Increased Mortality among Publicly Insured Participants in the HIV Outpatient Study (HOPS) Despite HAART Treatment

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ABSTRACT

Objective: Understanding mortality differences among HIV-infected patients can focus efforts to improve survival.

Design: We evaluated death rates, causes and associated factors among treated patients in the HOPS, a large, prospective, multicenter observational cohort of HIV-infected persons seen at diverse U.S. sites of care.

Methods: Among 3754 HOPS participants seen during 1996-2007 with ≥ 6 months of follow-up after initiating HAART and $\geq 75\%$ of time under observation receiving HAART (“substantially treated”), we calculated hazard ratios for death using proportional hazards regression models, death causes and comorbidities.

Results: Substantially treated participants, followed a median 4.7 years (IQR, 2.2-8.5), experienced 331 deaths. In multivariable analyses, higher mortality was associated with index CD4 < 200 counts/mm³ (adjusted hazard ratio [aHR], 2.86; 95% CI, 1.95-4.21), older age (aHR, 1.50 per 10 years; 95% CI, 1.33-1.70), log₁₀HIV RNA (aHR, 1.67 per log₁₀; 95% CI, 1.51-1.85), but not race/ethnicity (aHR, 0.99 for blacks vs whites, $p=0.92$).

Mortality was increased among publicly insured (PUB) vs privately insured participants (PRV

) when index CD4 ≥ 200 (aHR, 2.03; 95% CI, 1.32-3.14) but not when index CD4 < 200 cells/mm³ (aHR, 1.3, $p=0.13$). By death cause, PUB had significantly more cardiovascular events and hepatic disorders than PRV.

Comorbidities more frequent among PUB vs PRV decedents included cardiovascular disease, renal impairment and chronic hepatitis.

Conclusions: Among HAART treated participants with CD4 ≥ 200 cells/mm³, PUB experienced higher death rates than PRV. Non-AIDS death and disease causes predominated among publicly insured decedents, suggesting that treatable comorbidities contributed to survival disparities.

Introduction

Death rates among HIV-infected persons in the US decreased dramatically after the introduction of highly effective antiretroviral therapy (HAART)¹. Although lower and generally stable during the HAART era¹⁻³ compared with pre-HAART era, mortality rates for HIV-infected adults remain higher than rates for the general population.⁴ The benefits of HAART are not equally distributed among all groups; observational studies have noted demographic (e.g., gender, race/ethnicity) differences in the stage of HIV disease at clinical presentation^{5,6}, in HAART use⁷, in adherence to clinical care^{6,8,9}, in responses to therapy including viral suppression^{8,10}, and in overall survival^{3,5,7,11}. Few studies, however, have examined the extent to which survival and causes of death differ among adult HAART recipients who were under observation all or most of the time while prescribed HAART (i.e., “substantially treated”). In an era of national healthcare system reform, identification and characterization of disparities in survival, especially disparities that are associated with healthcare payer type or patient demographics (including descriptions of relationships between source of payment for medical care insurance and other socioeconomic variables such as age, ethnicity, income, and occupation) can inform and focus efforts to improve survival and quality of life for HIV-infected persons. In this report, we describe differences in mortality among HIV-infected persons in care and identify factors that may account for such differences.

Methods

Study Population and Data Sources

We analyzed data from the HIV Outpatient Study (HOPS), an ongoing, prospective, observational multicenter study of HIV-infected persons in care, funded by the Centers for Disease Control and Prevention

(CDC) since 1993¹². The study protocol is approved annually by the institutional review boards at the CDC and at each participating clinic. The 12 HOPS sites participating in 1996-2007 were in Washington DC, Tampa FL, Denver CO, Oakland CA, San Leandro CA, Chicago IL, Stony Brook NY, and Philadelphia PA, and included academic, public and private care centers. Participant data collected included laboratory results, clinical diagnoses, treatments, demographics, risk behaviors and information regarding death events.

For this analysis, we included participants who had ≥ 2 clinical visits between January 1, 1996 and December 31, 2007, using HOPS data updated as of September 30, 2009. We defined the baseline date as January 1, 1996 or the date of first HOPS visit thereafter. Observation was censored at whichever of the following occurred first: death, date of last contact plus 180 days, or December 31, 2007. We terminated observation at the end of 2007 to allow adequate time for identification and documentation of deaths. We restricted our analyses to patients who had received HAART continuously for at least six months and received HAART for $\geq 75\%$ of their observation time; we defined these patients as “substantially treated”. We excluded from modeling of mortality a small fraction of substantially treated patients who had clinical study-related or unknown payor or had “other” race or ethnicity. In addition to the baseline date when follow-up commenced, we defined an “index date” as the date on which a substantially treated participant first completed six months of continuous HAART. Vital status was corroborated using the Social Security Death Index. Only deaths occurring within six months after last HOPS contact and before December 31, 2007 were considered.

Definitions of Variables Analyzed

We calculated all-cause crude mortality rates as deaths per 100 person-years (py) of observation stratified by gender, race/ethnicity and insurance (i.e., primary payor of medical costs). Insurance was categorized as public, private, or other, according to that type documented during $\geq 75\%$ of visits during observation. We categorized the following as private: health maintenance organizations (HMOs), preferred

provider organizations (PPOs), point of service, and private insurance otherwise unspecified. We categorized the following as public: Medicare, Medicaid, Ryan White Care Act/AIDS Drug Assistance Program (ADAP) and public insurance otherwise unspecified. We categorized all other insurance types as other. If a patient had more than two types of insurance and none were in effect for $\geq 75\%$ of total HOPS visits, or if the primary medical care payor was a clinical research study, we also categorized insurance as other. CD4⁺ T-lymphocyte count (CD4) at death was defined as the last CD4 obtained during follow-up.

We defined HAART as any one of the following regimens: (a) any three antiretrovirals, one of which was either a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a fusion, integrase or entry inhibitor; (b) any three nucleoside reverse transcriptase inhibitors, one of which was abacavir or tenofovir (except for the regimens abacavir + tenofovir + lamivudine and didanosine + tenofovir + lamivudine); (c) two full-dose PIs; (d) a boosted PI with either an NNRTI or a fusion inhibitor; or, (e) an integrase inhibitor combined with either a PI, NNRTI, entry inhibitor or fusion inhibitor. If zidovudine and stavudine were present in the same regimen, they were removed from that regimen's total antiretroviral count due to their known antagonism.

Chronic comorbidities included cardiovascular disease, hypertension, diabetes mellitus, impaired glucose control, dyslipidemia, renal disorders, chronic obstructive pulmonary disease, hepatitis C virus (HCV) infection, chronic hepatitis B virus (HBV) infection, non-AIDS-defining cancers, and obesity. Obesity was defined as body mass index (BMI) ≥ 30 kg/m². Chronic comorbidities were defined based on the presence of diagnoses, treatments, procedures, or laboratory values pertinent to each condition (detailed appendix of classification available from the authors). The broad categories of causes of death were assigned after detailed review (by F.J.P. and R.B.) of systematically abstracted death data.

A patient was defined as HCV-infected if the medical record contained a positive result for HCV serology, or a report of a detectable HCV plasma viral load or an HCV genotype. A patient was defined as chronically HBV-infected if there was a positive test for serum HBV surface antigen, serum HBV e-antigen, or detectable plasma HBV DNA. Nadir CD4 was the lowest value prior to or within seven days after the index date. Index CD4 and HIV RNA were the values closest to the index date measured within six months prior to or within seven days after the index date. HIV resistance testing included both genotype and phenotype tests. All variables were defined as of the index date except for HIV resistance testing, which was analyzed as a time-varying variable from the index date.

Patients of Hispanic ethnicity were categorized as Hispanic, regardless of race. Patients of non-Hispanic ethnicity and Black or White race were classified as Non-Hispanic Blacks and Non-Hispanic Whites, respectively. All others races and unspecified ethnicities were classified as Other for race.

Statistical Analyses

Differences in crude mortality rates by race/ethnicity and payor categories and temporal trends in mortality were evaluated using general linear modeling. Continuous variables were compared statistically using the Wilcoxon rank sum test, and categorical variables using the Pearson chi-square test. Factors associated with mortality ($p < 0.10$) in univariate proportional hazards regression models were considered for inclusion in multivariable models. If two biologically related factors were strongly associated with each other in exploratory analyses (e.g., history of injection drug use [IDU] and HCV infection, nadir CD4 and history of AIDS), we included only one factor in the model, usually the factor for which available data were most complete. We derived final models by manually excluding covariates not significantly associated with mortality ($p > 0.05$) in adjusted analyses; however, we retained gender, race/ethnicity, HIV transmission risk group and year of

HAART initiation in all final models regardless of their statistical significance because of their *a priori* importance when considering survival outcomes. We explored interactions between index CD4 and payor, CD4 at HAART initiation and payor, CD4 at HAART initiation and race/ethnicity, year of HAART initiation and race/ethnicity, and race/ethnicity and payor.

For the deceased, we compared the distribution of causes of death and of chronic comorbidities diagnosed any time prior to death, stratified by race/ethnicity and payor using the Pearson chi-square test. We analyzed all-cause mortality and considered primary and secondary causes of death. In cause of death summaries, a patient could be represented in more than one cause of death category if multiple causes of death were present.

Results

From among 7338 HOPS participants who had ≥ 2 clinical visits between January 1, 1996 and December 31, 2007, we identified 3754 substantially treated participants for whom median observation time was 4.7 years (IQR, 2.2-8.5) and death rates were 1.60 deaths/100 person-years (py). The median percent of time on HAART during follow-up was 97.1% (IQR, 89.2%-100.0%).

In analyses restricted to 3569 (95%) of 3754 substantially treated patients who were black, white or Hispanic and did not have clinical study-related or unknown payors (Table 1), most participants were male (84.0%) and non-Hispanic white (white) (59.8%, compared with 28.6% non-Hispanic black [black] and 11.7% Hispanic), and were privately insured (56.6% compared with 32.1% who were publicly insured). Most (63.5%) participants were men who had sex with men (MSM); 21.7% were high-risk heterosexuals (HRH); 9.7% were injection drug users (IDU). Over one-third of participants had a history of AIDS at baseline (61.8%), 53.6% a history of tobacco use and 31.5% a history of substance abuse. There were 318 deaths.

In crude analyses of mortality rates, substantially-treated patients with public insurance/payor had significantly higher rates of mortality than patients with private insurance/payor ($p < 0.05$), while there were no statistical or clinically meaningful differences in mortality by race/ethnicity (Figure). Blacks had lower median index CD4 cell counts compared with all other patients combined (246 vs. 320 cells/mm³, $p < 0.0001$), as did publicly insured compared with privately insured patients (242 vs. 340 cells/mm³, $p < 0.0001$). Variables significantly associated with increased mortality hazard among substantially treated patients in unadjusted proportional hazards analyses included: older age, black race/ethnicity, IDU history, public insurance, AIDS, lower nadir and index CD4, lower CD4 at HAART initiation, higher index plasma HIV RNA, HCV infection or chronic HBV infection, tobacco smoking history, non-HAART exposure, and having not undergone antiretroviral resistance testing (Table 1).

We also identified an interaction between index CD4 (and CD4 at start of HAART) and insurance: although type of insurance was not associated with mortality rates among participants with CD4 < 200 cells/mm³, participants with public insurance had a higher mortality hazard than those with private insurance when their index CD4 (or CD4 at start of HAART) was ≥ 200 cells/mm³ (Table 2).

Table 3 outlines patient characteristics among substantially treated persons with baseline CD4 ≥ 200 cells/mm³, stratified by insurance type. In this group, compared to persons with private insurance, persons with public insurance were more likely ($p < 0.001$) to be female, Hispanic or non-Hispanic black race, have high-risk heterosexual risk for HIV, have a history of injection drug use, any recreational substance use, have a history of AIDS, chronic HCV infection, tobacco use, or to be cared for in a university clinic. Persons in this group with public insurance were less likely ($p < 0.001$) to ever achieve an undetectable plasma HIV RNA level, to be seen in a group practice setting, or to undergo HIV resistance testing ($p = 0.006$).

In adjusted models (Table 4) with interaction terms between index CD4 and insurance, or between CD4 at start of HAART and insurance, we also found increased mortality hazard among older patients, IDU compared with MSM, and persons with higher index HIV RNA levels; and reduced hazard for participants who underwent HIV resistance testing. Among patients with index CD4 ≥ 200 cells/mm³, those with public insurance had significantly higher hazard of death than those with private insurance (aHR, 2.03; 95% CI, 1.32-3.14); type of insurance was not associated with mortality hazard among patients with CD4 < 200 cells/mm³.

In another model, not presented here, we investigated whether insurance status remained associated with increased mortality among substantially treated participants if it was defined as of the index date rather than as the predominant insurance type during the study observation period. In this model, publicly insured participants still had higher mortality rates than privately insured participants (aHR, 3.14; 95% CI, 1.96-5.04) when index CD4 ≥ 200 cells/mm³. When the model controlled for CD4 at HAART initiation instead of index CD4 (for the smaller subset of participants who had that measurement available), mortality hazard for publicly compared with privately insured participants remained elevated but was not statistically significant (aHR, 1.36; 95% CI, 0.95-1.95).

Among substantially treated patients, 82% of the overall group, including 87% of the publicly insured and 89% of privately insured patients, remained covered by the same insurance/payor type during their entire observation. Of 2020 patients in the private insurance/payor group, only 2% had public or other/unknown insurance at their last visit; of 1146 persons in the public insurance/payor group, 1.4% had private or other/unknown insurance at their last visit.

Causes of death were available for 248 (78%) of participants who died: 77% of privately insured participants, 76% of publicly insured participants, 81% of whites, 69% of blacks, and 87% of Hispanics. Blacks were less likely than all other race/ethnicities to have a documented cause of death ($p = 0.025$). Among

participants with causes of death reported (Table 5), publicly insured participants had proportionately more ($p < 0.05$) deaths than privately insured patients from cardiovascular events (30.3% vs 15.1%) and hepatic disorders (23.8% vs 12.3%). Compared with whites, deaths among blacks were more likely ($p < 0.05$) to involve cardiovascular events (31.9% vs 19.7%) and renal disease (23.2% vs 6.6%) . In analyses of chronic non-AIDS comorbidities among participants who died (Table 6), publicly insured compared with privately insured participants were more likely to have ($p < 0.05$) cardiovascular disease (25.9% vs 13.1%), renal disease (24.5% vs 13.1%) and HCV or chronic HBV infection (48.2% vs 17.5%). Compared with whites, blacks were more likely ($p < 0.05$) to have had HCV or chronic HBV infection (38.0% vs 26.2%) or to have ever been obese (26.0% vs 13.4%).

Finally, for comparison with data for decedents, we undertook further analyses of all substantially treated HOPS participants with index CD4 cell counts ≥ 200 cells/mm³, and found that publicly insured participants were more likely ($p < 0.05$) than privately insured participants to have HCV or chronic HBV infection (28.5% vs 8.5%), hypertension (35.3% vs 18.7%), cardiovascular disease (6.8% vs. 2.2%), diabetes (6.8% vs 2.3%) and chronic obstructive pulmonary disease (5.8% vs 1.2%) at index date.

Discussion

In this large prospective observational study of a diverse cohort of HIV-infected patients seen in the US during the contemporary HAART era, substantially HAART-treated patients with CD4 ≥ 200 cells/mm³ whose principal access to medical care payment was through publicly-funded sources experienced a greater than two-fold adjusted mortality rate compared with similar patients whose healthcare costs were was paid by private entities. Significant differences in adjusted mortality rates by payor among similar patients with CD4 < 200 cells/mm³ were not apparent. In these adjusted analyses, race/ethnicity was not associated with increased mortality once CD4 cell counts, insurance/payor, and other factors were taken into account. Among

participants who died, several modifiable comorbid conditions and related causes of death were more prevalent among publicly than privately insured participants and among blacks than whites.

Our decision to focus this analysis on substantially treated patients was based upon preliminary findings (data not shown) of marked differences in the prevalence and persistence of HAART use among patient groups (e.g., publicly- compared with privately-insured, blacks compared with whites). We sought to minimize the impact of differential HAART exposure by evaluating more optimally treated patients. The substantially treated group differed from the overall cohort (see appendix); there was a somewhat lower proportion of black and publicly insured patients, median baseline and nadir CD4 were lower, and there was a higher prevalence of AIDS.

The independent association of public insurance with increased mortality risk was noted only in patients with either an index CD4 or a CD4 at HAART initiation ≥ 200 cells/mm³. This finding suggests that the increased risk of death was not a consequence of HIV-related morbidity per se but rather was associated with differences between the two groups in the rates or types of comorbid conditions or differences in the quality of medical care provided. We believe our analysis is the first to document an association between the types of medical coverage to which HIV–infected patients have access and patient survival.

There were differences in the CD4 ≥ 200 cells/mm³ group by insurance type in factors shown to be associated with mortality risk in univariate models, such as hepatitis C (which correlates with IDU and history of substance abuse) and tobacco smoking. We acknowledge that these factors could have contributed to observed mortality differences between publically and privately insured persons in this higher CD4 stratum; nevertheless, the independent and significant association of public insurance with increased mortality in adjusted models persisted after adjusting for key variables prognostic of the mortality in the HOPS.

Recent reports indicate that deaths and comorbidities during the contemporary treatment era are less likely to involve AIDS-defining (immunodeficiency-related or opportunistic) illnesses and are increasingly likely to occur as consequences of complications from chronic non-AIDS comorbidities^{2, 12-16}. In our cohort, nearly half of deaths were due to non-AIDS causes. Some of the most prevalent non-AIDS causes of death (e.g., cardiovascular, renal, and liver disease)² and comorbidities (e.g., viral hepatitis coinfection, obesity) occurred with greater frequency among both publicly insured and black participants who died. Obesity and viral hepatitis coinfection as well as many of the other comorbidities that were differentially increased among publicly insured and black participants represent preventable, often treatable conditions. Hence, timely identification and treatment of comorbidities has emerged as an important component of HIV medical care¹⁷.

We urge caution in interpreting our findings. We believe it would be improper to consider these findings as evidence that the quality of publicly funded healthcare provided was inferior and that it was primarily this inferiority that contributed to the greater mortality observed among publicly insured persons. Although we did not specifically examine the quality of healthcare delivered, our findings have important implications for healthcare reform because the population of persons whose access to healthcare was principally through public sources was significantly enriched in patients diagnosed with comorbidities – usually treatable and often preventable – that are known to be causes of the diseases that predominated as causes of death, especially for the publically insured. Although the associations between mortality and type of insurance among these HIV-infected adults may have been influenced by subtle differences in the quality of care, none were readily apparent in any comparisons of care indices (e.g., frequency of visits [data not shown]) among privately versus publicly funded patients at any HOPS site; it is more likely that the mortality/insurance associations were driven by an excess of underlying non-HIV related comorbid disease among persons whose healthcare was publicly funded. The extent to which having publicly funded healthcare was a marker for socioeconomic issues which themselves engendered greater risk for death (and disease) is unclear.

Our study has limitations. Since insurance/payor status was ascertained only at the time of clinic visits, we could not ascertain the precise timing of transition from private to public insurance/payor or vice-versa in the relatively small proportion of patients who had more than one primary payor type while under observation. For the same reason, we could not estimate percentage of follow-up time spent in each insurance category, and instead we assigned insurance/payor category based upon its presence at $> 75\%$ of the visits. We believe that it unlikely that this impacted our overall findings since the vast majority of patients analyzed had only one insurance/payor type throughout their observation. Furthermore, we could not find evidence that the association between public-coverage and increased mortality among patients with CD4 count ≥ 200 cells/mm³ was due to a systematic shift of patients from privately- to publicly-funded health coverage over time in association with advancing age or progression of their HIV disease. While we adjusted for key variables associated with mortality in our final parsimonious model, unmeasured or other unaccounted for confounders might exist that could explain the association of public insurance with increased mortality among patients with CD4 count ≥ 200 cells/mm³. For instance, we lack systematically collected data on antiretroviral adherence, clinical encounter length, missed clinical visits or comorbid disease prevention counseling administration. Also, we have tried to consider other aspects of care or sociodemographics for which “insurance payor” may be a proxy. For example, we did not have available to us data regarding specifically quality of life or income. Indeed, our findings suggest further research is needed to investigate these and other qualitative differences in HIV care that might be payor-based and their causal associations with mortality. Also, information on causes of death was not complete for all patients, and could have been inaccurately documented on death certificates in some cases, as has been observed in prior studies^{18 19, 20}.

Nevertheless, important strengths of our analysis include the use of data from a longitudinal observational cohort in which there were sufficient numbers of deaths to allow for relevant comparisons using sociodemographic variables. HOPS patients were cared for in real-world clinical settings (i.e., observations

were not derived from clinical trials or interval cohorts) by their own medical care providers and were sufficiently diverse in terms of gender, race/ethnicity and type of health insurance to permit meaningful analysis of factors that impacted survival.

The extent to which mortality rates among HIV-infected patients treated with HAART can be further reduced by routine and timely screening for and treatment of non-HIV-associated comorbid illnesses is not yet clear. While it is unknown at present whether such measures should commence at earlier ages for HIV-infected persons than HIV-uninfected persons, as HIV-infected patients live longer the incidence of these conditions will almost certainly increase. Pre-emptive risk reduction, early detection, and aggressive treatment of chronic comorbid diseases increasingly comprise routine medical care for HIV infection. Adoption of such measures as standard-of-care may bring us closer to “closing the gap” in survival expectancy that exists between diverse populations of HIV-infected persons, and between HIV-infected and HIV-uninfected patients in the U.S.

In conclusion, among contemporary HIV-infected U.S. patients substantially treated with HAART whose CD4 cell counts were ≥ 200 cells/mm³, we observed higher mortality among persons whose only access to medical care was through publicly funded sources, compared to persons who received privately funded medical care. After adjusting for type of healthcare insurance and other factors that impact survival, risk of mortality among substantially HAART-treated patients did not differ by race/ethnicity. Further, we found significantly higher frequencies of often preventable chronic comorbid conditions among publicly insured patients who died; however, further research is warranted to characterize how these factors may explain our principal observation. As our nation undergoes healthcare reform, we need to better understand how healthcare delivery and its financial reimbursement affect quality of care (including routine well-health screening and pre-emptive care) and mortality risk, particularly among groups of persons who have higher prevalence of illnesses that ultimately contribute to mortality regardless of insurance status. In the interim, screening for and addressing modifiable health risks associated with preventable and treatable medical conditions should guide clinical

practice and inform public health measures in our efforts to further improve survival and enhance overall health for all patients.

Reproducible Research Statement: *Study protocol and statistical code:* Available from the authors.

Data set: The HOPS is a public-use data set and is available to non-HOPS investigators. However, confidentiality protections that govern the HOPS data require HOPS authors to strip all record identifiers; it will therefore take some time to make these data available if requested. In addition, the CDC's heightened security procedures require persons who want to analyze HOPS data to 1) prepare a written proposal for CDC review and approval, 2) sign confidentiality and data use agreements, 3) conduct analyses with the CDC in Atlanta, and 4) go through CDC security clearance for access to facilities. The authors would be happy to facilitate these procedures for persons interested in conducting analyses with HOPS project data and welcome these requests.

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Appendix

The HIV Outpatient Study (HOPS) Investigators include the following persons and sites: John T. Brooks, Kate Buchacz, Tony Tong, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention (NCHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, GA; Kathleen C. Wood, Rose K. Baker, James T. Richardson, Darlene Hankerson, and Carl Armon, Cerner Corporation, Vienna, VA; Frank J. Palella, Joan S. Chmiel, Onyinye Enyia, and Caroline Studney, Feinberg School of Medicine, Northwestern University, Chicago, IL; Kenneth A. Lichtenstein and Cheryl Stewart, National Jewish Medical and Research Center Denver, CO; John Hammer, Benjamin Young, Kenneth S. Greenberg, Barbara Widick, and Joslyn D. Axinn, Rose Medical Center, Denver, CO; Bienvenido G. Yangco and Kalliope Halkias, Infectious Disease Research Institute, Tampa, FL; Douglas J. Ward and Charles A. Fiorentino, Dupont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, and Jane Esteves, State University of New York (SUNY), Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, Faye Ruley and Atiya Nimmons, Temple University School of Medicine, Philadelphia, PA; Richard M. Novak and Andrea Wendrow, University of Illinois at Chicago, Chicago, IL.

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Drs. Palella, Buchacz and Brooks had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclaimer: The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Role of Each Author

Dr. Palella: study concept, design, data interpretation, manuscript preparation

Ms. Baker: data collection, analysis and interpretation, manuscript preparation

Dr. Buchacz: study concept, design, data interpretation, manuscript preparation

Dr. Chmiel: study concept, design, data interpretation, manuscript preparation

Dr. Teldaldi: study concept, design, data interpretation, manuscript revision

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Dr. Brooks: study concept, design, data interpretation, manuscript preparation

Table 1. Death Rates and Univariate Hazard Ratios for Mortality by Participant Characteristics among Substantially Treated* Patients Observed after Index Date†, HIV Outpatient Study, 1996-2007.

Variable	Substantially Treated Patients	No. of Deaths	No. of Patient-years (py)	Deaths per 100 py‡	Hazard Ratio	P Value
No. of patients	3569	318	19543	1.6		
Median age at index date, years (IQR)	39 (34, 46)				1.50§	< .0001
Male, no. (%)	2996 (84.0)	271	16441	1.6	Referent	
Female, no. (%)	573 (16.0)	47	3101	1.5	0.92	.58
Race, no. (%)						
Non-Hispanic white	2133 (59.8)	187	12395	1.5	Referent	
Non-Hispanic black	1019 (28.6)	100	4970	2.0	1.33	.022
Hispanic	417 (11.7)	31	2177	1.4	0.94	.75
HIV Transmission Risk, no. (%)						
Men who have sex with men	2265 (63.5)	178	12733	1.4	Referent	
High-risk heterosexual contact	776 (21.7)	67	4084	1.6	1.17	.28
Injection drug use	346 (9.7)	54	1797	3.0	2.15	< .0001
Other	182 (5.1)	19	928	2.0	1.47	.11
Insurance/Payor¶, no. (%)						
Private	2020 (56.6)	137	11523	1.2	Referent	
Public	1146 (32.1)	143	5711	2.5	2.11	< .0001
Other	403 (11.3)	38	2309	1.6	1.39	.07
History of AIDS, no. (%)						
No	1362 (38.2)	60	7554	0.8	Referent	
Yes	2207 (61.8)	258	11988	2.2	2.74	< .0001
Nadir CD4 cell count at index, median cells/mm³ (IQR) (n= 3034)	180 (52, 327)				0.83	< .0001
CD4 cell count at index date, median cells/mm³ (IQR) (n=2799)	295 (160, 475)				0.83	< .0001
CD4 cell count at index date, no. (%)						
≥ 200 cells/mm³	1890 (53.0)	113	10476	1.1	Referent	
< 200 cells/mm³	909 (25.5)	155	4445	3.5	3.24	< .0001
Unknown	770 (21.6)	50	4622	1.1	1.00	.95
CD4 cell count at HAART initiation, median cells/mm³ (IQR) (n=2135)	216 (71, 378)				0.84	< .0001
CD4 cell count at HAART initiation, no. (%)						
≥ 200 cells/mm³	1124 (31.5)	59	6628	0.9	Referent	

Variable	Substantially Treated Patients	No. of Deaths	No. of Patient-years (py)	Deaths per 100 py‡	Hazard Ratio	P Value
< 200 cells/mm ³	1011 (28.3)	135	5492	2.5	2.77	<.0001
Unknown	1434 (40.2)	124	7423	1.7	1.87	<.0001
HIV RNA log ₁₀ copies/mL at index date, median (IQR) (n=2765)	2.3 (1.7, 3.4)				1.76	<.0001
Achieved undetectable plasma HIV RNA before index date, no. (%)						
Yes	2103 (58.9)	212	11173	1.9	Referent	
No	1466 (41.1)	106	8370	1.3	0.67	.0007
Achieved undetectable plasma HIV RNA before end of observation, no. (%)						
Yes	857 (24.0)	139	2832	4.9	Referent	
No	2712 (76.0)	179	16711	1.1	0.21	< .0001
Chronic HBV infection, no. (%)						
No	3422 (95.9)	298	18741	1.6	Referent	
Yes	147 (4.1)	20	801	2.5	1.58	.048
Chronic HCV infection, no. (%)						
No	3208 (89.9)	267	17778	1.5	Referent	
Yes	361 (10.1)	51	1765	2.9	1.93	< .0001
Chronic HBV or HCV infection, no. (%)						
No	3090 (86.6)	253	17128	1.5	Referent	
Yes	479 (13.4)	65	2414	2.7	1.83	< .0001
History of tobacco use, no. (%)						
Never	1656 (46.4)	121	9203	1.3	Referent	
Current or prior use	1913 (53.6)	197	10339	1.9	1.45	.001
History of substance use, no. (%)						
No	2446 (68.5)	206	13431	1.5	Referent	
Yes	1123 (31.5)	112	6111	1.8	1.20	.13
Year of HAART initiation, no. (%)						
< 2000	2394 (67.1)	279	15618	1.8	Referent	
≥ 2000	1175 (32.9)	39	3925	1.0	0.54	.0004
Antiretroviral exposure before index date, no. (%)						
HAART-only	1269 (35.6)	66	6092	1.1	Referent	
Any non-HAART	1690 (47.4)	206	10747	1.9	1.80	<.0001
Unknown/incomplete ARV history	610 (47.9)	46	2703	1.7	1.58	.02
Antiretroviral exposure to end of observation, no. (%)						

Variable	Substantially Treated Patients	No. of Deaths	No. of Patient-years (py)	Deaths per 100 py [‡]	Hazard Ratio	P Value
HAART-only	1121 (31.4)	58	5085	1.1	Referent	
Any non-HAART	1899 (53.2)	225	12132	1.9	1.65	.0007
Unknown/incomplete ARV history	549 (15.4)	35	2325	1.5	1.33	.17
Underwent HIV ARV resistance testing before index date, no. (%)						
No	3121 (87.4)	307	18103	1.7	Referent	
Yes	448 (12.6)	11	1440	0.8	0.44	.008
Underwent HIV ARV resistance testing before end of observation, no. (%)						
No	2281 (63.9)	232	11450	2.0	Referent	
Yes	1288 (36.1)	86	8092	1.1	0.57	< .0001

Abbreviations: ARV, antiretroviral; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range

* Patients were considered substantially treated if they received at least 6 months of continuous HAART and received HAART during at least 75% of their observation time following baseline.

[‡] Index date was the date at which 6 months of continuous HAART first completed and when observation for death outcome begins.

[§] Per 10-year age increment

[¶] Insurance status was classified according to the payor status in effect during at least 75% of visits

^{||} Per 50 cells/mm³ increment

Table 2. Interaction between CD4 Cell Count at Index Date* and Insurance Payor: Hazard Ratios for Mortality among Substantially Treated[^] Patients in the HIV Outpatient Study, 1996-2007.

Variable	No. (%)	No. of Deaths	No. of Person-years	Deaths per 100 py	Hazard Ratio	P Value [†]
<u>Interaction according to CD4 cell count at index date (N=2799)</u>						.06
CD4 $\geq$ 200 cells/mm ³ and insurance	1890	113	10475	1.08		
Private	1159 (61.3)	50	6613	0.76	Referent	
Public	513 (27.1)	48	2644	1.82	2.47	< .0001
Other	218 (11.5)	15	1218	1.23	1.65	.09
CD4 < 200 cells/mm ³ and insurance	909	155	4446	3.49		
Private	436 (48.0)	70	2207	3.17	Referent	
Public	346 (38.0)	64	1498	4.27	1.30	.13
Other	127 (14.0)	21	741	2.83	0.92	.73
<u>Interaction according to CD4 cell count at HAART initiation (N=1984)</u>						.02
CD4 $\geq$ 200 cells/mm ³ and insurance	1039	57	6180	0.92		
Private	657 (63.2)	22	3904	0.56	Referent	
Public	249 (24.0)	26	1449	1.79	3.18	<.0001
Other	133 (12.8)	9	827	1.09	1.93	.10
CD4 < 200 cells/mm ³ and insurance	945	128	5174	2.47		
Private	494 (52.3)	65	2800	2.32	Referent	
Public	314 (33.2)	44	1586	2.77	1.19	.38
Other	137 (14.5)	19	788	2.41	1.03	.90

Abbreviations: py, person-years

* Index date = date at which 6 months of continuous HAART first completed and when observation for death outcome begins.

[†] Obtained from Cox proportional hazards models including terms of CD4 count, insurance, and interaction between them.

[^] Patients were considered substantially treated if they received at least 6 months of continuous HAART and received HAART during

at least 75% of their observation time following baseline.

Table 3. Characteristics of Substantially Treated* Patients with Index† CD4 $\geq$ 200 by Insurance Status‡, HIV Outpatient Study, 1996-2007.

Characteristic	Total	Private	Public	Other/ unknown	P Value
No. of patients	1890	1159	313	218	
Median age at index date, years (IQR)	40 (34, 46)	39 (34, 45)	41 (35, 48)	41 (35, 47)	0.0001
	N (%)	n (%)	n (%)	n (%)	
Deaths	113 (6.0)	50 (4.3)	48 (9.4)	15 (6.9)	0.0003
Gender					
Male	1599 (84.6)	1082 (93.4)	334 (65.1)	183 (83.9)	<.0001
Female	291 (15.4)	77 (6.6)	179 (34.9)	35 (16.1)	
Race					
Non-Hispanic white	1197 (63.3)	887 (76.5)	184 (35.9)	126 (57.8)	<.0001
Non-Hispanic black	491 (26.0)	188 (16.2)	242 (47.2)	61 (28.0)	
Hispanic	202 (10.7)	84 (7.2)	87 (17.0)	31 (14.2)	
HIV Transmission Risk					
Men who have sex with men	1262 (66.8)	967 (83.4)	164 (32.0)	131 (60.1)	<.0001
High-risk heterosexual contact	381 (20.2)	121 (10.4)	208 (40.6)	52 (23.8)	
Injection drug use	161 (8.5)	35 (3.0)	107 (20.9)	19 (8.7)	
Other	86 (4.6)	36 (3.1)	34 (6.6)	16 (7.3)	
History of AIDS					
No	937 (49.6)	640 (55.2)	196 (38.2)	101 (46.3)	<.0001
Yes	953 (50.4)	519 (44.8)	317 (61.8)	117 (53.7)	
Achieved undetectable plasma HIV RNA before index date					
No	828 (43.8)	465 (40.1)	266 (51.8)	97 (44.5)	<.0001
Yes	1062 (56.2)	694 (59.9)	247 (48.2)	121 (55.5)	
Achieved undetectable plasma HIV RNA before end of observation					
No	303 (16.0)	150 (12.9)	113 (22.0)	40 (18.4)	<.0001
Yes	1587 (84.0)	1009 (87.1)	400 (78.0)	178 (81.6)	
Chronic HBV infection					
No	1807 (95.6)	1113 (96.0)	487 (94.9)	207 (95.0)	0.529
Yes	83 (4.4)	46 (4.0)	26 (5.1)	11 (5.0)	
Chronic HCV infection					
No	1685 (89.2)	1105 (95.3)	384 (74.8)	196 (89.9)	<.0001
Yes	205 (10.8)	54 (4.7)	129 (25.2)	22 (10.1)	
Chronic HBV or HCV infection					
No	1616 (85.0)	1061 (91.5)	367 (71.5)	188 (86.2)	<.0001

Characteristic	Total	Private	Public	Other/ unknown	P Value
Yes	274 (14.5)	98 (8.5)	146 (28.5)	30 (13.8)	
History of tobacco use					
Never	854 (45.2)	612 (52.8)	159 (31.0)	83 (38.1)	<.0001
Current or prior use	1036 (54.8)	547 (47.2)	354 (69.0)	135 (61.9)	
History of substance use					
No	1288 (68.2)	889 (76.7)	261 (50.9)	138 (63.3)	<.0001
Yes	602 (31.8)	270 (23.3)	252 (49.1)	80 (36.7)	
Year of HAART initiation					
< 2000	1246 (65.9)	775 (66.9)	316 (61.6)	155 (71.1)	0.026
≥ 2000	644 (34.1)	384 (33.1)	197 (38.4)	63 (28.9)	
Non-HAART exposure before index date					
No	667 (35.3)	417 (36.0)	165 (32.2)	85 (39.0)	0.004
Yes	923 (48.8)	573 (49.4)	241 (47.0)	109 (50.0)	
Unknown	300 (15.9)	169 (14.6)	107 (20.9)	24 (11.0)	
Non-HAART exposure before end of observation					
No	589 (31.2)	382 (33.0)	140 (27.3)	67 (30.7)	0.003
Yes	1028 (54.4)	623 (53.8)	276 (53.8)	129 (59.2)	
Unknown	273 (14.4)	154 (13.3)	97 (18.9)	22 (10.1)	
Underwent HIV ARV resistance testing before index date					
No	1600 (84.7)	970 (83.7)	433 (84.4)	197 (90.4)	0.042
Yes	290 (15.3)	189 (16.3)	80 (15.6)	21 (9.6)	
Underwent HIV ARV resistance testing before end of observation					
No	1184 (62.6)	741 (63.9)	294 (57.3)	149 (68.4)	0.006
Yes	706 (37.4)	418 (36.1)	219 (42.7)	69 (31.6)	
Type of site					
Clinic	225 (11.9)	159 (13.7)	36 (7.0)	30 (13.8)	<.0001
Group practice	870 (46.0)	654 (56.4)	137 (26.7)	79 (36.2)	
University clinic	795 (42.1)	346 (29.8)	340 (66.3)	109 (50.0)	

Abbreviations: ARV, antiretroviral; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range

* Patients were considered substantially treated if they received at least 6 months of continuous HAART and received HAART during at least 75% of their observation time following baseline.

† Index date was the date at which 6 months of continuous HAART first completed and when observation for death outcome begins.

¶ Insurance status was classified according to the payor status in effect during at least 75% of visits

Table 4. Risk of Mortality in Association with Selected Variables Among Substantially Treated Participants in the HIV Outpatient Study, Cox Proportional Modeling Results, 1996-2007.

	Using CD4 Cell Count at Index Date* (n = 2674, No. of events = 250)		Using CD4 Cell Count at HAART Initiation (n = 1944, No. of events = 178)	
Variable	Adjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
Age at index date (per 10-year increments)	1.50 (1.33-1.70)	< .0001	1.53 (1.32-1.76)	< .0001
Gender				
Male	Referent			
Female	0.75 (0.48-0.18)	.21	0.67 (0.39-1.12)	.13
Race				
Non-Hispanic white	Referent			
Non-Hispanic black	0.99 (0.72-1.34)	.92	0.80 (0.54-1.18)	.26
Hispanic	0.87 (0.55-1.37)	.55	0.93 (0.55-1.55)	.77
HIV Transmission risk				
Male sex with male	Referent			
High risk heterosexual	1.12 (0.74-1.70)	.58	1.12 (0.68-1.83)	.66
Injection drug use	1.53 (1.02-2.30)	.04	1.67 (1.01-2.78)	.05
Other HIV transmission risk	1.34 (0.79-2.27)	.28	1.43 (0.80-2.54)	.22
CD4 $\geq$ 200 cells/mm ³ at index date	Referent			
CD4 < 200 cells/mm ³ at index date	2.86 (1.95-4.21)	<.0001		
Overall interaction between CD4 at index and insurance/payor		.13		
CD4 $\geq$ 200 cells/mm ³ and insurance:				
- Private	Referent			
- Public	2.03 (1.32-3.14)	.001		
- Other	1.37 (0.76-2.47)	.29		
CD4 < 200 cells/mm ³ and insurance:				

- Private	Referent			
- Public	1.18 (0.81-1.73)	.39		
- Other	0.89 (0.53-1.49)	.65		
CD4 $\geq$ 200 cells/mm ³ at HAART initiation			Referent	-
CD4 < 200 cells/mm ³ at HAART initiation			3.41 (2.04-5.68)	<.0001
Overall interaction between CD4 at HAART initiation and insurance/payor				.02
CD4 $\geq$ 200 cells/mm ³ and insurance				
- Private			Referent	-
- Public			3.00 (1.61-5.60)	.0005
- Other			1.70 (0.77-3.78)	.19
CD4 < 200 cells/mm ³ and insurance				
- Private			Referent	-
- Public			1.05 (0.70-1.60)	.80
- Other			1.03 (0.61-1.72)	.92
Log ₁₀ HIV RNA (viral load) at index date	1.67 (1.51-1.85)	< .0001	1.76 (1.57-1.98)	< .0001
Year of HAART initiation				
< 2000	Referent	-	-	-
$\geq$ 2000	0.78 (0.52-1.56)	.21	1.01 (0.64-1.57)	.98
Underwent HIV antiretroviral resistance testing (time varying factor)	0.39 (0.29-0.52)	< .0001	0.38 (0.27-0.54)	< .0001

Abbreviations: CI, confidence interval; HAART, highly effective antiretroviral therapy

* Index date was the date at which 6 months of continuous HAART first completed and when observation for death outcome begins.

Persons with missing index viral loads were excluded.

Table 5. Causes of Death among Substantially Treated* Participants for whom at Least One Cause of Death was Reported[†], by Race and Payor, HIV Outpatient Study, 1996 – 2007.

	Deaths	AIDS		Bacteremia/ sepsis		Cardio-vascular Events		GI Disorders		Hematologic Disorders		Hepatic Disorders		Cancer (Non-AIDS)		Neurologic Disorders		Pulmonary Disease		Renal Disease	
	N	n	%	n	%	n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
Race																					
Overall	248	131	52.8	30	12.1	57	23.0	31	12.5	11	4.4	41	16.5	31	12.5	22	8.9	48	19.4	29	11.7
white	152	87	57.2	14	9.2	30	19.7	17	11.2	6	4.0	23	15.1	22	14.5	14	9.2	30	19.7	10	6.6
black	69	30	43.5	10	14.5	22	31.9	12	17.4	4	5.8	12	17.4	7	10.1	6	8.7	10	14.5	16	23.2
Hispanic	27	14	51.8	6	22.2	5	18.5	2	7.4	1	3.7	6	22.2	2	7.4	2	7.4	8	29.6	3	11.1
across races		p = .16		p = .12		p = .12		p = .30		p = .81		p = .64		p = .46		p = .95		p = .24		p = .002	
white vs. black		p = .58		p = .24		p = .048		p = .20		p = .54		p = .67		p = .38		p = .90		p = .35		p = .0004	
Insurance																					
Overall	215	110	51.2	26	12.1	49	22.8	28	13.0	10	4.6	39	18.1	27	12.6	19	8.8	44	20.5	27	12.6
Private	106	66	56.6	12	11.3	16	15.1	13	12.3	4	3.8	13	12.3	18	17.0	8	7.6	20	18.9	9	8.5
Public	109	50	45.9	14	12.8	33	30.3	15	13.8	6	5.5	26	23.8	9	8.3	11	10.1	24	22.0	18	16.5
		p = .12		p = .73		p = .01		p = .74		p = .55		p = .03		p = .05		p = .51		p = .57		p = .08	

Abbreviations: white, non-Hispanic white; black, non-Hispanic black; CVD, cardiovascular disease; GI, gastrointestinal

* Completed at least six continuous months of HAART and received HAART for at least 75% of study observation time.

[†] Patients could be included in more than one cause of death category (e.g., hepatic and cardiovascular; AIDS and GI disorder); see manuscript Methods for explanation how causes of death were ascertained and classified.

‡ Pearson chi-square test was used for 3-way and 2-way comparisons

Table 6. Comorbidities among Substantially Treated* Participants who Died by Race and Payor, HIV Outpatient Study, 1996 – 2007.

	Deaths	CVD†		Hypertension		Diabetes mellitus		Impaired Glucose Control		Dyslipidemia		Renal Disease		COPD		Cancer (Non-AIDS)		HBV or HCV Co-infection		Obesity‡	
	N	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Race																					
Overall	318	67	21.1	202	63.5	62	19.5	72	22.6	116	36.5	64	20.1	51	16.0	52	16.4	102	32.1	56	17.6
white	187	33	17.6	116	62.0	31	16.6	42	22.5	72	38.5	34	18.2	27	14.4	35	18.7	49	26.2	25	13.4
black	100	26	26.0	67	67.0	20	20.0	18	18.0	32	32.0	25	25.0	18	18.0	14	14.0	38	38.0	26	26.0
Hispanic	31	8	25.8	19	61.3	11	35.5	12	38.7	12	38.7	5	16.1	6	19.4	3	9.7	15	48.4	5	16.1
		p = .20§		p = .68		p = .048		p = .06		p = .53		p = .33		p = .64		p = .34		p = .02		p = 0.03	
white vs. black		p = .10		p = .40		p = .47		p = .38		p = .28		p = .17		p = .43		p = .31		p = .04		p = 0.01	
Insurance																					
Overall	280	55	19.6	180	64.3	55	19.6	62	22.1	97	34.6	53	18.9	49	17.5	47	16.8	93	33.2	49	17.5
Private	137	18	13.1	83	60.6	23	16.8	29	21.2	50	36.5	18	13.1	20	14.6	28	20.4	24	17.5	22	16.1
Public	143	37	25.9	97	67.8	32	22.4	33	23.1	47	32.9	35	24.5	29	20.3	19	13.3	69	48.2	27	18.9
		p = .01		p = .21		p = .24		p = .70		p = .52		p = .02		p = .21		p = .11		p < .0001		p = 0.53	

Abbreviations: CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; white, non-Hispanic white; black, non-Hispanic black

* Completed at least six continuous months of HAART and received HAART for at least 75% of study observation time.

† Comorbidities may have been documented any time during observation period. See manuscript Methods for explanation how comorbidities were ascertained.

‡ Ever had a BMI $\geq$ 30.

§ ‡Pearson chi-square test was used for 3-way and 2-way comparisons

Figure. Mortality among substantially-HAART treated patients in the HIV Outpatient Study, 1996-2007

a) by insurance/payor type

b) by race/ethnicity