Increased Persistence of Initial Treatment for HIV Infection With Modern Antiretroviral Therapy

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Background: Initiating antiretroviral therapy (ART) early improves clinical outcomes and prevents transmission. Guidelines for first-line therapy have changed with the availability of newer ART agents. In this study, we compared persistence and virologic responses with initial ART according to the class of anchor agent used.

Setting: An observational clinical cohort study in the Southeastern United States.

Methods: All HIV-infected patients participating in the UNC Center for AIDS Research Clinical Cohort (UCHCC) and initiating ART between 1996 and 2014 were included. Separate time-to-event analyses with regimen discontinuation and virologic failure as outcomes were used, including Kaplan–Meier survival curves and adjusted Cox proportional hazards models.

Results: One thousand six hundred twenty-four patients were included (median age of 37 years at baseline, 28% women, 60% African American, and 28% white). Eleven percent initiated integrase strand transfer inhibitor (INSTI), 33% non–nucleoside reverse transcriptase inhibitor (NNRTI), 20% boosted protease inhibitor, 27% other, and 9% NRTI only regimens. Compared with NNRTI-containing regimens, INSTI-containing regimens had an adjusted hazard ratio of 0.49 (95% confidence interval, 0.35 to 0.69) for discontinuation and 0.70 (95% confidence interval, 0.46 to 1.06) for virologic failure. All other regimen types were associated with increased rates of discontinuation and failure compared with NNRTI.

Conclusions: Initiating ART with an INSTI-containing regimen was associated with lower rates of regimen discontinuation and virologic failure.

Key Words: HIV, antiretroviral therapy, integrase inhibitors, prospective studies, United States

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INTRODUCTION

Initiating antiretroviral therapy (ART) early in HIV infection improves clinical outcomes and prevents transmission.[1,2] US treatment guidelines have changed with the availability of newer ART agents and currently recommend starting ART with a combination of 2 NRTIs, and an integrase strand transfer inhibitor (INSTI), or a boosted protease inhibitor (bPI).[3] The effectiveness of INSTI-containing regimens compared with previously available regimens has not been well characterized. In this study, we compared response to initial ART in the clinical setting including continuation of the initial regimen, known as persistence or durability, and virologic response.

METHODS

All patients initiating ART in the University of North Carolina (UNC) Center for AIDS Research HIV Clinical Cohort, 1996–2014, were included. This prospective cohort of all primary HIV care patients at the UNC Hospitals is representative of HIV-infected patients in care in North Carolina.[4] Patients were followed from the first ART initiation (baseline) until the first of outcome, loss to follow-up, death, or November 2015. The 2 primary outcomes evaluated were ART discontinuation, defined as change in anchor agent class or stopping ART for longer than 2 weeks, and virologic failure, defined as the first HIV RNA level ≥400 copies/mL after 24 weeks of therapy in an intention-to-treat approach, where patients lost to follow-up with HIV RNA <400 copies/mL were censored and changes in therapy were ignored. ART regimen categories were based

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TABLE 1. Baseline Patient Characteristics and Time to Discontinuation and Virologic Failure by Initial ART

		Initial ART Regimen					
	Total (n = 1624)	**INSTI (n = 173)**	**NNRTI (n = 536)**	**bPI (n = 331)**	**Other (n = 434)**	**NRTI (n = 150)**	***P****
Baseline characteristics							
Age y, median (IQR)	37 (29 to 46)	38 (26 to 48)	37 (29 to 46)	37 (29 to 47)	37 (29 to 45)	37 (31 to 45)	0.90
Women, No (%)	460 (28%)	30 (17%)	124 (23%)	107 (32%)	146 (34%)	53 (35%)	<0.001
Race†, No (%)							0.003
African American	979 (60%)	109 (63%)	328 (61%)	174 (53%)	268 (62%)	100 (67%)	
White	453 (28%)	52 (30%)	129 (24%)	112 (34%)	122 (28%)	38 (25%)	
Other	192 (12%)	12 (7%)	79 (15%)	45 (14%)	44 (10%)	12 (8%)	
CD4 cell count cells/mm^3, median (IQR)	277 (104 to 463)	403 (246 to 579)	279 (116 to 468)	230 (78 to 401)	237 (69 to 442)	341 (127 to 475)	<0.001
HIV RNA level $\log_{10}$ copies/mL, median (IQR)	4.8 (4.2 to 5.3)	4.4 (3.9 to 5.0)	4.8 (4.2 to 5.4)	4.9 (4.3 to 5.5)	4.9 (4.2 to 5.4)	4.6 (3.9 to 5.1)	<0.001
Calendar yr, median (IQR)	2005 (2000 to 2010)	2013 (2012 to 2014)	2007 (2002 to 2010)	2007 (2005 to 2010)	1999 (1998 to 2003)	1998 (1997 to 2001)	<0.001
Follow-up yrs, median (IQR)‡	5.5 (2.7 to 9.7)	2.3 (1.5 to 3.1)	5.5 (3.2 to 8.8)	5.5 (3.0 to 8.7)	6.6 (3.2 to 14.2)	9.7 (2.7 to 14.7)	<0.001
Lost to follow-up, No (%)	594 (37%)	29 (17%)	204 (38%)	121 (37%)	169 (39%)	71 (47%)	<0.001
Time to discontinuation§							
Unadjusted HR single model (95% CI)‖		0.48 (0.35 to 0.67)	1 (reference)	1.23 (1.04 to 1.46)	1.59 (1.37 to 1.85)	3.02 (2.48 to 3.68)	NA
Adjusted HR single model (95% CI)‖		0.49 (0.35 to 0.69)	1 (reference)	1.24 (1.05 to 1.47)	1.47 (1.24 to 1.75)	3.01 (2.40 to 3.78)	NA
Unadjusted HR separate models (95% CI)‖		0.56 (0.40 to 0.80)	1 (reference)	1.28 (1.08 to 1.52)	1.58 (1.35 to 1.85)	2.61 (1.98 to 3.43)	NA
Adjusted HR separate models (95% CI)‖		0.52 (0.34 to 0.80)	1 (reference)	1.28 (1.07 to 1.53)	1.39 (1.16 to 1.67)	2.76 (2.00 to 3.82)	NA
Time to virologic failure							
Unadjusted HR single model (95% CI)‖		0.46 (0.31 to 0.67)	1 (reference)	1.13 (0.92 to 1.38)	1.91 (1.61 to 2.27)	3.06 (2.46 to 3.81)	NA
Adjusted HR single model (95% CI)‖		0.70 (0.46 to 1.06)	1 (reference)	1.23 (1.00 to 1.51)	1.23 (1.02 to 1.50)	1.83 (1.44 to 2.34)	NA
Unadjusted HR separate models (95% CI)‖		0.74 (0.48 to 1.13)	1 (reference)	1.20 (0.97 to 1.47)	1.86 (1.55 to 2.23)	1.49 (1.10 to 2.01)	NA
Adjusted HR separate models (95% CI)‖		0.59 (0.34 to 1.03)	1 (reference)	1.25 (1.01 to 1.55)	1.28 (1.04 to 1.57)	1.39 (1.00 to 1.94)	NA

*P values from χ^2 and Kruskal–Wallis tests.

†Race for this study was based on medical record reviews and categorized by the investigators. We assessed race in this study given previous evidence of an association with HIV clinical outcomes.

‡Follow-up years defined as time from ART initiation until the first of death, loss to follow-up (last clinic visit plus 12 months), or administrative censoring (November 2015).

§Reasons for discontinuation included virologic failure and stopping ART for more than 2 weeks (23% and 37%, respectively) overall and for INSTI (5% and 54%), NNRTI (18% and 42%), bPI (20% and 35%), other (29% and 35%), and NRTI (29% and 26%).

‖Estimates from Cox proportional hazards models. Single model estimates based on 1 model including all patients initiating INSTI (raltegravir 53, dolutegravir 12, and elvitegravir 108); NNRTI (efavirenz 499 and rilpivirine 37); bPI (lopinavir 160, atazanavir 98, and darunavir 73); other (434); and NRTI (150). Separate model estimates based on fitting 4 separate models for patients initiating (1) INSTI and NNRTI between 2007 and 2014 (raltegravir 53, dolutegravir 12, elvitegravir 108, efavirenz 240, and rilpivirine 37); (2) bPI and NNRTI between 2000 and 2014 (lopinavir 154, atazanavir 98, darunavir 73, efavirenz 467, and rilpivirine 37); (3) other and NNRTI between 1998 and 2014 (other 359, efavirenz 499, and rilpivirine 37); and (4) NRTI and NNRTI between 1998 and 2005 (NRTI 83 and efavirenz 221). Adjusted models included age, sex, race, CD4 cell count, HIV RNA level, and calendar year, all measured at ART initiation.

IQR, interquartile range; NA, not applicable.

on anchor agent: INSTI (any INSTI), bPI (ritonavir-boosted atazanavir, darunavir, or lopinavir), non–nucleoside reverse transcriptase inhibitor (NNRTI, efavirenz, or rilpivirine), other (including unboosted and other bPI), and NRTI (regimens including only NRTIs). Patients provided written informed consent to participate in the clinical cohort, and the UNC Institutional Review Board approved both the cohort study and this secondary data analysis.

Separate time-to-event analyses were performed for each outcome of interest, including Kaplan–Meier survival curves and Cox proportional hazards models adjusted for baseline age, sex, race, CD4 cell count, HIV RNA level, and calendar year. We excluded patients missing baseline CD4 or HIV RNA measurements. In a sensitivity analysis, we included patients missing baseline measurements and used multiple imputations with Markov Chain Monte Carlo and 50

imputations based on age, sex, race, men who have sex with men status, injection drug use, year of ART initiation, and ART regimen. We included the calendar year using disjoint indicator variables for the periods 1996–2000, 2001–2005, 2006–2010, and 2011–2014. Because ART agent availability changed over time, we also fit separate models for INSTI, bPI, other, and NRTI, each in comparison with NNRTI, restricting to calendar years where both ART regimen types were available, including calendar years as a continuous variable. To account for shorter follow-up of INSTI-initiating patients, we also conducted sensitivity analyses, where we restricted follow-up time for all patients to 3 years after ART initiation. For all estimates, 95% confidence intervals (95% CIs) were calculated and P values were 2 sided; P values <0.05 were considered statistically significant. Analyses were performed in SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 1624 patients who initiated ART between 1996 and 2014 were 28% women, 60% African American, 28% white, and a median of 37 years old at baseline (Table 1). Eleven percent initiated INSTI, 33% NNRTI, 20% bPI, 27% other, and 9% NRTI only regimens. The most common NRTI backbone combinations were emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) among patients on INSTI (92%); FTC/TDF and zidovudine/lamivudine (3TC) among patients on NNRTI (59% and 22%, respectively); and TDF/FTC, zidovudine/3TC, and abacavir/3TC among patients on bPI (57%, 18%, and 9%, respectively). Patients initiating different ART regimens differed significantly on most baseline characteristics including sex, race, and year of starting ART. Notably, CD4 cell counts were statistically significantly different by ART regimen with a median of 403,

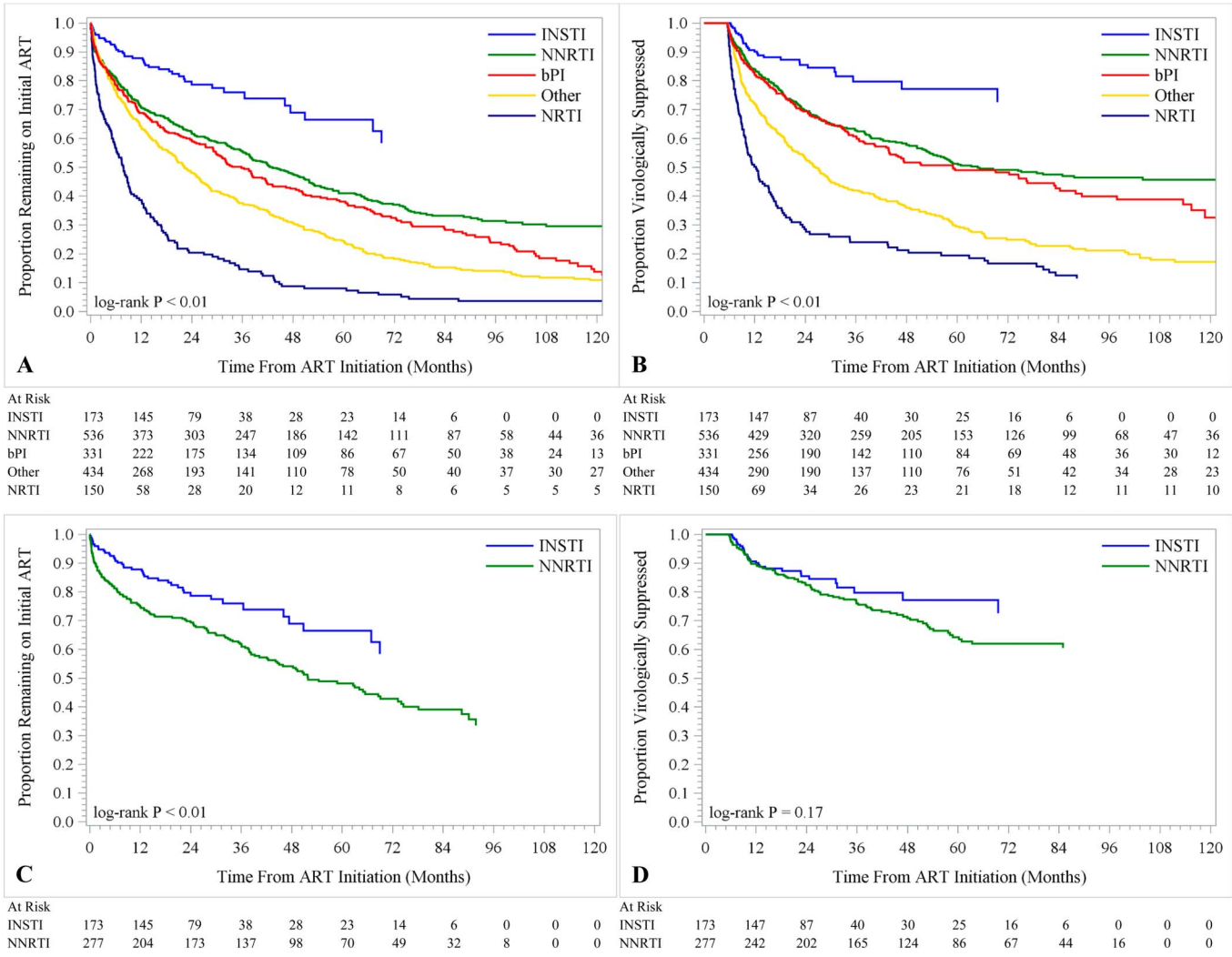

FIGURE 1. Primary endpoints. Shown are unadjusted Kaplan–Meier estimates of time to discontinuation of first ART (A), time to virologic failure of initial ART (B), and by ART regimen type. C and D show unadjusted Kaplan–Meier estimates of time to discontinuation and time to virologic failure, respectively, restricting to patients initiating INSTI and NNRTI regimens 2007 and later.

279, 230, 237, and 341 cells/mm^3 for patients starting INSTI, NNRTI, bPI, other, and NRTI regimens, respectively.

Median times to discontinuation and virologic failure for NNRTI patients were 3.5 and 5.1 years, respectively (Fig. 1A–B), compared with >7.4 years for INSTI patients for each of these events. Among 1111 patients who discontinued ART, 23% and 37% were because of virologic failure and ART interruption, respectively, and this varied with ART regimen. In unadjusted analyses, the estimated hazard ratio (HR) among those initiating an INSTI, as compared to an NNRTI, was 0.48 (95% CI: 0.35 to 0.67) for time to discontinuation and 0.46 (95% CI: 0.31 to 0.67) for time to virologic failure (Table 1). After adjustment, the estimated HR for patients initiating an INSTI versus an NNRTI was 0.49 (95% CI: 0.35 to 0.69) for time to discontinuation and 0.70 (95% CI: 0.46 to 1.06) for time to virologic failure. When comparing only patients initiating INSTI and NNRTI regimens between 2007 and 2014, INSTI regimens still fared better (Fig. 1C–D). In adjusted models restricted to years 2007–2014 and comparing only INSTI regimens to NNRTI, the HR was 0.52 (0.34 to 0.80) for time to discontinuation and 0.59 (0.34 to 1.03) for time to virologic failure. In this comparison, >90% of both INSTI and NNRTI regimens had TDF/FTC as the NRTI backbone. In a sensitivity analysis including patients missing CD4 and HIV RNA at baseline and using multiple imputation, in adjusted models restricted to 2007–2014 and comparing INSTI regimens (n = 180) with NNRTI (n = 295), the HR was 0.52 (95% CI: 0.34 to 0.79) for time to discontinuation and 0.57 (0.33 to 0.98) for time to virologic failure. Results were similar when follow-up was limited to 3 years after ART initiation, and when NRTI backbone was included as an adjustment variable (results not shown). Patients initiating bPI, other, or NRTI regimens fared worse in time-to-discontinuation and virologic failure analyses than patients initiating an NNRTI.

DISCUSSION

To our knowledge, this study demonstrates for the first time the dramatic increase in initial therapy virologic response and persistence with INSTI-containing regimens. Studies on initial ART duration before the availability of INSTI agents estimated median times on first therapy ranging from 1 to 2.9 years.[5–7] More recent reports have observed increases in durability with median times from 2.9 to 4.6 years, with patients initiated on NNRTIs remaining on their initial ART longer than those started on bPIs and other agents.[8,9] In this study, patients started on non-INSTI regimens had first ART durability comparable with these previous reports with similar associations observed between NNRTI and bPI regimens. Notably, we found that patients initiating INSTI-containing regimens remained on their initial regimen at least twice as long on average than patients initiating other types of ART. Our study is the first to examine specifically INSTI-containing regimens and to focus on changes of anchor class as regimen discontinuation. This definition likely reflects more relevant regimen modifications not related to simplification or to backbone agent changes.

The greater INSTI regimen persistence likely captures the contributions of favorable safety, efficacy, and tolerability profiles of INSTI regimens. Randomized clinical trials of INSTI agents have reported rare drug discontinuations because of adverse events, which were generally mild or moderate and lower than for NNRTI-based regimens and high virologic response rates and low failure rates that were comparable or better than NNRTI.[10–12] Our findings of INSTI effectiveness from routine clinical care therefore extend these previous results and suggest that more tolerable regimens with high efficacy result in increased initial ART persistence in a real-world setting and with longer observation.

Our findings are limited by smaller sample size and person-time available for INSTI initiators and possible residual confounding because of differences in baseline clinical covariates. In addition, specific reasons for discontinuation were not examined and may have varied across initial ART regimens. This study was also conducted at a single clinical site and, therefore, the generalizability of our results should be considered carefully. The demographic make-up of our clinical site is, however, very similar to the demographics of the HIV epidemic in Southeastern United States.[4] Expanding these analyses to national and international cohort collaborations and including future years of INSTI clinical care experience will be important to confirm these initial findings and inform clinical care practice.

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