Durability of Initial Antiretroviral Therapy in a Resource-Constrained Setting and the Potential Need for Zidovudine Weight-Based Dosing

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Background: Whereas access to antiretroviral therapy (ART) for HIV-infected individuals in the developing world is increasing, data on factors impacting initial regimen durability are lacking.

Methods: Retrospective review patients starting initial ART at Instituto de Medicine Tropical (Lima, Peru) April 1, 2004 to December 30, 2007. Survival methods (Kaplan–Meier, Cox proportional hazard) assessed factors associated with regimen durability including an interaction term between nucleoside reverse transcriptase inhibitor backbone and time.

Results: Decreased initial regimen durability was observed with weight <60 kg [hazards ratio (HR) = 1.77; 95% confidence interval (CI) = 1.25–2.51], CD4 <200 (HR = 1.73; 95% CI = 1.03–2.91), and zidovudine (AZT) use at <120 days (HR = 2.09; 95% CI = 1.22–3.57). In contrast, after 120 days, AZT use decreased risk of discontinuation (HR = 0.52; 95% CI = 0.28–0.95). Early (<120 days) toxicity-related discontinuation of AZT containing regimens was observed in 44% of patients <50 kg at baseline vs. 14% of those >70 kg. An increased risk of early toxicity-related discontinuation of AZT-containing regimens was observed for baseline weight <60 kg (HR = 2.52; 95% CI = 1.46–4.35).

Conclusions: Lower baseline weight and lower CD4 values at ART initiation were associated with decreased regimen durability. Compared with didanosine/stavudine, AZT use initially increased, then subsequently (>120 days) lowered hazards for regimen discontinuation. Weight <60 kg was associated with an increased risk of toxicity-related AZT discontinuation. As ART use expands globally, further study into maximally durable, least toxic regimens, and the role of weight-based AZT dosing is imperative.

Key Words: antiretroviral therapy, resource constrained, HIV, weight, zidovudine

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INTRODUCTION

Once thought impossible, the generosity and efforts of countless national and international agencies and dedicated individuals have led to the large scale deployment of HIV/AIDS therapy in developing nations.[1,2] The collective accomplishments are staggering, for example, as of March 2008 PEPFAR (President's Emergency Plan for AIDS Relief) sites reported the provision of life-saving antiretroviral therapy (ART) to 1.7 million individuals.[2] However, only an estimated 37% of HIV-infected individuals have received therapy in PEPFAR focus countries.[2]

The worldwide implementation of ART also provides an unprecedented opportunity to investigate therapeutic outcomes and comparative effectiveness of regimens in diverse populations. Such study findings will be critical to guide the selection of optimal ART regimens in different treatment settings.

In the present study, we studied 2 aspects of HIV care in Lima, Peru. First, we sought to determine factors associated

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with abbreviated first regimen durability among treatment-naive patients who started initial ART. As successive ART regimens exhibit progressively shorter durability, initial ART combinations offer the best opportunity for prolonged virologic suppression.[3] The selection of durable initial regimens directly benefits patients (reduced toxicity) and contributes to the financial sustainability of treatment programs due to the decreased need for costlier second or third line agents.[4]

Second, we set out to determine the factors associated with toxicity related discontinuation of AZT in our cohort. According to a World Health Organization report in June 2008, over 20% of all regimens used among adults in 2007 contained zidovudine (AZT). In our cohort, this drug is part of over 75% of initial regimens. A relationship between low body weight and lower AZT clearance has been previously reported, and at least one nation (Thailand) advocates the use of lower doses of AZT in those below 60 kg.[5–8] Though the relationship between low baseline weight and AZT dose has been reported, its impact on the durability of AZT containing ART regimens remains understudied. Further insight into this potential relationship is crucial before continued large scale expansion of AZT use in resource constrained settings.

METHODS

The Instituto de Medicina Tropical Alexander Von Humboldt HIV/AIDS Cohort—Universidad Peruana Cayetano Heredia (IMT), Hospital Nacional Cayetano Heredia, includes a nested cohort of over 1600 patients receiving HIV/AIDS care. This prospective cohort study captures detailed sociodemographic, psychosocial, and clinical information on patients receiving HIV/AIDS care at IMT. All HIV care occurs on site, and is coordinated by a team of IMT Infectious Disease specialists. After treatment is initiated, medications are dispensed directly to patients by a team of nurses. Medications are provided free of charge, though very rarely a patient may need to purchase a medication or drug formulation that is not in the formulary out of pocket. Patients receive a 1-week supply of ART medications at a time for the first 2 months of therapy and have face to face encounters with nurses on subsequent visits with direct adherence counseling. All laboratory and clinical information is stored in an electronic database. Institutional review boards at Universidad Peruana Cayetano Heredia and the University of Alabama at Birmingham approved this study.

Study Sample and Procedures

The present study is the result of a collaboration between the University of Alabama at Birmingham 1917 Clinic Cohort and the Instituto de Medicina Tropical Alexander Von Humboldt—Universidad Peruana Cayetano Heredia. All treatment-naive patients over 18 years of age initiating ART between April 1, 2004 and December 30, 2007 were included in the present study. Sociodemographic, psychosocial, and clinical variables were retrieved by direct chart abstraction from standardized clinic notes and antiretroviral prescribing documents. Laboratory data were extracted via Microsoft Access queries to the IMT database.

Study Variables

Patient level variables included age, sex, baseline weight, HIV risk factor, and height. Medical history including substance abuse (cocaine and marijuana included—no cases of intravenous drug use (IVDU) were observed in the study population), history of affective mental health (depression and/or anxiety), and alcohol abuse disorders, and past opportunistic infections were recorded via medical record abstraction. Laboratory variables included baseline $\log_{10}$ HIV RNA (copies/mL), CD4 cell count, creatinine, and hematocrit plus all subsequent values for these variables.

Antiretroviral regimen variables included regimen composition: nucleoside reverse transcriptase inhibitor (NRTI) backbone [azidothymidine (AZT), stavudine (d4T), or didanosine (DDI)] and third drug (NNRTI—nonnucleoside reverse transcriptase inhibitor and PI, protease inhibitor); and the dose and frequency of administration of each of these antiretroviral agents. All NRTI backbones in this study population contained lamivudine (100%).

The primary outcome measure was initial regimen durability, measured as the time from initial ART receipt to discontinuation for any reason. Survival methods were used in the calculation of initial regimen durability in a manner consistent with prior publications by the 1917 Clinic Cohort.[3,4] Initial ART regimens lasting longer than 14 consecutive days were included in analyses, whereas regimens of less than 14 days duration were excluded. A switch from individual drugs to the same drugs in a fixed-dose combination was not considered a regimen change. Regimen discontinuation reasons were abstracted from the medical records and documented categorically as death, adverse events, treatment failure, other (comorbid medical condition, could not afford, medication interaction, noncompliance, scheduled treatment interruption), and unknown. Three teams of medical records abstractors (C.T. and F. H.; J.W. and J.P.; G.H.) reviewed the primary records, all regimens were subsequently reviewed by J.W.

Statistical Analysis

Descriptive statistics were used to evaluate overall patient and regimen level characteristics to ensure that distributional assumptions for statistical tests were met. Kaplan–Meier (KM) plots of regimen durability were performed using the log-rank test to evaluate study variables association with regimen durability. A biphasic nature of the AZT durability curve on KM analysis was noted, with an inflection point observed approximately 120 days after regimen initiation reflecting an initial steep slope that later became more attenuated. Accordingly, to account for non-proportional hazards (non-PH), an interaction term between NRTI backbone (AZT vs. d4T or ddI) and time (120 days after regimen initiation) was included in the Cox PH analysis of factors associated with regimen discontinuation in ART-naive patients starting therapy. Sensitivity analyses varying the time of the interaction term were carried out. Subsequently, the frequency of short-term (120 days) discontinuation of AZT containing regimens as a function of baseline weight was evaluated and a Cox PH model was fit to determine factors associated with the discontinuation of AZT-containing

regimens before 120 days. All analyses were performed using SAS V9.1.3 software (SAS Institute, Cary, NC).

RESULTS

Overall, 546 patients who started initial ARV therapy between April 1, 2004 and December 31, 2007 are included in analyses. The majority of patients were men (69%) and heterosexual (73%). Affective mental health disorders were observed in over half of patients (60%), whereas substance abuse (21%) and alcohol abuse (46%) were less frequently reported. The mean (±SD) age was 36.2 ± 10.3, whereas mean baseline weight was 58 ± 11.1 kg; over half of patients weighed less than 60 kg (57%) at ART initiation. Baseline CD4 values were predominantly <200 cells/mm^3 (83%) and the mean baseline CD4 was 119 ± 112 cells/mm^3. Mean baseline $\log_{10}$ viral load was 5.1 ± 0.7, whereas mean baseline hematrocrit and creatinine values were 35 ± 6 and 0.8 ± 0.3, respectively (Table 1).

All NRTI backbones included lamivudine, which was most commonly combined with AZT (76%). NNRTIs (efavirenz = 210; nevirapine = 314) represented the overwhelming majority of third drugs prescribed (n = 524, 96%). PIs were used in 22 regimens (lopinavir/ritonavir = 19; atazanavir/ritonavir = 2; indinavir = 1). Laboratory surveillance of treatment effectiveness included the performance of a mean 1.8 ± 3.0 CD4 counts and 1.4 ± 2.3 viral load tests per year (Table 1).

The mean durability of initial regimens was 1.1 ± 1.0 years. Adverse events (65%) and treatment failures (11%) represented the most common discontinuation reasons (Table 1). Initial regimen durability was evaluated as a function of weight (<60 vs. >60 kg) utilizing KM plots and the log-rank test. Patients with baseline weights ≥60 kg had significantly longer regimen durability relative to those who initiated therapy with a weight of <60 kg (log rank, $P = 0.0002$; Fig. 1A).

Careful inspection of the KM plot for regimen durability stratified by NRTI backbone revealed a continuous gradual decline for ddI/d4T regimens, whereas the AZT curve reveals a sharp early drop in durability followed by an inflection point and subsequent linear decline with a markedly less steep slope (Fig. 1B).

To account for non-PH, an interaction term between NRTI backbone (AZT vs. ddI/d4T) and time was included in the Cox PH analysis of initial regimen durability. This interaction term was structured to allow the estimation of separate hazard ratios before and after 120 days. In multivariable analysis, baseline weights below 60 kg (HR = 1.77, 95% CI = 1.25–2.51) and baseline CD4 values of <200 cells/mm^3 (HR = 1.73, 95% CI = 1.03–2.91) increased the hazards for regimen discontinuation. In the first 120 days of therapy, the use of AZT in the NRTI backbone resulted in over twice the hazards of regimen discontinuation relative to d4T- or ddI-containing regimens (AZT vs. ddI/d4T <120 days HR = 2.09, 95% CI = 1.22–3.57). However, after 120 days of ART an NRTI backbone that included AZT rather than ddI/d4T was associated with a significantly reduced hazards of regimen discontinuation (AZT vs. ddI/d4T >120 days HR = 0.52, 95% CI = 0.28–0.95; Table 2). In summary, the utilization of AZT rather than ddI/d4T as part of an NRTI backbone was found to increase the early (<120 days) risk of regimen discontinuation, whereas beyond this initial period the selection of AZT over ddI/d4T was found to decrease the risk of regimen discontinuation.

Of the 546 regimens started, 195 (<120 days = 132, >120 days = 63) had been discontinued by the end of the study period. In the first 120 days of therapy, 80% of all regimen discontinuations were due to toxicity (n = 106 of 132). These early toxicity related regimen discontinuations occurred more frequently when AZT was part of the NRTI backbone (n = 96; anemia = 78, hepatotoxicity = 2, neutropenia = 1, rash = 13, unknown = 2) than d4T/ddI (n = 10; neuropathy = 2, rash = 3, unknown = 2, hepatotoxicity = 1, dizziness = 1, arthralgias/myalgias = 1). After 120 days of therapy, 35% of regimen discontinuations were toxicity related (n = 22 of 63 discontinuations). Of these latter (>120 days) toxicity-related discontinuations, 14 regimens included AZT (anemia = 11, hepatotoxicity = 3) and 8 included d4T/ddI (lipodystrophy = 3, neuropathy = 3, dyslipidemia = 1, CNS toxicity = 1) as part of the NRTI backbone.

As AZT-containing regimens accounted for most early (<120 days) toxicity-related regimen discontinuations (96 of 106), a Cox PH model was fit to further characterize factors associated with early toxicity-related discontinuation of regimens that contained AZT. In multivariable analysis, baseline weight of <60 kg was found to more than double the risk of early discontinuation of AZT-containing regimens (HR = 2.52, 95% CI = 1.46–4.35), whereas other factors were not statistically significant (Table 3). Figure 2 details the relationship between baseline weight and the frequency of early discontinuation for AZT-based regimens. Discontinuation rates increased dramatically with lower baseline weights (>70 kg 14%; 60–70 kg 16%; 50–59 kg 26%; <50 kg 44%, P for trend <0.05; Fig. 2).

DISCUSSION

In our sample of treatment-naive individuals initiating ART in a resource constrained setting, lower baseline weight (<60 kg) and lower baseline CD4 values (<200 cells/mm^3) were associated with shorter regimen durability. The increased risk of regimen discontinuation with lower baseline CD4 values underscores the importance of early diagnosis and ART initiation. NRTI backbone selection also played a significant role in the durability of initial ART. Relative to d4T- or ddI-containing regimens, AZT use was associated with an increased risk for regimen discontinuation in the first 120 days of therapy, whereas patients remaining on AZT beyond 120 days were significantly less likely to discontinue treatment compared with those on d4T or ddI. In a separate analysis, low baseline weight was found to significantly increase the risk of early toxicity-related discontinuation of AZT-containing regimens within 120 days of treatment initiation. 2007 World Health Organization estimates indicated that only 31% of those infected in low- and middle-income countries had access to ART.[1,9,10] As work to propagate ART in resource-constrained settings continues, data on factors related to prolonged regimen durability, toxicity, comparative regimen

TABLE 1. Baseline Characteristics of 546 Antiretroviral-Naive Patients Starting Their Initial ART Regimen At the Instituto Tropical Alexander Von Humboldt in Lima, Peru; May 1, 2004–December 31, 2007

Characteristic	Mean ± SD or N (%)
Age	36.2 ± 10.3
Sex	
Female	168 (31%)
Male	378 (69%)
Baseline weight (kg)	58 ± 11.1
Height (cm)	162 ± 9.2
BMI	22 ± 3.8
Baseline weight*	
<60 kg	294 (57%)
≥60 kg	224 (43%)
History of affective mental health disorder	
Yes	245 (60%)
No	163 (40%)
HIV risk factor	
Heterosexual	388 (73%)
MSM	146 (27%)
History of substance abuse	
Yes	110 (21%)
No	413 (79%)
History of alcohol abuse	
Yes	241 (46%)
No	285 (54%)
History of prostitution	
Yes	20 (4%)
No	499 (96%)
History of opportunistic infection	
Yes	345 (63%)
No	201 (37%)
Baseline CD4 (cells/mm^3)	119 ± 112
Baseline CD4	
<200 cells/mm^3	399 (83%)
≥200 cells/mm^3	80 (17%)
Log_{10}VL	5.1 ± 0.7
Baseline hematocrit (HCT)	35 ± 6
Anemia*	
Yes	304 (77%)
No	92 (23%)
Number of CD4 measures first year of therapy	1.8 ± 3.0
Number of VL measures first year of therapy	1.4 ± 2.3
Duration of the initial regimen (yrs)	1.1 ± 1.0
Creatinine (mg/dL)	0.8 ± 0.3
NRTI backbone	
AZT	417 (76%)
ddI or d4T	129 (24%)
Initial regimen composition†	
NNRTI	524 (96%)
PI	22 (4%)
Discontinuation reasons‡	
Death	15 (8%)
Adverse events	128 (65%)
Treatment failure	21 (11%)
Other§	19 (10%)
Unknown	12 (6%)

*Anemia = HCT < 41 men, HCT < 36 women.

†NNRTIs (efavirenz = 210, nevirapine = 314); PIs (lopinavir/ritonavir = 19; atazanavir/ritonavir = 2; indinavir = 1).

‡A total of 195 of 547 patients discontinued their initial ART regimen during the study period (36%).

§Other discontinuation reasons includes lost to follow-up (n = 3), comorbid medical condition (n = 4), could not afford (n = 4), medication interaction (n = 1), noncompliance (n = 4), scheduled treatment interruption (n = 2), transfer of care (n = 1).

effectiveness and outcomes throughout the globe, will enable policy makers to select drug formularies best suited to maximize the durable success of therapy in distinct settings at both individual and programmatic levels.

The temporal association of the risk for regimen discontinuation seen with AZT (first 120 days) and d4T/ddI (after 120 days) corresponds to existing data on the common toxicity of these agents. AZT use has been associated with a relatively increased rate of early treatment limiting side effects largely related to GI and bone marrow toxicity, whereas serious treatment limiting side effects more commonly occur after prolonged exposure with d4T including peripheral neuropathy and lipoatrophy.[11,12] Despite their predominant role for first-line therapy in resource limited settings, agents such as d4T, AZT, ddI, and nevirapine are not currently recommended as part of initial ART in the United States.[1,10] The increased toxicity associated with these agents is well documented in industrialized nations, data that are increasingly echoed by mounting evidence from resource-limited settings.[13–19] A study of regimen durability at the University of Alabama at Birmingham found a significant impact of initial NRTI backbone selection on regimen durability (median durability of 1253 days tenofovir/abacavir; 791 days AZT; 405 days ddI/d4T).[4] Initiating ART with agents with greater toxicity may lead to intermittent adherence and drug resistance, hampering future therapy under limited drug formularies.[17,20–22] Though the reduced financial costs associated with these agents have contributed to the dissemination of ART, the true costs of selecting these less durable agents in terms of resistance, limitation of future drug options, cost of monitoring/treating medication-related toxicities, and ultimately the transmission of drug resistant virus in resource limited settings remain to be seen.[21–23]

Baseline weight of <60 kg was associated with an increased risk of regimen discontinuation in our study population. As early as 1989, the American Dietetic Association emphasized nutrition intervention and education as part of care for HIV-infected patients in all stages of disease.[24] Adequate

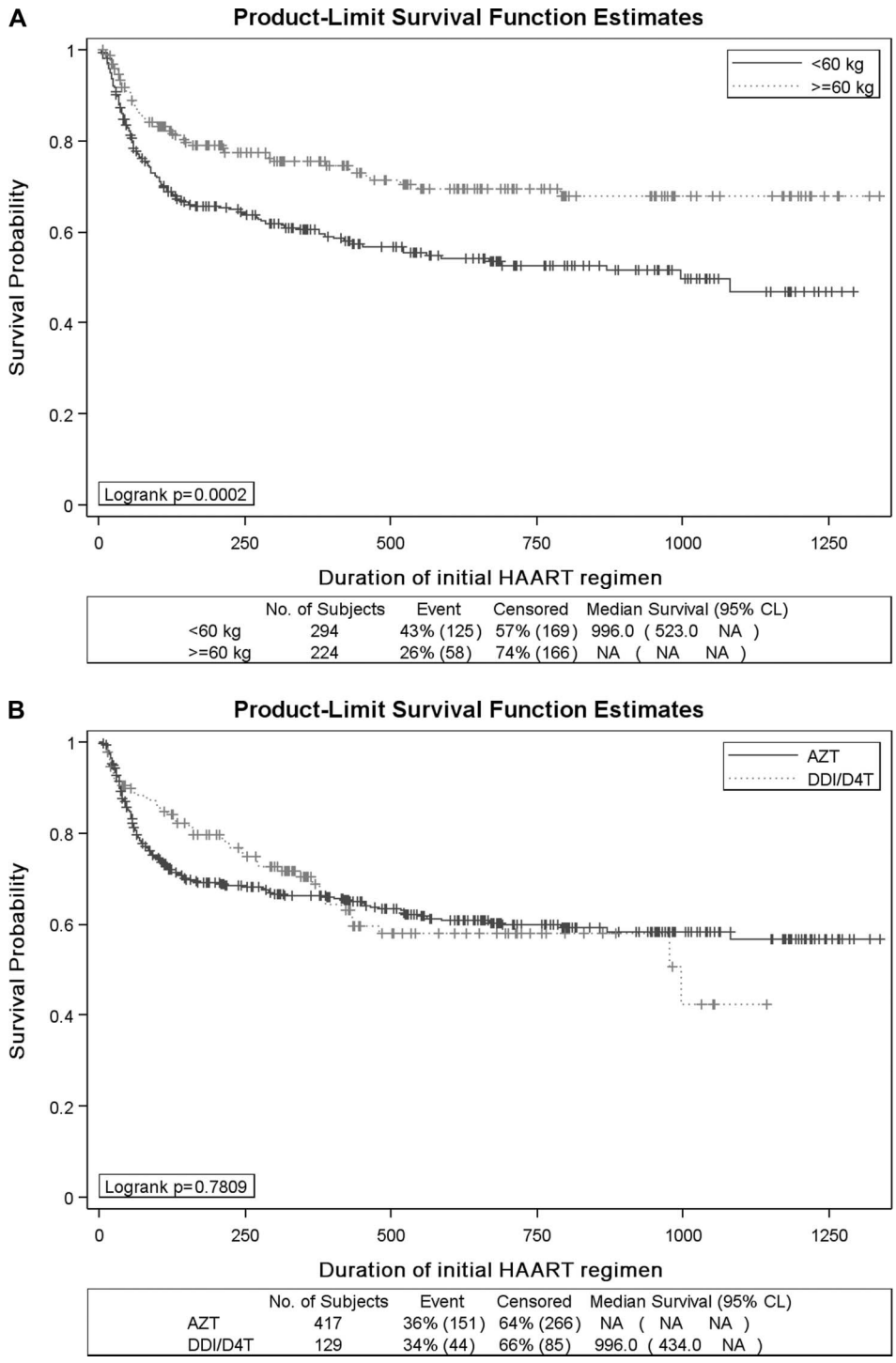

FIGURE 1. Kaplan Meier analyses of initial regimen durability as a function of weight (1a) and nucleoside reverse transcriptase inhibitor (1b) backbone (AZT vs DDI or D4T) among antiretroviral-naïve patients starting initial ART regimens at the Instituto Tropical Alexander Von Humboldt in Lima, Peru; April 1, 2004-December 31, 2007.

nutrition continues to be an important part of successful HIV therapy worldwide and weight loss remains an independent predictor of mortality in HIV-infected individuals.[25–28] Some studies have noted accentuated ART-related side effects after treatment initiation in malnourished individuals.[25,26] The combination of an increased risk for treatment-related side-effects, morbidity, and death are likely contributors to early regimen discontinuation in patients with low baseline weight.

Hematologic toxicity is an important side effect of AZT therapy and baseline hematocrit was not found to be significant in our model. The mean hematocrit of patients with ddI/d4T as part of the NRTI backbone was 30% compared with 36% in those utilizing AZT. This suggests that providers avoided AZT in patients with lower baseline hematocrit values. An association between lower baseline weight and toxicity-related discontinuation of AZT-containing regimens in the first 120

TABLE 2. Univariate and Multivariable Cox PH Analyses of Factors Associated With Regimen Discontinuation Among Antiretroviral-Naive Patients Starting Initial ART Regimens at the Instituto Tropical Alexander Von Humboldt in Lima, Peru; April 1, 2004–December 31, 2007

	Crude HR (95% CI)	Adjusted HR (95% CI)
Age (per 10 yrs)	0.97 (0.84–1.11)	—
Sex		
Female vs. male	1.11 (0.83–1.49)	0.92 (0.65–1.31)
Baseline weight		
<60 kg vs. ≥60 kg	1.78 (1.30–2.43)	1.77 (1.25–2.51)
Anemia*		
Yes vs. no	1.25 (0.82–1.89)	—
HIV risk factor		
MSM vs. heterosexual	0.72 (0.51–1.01)	—
Baseline CD4		
<200 vs. ≥200	1.91 (1.14–3.20)	1.73 (1.03–2.91)
AZT vs. ddI/d4T before 120 d	1.80 (1.12–2.91)	2.09 (1.22–3.57)
AZT vs. ddI/d4T after 120 d	0.43 (0.26–0.72)	0.52 (0.28–0.95)
Log10 VL	1.22 (0.94–1.58)	—
History of affective mental health disorder		
Yes vs. no	1.18 (0.83–1.66)	—
History of substance abuse		
Yes vs. no	1.03 (0.72–1.48)	—
History of opportunistic infection		
Yes vs. no	0.96 (0.72–1.28)	—
Initial regimen composition		
NNRTI vs. PI	1.02 (0.51–2.08)	—

*Anemia = HCT <41 men, HCT <36 women.

TABLE 3. Univariate and Multivariable Cox PH Analyses of Factors Associated With Toxicity Related Discontinuation of AZT-Containing Regimens During Their First 120 Days Among Antiretroviral-Naive Patients Starting Initial ART Regimens at the Instituto Tropical Alexander Von Humboldt in Lima, Peru; April 1, 2004–December 31, 2007

	Crude HR (95% CI)	Adjusted HR (95% CI)
Age (per 10 yrs)	0.89 (0.71–1.11)	0.83 (0.62–1.11)
Sex		
Female vs. male	0.88 (0.54–1.42)	0.60 (0.32–1.15)
Baseline weight		
<60 kg vs. ≥60 kg	2.13 (1.35–3.36)	2.52 (1.46–4.35)
Baseline anemia*		
Yes vs. no	1.31 (0.71–2.39)	—
Baseline CD4		
<200 vs. ≥200	2.84 (1.03–7.80)	2.62 (0.95–7.23)
History of affective mental health disorder		
Yes vs. no	1.14 (0.70–1.88)	—
History of substance abuse		
Yes vs. no	1.30 (0.80–2.11)	—
Third drug		
NNRTI vs. PI	2.36 (0.33–16.93)	1.17 (0.16–8.55)
Baseline viral load		
>100,000 vs. <100,000	1.34 (0.75–2.39)	—

*Anemia in men hematocrit <41, in women hematocrit <36.

days of ART was observed (HR 2.52 for <60 kg vs. >60 kg; 95% CI = 1.46–4.35). A relationship between low body weight and lower AZT clearance has previously been reported.[6,8] Further, a small study in Thailand study found doses of AZT 200 mg twice daily achieved plasma levels equivalent to the standard international 300 mg twice daily dose in individuals weighing <60 kg.[7] Due to these findings Thai National Treatment Guidelines advocate AZT doses of 200 mg twice daily in patients with baseline weights below 60 kg.[5] The association between lower baseline weight and AZT toxicity found in Thailand and echoed in our findings merits further study particularly as combination tablets with the established 300-mg international standard dose are increasingly used throughout the developing world.

The findings of our study should be interpreted within the context of the study limitations. As a single treatment center study in Lima, Peru, the results may not be generalizable to other regions of Peru or to other international locations. However, the thorough capture and richness of the IMT data set provided high quality data for analyses. Because of our modest sample size, we were not able to compare the durability of initial ART regimens at the individual regimen level. However, the preferred regimens utilized in our cohort are in concordance with those most commonly used throughout the developing world. Though a trend toward higher AZT-related discontinuation with lower baseline weights was found, this important finding awaits further confirmation via large scale study, optimally with data across multiple geographic treatment settings and ultimately this association will require pharmacokinetic confirmation.

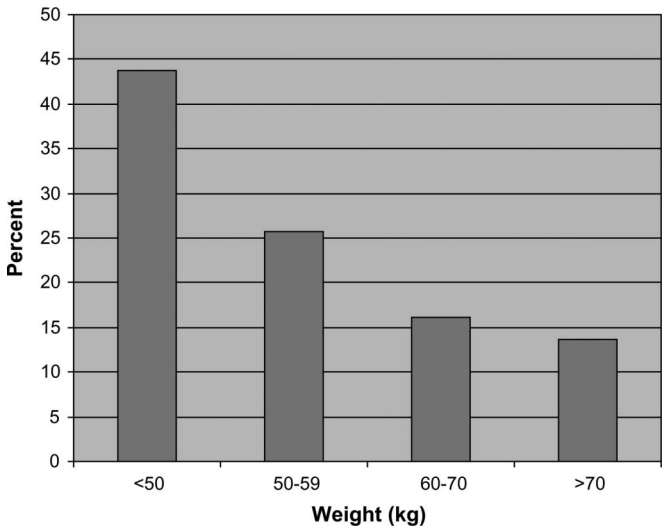

FIGURE 2. Discontinuation of zidovudine containing regimens due to toxicity in the first 120 days per baseline weight group among antiretroviral-naïve patients starting ART in the Instituto Tropical Alexander Von Humboldt in Lima, Peru; April 1, 2004–December 31, 2007.

In summary, this study outlines factors compromising the durability of initial ART in treatment-naive patients initiating therapy in a resource-constrained setting. The durability of initial ART in Peru lags behind that seen with newer once daily treatment options in our previous work at the 1917 Clinic Cohort in Birmingham, AL.[4] The question of whether we are using the regimens best suited to maximize ART durability in resource-constrained settings must be asked, particularly as restricted drug formularies limit future treatment options. As the global fight against the AIDS pandemic continues to expand, the potential for adverse consequences of inappropriately dosed AZT use will likewise increase. In the context of avoiding patient harm, further study into the role of weight-based AZT dosing is imperative.

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