Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy

James H. Willig[a], Sarah Abroms[b], Andrew O. Westfall[c], Justin Routman[a], Sunil Adusumilli[a], Mohit Varshney[a], Jeroan Allison[d], Ashlee Chatham[a], James L. Raper[a], Richard A. Kaslow[e], Michael S. Saag[a] and Michael J. Mugavero[a]

Introduction: Data on initial antiretroviral regimen longevity predates the arrival of newer nucleoside reverse transcriptase inhibitor backbones and once-daily regimens. Modern regimens are thought to possess greater tolerability and convenience. We hypothesized this would translate into greater durability.

Methods: Retrospective study of antiretroviral-naive patients starting treatment at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic 1 January 2000–31 July 2007. Two periods of antiretroviral initiation were identified, prior and after August 2004 (arrival of once-daily fixed-dose regimens). Kaplan–Meier survival analyses of regimen durability by time period and regimen characteristics were performed. Staged Cox proportional hazards models evaluated the roles of dosing complexity and composition in explaining differences in regimen durability between study periods.

Results: Overall 542 patients started antiretroviral drugs ($n = 309$, January 2000–July 2004; $n = 233$, August 2004–July 2007). Median durability was 263 days longer in after August 2004 regimens. Regimens started before August 2004 had increased hazards for discontinuation relative to after August 2004 regimens [hazard ratio (HR) = 1.44; 95% confidence interval (CI) = 1.03–2.02]. Time period of initiation lost statistical significance when the model included dosing frequency (HR = 1.92 for at least twice daily vs. daily; 95% CI = 1.29–2.88). As regimen composition variables were added, time period and dosing frequency lost significance. Increased hazards of discontinuation were observed with didanosine or stavudine relative to abacavir or tenofovir use (HR = 1.92; 95% CI = 1.29–2.88) and all third drugs compared with non-nucleoside reverse transcriptase inhibitor-based regimens (triple-nucleoside reverse transcriptase inhibitor HR = 1.76; 95% CI = 1.14–2.73; unboosted-protease inhibitor HR = 1.58; 95% CI = 1.02–2.46; boosted-protease inhibitor HR = 1.57; 95% CI = 1.02–2.41). Affective mental health disorders increased the hazard of discontinuation in all models.

Conclusion Durability of contemporary once-daily fixed-dose antiretroviral regimens has significantly eclipsed the duration of earlier antiretroviral drug options. Our results indicate this is due to both more convenient dosing and improved tolerability of modern antiretroviral regimens.

AIDS 2008, **22**:1951–1960

Keywords: antiretroviral therapy, durability, highly active antiretroviral therapy, HIV, regimen

[a]Division of Infectious Diseases, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, [b]University of Pennsylvania, Philadelphia, [c]Department of Biostatistics, [d]Division of General Internal Medicine, Department of Medicine, and [e]Departments of Epidemiology and International Health, University of Alabama at Birmingham, Birmingham, Alabama, USA.

Correspondence to James H. Willig, MD, CCB 174, 908 20th Street South, Birmingham, AL 35294-2050, USA.

Tel: +1 205 996 5753; fax: +1 205 975 8273; e-mail: jwillig@uab.edu
Received: 31 March 2008; revised: 14 June 2008; accepted: 27 June 2008.

DOI:10.1097/QAD.0b013e32830efd79

Introduction

Antiretroviral therapy (ART) has transformed HIV infection from a uniformly fatal disease to a chronic medical condition for the majority of individuals with access to treatment. Although debate persists on the optimal timing of treatment initiation, studies have shown deviation from the current paradigm of uninterrupted, lifelong treatment following the initiation of ART results in increased morbidity and mortality [1–3]. Thus, contemporary HIV management calls for indefinite ARV administration in the face of a growing, but exhaustible number of antiretroviral drug options [4]. The spectrum of available antiretroviral drugs must be utilized to provide lifelong therapy whereas contending with the challenges to treatment regimen longevity posed by toxicity and drug resistance [5–8].

Prolonging antiretroviral regimen durability is a key tenet to achieving long-term treatment success in the management of HIV-infected patients. Because successive antiretroviral regimens have exhibited progressively shorter durability [9,10], optimizing the duration of the first regimen in treatment-naive patients is of the utmost importance. Because previous studies of antiretroviral regimen longevity were conducted during study periods before the widespread availability of once-daily fixed-dose nucleoside reverse transcriptase inhibitor (NRTI) combinations, little is known about the durability of regimens built with these drugs. Importantly, new co-formulated agents are composed of antiretroviral drugs that exhibit better toxicity profiles than earlier NRTI backbones [9–12]. In recent years, zidovudine (ZDV), stavudine (D4T), and didanosine (DDI) have largely been replaced by tenofovir (TDF) and abacavir (ABC) as agents paired with emtricitabine (FTC) or lamivudine (3TC) in industrialized countries for the treatment of antiretroviral-naive patients [13].

In a previous study on regimen durability, our group reported a duration of 1.6 years for initial antiretroviral regimens started in treatment-naive patients between 1996 and 2001 [10]. For the present study, we compared the durability of antiretroviral regimens started from January 2000 to July 2004 to those started after August 2004, which marks the release of once-daily fixed-dosed combination NRTIs (Epzicom and Truvada). When combined with a number of third drug options, these NRTI backbones have made numerous once-daily regimens available for use in routine clinical care. We hypothesized that the decreased regimen complexity (smaller pill burdens and less frequent dosing) and improved tolerability of newer antiretroviral regimens owing to better toxicity profiles would prolong durability of initial antiretroviral regimens in treatment-naive patients starting therapy.

Methods

The University of Alabama at Birmingham (UAB) 1917 HIV/AIDS Clinic Cohort Observational Database Project is a prospective cohort study that contains detailed sociodemographic, psychosocial, and clinical information from over 6000 clinic patients dating back to 1988. Currently, over 1500 patients receiving primary and subspecialty HIV care at the clinic participate in the Institutional Review Board (IRB) approved observational, clinical cohort project. The 1917 Clinic uses a locally programmed electronic medical record that imports all laboratory values from the central UAB laboratory, requires electronic prescription for all medications, and contains detailed encounter notes. The electronic medical record and database are 100% quality controlled, with all provider notes reviewed within 72 h of entry into the system to ensure appropriate data capture regarding diagnoses and medications, including start and stop dates for antiretrovirals and all other prescribed drugs. This retrospective cohort study nested in the UAB 1917 HIV/AIDS Clinic Cohort Observational Database Project was approved by the UAB Institutional Review Board.

Study sample and procedures

For this analysis, two teams of medical record abstracters (S.A., M.V. and J.R., S.A.) independently reviewed charts of all new patients entering care at the 1917 Clinic between 1 January 2000 and 31 July 2007 to determine whether patients establishing care were naive to ART upon initial presentation. Patients with a history of prior exposure to antiretroviral drugs were excluded from this study, including those who had received agents transiently for the purpose of blocking mother-to-child HIV transmission, or those who received drugs also used in HIV care for hepatitis B infection. Any discrepancies in the conclusions of the chart abstraction teams were arbitrated by a third team consisting of two clinic providers (J.H.W. and M.J.M.) who reviewed the discrepant medical records and made the final determination on antiretroviral exposure status. Patient data were retrieved through a combination of UAB 1917 Clinic Cohort Database queries, supplemented by manual medical record abstraction to corroborate details regarding antiretroviral medication histories (e.g. discontinuation reason).

Study variables

Patient-level characteristics including age, gender, race, HIV risk factor, baseline $\log_{10}$ plasma HIV RNA (copies/ml), baseline CD4 cell count, and health insurance status at cohort entry (public, private or uninsured) were recorded. Diagnosis of affective mental health disorders, substance abuse disorders, and alcohol abuse disorders were also recorded from the database. Regimen level characteristics included date of initiation,

pill burden, dosing frequency (once daily vs. twice daily or more), NRTI backbone and third drug composition [triple NRTI, nonnucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor, boosted-protease inhibitor], use of fixed-dose combination antiretroviral agents and regimen end date (discontinuation or censoring date). NRTI backbones were assigned to three groups: DDI or D4T-containing regimens, ZDV-containing regimens, and regimens containing ABC or TDF. These NRTIs were typically combined with either FTC or 3TC (98% of regimens); therefore, these latter agents were not evaluated separately for study purposes. If a regimen contained NRTIs from more than one group (e.g. DDI and ZDV), the regimen was assigned to one group using a standardized hierarchy; DDI or D4T, then ZDV, and finally ABC or TDF.

The primary outcome measure was initial regimen duration. Regimens were assigned into one of two time periods based upon the date of regimen initiation: 1 January 2000–31 July 2004 and 1 August 2004–31 July 2007. The second time period coincided with the availability of once-daily fixed-dose NRTI combination antiretroviral agents. Initial regimens lasting for 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 (e.g. ZDV and 3TC to Combivir). Regimen discontinuation reasons were abstracted from the medical records by the abstraction teams and included: virologic failure, adverse event or toxicity, and lost to follow-up. Active regimens were censored at the end of the study period or 6 months after a patient's last contact with the clinic, whichever came first.

Statistical analysis

Descriptive statistics were employed to evaluate overall patient and regimen level characteristics to ensure distributional assumptions for statistical tests were met. Chi-squared and *t*-test analyses were used to compare patient and regimen characteristics between individuals initiating ART during the two time periods of interest. Kaplan–Meier survival analyses of regimen duration were performed comparing period of antiretroviral initiation, regimen complexity [daily (q.d.) vs. at least twice a day (b.i.d.); pill count], and regimen composition (third drug and NRTI backbone). The first Kaplan–Meier curve displays regimen durability as a function of time period of regimen initiation. Though the focus of these analyses was on more contemporary antiretroviral regimens (after 2000), a curve for the duration of antiretroviral regimens in the time period 1 January 1996–31 December 1999 in our cohort is also included as a point of reference.

Univariate analyses were performed to identify factors affecting initial regimen longevity. Next, three-staged multivariable Cox proportional hazard models were used to evaluate factors associated with regimen longevity whereas adjusting for covariates. The first Cox model assessed the role of time period of regimen initiation on regimen longevity. The second Cox model addressed the role of regimen dosing complexity, which is represented by pill burden and dosing frequency. Dosing frequency (q.d. vs. at least b.i.d.) was utilized as a measure of regimen complexity as a once-daily option was not available during the evaluation periods of earlier regimen durability studies. We feel it also avoids the issue of overlap in pill burdens between time periods [e.g. Combivir + efavirenz in the earlier time period and ritonavir boosted-atazanavir + efavirenz in the latter time period share pill burdens (three pills per day) but not dosing frequencies b.i.d vs. q.d.]. The final Cox model introduced regimen composition variables (NRTI backbone and third drug) into the assessment of factors related to regimen durability between the time periods under study. All analyses were performed using SAS V9.1.3 software (SAS Institute, Cary, North Carolina, USA).

Results

Overall, 542 patients who started initial ART during the study period met eligibility criteria and are included in this study. Patient and regimen characteristics were calculated for the overall sample, and then by time period of ART initiation (Table 1). The majority of patients were black (55%), men (77%) and lacked private health insurance (51%). The mean age of the sample was 37.9 ± 9.9 years, and intravenous drug use was an infrequently reported HIV risk factor (8%), whereas a history of men having sex with men (50%) was most commonly reported. Affective mental health disorders were diagnosed in 45% of the sample, whereas 23% had substance abuse disorders. The baseline $\log_{10}$ plasma HIV RNA was 4.7 ± 1.0 copies/ml and 56% of patients had initial CD4 cell counts less than 200 cells/μl. Compared with patients starting ART between 1 January 2000 and 31 July 2004, those starting after August 2004 were less likely to have private health insurance, less likely to have alcohol abuse disorders, and had higher baseline CD4 cell counts (Table 1).

In the overall evaluation of regimens prescribed during the study period, NNRTI-based therapy was most commonly used (Table 1). Two-thirds of regimens consisted of three or fewer pills, and 85% contained a fixed-dose combination antiretroviral agent. A marked and statistically significant increase in the use of fixed-dose combination antiretrovirals (77–95%) and once-daily regimens (12–82%) was noted when comparing regimens started in the earlier time period with those started after August 2004. The use of ABC or TDF as part of an NRTI backbone grew from 6% in the earlier period

Table 1. Baseline characteristics of 542 antiretroviral-naive patients starting their initial antiretroviral regimen at the UAB 1917 HIV/AIDS Clinic; January 2000–July 2007.

Characteristic	Overall	Mean ± standard error or *N* (%) for those starting ART 1/1/2000–7/31/2004	Mean ± standard error or *N* (%) for those starting ART 8/1/2004–7/31/2007	*P* value[a]
Patient characteristics				
Age (years)	37.9 ± 9.9	38.7 ± 9.4	37.0 ± 10.4	0.04
Sex				0.33
Male	417 (76.9%)	233 (75.4%)	184 (79.0%)	
Female	125 (23.1%)	76 (24.6%)	49 (21.0%)	
Race				0.60
White	242 (44.6%)	135 (43.7%)	107 (45.9%)	
Black	300 (55.4%)	174 (56.3%)	126 (54.1%)	
HIV risk factor				0.08
MSM	269 (50.4%)	145 (47.8%)	124 (53.7%)	
Heterosexual	225 (42.1%)	129 (42.6%)	96 (41.5%)	
i.v.DU	40 (7.5%)	29 (9.6%)	11 (4.8%)	
Health insurance				<0.01
Private	265 (48.9%)	164 (53.1%)	101 (43.4%)	
Public	80 (14.8%)	52 (16.8%)	28 (12.0%)	
Uninsured	197 (36.3%)	93 (30.1%)	104 (44.6%)	
History of affective mental health disorder				0.08
No	293 (54.1%)	157 (50.8%)	136 (58.4%)	
Yes	249 (45.9%)	152 (49.2%)	97 (41.6%)	
History of substance abuse				0.12
No	420 (77.5%)	232 (75.1%)	188 (80.7%)	
Yes	122 (22.5%)	77 (24.9%)	45 (19.3%)	
History of alcohol abuse				
No	455 (84.0%)	248 (80.3%)	207 (88.8%)	<0.01
Yes	87 (16.0%)	61 (19.7%)	26 (11.2%)	
History of opportunistic infection				<0.01
No	366 (67.5%)	194 (62.8%)	172 (73.8%)	
Yes	176 (32.5%)	115 (37.2%)	61 (26.2%)	
Baseline CD4 cell count				<0.01
<50 cells/μl	160 (31.0%)	109 (37.4%)	51 (22.7%)	
50–199 cells/μl	134 (26.0%)	68 (23.4%)	66 (29.3%)	
200–350 cells/μl	111 (21.5%)	62 (21.3%)	49 (21.8%)	
>350 cells/μl	111 (21.5%)	52 (17.9%)	59 (26.2%)	
Baseline $\log_{10}$ plasma HIV RNA (copies/ml)	4.7 ± 1.0	4.7 ± 0.97	4.7 ± 1.03	0.90
Regimen characteristics				
Initial regimen				<0.01
Triple NRTI	50 (9.2%)	50 (16.2%)	0 (0.0%)	
NNRTI based	378 (69.7%)	210 (68.0%)	168 (72.1%)	
Protease inhibitor based	38 (7.0%)	26 (8.4%)	12 (5.2%)	
Boosted-protease inhibitor based	76 (14.0%)	23 (7.4%)	53 (22.8%)	
NRTI backbone				<0.01
Abacavir or tenofovir	217 (40.0%)	18 (5.8%)	199 (85.4%)	
Zidovudine	271 (50.0%)	239 (77.4%)	32 (13.7%)	
Didanosine or stavudine	54 (10.0%)	52 (16.8%)	2 (0.9%)	
Pill burden of initial regimen				<0.01
≤3	358 (66.0%)	186 (60.2%)	172 (73.8%)	
4–5	117 (21.6%)	73 (23.6%)	44 (18.9%)	
≥6	67 (12.4%)	50 (16.2%)	17 (7.3%)	
Regimen dosing frequency				<0.01
q.d.	228 (42.1%)	37 (12.0%)	191 (82.0%)	
≥ b.i.d.	314 (57.9%)	272 (88.0%)	42 (18.0%)	
Initial fixed-dose combination				<0.01
No	82 (15.1%)	70 (22.7%)	12 (5.2%)	
Yes	460 (84.9%)	239 (77.3%)	221 (94.8%)	
Discontinuation of initial regimen within 90 days				<0.01
No	463 (89.0%)	262 (85.6%)	201 (93.9%)	
Yes	57 (11.0%)	44 (14.4%)	13 (6.1%)	

ART, antiretroviral therapy; b.i.d., twice daily; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; q.d., daily.
[a]*P* value based on chi-squared statistic or *t*-test.

to 85% for regimens started after August 2004, whereas ZDV use dropped from 77 to 14% in the latter time period. Increased use of both boosted protease inhibitor (7–23%) and NNRTI regimens (68–72%) was observed, whereas triple NRTI regimen use ceased altogether (16 to 0%) in the study period after August 2004. Finally, a

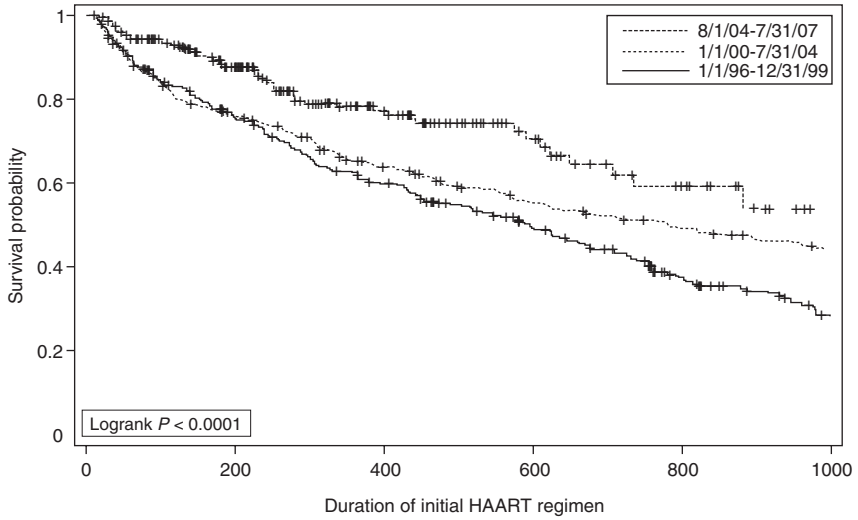

Fig. 1. Regimens started after 8/1/04 ($n = 233$) achieved a median durability of 1043 days (95% CI = 735–NA) vs. 780 days (95% CI = 593–992) for regimens started between 1 January 2000 and 31 July 2004 ($n = 309$). The final curve represents regimens started during the time period 1 January 1996–31 December 1999 ($n = 293$), which is included for comparative purposes and not evaluated in statistical analyses for this manuscript. Strikingly, the median regimen durability of 595 days (95% CI = 453–707) seen during this early time period is almost half of that seen after August 2004 when new once-daily, more tolerable, fixed-dosed combination NRTIs became widely available. CI, confidence interval; HAART, highly active antiretroviral therapy; NRTIs, nucleoside reverse transcriptase inhibitor.

statistically significant decline in regimen discontinuation within 90 days of initiation ($P < 0.01$) was observed between the earlier and latter time periods (14 vs. 6%).

The median duration of the initial ART regimen increased by 263 days between the earlier (780 days) and more recent (1043 days) study periods (Fig. 1). Initial ART regimen duration for both periods eclipsed the observed median of 595 days for regimens initiated between 1 January 1996 and 31 December 1999.

Next, we evaluated the roles of dosing complexity and antiretroviral composition of regimens as they relate to initial ART regimen durability using Kaplan–Meier plots and the log rank test. First, we evaluated regimen duration as a function of pill burden, demonstrating that regimens containing three pills or less achieved the greatest longevity (median 1218 days) and those consisting of at least six pills, the shortest (median 340 days) (Fig. 2a). Once-daily regimens (1253 days) lasted a median of 541 days longer than regimens dosed at least twice a day (712 days) (Fig. 2b). Next, the composition of regimens was evaluated. Regimens containing DDI or D4T exhibited the shortest durability (450 days), whereas regimens including ABC or TDF had the longest durability (median 1253 days) (Fig. 3a). Finally, when comparing third drugs by class, NNRTI-based regimens (median 1132 days) had the greatest longevity followed by boosted-protease inhibitor (median 1043 days), triple NRTI (median 662 days), and unboosted protease inhibitor regimens (median 382 days) (Fig. 3b).

Staged Cox proportional hazard models were fitted to first evaluate the role of study period on regimen longevity when controlling for patient factors, and then sequentially adding dosing frequency (b.i.d. vs. q.d.) and antiretroviral composition of regimens (NRTI agents and third drug class) to successive models to evaluate the role of these factors in contributing to greater longevity of regimens started in more recent years (Table 2). When controlling for patient factors, regimens started between 1 January 2000 and 31 July 2004 had significantly increased hazards of discontinuation relative to regimens started after August 2004 [HR 1.44, 95% confidence interval (CI) 1.03–2.02] (Table 2, Model 1). When dosing frequency was added to the model (Table 2, Model 2), time period of antiretroviral drug initiation was no longer significant, whereas at least twice daily dosing frequencies had nearly double the hazard of regimen discontinuation relative to once-daily regimens (HR 1.92, 95% CI 1.29–2.88). In the final model regimen composition, variables were added to the model (Table 2, Model 3). All third drug classes were found to have greater hazards of discontinuation relative to NNRTI-based regimens (triple NRTI HR 1.76, 95% CI 1.14–2.73; unboosted-protease inhibitor HR 1.58, 95% CI 1.02–2.46; boosted-protease inhibitor HR 1.57, 95% CI 1.02–2.41). The use of the NRTIs DDI or D4T was also found to increase the hazards of regimen discontinuation when compared with ABC or TDF use (HR 2.16, 95% CI 1.09–4.26). In this final model, time period of ART initiation remained nonsignificant, and regimen-dosing frequency lost statistical significance. The only patient characteristic associated with regimen longevity in

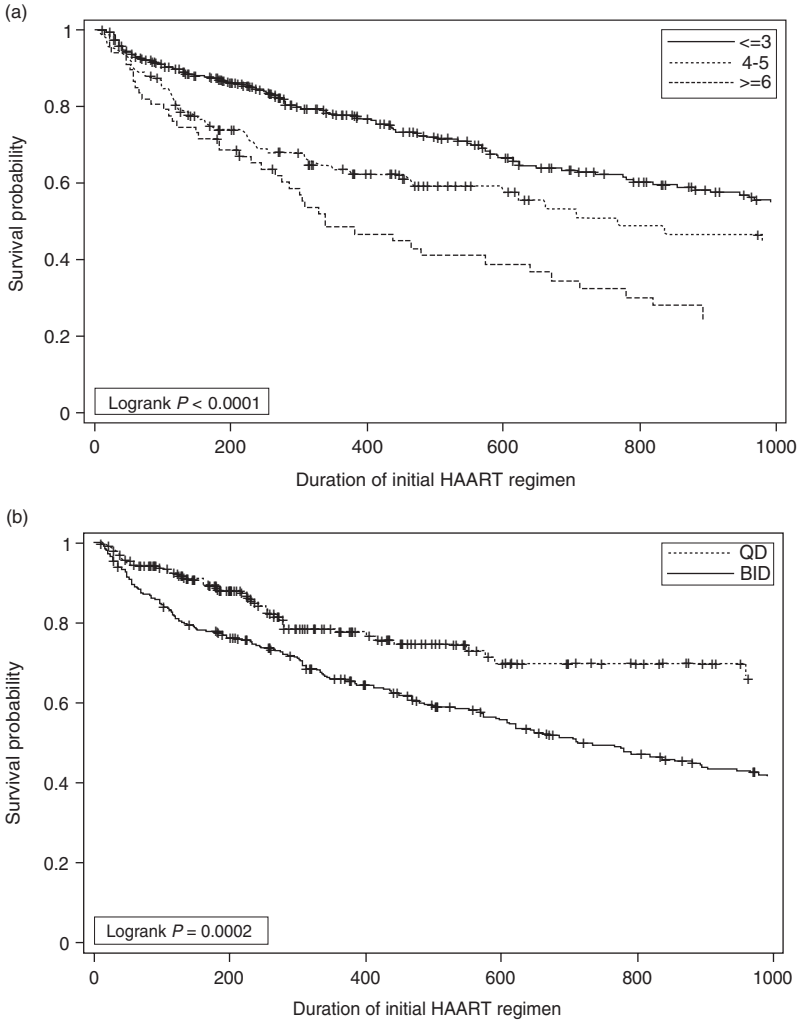

Fig. 2. Duration of initial antiretroviral regimens as a function of regimen dosing complexity. (a) Pill burden: regimens three pills per day or less ($n = 358$) achieved a median durability of 1218 days (95% CI = 961–1724) as compared with a median durability of 766 days (95% CI = 468–1263) for 4–5 pills per day ($n = 117$) and 340 days if the regimen was at least six pills ($n = 67$) per day (95% CI = 274–640). Overall, as regimens increase in total daily pill count duration is truncated. (b) Dosing frequency: once-daily regimens ($n = 228$) achieved a median durability of 1253 days (95% CI = 1055–NA), outlasting at least twice a day ($n = 314$) alternatives whose median durability was 712 days (95% CI 597–905). This variable demonstrates the aggregate effect of newer more tolerable medications as well as the effect of a more convenient dosing scheme. BID, twice daily; CI, confidence interval; HAART, highly active antiretroviral therapy; QD, daily.

multivariate Cox proportional hazard analyses was affective mental health disorder, which increased the hazards of early regimen discontinuation across all three models (Table 2).

All-cause regimen discontinuation was greater in earlier regimens (1 January 2000–31 July 2004) relative to those used after August 2004 (14 vs. 6% at 90 days, 38 vs. 30% at 360 days). Among discontinued regimens, medication-related toxicity was the most commonly cited reason, accounting for a greater proportion of discontinued regimens in the early vs. after August 2004 time periods (80 vs. 62% at 90 days, 64 vs. 43% at 360 days) (Data not shown).

Discussion

In treatment-naive patients starting ART, contemporary initial regimens are more durable than those initiated prior to August 2004. However, the time period of starting ART was no longer associated with regimen longevity after adding dosing frequency to the model, thus indicating that once-daily regimens had greater longevity than those taken twice daily. or more frequently. In further analysis, adding antiretroviral regimen composition to the model revealed that NNRTI-based options lasted longer than other third drugs, and regimens containing D4T or DDI were more short-lived relative to those containing ABC or TDF.

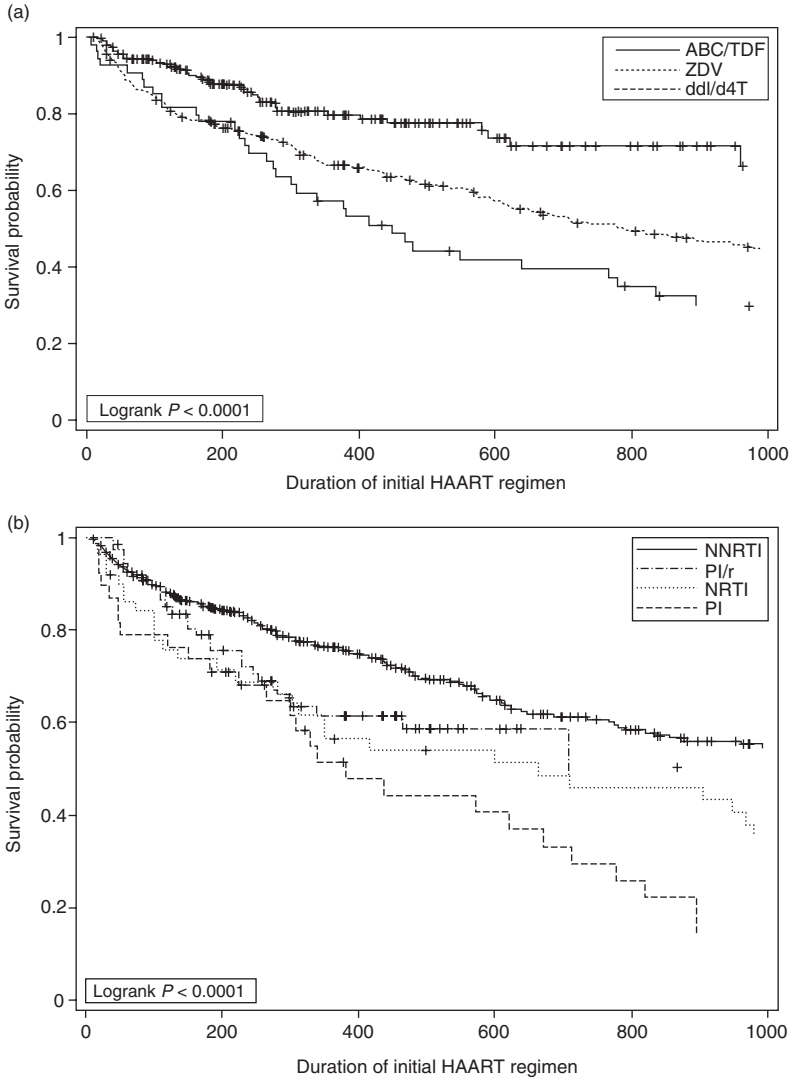

Fig. 3. Duration of initial antiretroviral regimens per regimen composition. (a) NRTI: regimens containing D4T and/or DDI ($n = 54$) have the shortest median duration 405 days, whereas those utilizing ZDV ($n = 271$) achieved a median duration of 791 days. Regimens including the NRTIs ABC or TDF ($n = 217$) had the most prolonged median duration at 1253 days. These NRTIs were combined with either lamivudine or emtricitabine in 98% of regimens. (b) Third drug class: NNRTI-based regimens (median 1132 days) had the most prolonged duration whereas unboosted protease inhibitor regimens (median 382 days) had the shortest durability. ABC, abacavir; ZDV, zidovudine; D4T, stavudine; DDI, didanosine; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TDF, tenofovir.

Taken together, our results suggest the more convenient once-daily fixed-dosed drug regimens and improved drug tolerability of contemporary regimens has allowed for significant gains in initial regimen durability. We suggest that August 2004 ushered in a new treatment era for antiretroviral-naive patients initiating ART.

Prior studies [9,10,12,14] assessing initial antiretroviral regimens in US populations have reported regimen durations from 11.8 months to 1.6 years [9,10]. The time periods evaluated in these studies predate the availability of once-daily, fixed-dose combination antiretroviral agents. In addition to decreasing regimen complexity by making once-daily regimens widely available, we suspect that newer NRTI agents have contributed to greater regimen longevity due to decreased toxicity. Previous studies have demonstrated high discontinuation rates of regimens containing ZDV, primarily due to bone marrow suppression, and D4T and DDI, often related to mitochondrial toxicity (e.g. peripheral neuropathy or lactic acidosis). Although third drug selection remained relatively stable in our study periods (NNRTIs 68 vs. 72%), the use of ABC or TDF as NRTI backbones increased dramatically (6 vs. 85%). We suggest this shift in NRTI backbone selection accounts for the diminished proportion of

Table 2. Initial antiretroviral regimen longevity as a function of patient characteristics, time period of antiretroviral initiation, regimen complexity and antiretroviral regimen composition among antiretroviral-naïve patients starting initial antiretroviral regimens at the UAB 1917 HIV/AIDS Clinic; January 2000–July 2007.

		Adjusted HR (95% CI)		
	Crude HR (95% CI)	Model 1	Model 2	Model 3
Age (per 10 years)	0.92 (0.80–1.05)	0.95 (0.82–1.10)	0.94 (0.82–1.09)	0.95 (0.82–1.11)
Sex				
Female vs. male	1.57 (1.18–2.09)	1.38 (0.94–2.02)	1.45 (0.99–2.13)	1.31 (0.88–1.94)
Race				
Black vs. white	1.26 (0.97–1.63)	1.15 (0.84–1.58)	1.20 (0.87–1.65)	1.26 (0.91–1.74)
Insurance				
Public vs. private	1.77 (1.24–2.51)	1.41 (0.93–2.13)	1.44 (0.96–2.18)	1.41 (0.93–2.13)
Noninsured vs. private	1.33 (1.00–1.77)	1.25 (0.92–1.70)	1.22 (0.90–1.66)	1.19 (0.87–1.63)
HIV risk factor				
Heterosexual vs. MSM	1.27 (0.96–1.67)	0.98 (0.69–1.39)	0.93 (0.65–1.33)	0.95 (0.66–1.36)
i.v.DU vs. MSM	1.78 (1.16–2.74)	1.34 (0.77–2.33)	1.37 (0.79–2.38)	1.19 (0.68–2.08)
Baseline CD4 cell count				
<50 vs. >350 cells/μl	1.17 (0.81–1.67)	1.17 (0.80–1.70)	1.25 (0.86–1.83)	1.31 (0.88–1.94)
50–199 vs. >350 cells/μl	0.93 (0.63–1.36)	1.01 (0.68–1.50)	1.06 (0.71–1.57)	1.04 (0.69–1.56)
200–350 vs. >350 cells/μl	0.74 (0.48–1.14)	0.76 (0.49–1.17)	0.75 (0.49–1.17)	0.72 (0.46–1.12)
History of affective mental health disorder				
Yes vs. no	1.51 (1.17–1.95)	1.43 (1.07–1.91)	1.44 (1.08–1.93)	1.43 (1.06–1.93)
History of substance abuse				
Yes vs. no	1.25 (0.93–1.67)	0.98 (0.66–1.44)	0.96 (0.65–1.42)	1.04 (0.70–1.55)
Time period of antiretroviral initiation				
1/1/2000–7/31/2004 vs. 8/1/2004-7/31/2007	1.61 (1.17–2.21)	1.44 (1.03–2.02)	0.97 (0.64–1.45)	0.79 (0.49–1.26)
Regimen dosing frequency				
≥ b.i.d. vs. q.d.	1.84 (1.34–2.55)	–	1.92 (1.29–2.88)	1.49 (0.85–2.62)
NRTI backbone				
ZDV vs. ABC or TDF	1.90 (1.34–2.70)	–	–	1.48 (0.75–2.93)
DDI or D4T vs. ABC or TDF	2.76 (1.77–4.29)	–	–	2.16 (1.09–4.26)
Initial regimen composition				
Triple NRTI based vs. NNRTI	1.66 (1.14–2.43)	–	–	1.76 (1.14–2.73)
Protease inhibitor based vs. NNRTI	2.47 (1.65–3.68)	–	–	1.58 (1.02–2.46)
Boosted protease inhibitor vs. NNRTI	1.39 (0.93–2.08)	–	–	1.57 (1.02–2.41)

ABC, abacavir; ZDV, zidovudine; b.i.d., twice daily; CI, confidence interval; D4T, stavudine; DDI, didanosine; HR, hazard ratio; i.v.DU, intravenous drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; q.d., daily; TDF, tenofovir.

regimens stopped for drug toxicity in after August 2004 regimens. After August 2004, once-daily, fixed-dose NRTI combinations of TDF or ABC (co-formulated with emtricitabine and lamivudine, respectively) provide simpler, better tolerated therapeutic options [15–17], and were found to outlast ZDV and DDI or D4T regimens by a median of 461 and 803 days, respectively.

The only patient characteristic associated with shorter longevity of the initial antiretroviral regimens was a history of affective mental health disorder ($n = 249$), which increased the hazards for early regimen discontinuation across all three-staged Cox proportional hazard multivariate models (Table 2).

We further evaluated specific affective mental health disorders and found the majority of patients in this group had depressive disorders ($n = 185$) and anxiety disorders ($n = 85$), with both categories diagnosed in 48 patients. Kaplan–Meier analyses evaluating median regimen longevity in patients with depressive disorders and anxiety disorders yielded similar findings to the median duration observed in the overall analysis of affective mental health disorders category.

Multiple studies have linked the presence of affective mental health disorders with poor adherence to antiretroviral regimens [18–20]. Poor adherence to therapy in turn is strongly associated to virologic treatment failure, which typically results in a discontinuation and change of a given antiretroviral regimen [6–8,21]. Screening and timely intervention for affective mental health disorders may serve as a key component to prolonging initial regimen duration and ultimately to the long-term success of ART.

The enhanced durability of more modern regimens is encouraging in light of recent data highlighting the importance of uninterrupted ART following the initiation of treatment. Our findings regarding the enhanced duration of newer regimens is reason for hope that a majority of HIV-infected patients will be able to achieve and sustain long-term virologic suppression, whereas experiencing less toxicity than patients in earlier antiretroviral treatment eras. Although there is much

promise in this era of once-daily fixed-dose combination ART, it remains to be seen how approaches to antiretroviral treatment for naive patients will evolve, and if even greater regimen longevity may be achieved in years to come with the addition of new drugs and drug classes to the antiretroviral armamentarium such as integrase and chemokine (C-C motif) receptor 5 (CCR5) inhibitors.

The findings of our study should be interpreted within the context of the study limitations. As a single academic HIV treatment center in the southeastern United States, the results may not be generalizable to other regions of the country or to international locations. Because of our modest sample size, we were not able to compare longevity of initial antiretroviral regimens at the individual regimen level. Future studies with larger samples addressing longevity at the regimen level may provide greater insight, particularly as it relates to individual third drugs rather than classes of agents. Finally, adherence to antiretroviral regimens is not captured systematically at our clinic. Accordingly, we were unable to gauge the impact of adherence on regimen durability, although we expect that poor adherence was likely associated with shorter longevity of initial antiretroviral regimens among our sample.

In summary, this study illustrates that the shift to newer, more convenient, and better-tolerated therapeutic options over the last few years is associated with a remarkable increase in the durability of first regimens. Further studies are needed to determine the relative benefit of one regimen over another and to determine the generalizability of these findings.

Acknowledgements

We thank the University of Alabama at Birmingham 1917 Clinic HIV/AIDS Clinic Cohort management team for their assistance with this project.

University of Alabama at Birmingham Center for AIDS Research (grant P30-AI27767), the Mary Fisher CARE Fund and the CFAR Network of Integrated Clinical Sites (CNICS; grant 5R24-AI067039). J.W. received financial support for this study from a Ruth L. Kirschstein National Research Service Award (grant 5T32AI52069) and the Bristol Myers Squibb Virology Fellows Research Program 2007–2008.

J.H.W. led the conception and design of this investigation, contributed to data acquisition and interpretation, and prepared the initial draft of the manuscript. A.O.W. contributed to study design, conducted all analyses, contributed to data interpretation and provided critical revision of the manuscript. Remaining authors provided substantial contributions to the design, data acquisition or interpretation of data and critically revised the intellectual content of the manuscript. All authors approved the final version of the manuscript.

J.H.W. has received research funding from the Bristol-Myers Squibb Virology Fellows Research Program for the 2006–2008 academic years. M.J.M. has received recent research funding from Tibotec. M.S.S. has received recent research funding or consulted for Adrea Pharmaceuticals, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Monogram Biosciences, Panacos, Pfizer, Progenics, Roche, Serono, Tanox, Tibotec, Trimeris, and Vertex. All other authors have no conflicts of interest related to this manuscript.

Data Presented at 12th International Workshop on HIV Observational Databases; Malaga, Spain; 27–30th March 2008.

References

1. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, *et al*. **CD4+ count-guided interruption of antiretroviral treatment.** *N Engl J Med* 2006; **355**:2283–2296.
2. Jacobson JM, Turner BJ, Abrutyn E. **Trials that matter: CD4+ T-lymphocyte count-guided interruption of antiretroviral therapy in HIV-infected patients.** *Ann Intern Med* 2007; **146**:682–683.
3. Ruiz L, Paredes R, Gomez G, Romeu J, Domingo P, Perez-Alvarez N, *et al*. **Antiretroviral therapy interruption guided by CD4 cell counts and plasma HIV-1 RNA levels in chronically HIV-1-infected patients.** *AIDS* 2007; **21**:169–178.
4. Hammer SM, Saag MS, Schechter M, Montaner JS, Schooley RT, Jacobsen DM, *et al*. **Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel.** *Jama* 2006; **296**:827–843.
5. d'Arminio Monforte A, Lepri AC, Rezza G, Pezzotti P, Antinori A, Phillips AN, *et al*. **Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients.** *AIDS* 2000; **14**:499–507.
6. Mocroft A, Phillips AN, Soriano V, Rockstroh J, Blaxhult A, Katlama C, *et al*. **Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen: increased incidence of stopping due to toxicity or patient/physician choice in patients with hepatitis C coinfection.** *AIDS Res Hum Retroviruses* 2005; **21**:527–536.
7. Sabundayo BP, McArthur JH, Langan SJ, Gallant JE, Margolick JB. **High frequency of highly active antiretroviral therapy modifications in patients with acute or early human immunodeficiency virus infection.** *Pharmacotherapy* 2006; **26**:674–681.
8. Yuan Y, L'Italien G, Mukherjee J, Iloeje UH. **Determinants of discontinuation of initial highly active antiretroviral therapy regimens in a US HIV-infected patient cohort.** *HIV Med* 2006; **7**:156–162.
9. Palella FJ Jr, Chmiel JS, Moorman AC, Holmberg SD. **Durability and predictors of success of highly active antiretroviral therapy for ambulatory HIV-infected patients.** *AIDS* 2002; **16**:1617–1626.
10. Chen RY, Westfall AO, Mugavero MJ, Cloud GA, Raper JL, Chatham AG, *et al*. **Duration of highly active antiretroviral therapy regimens.** *Clin Infect Dis* 2003; **37**:714–722.
11. Fletcher C. **Translating efficacy into effectiveness in antiretroviral therapy: beyond the pill count.** *Drugs* 2007; **67**:1969–1979.
12. Medeiros R, Diaz RS, Filho AC. **Estimating the length of the first antiretroviral therapy regiment durability in Sao Paulo, Brazil.** *Braz J Infect Dis* 2002; **6**:298–304.

13. Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 29 January 2008; 1–128. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. [Accessed 9 March 2008]
14. Gratacòs LTM, Codina C, Miró JM, Mallolas J, Miserachs N, Martín-Conde MT, *et al*. **Antiretroviral therapy of HIV infection: duration and reasons for changing the first therapeutic regimen in 518 patients.** *Med Clin (Barc)* 2006; **126**:241–245.
15. McComsey GA, Paulsen DM, Lonergan JT, Hessenthaler SM, Hoppel CL, Williams VC, *et al*. **Improvements in lipoatrophy, mitochondrial DNA levels and fat apoptosis after replacing stavudine with abacavir or zidovudine.** *AIDS* 2005; **19**:15–23.
16. Milinkovic A, Martinez E, Lopez S, de Lazzari E, Miro O, Vidal S, *et al*. **The impact of reducing stavudine dose versus switching to tenofovir on plasma lipids, body composition and mitochondrial function in HIV-infected patients.** *Antivir Ther* 2007; **12**:407–415.
17. Llibre JM, Domingo P, Palacios R, Santos J, Perez-Elias MJ, Sanchez-de la Rosa R, *et al*. **Sustained improvement of dyslipidaemia in HAART-treated patients replacing stavudine with tenofovir.** *AIDS* 2006; **20**:1407–1414.
18. Horberg MA, Silverberg MJ, Hurley LB, Towner WJ, Klein DB, Bersoff-Matcha S, *et al*. **Effects of depression and selective serotonin reuptake inhibitor use on adherence to highly active antiretroviral therapy and on clinical outcomes in HIV-infected patients.** *J Acquir Immune Defic Syndr* 2008; **47**:384–390.
19. Lima VD, Geller J, Bangsberg DR, Patterson TL, Daniel M, Kerr T, *et al*. **The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART.** *AIDS* 2007; **21**:1175–1183.
20. Pence BW, Miller WC, Gaynes BN, Eron JJ Jr. **Psychiatric illness and virologic response in patients initiating highly active antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2007; **44**:159–166.
21. Mocroft A, Youle M, Moore A, Sabin CA, Madge S, Lepri AC, *et al*. **Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre.** *AIDS* 2001; **15**:185–194.