampled (200 men, 100 women).

The sample size calculation was based on a confidence interval (CI) of 95%, power of 80%, and combination antiretroviral use by 79% of control patients to detect an odds ratio (OR) of at least 2.5.

Data Collection

Trained public health staff familiar with AIDS surveillance data abstraction collected data for 1995 and 1996. Several data sources were used: HARS, records from facilities concerning AIDS diagnosis/death, death certificates, and records from additional facilities identified through chart reviews or through a CD4 reporting mechanism by which laboratories report counts less than 200 cells/μL to HARS. Viral load testing was not the standard of practice during the study period; therefore, results were not available for the majority of patients. Standardized data collection forms were used. Patient interviews were not performed.

Statistical Analysis

We categorized antiretroviral therapy based on the most advanced regimen used as none, monotherapy, HAART (defined as an antiretroviral combination that included at least one protease inhibitor), and combination therapy other than HAART. Subjects were excluded from the analysis of medication use if no such information was available. The baseline CD4 count closest to the time of AIDS diagnosis was used for all analyses.

A stepwise logistic regression model was used to assess the association between antiretroviral therapy and AIDS survival while controlling for continuous variables (age, baseline CD4 count) and categorical variables (gender, race, health insurance status, human immunodeficiency virus [HIV] transmission category, and year of AIDS diagnosis).

SAS 6.12 (SAS Institute, Cary, NC) and Epi Info 6.04 (CDC, Atlanta, GA) were used for data analyses. All statistical tests were two sided, and a P value less than .05 was considered to indicate statistical significance.

RESULTS

Of the 300 patients, 21 were excluded from the analysis: Two control patients could not be identified adequately because of conflicting demographic data, 3 control patients had received their medical care outside New York City, and 8 patients from each group actually were diagnosed with AIDS before 1994. These excluded patients did not differ significantly from the rest of the sample in age, gender, HIV transmission category, health insurance status, and baseline CD4 count. There were slightly fewer minorities in the excluded group (62% vs. 82%, $P = .04$).

Patient Characteristics

The patients in our sample were similar to the AIDS population in New York City from which they were selected after taking into account differences in race and transmission categories inherent in the intentional oversampling of women (Table I). Cases were similar to controls in age, gender, race, HIV transmission category, and health insurance coverage.

Predictors of AIDS Survival

The median baseline CD4 count was 30 cells/μL for those who died and 103 cells/μL for the survivors ($P < .001$). Those who died were more likely to have been diagnosed with AIDS before 1996 ($P < .05$) (Table II).

In univariate analysis, antiretroviral therapy status was associated with survival (Table III). Those who survived were more likely to have been prescribed antiretrovirals compared to those who died (OR = 3.5, 95% CI 1.8–6.7). In particular, they were more likely to have been prescribed HAART (OR = 5.1, 95% CI 2.5–10.2). The above association persisted after stratification by year of AIDS diagnosis or by baseline CD4 count; HAART was associated with increased survival even in those with very low CD4 count (<50 cells/μL). To allow cases a greater opportunity to initiate HAART in 1996 when it first became available, we compared those cases who survived through at least the first 6 months in 1996 to the controls. HAART remained associated with increased survival (OR = 2.3, 95% CI 1.1–5.1) (Table II).

In multivariate analysis controlling for gender, age, race, health insurance status, HIV transmission category, years of AIDS diagnosis, baseline CD4 count, and antiretroviral therapy, the prescription of HAART in 1996 had the strongest

TABLE I Baseline Characteristics of Cases and Controls*

	Case (N = 142) (Died)	Control (N = 137) (Survived)	P
Median age in years (25th to 75th percentile)	40 (35–45)	38 (34–45)	0.34
Sex			
Male	96 (68)	91 (66)	
Female	46 (32)	46 (34)	0.93
Race			
White	25 (18)	22 (16)	
Black	59 (41)	65 (47)	0.3
Hispanic	55 (39)	50 (36)	
Other	3 (2)	0 (0)	
HIV transmission category			
Men who have sex with men	27 (19)	24 (17)	
Injection drug users	79 (56)	71 (52)	0.71
Heterosexual transmission	18 (13)	18 (13)	
Other/unknown	18 (13)	24 (17)	
Health insurance†			
Public funding	100 (73)	77 (69)	
Private insurance	21 (15)	17 (15)	0.54
Other	1 (1)	5 (5)	
No coverage	15 (11)	13 (12)	

*Values are number (percentages) of subjects unless otherwise stated.
†Health insurance status was unknown for 29 patients.

association with survival (adjusted OR = 8.6, 95% CI 3.5–20.7) (Table IV). Prescription of combination therapy other than HAART in 1996 and baseline CD4 count were associated less strongly with survival.

Despite extensive chart reviews at each treatment facility, antiretroviral data were missing for 51 patients. To ensure that the missing data would not have changed the conclusions of the study, we repeated the univariate analyses using two assumptions. First, we assumed that none of those with missing information were prescribed antiretrovirals. The analysis was then repeated assuming that all these 51 patients were prescribed HAART. In both scenarios, the strong association between survival and HAART remained ($P < .001$) (Table V).

DISCUSSION

Clinical trials have shown that HAART can reduce mortality in highly selected and closely monitored HIV-infected patients in ideal research settings.[4,5] Subsequently, observational studies have suggested survival benefits in patients attend-

TABLE II Significant Predictors of AIDS Survival in 1996: Univariate Analysis

	Case (Died)	Control (Survived)	OR* (95% CI)
Any antiretroviral†	73/129 (56%)	81/99 (82%)	3.5 (1.8–6.7)
HAART (unstratified)	17/129 (13%)	43/99 (44%)	5.1 (2.5–10.2)
HAART, stratified by baseline CD4 count			4.3 (2.2–8.4) (Mantel-Haenszel)
CD4 <50 cells/μL	7/82 (9%)	5/23 (22%)	8.9 (2.8–29.0)
CD4 ≥50 cells/μL	9/42 (21%)	26/62 (42%)	2.7 (1.0–7.2)
HAART, stratified by year of AIDS diagnosis			5.0 (2.6–9.7) (Mantel-Haenszel)
1996	4/25 (16%)	14/36 (39%)	3.3 (1.0–13.2)
1994–1995	13/104 (14%)	29/63 (46%)	6.0 (2.6–13.9)
HAART, limited to cases who died in the second half of 1996	14/56 (25%)	43/99 (44%)	2.3 (1.1–5.1)
Year of AIDS diagnosis			
1996	27/142 (19%)	43/137 (31%)	
1994–1995	115/142 (81%)	94/137 (69%)	2.0 (1.1–3.5)
Median baseline CD4 count‡ (cells/μL) (25th to 75th percentile)§	30 (10–70)	103 (34–171)	—

*Crude OR except as indicated.

†Monotherapy and antiretroviral combinations other than HAART were not significantly associated with survival in univariate analysis.

‡CD4 count was unknown for 20 patients.

§Median, $P < .001$.

TABLE III Antiretroviral Therapy Prescribed Based on the Most Advanced Regimens Used by Cases and Controls in 1996*

	Case (N = 129)† (Died)	Control (N = 99)† (Survived)
None	56 (44%)	18 (18%)
Monotherapy	21 (16%)	11 (11%)
Combination other than HAART	35 (27%)	27 (27%)
HAART	17 (13%)	43 (44%)

*51 patients with missing antiretroviral data were excluded from analysis of antiretroviral use.

†$P < .001$.

TABLE IV Predictors of AIDS Survival in 1996: Multivariate Analysis*

	Adjusted OR	95% CI
HAART	8.6	3.5–20.7
Antiretroviral combination other than HAART	2.6	1.1– 6.2
Baseline CD4 (per 50/μL increment)	1.6	1.3– 2.0

*Controlled for gender, age, race, health insurance status, HIV transmission category, year of AIDS diagnosis, baseline CD4 count, and antiretroviral therapy.

ing outpatient clinics.[10–15] Many of these studies include either predominantly men, MSM, or individuals who belong to higher socioeconomic strata, but there is an under-representation of women, minorities, and IDUs. It may not be possible to generalize the results of these studies to all HIV populations. For example, Palella et al.[13] demonstrated survival benefit in a cohort of 1255 patients seen at nine HIV clinics in the US. However, the study included predominantly Caucasian MSM (12% female and 14% IDUs). Similarly, McNaghten et al.[15] included only 15% females and 16% IDUs. In addition, by being involved in a study or attending a clinic, cohort study patients may be more adherent or have better access to information and therapy compared with patients in the general population. As new therapy often diffuses slowly into the general population, especially for women, IDUs, and other socioeconomically disadvantaged groups, these clinical benefits may not translate into public health impact in the wider population with different demographics, different degrees of adherence, and different access to care.[15–18]

Our population-based case-control study included a large number of IDUs and a full spectrum of socioeconomic status, access to care, stages of immunosuppression, and adherence to therapy. In New York City, the AIDS Drug Assistance Program and funding from the Ryan White Comprehensive AIDS Resources Emergency Act have provided broad access to treatment for HIV-infected patients, particularly the disadvantaged. Unlike other population studies involving health care delivery systems different from those in the US,[20,21] ours included a

TABLE V Analytic Technique Addressing Missing Antiretroviral Data

Patients with Missing Antiretroviral Data Were	No. of Cases on HAART (%)	No. of Controls on HAART (%)	OR	95% CI
Assumed to be prescribed no antiretrovirals	17/142 (12)	43/137 (31)	3.4	1.7– 6.6
Assumed to be prescribed HAART	30/142 (21)	81/137 (67)	5.4	3.1– 9.5
Excluded from analysis	17/129 (13)	43/99 (44)	5.1	2.5–10.2

larger number of women (33% of sample) and minorities (82% of sample). We confirmed that survival benefit extends beyond the confines of highly educated Caucasians or MSM into the population level, across lines of gender, ethnicity, injection drug use, and health insurance status.

Some limitations of our study need to be discussed. Our study does not take into account frequent antiretroviral regimen changes, regimen duration, or variations in drug dosage. To address the potential survivor treatment selection bias, we compared those cases who died in the last half of 1996 to the controls. HAART remained associated with increased survival. In addition, as HAART coverage increased in New York City after the study period, AIDS mortality continued to decline.[22]

In conclusion, the decline in AIDS deaths in New York City in 1996 was rapid and coincided with the introduction of HAART. Our study findings support the hypothesis that the introduction of HAART in 1996 played a primary role in the decline in AIDS mortality in New York City.

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