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Journal of Clinical Epidemiology 57 (2004) 89–97

Journal of Clinical Epidemiology

Disease progression in HIV-infected patients treated with stavudine vs. zidovudine

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Accepted 18 February 2003

Abstract

Background and Objectives: This prospective, observational study compared disease progression and death in HIV-1 patients treated with stavudine vs. zidovudine in the Collaborations in HIV Outcomes Research/U.S. (CHORUS) cohort.

Methods: Patients with a first occurrence of CD4 count <500 cells/μL (n = 3301) were grouped as: no nucleoside reverse transcriptase inhibitor (NRTI) use; other NRTI without stavudine or zidovudine; stavudine with no zidovudine, with or without other NRTIs; and zidovudine with no stavudine, with or without other NRTIs. The risk for death or disease progression was evaluated in unadjusted analyses and using a Cox proportional hazards model, adjusting for: study site, age, gender, race, route of HIV infection, previous AIDS-defining conditions, number of previous antiretroviral regiments, CD4 count, HIV-1 RNA, and treatment variables. Sensitivity analyses were conducted to determine the sensitivity of the results to major modeling assumptions. A landmark analysis was conducted to determine the absolute difference in time to event.

Results: During a median follow-up of 2.4 years, there were 57 deaths and 348 AIDS-defining conditions in 405 patients. Stavudine treatment compared with zidovudine resulted in a greater percentage of patients with AIDS-defining events (14.5 vs. 10.9%; P = .013), and an increased risk of disease progression (HR = 1.30; 95% CI: 1.01,1.7; P = .04). This result was not sensitive to modeling assumptions. Landmark analysis demonstrated an absolute difference in time to 95% event-free survival of 2.7 months for those with a CD4 ⩽200 cells/μL and 11 months for those 6 months after model entry.

Conclusions: In unadjusted and adjusted analyses of 3301 HIV-1 infected patients, stavudine containing combination therapy was associated with an increased risk of disease progression or death compared to therapy containing zidovudine. Most of the difference was attributable to new cases of wasting.

Keywords: Stavudine; Zidovudine; Disease progression; Longitudinal study; CHORUS; HIV wasting

1. Introduction

Nucleoside reverse transcriptase inhibitors (NRTIs) are the bedrock of Highly Active Antiretroviral Therapy (HAART). However, NRTIs have been associated with significant toxic effects, including myopathy [1,2] and hematopoetic toxicity with zidovudine [3,4]; pancreatitis and peripheral neuropathy with didanosine, zalcitabine, and stavudine [5–7]; and hepatic steatosis and lactic acidosis with zidovudine, didanosine, and stavudine [8–12].

Although the mechanism for these toxicities is not completely understood, one hypothesized mechanism is defective mitochondrial DNA replication possibly resulting from mitochondrial DNA polymerase-γ inhibition by nucleoside analogs [13–17]. All NRTIs have varying degrees of mitochondrial toxicity *in vitro* [15–17]. Attribution of these toxicities to particular NRTIs is difficult, as most patients on HAART are on at least two NRTIs at a time; the most common combinations are zidovudine with lamivudine and stavudine with lamivudine. Although zidovudine and

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0895-4356/04/$ – see front matter
doi: 10.1016/S0895-4356(03)00245-2

stavudine are often considered interchangeable [18–21], there is some evidence of an increased incidence of lipodystrophy and wasting in patients who receive stavudine when compared with other NRTIs [22–27]. Consistent with this clinical observation is that stavudine has demonstrated more potent cytotoxicity and mitochondrial toxicity than didanosine [16] or zidovudine [17] in lymphoblastoid cell cultures.

We postulated that these laboratory differences may result in differences in clinical outcomes in patients on HAART even if the virologic and immunologic effects of the agents were similar. Therefore, we compared the clinical outcomes associated with stavudine and zidovudine containing regimens in the Collaborations in HIV Outcomes Research/U.S. (CHORUS) observational database, an ongoing, community-based observational study of HIV-1 infected patients in the United States. Because lamivudine is used in nearly all HAART regimens, it could not be studied separately.

2. Methods

2.1. Patients

CHORUS is an observational database designed to follow longitudinal clinical outcomes in a large cohort of HIV/AIDS patients enrolled at four outpatient sites. Sites include: Comprehensive Care Center (Nashville, Tennessee), Liberty Medical Group (New York, New York), Pacific Horizon Medical Group (San Francisco, California), and Pacific Oaks Medical Group (Los Angeles, California). All patients included in this analysis gave written informed consent, and this study was approved by the Institutional Review Boards at Research Triangle Institute (Research Triangle Park, North Carolina) and Vanderbilt University (Nashville, Tennessee).

2.2. Data collection

Medical information for each patient in the cohort was maintained on a computerized patient record system developed by Healthmatics, Inc. (Cary, North Carolina) for use in physicians' offices at the time of the patient encounter. This system electronically captures detailed demographics; laboratory and procedure data; assessment and plan, history, and physical reporting; and prescription ordering. The computerized patient record was electronically transferred via a secure connection to an independent data aggregation and analysis facility at Research Triangle Institute in Research Triangle Park, North Carolina. Only aggregated nonidentifiable patient data was used in the analysis to maintain patient confidentiality. Data quality was maintained through a quality management plan encompassing acceptance testing, ongoing site monitoring, best entry practices training, data edit checks, and data validation. An independent Advisory Board (listed in the Acknowledgments Section) oversaw the project and the analysis of data. The Board is comprised of physicians and researchers from the participating sites, members of the HIV community, academic experts, personnel from the analysis center, and sponsor representatives.

2.3. Study design

Patients in CHORUS whose CD4 cell counts dropped below 500 cells/μL after August 29, 1996 (the date retrospective data collection began in CHORUS), and who had HIV-1 RNA data at this time, were entered in the analysis. Baseline (model entry) was defined as the first point at which the CD4 dropped below 500 cells/μL after August 29, 1996. Patients were excluded if they were taking stavudine and zidovudine concurrently at baseline or at any time during the follow-up period. The primary outcome was defined as death or a new occurrence of a clinical AIDS-defining condition after baseline. No CD4 count definitions of AIDS were used in this analysis. Patients were followed until the earliest event, withdrawal from the study, or the freeze date of the database (July 10, 1999).

Baseline CD4 cell count and HIV-1 RNA data were summarized for all patients. All follow-up laboratory tests were included regardless of the number of tests per patient. If multiple HIV-1 RNA results were available for the same time point, the maximum of the PCR, bDNA, and NASBA tests was included. If none of these were available, ultrasensitive test results were included. All HIV-1 RNA data were $\log_{10}$ transformed.

Based on NRTI use, patients were categorized into the following mutually exclusive groups: (1) no NRTI; (2) other NRTI without stavudine or zidovudine; (3) stavudine with no zidovudine, with or without other NRTIs; and (4) zidovudine with no stavudine, with or without other NRTIs. Analyses were focused on groups 3 and 4. The number of antiretroviral therapy (ART) regimens patients received prior to baseline was categorized as 0, 1, or greater than or equal to 2 rounds of prior ART therapy, and was increased by one with each new ART regimen during the follow-up period in the time-dependent models.

Demographic data (gender, ethnicity, age at baseline, probable route of HIV infection), indicator variables for previous AIDS-defining conditions, prior ART use, and number of prior ART regimens were summarized by each baseline NRTI group. Patients receiving primary or secondary prophylaxis medications for *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* complex (MAC), and herpes at baseline or during the follow-up period and possessing a CD4 $<$250 cells/μl for PCP or CD4 $<$100 cells/μL for MAC were defined as receiving prophylaxis and also identified. The number of new AIDS-defining events was also summarized for each baseline NRTI.

2.4. Statistical analyses

Unadjusted comparisons between patients on stavudine or zidovudine containing regimens were made using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Cox proportional hazards

regression models were used to quantify the adjusted risk relationship between treatment and the outcome. The primary analysis omitted time-dependent variables and counted events in the treatment group that the patient was in at baseline regardless of later changes in regimen. This approach was used because it most closely approximates the clinical decision-making perspective.

Adjustment was made for study site, age (per 10 years), gender, ethnicity (Caucasian vs. other), probable route of HIV infection (IDU vs. other), previous AIDS-defining conditions (yes/no), number of previous ART regimens (0, 1, 2+), use of antiherpetics, PCP, or MAC prophylaxis, CD4 counts (per 50 cells), and HIV-1 RNA results (log10) at baseline. Medication exposure was modeled as follows: four NRTI indicators (stavudine use, zidovudine use, lamivudine use, and other NRTI use); a PI indicator, and an NNRTI indicator. In time-dependent models, the values of these therapy indicators were updated each time there was a change in ART use during follow-up until the time of an event or censoring. Thus, patients were counted in the therapy group they were in at the time of an event. Hazard ratios and 95% confidence intervals are reported from the model with statistical significance determined by the Wald chi-square test.

2.5. Sensitivity analyses

In addition to the primary baseline Cox model, several secondary models were fit to determine the sensitivity of the comparison between stavudine and zidovudine to model assumptions. First, the baseline model was refit to the outcome redefined to exclude Kaposi's sarcoma. Next, models which included time-dependent covariates were fit to a variety of outcomes: the primary outcome, the primary outcome with Kaposi's sarcoma excluded, a new clinical AIDS-defining condition alone, death alone, only death or wasting, and only death or wasting among the subset of patients with no history of wasting prior to baseline. Additionally, the model was fit to the primary outcome separately for patients with and without any AIDS-defining condition prior to baseline.

In all of these models, CD4 count, HIV-1 RNA, prophylaxis use indicators, indicators for ART use, and number of previous regimens were entered as time-dependent covariates. Number of previous regimens were increased by one with each new ART regimen received during the follow-up period. Indicators for therapy use were updated each time there was a change in ART use during follow-up until the time of an event or censoring. Thus, patients were counted in the therapy group they were in at the time of an event (an "as treated" approach). A final time-dependent model was fit to the primary outcome and included time-dependent covariates as previously with the exception that the NRTI indicators were allowed to vary only until each patient started on a stavudine or zidovudine-containing regimen (an "intent to treat" approach). Patients were counted in whichever of these two NRTI groups they entered first, starting at baseline for some and later for those not receiving stavudine or zidovudine at baseline.

Finally, models were fit to the primary outcome using a stepwise procedure to select significant predictors from among baseline values of the covariates and additionally following a forward selection of variables. Forward selection proceeded in a preplanned order by including disease severity variables (CD4 count, HIV-1 RNA, number of previous regimens; all treated as time-dependent covariates) incrementally to a model containing all ART regimen indicators as well as adjustment for study site.

2.6. Landmark analyses

Time-dependent multivariable Cox models provide an estimate of the relative survival risk (or hazard) associated with use of stavudine or zidovudine containing regimens but do not provide an estimate of the absolute difference in the survival time (time to first event). Landmark analyses were conducted to address this question. In these analyses, participants must have survived to one of the two landmark time points (6 months after baseline or CD4 $\leqslant$200 cells/μL), chosen because they represented an early and a late event after starting antiretroviral therapy. Patients were categorized into NRTI groups based on ART regimen at the time of the landmark. Because the populations differ over time and because of selection biases, we adjusted for prognostic risk factors (covariates) as of the landmark but there was no adjustment at subsequent time points to plot estimated survival curves. To adjust for these prognostic risk factors, the mean value of the continuous covariates at the time of the landmark were used and the dichotomous covariates were set to discrete values.

For the 6-month landmark, the mean values for the subcohort were 40 years of age, 325 CD4 lymphocyte cells/μL, and 3.4 log copies/mL HIV-1 RNA. The dichotomous values were set to male, Caucasian, without prior AIDS-defining conditions, probable route other than IDU, $\geqslant$2 prior ART regimens, and taking a PI and 3TC with their thymidine analog. For the CD4 $\leqslant$200 landmark, the mean values for the subcohort were 40 years of age, 115 CD4 lymphocyte cells/μL and 4.1 log copies/μL HIV-1 RNA. The dichotomous variables were set to male, Caucasian, without prior AIDS-defining conditions, probable route of infection other than IDU, with $\geqslant$2 prior ART regimens, and prescribed a PI and 3TC in addition to their thymidine analog with PCP prophylaxis. Based on these assumptions, survival curves were estimated and compared for patients using stavudine and zidovudine.

3. Results

3.1. Demographics, prophylaxis use, antiretroviral therapy, and laboratory measures

As of July 10, 1999, the number of patients consented in CHORUS was 4,390. Of these, 3,713 (84%) experienced a

CD4 count of <500 cells/μL after August 29, 1996. Furthermore, 133 patients (4%) were excluded for lack of a baseline HIV-1 RNA value, 55 (1%) for missing medication records, and 224 (6%) for concurrent use of stavudine and zidovudine at baseline or during follow-up. A total of 3,301 patients (75%) were categorized into one of four mutually exclusive groups: (1) no NRTI (n = 966, 29%); (2) other NRTI without stavudine or zidovudine (n = 225, 7%); (3) stavudine with no zidovudine, with or without other NRTIs (n = 1,004, 30%); and (4) zidovudine with no stavudine, with or without other NRTIs (n = 1,106, 34%). Baseline characteristics of the stavudine containing and zidovudine containing regimens are presented (groups 3 and 4, Table 1).

Baseline characteristics showed that the population in both treatment groups was predominantly male and Caucasian (Table 1). When compared with patients in the zidovudine group, a higher percentage of patients in the stavudine group had AIDS-defining conditions prior to baseline, had received prophylaxis for MAC and herpes, and were treated with PIs, NNRTIs, and other NRTIs. A greater percentage of patients in the zidovudine group were treated with lamivudine. The median number of prior ART regimens was greater in the stavudine group when compared with the zidovudine group. All other variables including median HIV-1 RNA and CD4 counts did not differ significantly between the two groups.

Table 1
Demographics and summary characteristics of patients at baseline

Characteristic	Stavudine	Zidovudine	P-value
Number of patients	1004	1106	
Age, median, years	40	39	0.21
Sex (n (%) male)	951 (95)	1000 (90)	0.001
Ethnicity, n (%)			0.002
Caucasian	788 (78)	827 (75)	
African–American	97 (10)	167 (15)	
Hispanic	82 (8)	80 (7)	
Other	37 (4)	32 (3)	
Probable route of infection [n (%) IDU]	25 (2)	52 (5)	0.007
Prior AIDS-defining condition, n (%)	342 (34)	313 (28)	0.004
Median follow-up time (months)	31	31	0.08
PCP prophylaxis, n (%)	377 (38)	384 (35)	0.18
MAC prophylaxis, n (%)	92 (9)	76 (7)	0.05
Anti-herpetics, n (%)	315 (31)	282 (26)	0.003
PI use, n (%)	670 (67)	614 (56)	0.001
NNRTI use, n (%)	92 (9)	47 (4)	0.001
Lamivudine use, n (%)	799 (80)	976 (88)	0.001
Other NRTIs use, n (%)	161 (16)	100 (9)	0.001
ART use prior to baseline, n (%)	971 (97)	1061 (96)	0.34
Median prior ART use (months)	31	29	0.12
Median prior ART regimens	2	1	0.0001
Log_{10} HIV-1 RNA, copies/mL			0.33
Mean ± SE	3.4 ± 0.03	3.5 ± 0.03	
Median	3.1	3.2	
Range	1.3–7.1	3.2–6.5	
CD4 cell count, cell/μL			0.11
Mean ± SE	277 ± 4.5	288 ± 4.2	
Median	291	305	
Range	2–499	1–499	

Abbreviations: ART = antiretroviral therapy; IDU = intravenous drug use; MAC = mycobacterium avium complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PCP = pneumocystis carinii pneumonia; PI = protease inhibitor.

3.2. Events

A total of 405 patients experienced an event including 57 deaths and 348 new occurrences of an AIDS-defining condition during the follow-up period. The total number of events in the stavudine and zidovudine groups were 146 and 121, respectively (Table 2). In unadjusted analyses, patients in the stavudine group experienced a significantly greater frequency of events (14.5%) than those in the zidovudine group (10.9%)(P = .013). The incidence of death as a first event was similar in both groups. HIV wasting syndrome was the most common new AIDS-defining condition among patients exposed to NRTIs. The incidence of wasting was significantly higher in the stavudine group (P = .004). PCP was a relatively uncommon event among patients exposed to NRTIs; however, PCP was more common in the zidovudine group compared to the stavudine group (P = .01).

3.3. Hazard ratios for disease progression

3.3.1. Univariate baseline models

Each variable from the primary analysis was entered separately into a proportional hazards model containing only that variable and site indicators. Variables associated with increased risk of disease progression included age, prior AIDS conditions, higher HIV-1 RNA viral load, PCP, and MAC prophylaxis use, antiherpetics, and use of NNRTIs (Table 3). Variables associated with a decreased risk of disease progression included higher CD4 cell count, prior antiretroviral therapy, PI use, and use of NRTIs. The hazard ratio for stavudine compared to zidovudine indicated a significantly increased risk for disease progression in the stavudine treated patients (HR: 1.5; CI: 1.2, 2.0; P < .002).

Table 2
Frequency [n (%)] of most common AIDS-defining events and death in patients by baseline treatment group.

Event	Stavudine n = 1004	Zidovudine n = 1106	P-value[a]
Cytomegalovirus retinitis	11 (1.1)	6 (0.5)	0.17
Candidial esophagitis	10 (1.0)	12 (1.1)	0.84
Death	19 (1.9)	19 (1.7)	0.76
HIV encephalopathy	1 (0.1)	5 (0.5)	0.13
HIV wasting	83 (8.3)	57 (5.2)	0.004
Kaposi's sarcoma	5 (0.5)	4 (0.4)	0.63
Pneumocystis carinii pneumonia	1 (0.1)	10 (0.9)	0.01
Total number of events	146 (14.5)	121 (10.9)	0.013

[a] P-value from unadjusted chi-square test for difference between stavudine and zidovudine groups.

Table 3
Significant predictors for disease progression from the univariate models[a]

	Univariate models		
Variables	HR	95% CI	*P*-value
Age (per 10 years)	1.1	1.02, 1.3	0.02
Prior AIDS conditions	2.2	1.8, 2.7	0.0001
CD4 count (per 50 cells)	0.79	0.77, 0.82	0.0001
Log_{10} HIV-1 RNA	1.8	1.6, 1.9	0.0001
PCP prophylaxis	2.1	1.8, 2.6	0.0001
MAC prophylaxis	3.3	2.6, 4.1	0.0001
Antiherpetics	1.4	1.1, 1.7	0.004
Prior ART therapy (=1)	0.66	0.44, 0.98	0.04
PI use	0.80	0.65, 0.99	0.04
NNRTI use	1.4	1.1, 1.8	0.01
NRTI use	0.58	0.46, 0.73	0.0001
Zidovudine use	0.53	0.42, 0.67	0.0001
Lamivudine use	0.58	0.47, 0.70	0.0001
Stavudine vs. Zidovudine use	1.5	1.2, 2.0	0.002

[a] Each variable from the primary baseline analysis was entered separately into a model containing only that variable and site indicators.

Abbreviations: ART = antiretroviral therapy; HR = hazard ratio; MAC = mycobacterium avium complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PCP = pneumocystis carinii pneumonia; PI = protease inhibitor.

3.3.2. Multivariable baseline model

When all variables were entered into the primary proportional hazards model, the association between stavudine and an increased risk for disease progression remained significant (HR: 1.30; CI: 1.01, 1.7; $P = .04$). Higher CD4 counts, decreased viral load, younger age, and lack of prior AIDS-defining conditions were associated with a decreased risk of disease progression, while other covariates were not (Table 4).

There were no significant differences in period (year of entry into analysis cohort between stavudine and zidovudine groups, $P = .8$). When the baseline model was rerun with site as a random effect, results were not substantially different. The variance of the random effect was low (0.245). The coefficients for stavudine and zidovudine and their standard errors were similar to those of the original analysis, and therefore, the hazard ratio for stavudine vs. zidovudine remained 1.3.

3.4. Sensitivity analyses

The major limitation of observational data is unadjusted confounding. Because any single approach to multivariable adjustment has limitations, we felt it important to assess the sensitivity of our results to the method of adjustment. Models in which CD4 count, HIV-1 RNA, prophylaxis use, ART use, and number of previous regimens were treated as time-dependent covariates and which were fit to a variety of outcomes consistently indicated an increased risk for disease progression among patients receiving stavudine-containing regimens compared to those receiving zidovudine-containing regimens (Fig. 1). In the time-dependent model fit to the primary outcome the hazard ratio comparing the two groups was 1.44 (CI: 1.1, 1.9; Table 4). When the outcome was death only, the hazard ratio was higher but the confidence interval was wider and a statistical difference was not detected (HR: 1.73, CI: 0.82, 3.7; $P = .15$).

When employing forward selection modeling, increasing adjustment for disease severity resulted in minimal changes in the hazard ratio for the comparison of stavudine to zidovudine; with addition of CD4 (HR = 1.49; $P = .003$), then HIV-1 RNA (HR = 1.56; $P = .003$), then regimen count (HR = 1.45; $P = .006$). The stepwise selection model resulted in the following significant variables: lower CD4 count ($P = .0001$), presence of AIDS-defining condition prior to baseline ($P = .002$), higher viral load ($P = .0006$), use of stavudine ($P = .014$), and older age ($P = .02$).

3.5. Landmark analyses

The two landmark time points were 6 months after baseline (see Study Design) and the time of reaching a CD4 lymphocyte count of ⩽200 cells/μL. In Fig. 2, multivariable Cox models, based on data after the landmark, are used to estimate survival curves for the two groups. In the analysis

Table 4
Hazard ratio for significant covariates[a] of disease progression

	Baseline model[b]			Fully time-dependent model[c]		
Variables	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Stavudine vs. Zidovudine	1.30	1.01,1.7	0.04	1.44	1.1,1.9	0.006
CD4 cells (per 50 cells)	0.83	0.80,0.88	0.0001	0.85	0.81,0.88	0.0001
Log_{10} HIV-1 RNA	1.2	1.1,1.4	0.0002	1.4	1.3,1.5	0.0001
Age (per 10 years)	1.1	1.01,1.3	0.03	1.1	1.01,1.3	0.04
Prior AIDS conditions	1.3	1.1,1.7	0.01	1.3	1.01,1.6	0.04
PI use	1.04	0.81,1.3	0.33	0.7	0.59,0.94	0.01

[a] A Cox Proportional Hazards Model was used (see Methods) for time to first occurrence of clinical AIDS events or death.

[b] Baseline Model = no time-dependent variables were used and events were counted in whichever treatment group the patient was in at baseline regardless of later changes in regimen.

[c] Fully time-dependent model = indicators for antiretroviral use, number of previous ART regimens, CD4 count, HIV-1 RNA, and prophylaxis use, were included as time-dependent variables and events were counted in the treatment group in use at the time of the event.

Abbreviations: CI = confidence interval; HR = hazard ratio; PI = protease inhibitor.

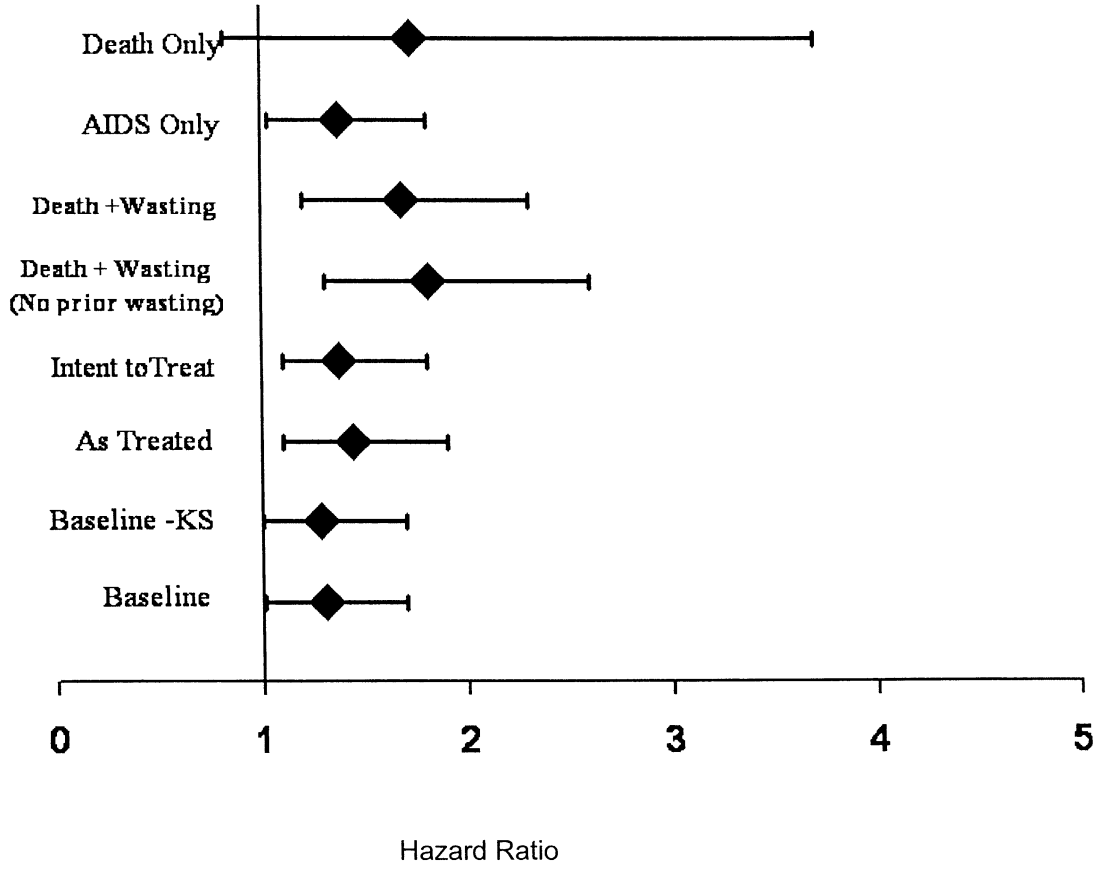

Fig. 1. Hazard ratio for disease progression of stavudine versus zidovudine using a variety of outcomes. Hazard ratios derived from Cox proportional hazard models. All models were time-dependent except those labeled baseline. A hazard greater than 1 indicates an increased risk for disease progression in stavudine-treated patients vs. zidovudine treated patients. KS = Kaposi's sarcoma; Wasting = HIV wasting syndrome.

using a landmark of 6 months after baseline the cumulative event incidence rates are 8.8% ($n = 1230$) and 5.6% ($n = 1144$), respectively. The use of a stavudine or zidovudine containing regimen at the landmark gave 95th percentile times of 408 and 750 days (HR = 1.44, CI: 1.04, 1.98; $P = .03$), or a difference of 11 months to time of first AIDS-defining condition or death after the landmark. Using a landmark of time of reaching a CD4 count of ⩽200 cells/μL, the cumulative event incidence rates are 19.7% ($n = 462$) and 14.3% ($n = 428$), respectively. The use of a stavudine or zidovudine containing regimen at the landmark gave 95th percentile times of 107 and 189 days (HR = 1.41, CI: 1.004, 1.97; $P = .047$), representing a difference of time to first AIDS-defining condition or death after the landmark of 2.7 months.

4. Discussion

In univariate, multivariate, and landmark analyses, stavudine was consistently associated with poorer clinical outcomes than zidovudine. This association was not sensitive to a wide range of modeling assumptions. It remained in baseline and time-dependent models, on-treatment and intent-to-treat models, models with Kaposi's sarcoma included or excluded, and models with a combined end point of death or new AIDS-defining conditions, models with death or AIDS-defining conditions alone, as well as models employing stepwise variable selection. When death was considered as an isolated outcome, the trend remained but did not reach statistical significance due to a limited number of deaths in the sample. Landmark analyses were used to calculate the absolute differences in time to new AIDS-defining condition or death between treatment groups. The estimated length of the additional time to a new AIDS-defining condition or death (95th percentile) in the zidovudine exposed group was 2.7 months for those with a CD4 ⩽200 and 11 months for those reaching 6 months after model entry.

Although prior short-term trials of stavudine-containing combination regimens indicated no major differences in HIV-1 RNA or CD4 cell count changes compared to other nucleoside therapies [20,21], this effect may not translate into equivalent clinical outcome. Many groups have demonstrated a significant association between stavudine and increased risk of lipodystrophy, wasting, and other clinical events [22–27].

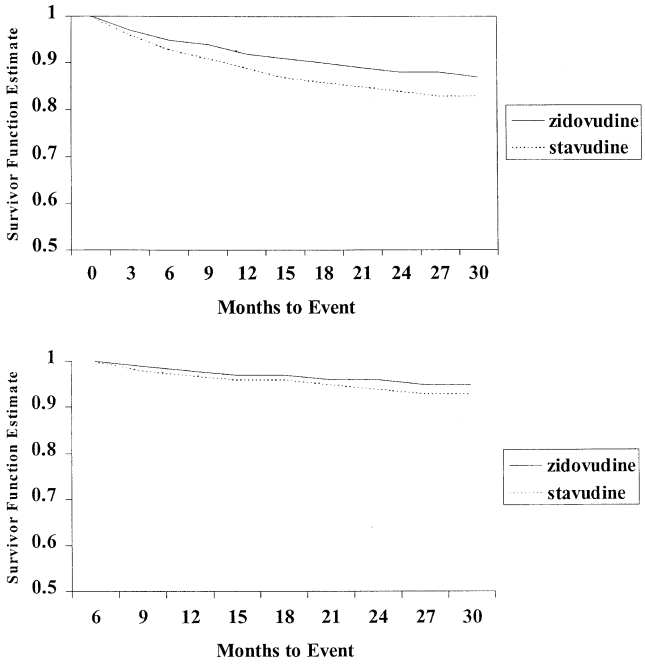

Fig. 2. (Top) Landmark analysis using CD4 ⩽200 cells/μL as the landmark. Estimated distributions of time from reaching a CD4 count ⩽200 cells/μL to a new AIDS-defining condition or death among participants with no events prior to reaching the landmark. (Bottom) Landmark analysis using 6 months after baseline as the landmark. Estimated distributions of time from 6 months after baseline to a new AIDS-defining condition or death among participants with no events prior to reaching the landmark.

Lipodystrophy is a syndrome characterized by abnormal fat distribution and peripheral loss of fatty tissue, primarily associated with the use of PIs [28–30], and has recently been reported to occur with NRTI therapy even in the absence of PIs [25,27]. Although the precise mechanism underlying this syndrome is not clear, the potential for NRTIs to cause mitochondrial toxicity has been postulated as a hypothesis for the fat wasting and related metabolic changes observed in this syndrome [31,32]. This seems plausible, given that genetic mitochondrial syndromes are characterized by failure to thrive in infants [33] and thin-body habitus in older individuals [34]. Others [35] have speculated that stavudine may exert a direct effect on β-oxidation based on its unique phosphorylation to mono-, di-, and triphosphate forms in isolated mitochondria [36].

Several recent studies have shown that, in patients treated with NRTIs, therapy with stavudine demonstrated a significantly higher risk of lipodystrophy (fat-wasting predominant) compared to other NRTIs [22–27,37–39]. Specifically, therapy with stavudine-containing regimens was found to be more strongly associated with fat wasting than therapy with zidovudine-containing regimens [25,37,38]. In confirmation of our findings, Mallal et al. recently reported that stavudine increased the risk of fat wasting by 265% per year compared with zidovudine [35]. However, this and other previous studies have been limited to single clinical events, single sites, or samples not on current antiretroviral regimens. The strength of this study is that it offers an integrated assessment of the overall clinical effect of stavudine relative to another commonly used NRTI at four geographically diverse community sites from 1996 to 1999.

Additionally, there may be other factors contributing to the observed association between stavudine exposure and HIV wasting. HIV wasting could be a marker for HAART failure and disease progression in an era of potent prophylaxis when traditional opportunistic infections (e.g., PCP) are more rarely evident. It is likely that more than one mechanism is contributing to these observations. Teasing out the contribution of these factors will require further study in other large, mature HIV cohorts.

This study has three major limitations. The first is the use of a combined outcome or end point of death or a new AIDS-defining condition. The problem with combining clinical end points as a single end point in statistical modeling is that it violates a basic assumption of the model, that is, that all the events are equally associated with the predictor variables in the model [40]. We know this is not the case. We demonstrated that the risk of wasting is much more influenced by stavudine use than the relative hazard for other AIDS defining conditions or death. Furthermore, it is possible that the clinical diagnosis of "HIV wasting" includes some fat wasting associated with lipodystrophy from the period prior to a definitive diagnostic criteria for lipodystrophy. We do not yet know whether the fat wasting associated with lipodystrophy has an equally poor prognosis as that established for HIV wasting. Thus, combining clinical events is problematic. It has, nevertheless, been a common practice in HIV research since the first antiretroviral trial. It will be valuable to repeat this analysis in subsequent years once sufficient deaths have occurred, using death as a single end point.

The second limitation is that of our use of observational data. Studies based upon observational data must carefully consider the potential for confounding by the indication for treatment [41]. Specifically there may be information influencing a clinician's decision to treat with a particular NRTI, which is not reflected in the variables available for analysis and therefore not adjusted for in these analyses. This is particularly a concern when measured variables demonstrate important and consistent differences in important prognostic factors between groups. In some ways, patients treated with stavudine appear to have had better prognostic factors at baseline, as they were more likely to be male, Caucasian, receive prophylaxis, and receive protease inhibitors. In contrast, the stavudine group was also more likely to have had prior AIDS-defining conditions and to have been treated with ART (these variables were associated with a poorer outcome). When we adjusted for these differences using a variety of multivariable models, the relative risk associated with stavudine was not substantially altered.

The third limitation of these analyses is that wasting was determined by clinician assessment and may have been

variably diagnosed; however, we have no evidence that wasting was preferentially diagnosed among patients receiving stavudine compared to zidovudine. If there is no preferential assignment, imprecision in measurement would bias the conclusions toward that of no difference between groups. We found a strong and consistent difference despite a possible bias toward the null, suggesting the actual difference might be greater than the one reported.

In conclusion, stavudine is associated with a higher risk of disease progression when compared with zidovudine. This was primarily due to increased rates of wasting among stavudine-treated patients. Future analyses should confirm whether stavudine is associated with an increased risk of wasting, lipodystrophy, and other mitochondrial toxicities including mortality.

Acknowledgments

We thank the following individuals for their contributions to the study: Shehnaz Gangjee, Richard Fleenor, Kris Batts, Suzy Holmes, Robin Beckerman, Bernard Most, Nancy Jenkins, and the CHORUS Program Team (listed below). Additionally, we would like to thank all the patients and their caregivers for sharing their information with us. **CHORUS program team—***Sites:* The Comprehensive Care Center, Nashville, TN: Stephen Raffanti, MD (principal investigator); Wendy Mangialardi, MD. Liberty Medical Group, New York, NY: Douglas T. Dieterich, MD (principal investigator); James F. Braun, DO. Pacific Horizon Medical Group, San Francisco, CA: Stephen L. Becker, MD (principal investigator); Jeremy Berge, MD. Pacific Oaks Medical Group, Los Angeles, CA: Anthony Scarscella, MD (principal investigator); Laurie Shaker-Irwin PhD. ***Consultants:*** Amy C. Justice, MD, PhD: University of Pittsburgh and VA Pittsburgh Healthcare System, Pittsburgh, PA; Michael S. Saag, MD: University of Alabama–Birmingham, Birmingham, AL; Richard Moore, MD: Johns Hopkins University, Baltimore, MD; Kevin Frost: American Foundation for AIDS Research, New York, NY; Dawn Averitt: AIDS Treatment Advocate, Raleigh, NC; Winston Liao, PhD: Research Triangle Institute, Research Triangle Park, NC; Neil Graham, MD, Jeff Chulay, MD, and Gregory P. Fusco, MD, MPH: Glaxo Wellcome, Inc. Presented in part: 7th Conference on Retroviruses and Opportunistic Infections, Chicago, IL, February 2, 2000; #756. Financial support was provided by GlaxoSmithKline.

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