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Unanticipated Effects of New Drug Availability on Antiretroviral Durability: Implications for Comparative Effectiveness Research

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Background. Durability of antiretroviral (ARV) therapy is associated with improved human immunodeficiency virus (HIV) outcomes. Data on ARV regimen durability in recent years and clinical settings are lacking.

Methods. This retrospective follow-up study included treatment-naive HIV-infected patients initiating ARV therapy between January 2007 and December 2012 in a university-affiliated HIV clinic in the Southeastern United States. Outcome of interest was durability (time to discontinuation) of the initial regimen. Durability was evaluated using Kaplan-Meier survival analyses. Cox proportional hazard analyses was used to evaluate the association among durability and sociodemographic, clinical, and regimen-level factors.

Results. Overall, 546 patients were analyzed. Median durability of all regimens was 39.5 months (95% confidence interval, 34.1–44.4). Commonly prescribed regimens were emtricitabine and tenofovir with efavirenz (51%; median duration = 40.1 months) and with raltegravir (14%; 47.8 months). Overall, 67% of patients had an undetectable viral load at the time of regimen cessation. Discontinuation was less likely with an integrase strand transfer inhibitor (adjusted hazards ratio [aHR] = 0.35, $P = .001$) or protease inhibitor-based regimen (aHR = 0.45, $P = .006$) and more likely with a higher pill burden (aHR = 2.25, $P = .003$) and a later treatment era (aHR = 1.64, $P < .001$).

Conclusions. Initial ARV regimen longevity declined in recent years contemporaneous with the availability of several new ARV drugs and combinations. Reduced durability mostly results from a preference for newly approved regimens rather than indicating failing therapy, as indicated by viral suppression observed in a majority of patients (67%) prior to regimen cessation. Durability is influenced by extrinsic factors including new drug availability and provider preference. Medication durability must be interpreted carefully in the context of a dynamic treatment landscape.

Keywords. antiretroviral; durability; persistence; prescribing patterns.

Early in the treatment era of the human immunodeficiency virus (HIV) epidemic (late 1990s–early 2000s), antiretroviral (ARV) durability, also known as persistency, was adopted as a method to compare treatments for persons living with HIV (PLWH). In recent studies, ARV durability, defined as the time from regimen initiation to discontinuation, has been associated with improved outcomes: virologic control, reduced drug resistance, and lower morbidity and mortality [1, 2]. In addition to efficacy, ARV durability is an indirect measure of tolerability and adherence because side effects may be treatment-limiting and/or reduce adherence leading to resistance and viral failure. Patient-reported side effects, viremia, and/or resistance will then prompt providers to discontinue the ARV regimen in favor of an alternative. Today, there are considerably more treatment options for PLWH, but data on initial ARV regimen durability in recent years and clinical settings are lacking.

Although randomized-controlled trials have evaluated the durability and tolerability of newer regimens, it is unclear whether these findings will be replicated in routine clinical practice [3]. In previous studies, nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based regimens were found to be the most durable [1, 4, 5]. However, several new ARV drugs and fixed-dose combinations (FDCs) have entered the marketplace since these studies, including an entirely new class, integrase strand transfer inhibitors (ISTIs), and single-tablet regimens (STRs) Stribild and Triumeq. It is unclear how ARV regimen durability will be impacted by the evolving treatment landscape.

Additional research is needed to understand the durability of new drug classes, combinations, and dosing schedules in routine outpatient settings. Knowledge of intrinsic drug properties and extrinsic factors impacting regimen longevity will aid initial regimen selection and improve patient care. Durability has been used to compare the effectiveness of treatments for many

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chronic conditions such as insomnia, pain, infections, and bowel disease; understanding extrinsic influences on drug durability has broad implications [6–9]. We conducted this study to examine durability of initial regimens in the contemporary ARV treatment era and factors associated with their discontinuation in treatment-naive PLWH.

METHODS

Study Design and Population

This retrospective follow-up study was conducted at the 1917 Clinic, the University of Alabama at Birmingham (UAB)-affiliated clinic, which currently serves more than 3000 PLWH. The 1917 HIV/AIDS Clinic Cohort (http://www.uab.edu/medicine/1917cliniccohort/) is a prospective cohort capturing clinical, sociodemographic, and behavioral information. A majority of patients are assessed for patient-reported outcomes such as depression and substance use when they initiate care through Project CONNECT, the Client-Oriented New Patient Navigation to Encourage Connection to Treatment.

The UAB 1917 Clinic Cohort database was queried for treatment-naive patients entering care between January 1, 2007 and December 31, 2012. Medical record review identified treatment-naive patients. Patients were included if they initiated an ARV regimen (3 or more drugs) for at least 14 days and were not pregnant at the time of initiation. Research study participants involved in trials comparatively evaluating ARV regimens were included only if the study was unblinded at the time of data analysis, because analyses required knowledge of ARV drug regimen. The study was approved by the UAB Institutional Review Board.

Study Variables

Outcome of interest was time to discontinuation of the initial regimen. Investigator E. F. E. and a research technician manually reviewed electronic records to confirm ARV start and stop dates and documented indications for discontinuation. Reasons for discontinuation included side effects, drug-drug interaction, treatment failure, loss to follow up (no visit 6 months after last arrived visit), regimen simplification, study-related prescription change, and death. Poor adherence, resistance, and virologic failure were deemed "treatment failure" due to the complex relationships and overlap between these events. A chart review protocol was followed to ensure consistency in record abstraction. Changes in ARV, excluding dosage adjustment, lasting more than 14 days were considered discontinuation of initial regimen. If an individual was switched from individual drugs to a FDC of the same constituent drugs, the regimen was considered continued.

Antiretroviral regimen was categorized according to drug class, pill count (1, 2, or ≥3 pills/24 hour), once- or twice-daily dosing frequency, calendar start and stop dates, and presence of an FDC (Atripla, Truvada, Combivir, Complera, Epzicom, or Stribild). Most regimens relied on a combination of 2 nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs) and a third drug. Regimen drug class was assigned based on the third drug: NNRTI, protease inhibitor (PI), or ISTI. Six participants were started on 3 drug regimens containing an NNRTI and ISTI, which were categorized as ISTI-based.

Age, sex, race, HIV transmission risk factor, and insurance status were obtained from the first orientation visit, along with baseline CD4 cell count and HIV ribonucleic acid (RNA) viral load (VL). Race was defined by patient report. All VL values during the study were collected. Patient-reported outcomes related to alcohol and substance use, depression, and anxiety at entry to care were captured. Depression was identified by Patient Health Questionnaire (PHQ-9) Score and was considered "none/mild" if PHQ9 score <10 or "depressed" if PHQ9 ≥10 [10]. Anxiety was present if PHQ9A ≥10 [11]. Substance abuse, both drug and alcohol abuse, were classified as "current" or "not current" according to ASSIST Substance Abuse Scores and AUDIT-C Alcohol Scores, respectively [12].

Statistical Analyses

Descriptive evaluation was performed by grouping patients as "Discontinued" or "Continued" depending upon the regimen discontinuation status. Continuous variables were reported as means (with standard deviations [SDs]) when the distribution was "normal" and as medians (with quartiles, Q1 = first quartile, Q3 = third quartile) for "non-normal/skewed" distribution. Categorical variables were reported as frequencies (with percentages) and compared between 2 groups using χ^2 test of 2-proportions.

Time to discontinuation of the initial regimen (durability) was evaluated using Kaplan-Meier survival curves. Median durability time was reported in months and compared across stratified variables using the log-rank test examining statistically significant differences. Those who discontinued for various reasons (including death and lost to follow-up [LTFU]) were considered to have experienced the "event" referenced above. Data were censored at the end of follow-up period (December 2014) if the patients continued to be on the initial regimen. Because we selected December 2014 as the end of follow-up period, a patient initiating ARV in December 2012 had a potential 2 years of durability prior to censoring. For patients who were LTFU for greater than or equal to 6 months, their regimen was considered discontinued 6 months from their last HIV provider visit, because this is the typical number of prescribed refills at a visit.

Association of various factors with durability of the initial regimen was evaluated by univariate and multivariable Cox proportional hazard (PH) analyses and reported with crude and adjusted hazard ratios (aHRs), respectively, and 95% confidence intervals (CIs). Proportional hazard assumption was tested by entering interaction (product) terms of factors and natural logarithm of durability (months) in the models; no evidence of deviation from this assumption was found. Clinically important factors were included in the multivariable model. Along with drug class, we included sociodemographic variables such as age, sex, race, transmission risk factor (men who have sex with men

[MSM], intravenous drug use, heterosexuality), insurance (private, public, uninsured), laboratory values (CD4 count and VL), mental health factors (depression, substance use, alcohol use), and regimen factors (year of initiation, pill burden).

As mentioned earlier, those who were LTFU were included in the discontinuation group as events along with those who discontinued for reasons such as side-effects, drug interactions, and other. However, because LTFU could be considered different than other discontinuation reasons, a sensitivity analysis considering LTFU as a competing risk was performed. For the competing risk analysis, 2 separate event-specific Cox PHs models were fit: one with only LTFU as the event and the other with only the other discontinuation reasons as the event (LTFU treated as censored with those who continued the regimen). A likelihood-ratio-based χ^2 statistic was calculated to test for an overall difference in the resulting HRs between the 2 models and the overall model [13].

Statistical significance was set at 0.05 (2-tailed). All analyses were performed using SAS statistical software, version 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of 561 patients met the inclusion criteria. We excluded 15 patients whose race was other/unknown. The remaining 546 patients were included in the final analysis, of which 348 (64%) discontinued the initial ARV regimen. The mean age of the study sample was 36 years (SD = 11 years), 83% were male, and 61% were African American (Table 1). Major transmission risk factors were MSM (59%) and heterosexual sex (35%), and 47% were uninsured. The median pre-ARV CD4 count (cells/μL) was 286 (Q1 = 111, Q3 = 466), and 35% had an initial CD4 count <200 cells/μL. Median pre-ARV VL was 4.8 log copies/mL. Twenty-three percent of patients reported depression and 19% reported anxiety. Active substance and alcohol abuse was reported in 12% and 16% of the participants, respectively.

Treatment Share

Regimens most commonly prescribed included emtricitabine and tenofovir combined with efavirenz (51% of treatment share) followed by raltegravir (14%) (Table 2). Overall, 52% received an STR, and 81% received a once-daily regimen. Prescribing practices changed over time (2007–2009 vs 2010–2012): emtricitabine/tenofovir/efavirenz use as initial therapy declined from 70.1% to 36.8% ($P < .001$); emtricitabine/tenofovir/ritonavir/atazanavir use declined modestly, from 9.7% to 8.2%. The other emtricitabine/tenofovir-containing regimens increased in usage (2007–2009 vs 2010–2012): rilpivirine 0%–9.4% ($P < .001$), raltegravir 7.5%–18.2% ($P < .001$), and ritonavir-boosted darunavir 3.1%–17.0% ($P < .001$) (Figure 1).

Regimen Durability

The median durability of all regimens was 39.5 months (95% CI, 34.1–44.4). Initial regimen longevity in order of increasing

Table 1. Characteristics of the Treatment-Naive HIV-Infected Patients Initiating Therapy Between January 2007 and December 2012 at the UAB HIV Clinic[a]

Characteristic	Total (N = 546) n (%)	Discontinued[b] (N = 348) n (%)	Continued[b] (N = 198) n (%)
Age (years)			
<30	197 (36)	127 (36)	70 (35)
30–45	227 (42)	151 (43)	76 (38)
>45	122 (22)	70 (20)	52 (26)
Sex			
Female	95 (17)	65 (18)	30 (15)
Male	451(83)	283 (81)	168 (85)
Race			
Black/AA	334 (61)	215 (62)	119 (60)
White	212 (39)	133 (38)	79 (40)
HIV transmission risk			
MSM	320 (59)	208 (60)	112 (57)
Heterosexual	189 (35)	116 (33)	73 (37)
IVDU	35 (6)	23 (7)	12 (6)
Insurance			
Private	227 (43)	122 (36)	105 (54)
Public	56 (10)	46 (14)	10 (5)
Uninsured	250 (47)	169 (50)	81 (41)
Education			
≤12th Grade	172 (32)	111 (32)	61 (31)
>12th Grade	269 (49)	160 (46)	109 (55)
Unknown	105 (19)	77 (22)	28 (14)
History of prison			
No	300 (55)	190 (55)	110 (56)
Yes	35 (6)	22 (6)	13 (7)
Unknown	211 (39)	136 (39)	75 (38)
CD4 cell count (cells/μL)			
<200	191 (35)	134 (39)	57 (29)
≥200	276 (51)	163 (47)	113 (57)
Missing	79 (14)	51 (15)	28 (14)
Log viral load (copies/mL)			
<log 4	71 (13)	49 (14)	22 (11)
≥log 4	401 (73)	249 (72)	152 (77)
Missing	74 (14)	50 (14)	24 (12)
Hepatitis C coinfection			
Yes	39 (7)	28 (8)	11 (6)
No	507 (93)	320 (92)	187 (94)
Depression			
Yes	125 (23)	84 (24)	41 (21)
No	248 (45)	141 (41)	107 (54)
Missing	173 (32)	123 (35)	50 (25)
Anxiety			
Yes	103 (19)	68 (20)	35 (18)
No	279 (51)	166 (48)	113 (57)
Missing	164 (30)	114 (33)	50 (25)
Current substance use			
Yes	65 (12)	45 (13)	20 (10)
No	328 (60)	199 (57)	129 (65)
Missing	153 (28)	104 (30)	49 (25)
Current alcohol abuse			
Yes	87 (16)	51 (15)	36 (18)
No	300 (55)	187 (54)	113 (57)
Missing	159 (29)	110 (32)	44 (25)

Abbreviations: AA, African American; HIV, human immunodeficiency virus; IVDU, intravenous drug use; MSM, men who have sex with men; SD, standard deviation; UAB, University of Alabama at Birmingham.

[a] Missing data: HIV transmission risk = 2 (discontinued = 1; continued = 1); insurance = 13 (discontinued = 11; continued = 2).

[b] Initial regimen.

Table 2. Initial Antiretroviral Regimens of HIV-Infected Patients Starting Therapy Between January 2007 and December 2012 at the UAB HIV Clinic

Initial Regimen Characteristics	Total (N = 546) n (%)	Discontinued[a] (N = 348) n (%)	Continued[a] (N = 198) n (%)
Regimen composition			
Efavirenz/Emtricitabine/Tenofovir	277 (51)	186 (60)	91 (50)
Emitricitabine/Raltegravir/Tenofovir	75 (14)	40 (13)	35 (19)
Darunavir/Emtricitabine/Ritonavir/Tenofovir	61 (11)	30 (10)	31 (17)
Atazanavir/Emtricitabine/Ritonavir/Tenofovir	48 (9)	37 (12)	11 (6)
Emtricitabine/Rilpivirine/Tenofovir	30 (5)	15 (5)	15 (8)
Class			
ISTI-based	95 (17)	52 (15)	43 (22)
NNRTI-based	322 (59)	213 (61)	109 (55)
PI-based	129 (24)	83 (24)	46 (23)
Era of initiation			
2007–2009	228 (42)	161 (46)	67 (34)
2010–2012	318 (58)	187 (54)	131 (66)
Pill burden			
One	286 (52)	180 (52)	106 (54)
Two	29 (5)	22 (6)	7 (4)
≥Three	231 (42)	146 (42)	85 (43)
Dosing frequency			
Daily	441 (81)	282 (81)	159 (80)
Twice daily	105 (19)	66 (19)	39 (20)

Abbreviations: HIV, human immunodeficiency virus; ISTI, integrase strand transfer inhibitors; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; UAB, University of Alabama at Birmingham.

[a] Initial regimen.

median durability was as follows: emtricitabine/tenofovir in combination with ritonavir and atazanavir (31.9 months), with rilpivirine (36.3 months), with efavirenz (40.1 months), with raltegravir (47.8 months), and with ritonavir and darunavir (47.8 months). The NNRTI- and PI-based regimens had similar median durability (39 and 38 months, respectively), and ISTI-based regimens were more durable (47.8 months).

Once- and twice-daily regimens had a median durability of 41 and 33.8 months, respectively ($P = .74$). The median durability of 1, 2, and greater than or equal to 3 pills was 41.8, 33.7, and

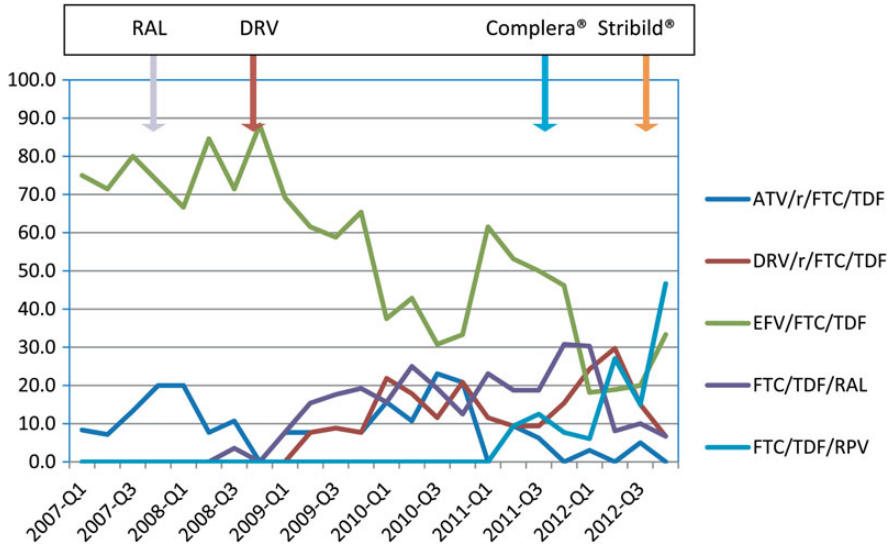

Figure 1. Proportion of treatment-naive human immunodeficiency virus (HIV)-infected patients starting antiretroviral (ARV) regimen by quarter and US Food and Drug Administration approval date at the University of Alabama at Birmingham HIV clinic between January 2007 and December 2012. *Other regimens not shown (N = 55). Abbreviations: ATV, atazanavir; DRV, darunavir; EFV, efavirenz; FTC, emtricitabine; r, ritonavir; RAL, raltegravir; rPV, rilpivirine; TDF, tenofovir.

38.1 months, respectively ($P = .60$). Those prescribed any FDC had a median durability of 41 months, whereas those not on a FDC had a much shorter durability of 16.5 months (Figure 2A). It is of interest to note that regimens started from 2010 to 2012 were less durable (33.6 months, $P = .007$) than those started earlier (47.2 months) (Figure 2B).

Regimen Discontinuation

The most common indications for discontinuation were side effects (n = 115, 33%), LTFU (124, 36%), and regimen failure (53, 15%); few regimens (11, 3%) were discontinued without a documented indication. Side effects and drug failure declined over the study period from 27.6% to 16.4% ($P = .001$) and 11.4% to 8.5%

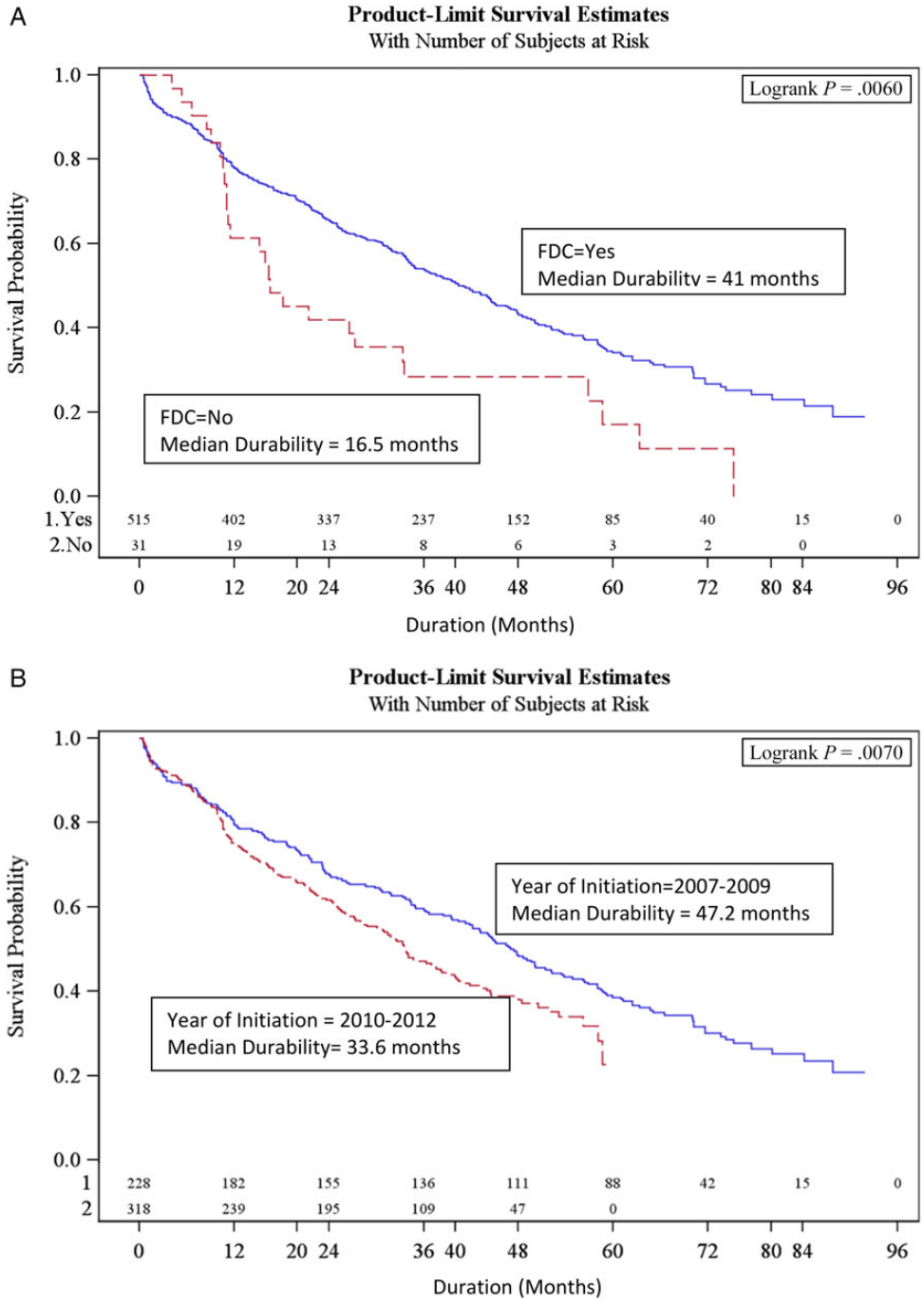

Figure 2. (A) Duration of initial antiretroviral (ARV) regimen with and without fixed-dose combination (FDC) pill in treatment-naive HIV-infected study patients starting therapy between January 2007 and December 2012 at the University of Alabama at Birmingham (UAB) HIV clinic. (B) Duration of initial ARV regimen by year of initiation at the UAB HIV clinic between January 2007 and December 2012.

($P = .26$), respectively, but LTFU was unchanged (23.3%–22.3%, $P = .80$). Analysis of HIV RNA VL preceding regimen discontinuation demonstrated that 67% of patients had a VL <200 copies/mL. The percentage of patients with <200 copies/μL at the time of regimen discontinuation is as follows: emtricitabine and tenofovir with efavirenz 62.8%; with ritonavir and atazanavir 62.9%; with rilpivirine 73.3%; with ritonavir-boosted darunavir 79.3%; with raltegravir 84.6%; all other regimens 65%.

When graphing the frequency of regimen discontinuations over time concurrent with US Food and Drug Administration (FDA) approval dates of raltegravir, darunavir, Complera, and Stribild, discontinuations of emtricitabine/tenofovir/efavirenz are most common and increased in frequency following the approval dates of new ARV drugs (Figure 3). Most discontinuing emtricitabine/tenofovir/efavirenz did so in the third quarters of 2009 and 2010, the 4th quarter of 2011, and the 2nd quarter of 2013 and were switched to a regimen containing raltegravir (n = 13), atazanavir (8), darunavir (5), or Complera (4). A small number of patients were switched to Stribild (3).

Predictors of Regimen Durability (Time to Discontinuation)

Table 3 presents univariate and multivariable Cox PH models of factors associated with initial ARV regimen durability. In the multivariable model, female sex (aHR = 1.47; 95% CI, 1.02–2.13), heterosexuality as transmission risk factor (aHR = 0.67; 95% CI, .49–.93), public insurance (aHR = 1.86; 95% CI, 1.29–2.68), or being uninsured (aHR = 1.38; 95% CI, 1.07–1.77) were significantly associated with discontinuation. Compared with

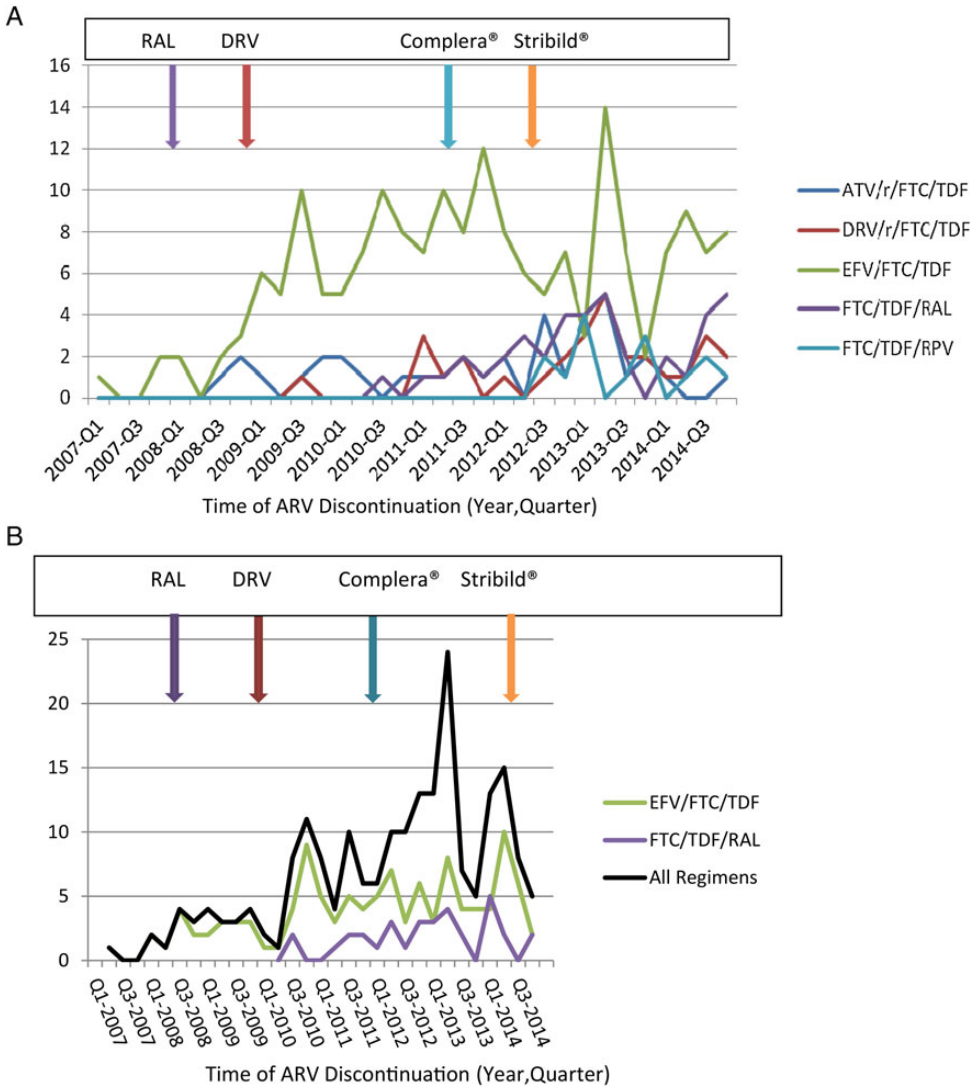

Figure 3. (A) Number of antiretroviral (ARV) regimen discontinuations by quarter and US Food and Drug Administration (FDA) approval at the University of Alabama at Birmingham (UAB) human immunodeficiency virus (HIV) clinic between January 2007 and December 2012. *Other regimens not shown (N = 55). (B) Number of ARV regimen discontinuations in patients with viral load ≤200 copies/mL by quarter and FDA approval at the UAB HIV clinic between January 2007 and December 2012. Abbreviations: ATV, atazanavir; DRV, darunavir; EFV, efavirenz; FTC, emtricitabine; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir.

Table 3. Association of Various Characteristics With the Initial Antiretroviral Regimen Discontinuation in the Treatment-Naive HIV-Infected Study Patients Starting Therapy Between January 2007 and December 2012 at the UAB HIV Clinic[a]

Characteristic	Univariate Analysis[b]		Multivariable Analysis[b,c]	
	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Sex				
Male[d]	1.00	—	1.00	—
Female	1.18 (.90–1.55)	.22	**1.47 (1.02–2.13)**	**.04**
Transmission risk				
MSM[d]	1.00	—	1.00	
Heterosexual	0.89 (.71–1.12)	.33	**0.67 (.49–0.93)**	**.02**
IVDU	1.06 (.69–1.63)	.79	0.73 (.45–1.19)	.21
Insurance				
Private[d]	1.00	—	1.00	—
Public	**1.92 (1.37–2.70)**	**<.001**	**1.86 (1.29–2.68)**	**.001**
Uninsured	**1.42 (1.12–1.79)**	**.003**	**1.38 (1.07–1.77)**	**.01**
CD4 cell count				
<200[d]	1.00	—	1.00	—
≥200	0.84 (.66–1.05)	.12	0.79 (.61–1.02)	.07
Missing	0.99 (.72–1.37)	.96	0.68 (.29–1.60)	.38
Depression		—		
No[d]	1.00		1.00	—
Yes	**1.35 (1.03–1.77)**	**.03**	1.28 (.96–1.70)	.09
Missing	**1.29 (1.01–1.64)**	**.04**	**1.64 (1.00–2.68)**	**.05**
Current substance use				
No[d]	1.00	—	1.00	—
Yes	1.25 (.91–1.73)	.17	1.40 (.98–2.02)	.07
Missing	1.16 (.92–1.48)	.21	1.23 (.66–2.28)	.51
Class				
NNRTI[d]	1.00	—	1.00	—
ISTI	0.85 (.63–1.16)	.30	**0.35 (.20–.63)**	**.001**
PI	1.09 (.84–1.41)	.50	**0.45 (.25–.80)**	**.006**
Year of initiation				
2007–2009[d]	1.00	—	1.00	—
2010–2012	**1.37 (1.09–1.72)**	**.01**	**1.64 (1.26–2.14)**	**<.001**
Pill burden				
One[d]	1.00	—	1.00	—
Two	1.20 (.77–1.86)	.43	1.16 (.70–1.94)	.56
≥Three	1.09 (.88–1.36)	.43	**2.25 (1.32–3.82)**	**.003**

Abbreviations: CI, confidence interval; HR, hazard ratio; ISTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, nonnucleotide reverse-transcriptase inhibitor; PI, protease inhibitor; UAB, University of Alabama at Birmingham.

[a] Missing data: HIV transmission risk = 2 (discontinued = 1; continued = 1); insurance = 13 (discontinued = 11; continued = 2). Bold items statistically significant at 0.05 level.

[b] Cox proportional hazards analysis.

[c] Multivariable model (N = 531) also adjusted for age, race, viral load, and alcohol use (all $P > .20$).

[d] Reference category.

NNRTI, being prescribed ISTI (aHR = 0.35; 95% CI, .20–.63) or PI (aHR = 0.45; 95% CI, .25–.80) was associated with lower likelihood of discontinuation. Regimens initiated in the 2010–2012 era were more likely to be discontinued than those initiated from 2007 to 2009 (aHR = 1.64; 95% CI, 1.26–2.14).

For the competing risk analysis (results not shown), when event-specific hazard models were compared with the overall model (described above), no statistically significant difference was observed; the likelihood ratio χ^2 was 20.00 with *P* value of .36 at 23 degrees of freedom.

DISCUSSION

In previous studies, virologic failure and drug toxicity accounted for a large proportion of initial ARV discontinuations in treatment-naive PLWH [14–16]. In patients initiating therapy between 1997 and 2001, O'Brien et al [15] found that only 21% of patients who discontinued their initial regimen had an undetectable VL. In our study, 67% had a VL <200 copies/mL at the time of initial regimen discontinuation. This finding, along with the recent abbreviated regimen durability (2010–2012 vs 2007–2009), suggests that contemporary regimens are being usurped in favor of alternative regimens, due to real or perceived improvements in simplicity or tolerability. This contrasts with historical reasons for regimen failure including virologic failure and intolerance. Of those discontinuing the efavirenz-based regimen, most (62.8%) had a VL <200 copies/mL at the time of discontinuation and were switched to a newer regimen including darunavir, raltegravir, Complera or Stribild. Such discontinuations of the Efavirenz-based regimen, which made up 86% of NNRTI regimens, and subsequent prescribing patterns are reflected in the abbreviated durability and increased hazard of discontinuation of NNRTIs (relative to ISTI and PI) observed in recent years.

The shifting diversity of regimens prescribed in our study reflects the approval and uptake of newly approved ARV regimens. Efavirenz-based regimen prescriptions made up only 51% of the treatment share, a significant decrease compared with the 85% observed by McKinnell et al [17] in 2007. The remaining 49% of prescriptions were divided approximately equally between 4 regimens and "other" regimens. The increased variability reflects the introduction of new ARVs: raltegravir, darunavir, and new STRs (Complera, Stribild). The number of efavirenz-based prescriptions declined after the FDA approval of these ARV regimens (Figure 2). As a result, treatment share differed dramatically according to year of initiation with a sharp drop in efavirenz-based regimens in the most recent study years; this decline preceded treatment guideline changes that no longer recommend efavirenz in first-line therapy [18]. The increasing percentage of treatment-naive patients started on rilpivirine (0%–10%), raltegravir (8%–20%), and darunavir (3%–19%) based regimens over the study period suggests they became preferable to patients and providers for initial HIV treatment.

Durability decreased for those starting therapy between 2010 and 2012 (33.6 months) relative to 2007–2009 (47.2 months). Reduced durability cannot be blamed on less efficacious regimens: 67% of patients were virally suppressed at the time of regimen discontinuation. Rather, this decline in ARV durability followed the FDA approval of novel ARV options allowing patients and providers to discontinue older regimens and initiate newer ones. After the approval of new drugs, including Complera, darunavir,

and raltegravir, the number of discontinuations of the efavirenz-based regimen increased (Figure 3). A subanalysis of those discontinuing this regimen revealed that a majority were switched to the aforementioned novel regimens. The abbreviated ARV durability seen in the more recent era (2010–2012) results largely from the introduction of newer treatment options, rather than a lack of efficacy of the initial regimen. Thus, "durability" is not an intrinsic characteristic of an ARV drug or regimen but a marker of an evolving treatment landscape with other available options.

Moreover, in contrast to prior cohort studies, NNRTI-based regimens were most likely to be discontinued, which is likely a reflection of the changing reasons for regimen discontinuation [4, 5]. Our study reveals a demonstrable reduction in prescriptions of NNRTI-based regimens and a rise in ISTI- and PI-based regimens for naive patients. If a preference for newer regimens influenced prescriptions for treatment-experienced patients as well, then NNRTI-based regimens would have been discontinued, perhaps prematurely, in favor of newer alternatives. This theory is supported by subanalysis of efavirenz discontinuations. Of interest, most ISTI prescribed were twice-daily raltegravir (N = 87) rather than daily dolutegravir (N = 4), and both PI-based regimens included ≥3 pills/24 hours. Despite increased complexity, these regimens had lower hazards for discontinuations than NNRTI-based FDC, Complera and Atripla. Since our study's conclusion, Triumeq (FDC containing dolutegravir) and FDC of darunavir and atazanavir with cobicistat have been approved by the FDA [19]. The durability of these new regimens in real-world settings remains to be seen as does the influence of their adoption on the durability of other regimens.

It is plausible that changes in drug availability and prescribing practices have influenced ARV durability reported previously. For example, the FDA approval of Atripla (2006) and Complera (2011), both NNRTI-based regimens, may have affected the abbreviated durability of alternative regimens in prior studies [4, 5]. Atripla was rapidly adopted for treatment-naive patients after FDA approval [17]. In addition to dominating the treatment share for treatment-naive patients, it was likely prescribed for treatment-experienced patients for regimen simplicity. If providers discontinued older, multitablet NRTI- and PI-based regimens in favor of newer FDC, this would have contributed to the shorter durability of these regimens relative to NNRTIs in prior studies [4, 5]. Did reports of superior durability of NNRTI-based regimens reflect uptake of Atripla and Complera in treatment-experienced patients just as the availability of novel PI- and ISTI-based regimens reduced NNRTI durability in the current study?

Limitations include the modest patient sample size at a single site, academically affiliated HIV clinic in the Southeastern United States. A majority of patients were either privately insured or eligible for Alabama's AIDS Drug Assistance Program, which provides funding and access to new regimens. Therefore, results may be less generalizable to populations with different demographics and limited ARV availability. The study duration (2007–2014) and use of more recently approved regimens in a real-world setting make it unique and significant.

As the HIV treatment landscape has evolved, prescribing patterns have changed and regimen durability has declined. In addition, more patients are virally suppressed at the time of their regimen discontinuation. The recent decline in durability is the result of new regimen availability and uptake, rather than a marker of therapy failure or an intrinsic trait of a drug or regimen. Treatment landscape influences regimen longevity yet is harder to quantify than regimen-specific factors such as tolerability and failure. Durability, when defined as time from regimen initiation to discontinuation, does not capture the complexity of the concept and should be used with caution as a metric of success in contemporary outcome studies. An ideal comparative effectiveness study would incorporate extrinsic factors and subsequent ARV selection to understand which regimens are discontinued due to provider preference or regimen simplification alone.

CONCLUSIONS

In conclusion, the dynamic field of HIV treatment has had a considerable impact on the selection and durability of initial ARV regimens. Additional research is needed to understand the long-term clinical implications associated with these shifts. Studies of other chronic conditions, such as Crohn's disease, chronic pain, and insomnia, have used durability to compare treatment options. Relying on durability without considering the complex treatment landscape leads to an oversimplified and flawed comparative effectiveness assessment, which has broad implications for understanding chronic disease management.

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