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Integrase inhibitor-based regimens result in more rapid virologic suppression rates among treatment-naïve human immunodeficiency virus–infected patients compared to non-nucleoside and protease inhibitor–based regimens in a real-world clinical setting

A retrospective cohort study

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Abstract

The integrase strand transfer inhibitor (INSTI) class of antiretroviral therapy (ART) may result in faster time to virologic suppression compared with regimens that contain protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs). However, differences in time to achieve virologic suppression are not well-defined in routine clinical settings with contemporary antiretroviral agents.

Study was a retrospective single-center study of treatment-naïve human immunodeficiency virus (HIV) patients initiating ART between 2013 and 2016. Among patients on different ART regimen types, we compared rates of and median time to virologic suppression [viral load (VL) <50 copies/mL].

A total of 155 patients—45 (29%) female and 110 (71%) male—met study inclusion criteria. Median age was 42 years (interquartile range 31–52), and median baseline CD4 count was 288 cells/μL and VL was 60,000 copies/mL. Seventy-one (46%) initiated an INSTI-based regimen, 58 (37%) were on NNRTI-based regimens, and 26 (17%) on PI-based regimens. In total, 112 (72%) patients achieved virologic suppression at 12 months. Patients on INSTI-based regimens were more likely to achieve virologic suppression by 3, 6, and 12 months ($P < .01$), and had lower median time to suppression (60 vs 137 days on NNRTI-based regimens and 147 days on PI-based regimens, $P < .01$).

Patients on INSTI-based ART regimens in a real-world setting experienced higher rates of virologic suppression and shorter time from ART initiation to virologic suppression. For HIV patients on INSTI-based ART regimens, virologic failure should be suspected in those with VLs >50 copies/mL before the current recommendation of 48 weeks.

Abbreviations: AIDS = acquired immunodeficiency syndrome, ART = antiretroviral therapy, BMI = body mass index, DHHS = Department of Health and Human Services, HIV = human immunodeficiency virus, IDU = injection drug use, INSTI = integrase strand transfer inhibitor, IQR = interquartile range, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, VL = viral load, YNHH = Yale-New Haven Hospital.

Keywords: human immunodeficiency virus/acquired immunodeficiency syndrome, integrase inhibitor, nucleoside (tide) reverse transcriptase inhibitors, protease inhibitor, virologic failure

1. Introduction

In the United States and worldwide, more human immunodeficiency virus (HIV)-infected individuals are taking combination antiretroviral therapy (ART) than ever before.[1] This has led to improved outcomes for patients including extended life expectancy compared to historical observations.[2] There are now 7 classes of antiretroviral drugs available and approved by the United States Federal Drug Administration for the treatment of HIV-1 infection, providing multiple treatment options for individuals who are newly infected or diagnosed.[3]

The antiretroviral agents approved for treatment of HIV-1 infection differ widely in their mechanism of action, pharmacokinetic properties, drug interaction potentials, side effect profiles, and dosing frequency. All of these are important considerations for providers initiating therapy for treatment-naïve HIV-infected individuals. A principal goal of HIV therapy is to achieve rapid suppression of the HIV virus, which allows restoration of the immune system to protect against acquired immunodeficiency syndrome–associated opportunistic infections and also decreases

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the time of infectivity thereby preventing disease transmission from infected individuals.[4,5] Thus, one important measure of the efficacy of a chosen ART regimen is the time to full virologic suppression.

Virologic failure is defined in US Department of Health and Human Services (DHHS) guidelines as failure to achieve or maintain full virologic suppression (<200 copies/mL) at 48 weeks after initiation of ART.[6] Virologic failure may occur as a result of various factors including poor medication adherence, development of drug resistance, and unrecognized drug-drug interactions that can affect ART pharmacokinetics and efficacy. Intensive virologic monitoring after treatment initiation allows for identification of individuals who are at risk of virologic failure and provides opportunities to address its potential causes.

Contemporary ART regimens for the treatment of HIV that include the integrase strand transfer inhibitor (INSTI) class of ART have demonstrated high efficacy, tolerability, and in initial clinical trials, have resulted in faster time to virologic suppression compared to that historically documented for ART regimens based on protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes.[7,8] However, these differences are not well-defined in routine clinical settings.

Therefore, our study aimed to describe the time from treatment initiation to full virologic suppression among HIV-infected treatment-naïve individuals in a real world setting and compare regimens by base ART class.

2. Methods

2.1. Study aims

We performed a retrospective single-center chart review of antiretroviral-naïve patients with HIV who initiated ART at any Yale-New Haven Hospital (YNHH) System site from January 1, 2013 to December 31, 2016. The aim of the study was to compare rates of and time to virologic suppression among HIV-infected patients initiating INSTI-, PI-, and NNRTI-based ART regimens in a routine clinical setting.

2.2. Eligibility criteria

Included in the study were all patients with diagnosed HIV infection who were ART naïve and initiated on a typical ART regimen consisting of an NNRTI, PI, or INSTI in combination with 2 nucleoside/nucleotide reverse transcriptase inhibitors. Patients who did not have both baseline (at treatment initiation) and subsequent viral load (VL) values available (at least 1 VL measurement within 3, 6, and between 6 and 12 months of ART initiation), who had provider-documented nonadherence to their prescribed ART medication upon chart review, who were started on an atypical antiretroviral regimen (i.e., not meeting criteria for typical regimen described above, for example, a regimen containing both a PI and NNRTI together), and who switched regimens during the study period were excluded.

2.3. Patient selection and data collection

With the help of YNHH's Joint Data Analytics Team, HIV-infected patients who were newly prescribed any antiretroviral medication within the study period were identified in the electronic medical record system. A subsequent chart review was conducted to confirm eligibility criteria and collect data on patient demographics, comorbidities, HIV-related clinical factors including presence of opportunistic infection(s) (as defined by DHHS guidelines),[9] CD4+ T-lymphocyte count, and HIV RNA VL measurements up to 1 year after treatment initiation. Our laboratory uses COBAS Ampliprep/COBAS Taqman, version 2.0, Linear range: 20 to 10,000,000 copies/mL (Roche Diagnostics, Indianapolis, IN) for VL estimation and flow cytometry for CD4 counts.

2.4. Data analysis

HIV VLs at baseline and closest to 3-, 6-, 9-, and 12-month time points after ART initiation were recorded and entered into a database for the study analysis. Virologic suppression was defined as a VL <50 copies/mL on HIV-RNA quantitative assay, according to currently accepted clinical practice. Analysis was also performed on time to VL <200 copies/mL, which is the cutoff specified in current DHHS guidelines.[9] Time to virologic suppression was calculated as period (in days) from initiation of ART to achievement of virologic suppression.

We compared rates of achievement of virologic suppression among patients on INSTI-, NNRTI-, and PI-based regimens at 3-, 6-, and 12-month time points using Chi-square test. We also compared time to virologic suppression using independent samples median testing and Kaplan-Meier analysis. We assessed for variables that were associated with virologic suppression at 12 weeks using Cox regression analysis. Statistical significance was set at P value <.05. Statistics were performed using IBM SPSS software version 24.0.

2.5. Study approval

The study was approved by Yale University human investigations committee.

3. Results

3.1. Eligibility screen

Of 1388 screened for eligibility, 193 were found to be ART naïve and had at least 2 VL tests on record in the post-ART initiation period. Of these, 6 patients were initiated on a nontraditional ART regimen and 32 were documented to be nonadherent to therapy and were not included. Therefore, 155 patients were included in the analysis.

3.2. Demographics

In total, 155 patients—45 (29.0%) females and 110 (71%) males—met study inclusion criteria. The relative proportion of men in the INSTI group (83%) was higher than that of NNRTI (66%) and PI-based (50%) ART groups. Forty-three (28%) were white, 73 (47%) were black, 32 (21%) Hispanic, and 7 (5%) of other ethnicity/race. Median age at ART initiation was 42 years [interquartile range (IQR) 31–52] and median body mass index (BMI) was 26 (IQR 23–30) with no difference between the different ART groups (Table 1).

3.3. HIV status and comorbidities

Before ART initiation, median CD4 was 288 cells/μL and median VL was 60,100 copies/mL (4.8 log10 copies/mL). Thirteen (8%) patients had an opportunistic infection diagnosed at time of ART initiation. Seventy-one (46%) initiated an INSTI-based ART regimen (Table 1), of which 56 initiated a dolutegravir-based regimen, 12 initiated a raltegravir-based regimen, and 3 initiated

Table 1

Patient demographics, clinical characteristics, and time to viral suppression.

Patient characteristic	All n = 155	INSTI regimen n = 71	PI regimen n = 26	NNRTI Regimen n = 58	*P*
Median age	42 (31–52)	40 (30–52)	44 (32–50)	45 (31–52)	.22
Male sex	110 (71%)	59 (83%)	13 (50%)	38 (66%)	<.01
Race/ethnicity					
Hispanic	32 (21%)	17 (24%)	4 (15%)	11 (19%)	.48
White	43 (26%)	21 (30%)	5 (19%)	17 (29%)	
Black	73 (47%)	31 (44%)	14 (54%)	28 (48%)	
Other	7 (5%)	2 (3%)	3 (12%)	2 (3%)	
Married	20 (13%)	11 (16%)	2 (8%)	7 (12%)	.59
Median BMI	26 (23–30)	26 (23–30)	26 (20–31)	26 (23–29)	.72
Median pre-ART CD4 cells/μL	288 (89–462)	257 (75–462)	320 (99–485)	330 (140–500)	.52
Median pre-ART CD8 cells/μL	730 (464–1116)	686 (373–1101)	811 (464–1337)	739 (524–1098)	.75
Median pre-ART HIV RNA copies/mL	60,000 (25,000–205,000)	109,000 (35,000–208,000)	55,000 (18,000–424,000)	56,000 (19,000–166,000)	.03
OI present at time of ART initiation	13 (8%)	8 (11%)	3 (11%)	2 (3%)	.23
Treatment outcome					
HIV RNA <50 copies/mL within 3 mo	51 (33%)	36 (51%)	2 (8%)	13 (22%)	<.01
HIV RNA <200 copies/mL within 3 mo	102 (66%)	57 (80%)	10 (39%)	35 (60%)	<.01
HIV RNA <50 copies/mL within 6 mo	88 (57%)	47 (66%)	9 (35%)	32 (55%)	<.01
HIV RNA <200 copies/mL within 6 mo	127 (82%)	63 (89%)	15 (58%)	49 (85%)	<.01
HIV RNA <50 copies/mL within 12 mo	112 (72%)	54 (76%)	14 (54%)	44 (76%)	<.01
HIV RNA <200 copies/mL within 12 mo	139 (90%)	66 (93%)	18 (69%)	55 (95%)	<.01
Median days to HIV RNA <50 copies/mL	105 (50–164)	60 (40–120)	147 (121–239)	137 (80–186)	<.01
Median days to HIV RNA <200 copies/mL	57 (34–98)	43 (28–67)	84 (54–142)	69 (35–105)	<.01

Cell values represent median value (interquartile range) or number (%).Virologic suppression defined as achieving viral load <50 copies/mL. P values are presented for chi-square and nonparametric testing. ART = antiretroviral therapy, BMI = body mass index, HIV = human immunodeficiency virus, INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, OI = opportunistic infection, PI = protease inhibitor.

an elvitegravir-based regimen. Fifty-eight (37%) initiated an NNRTI-based regimen, of which 37 initiated an efavirenz-based regimen and 21 initiated a rilpivirine-based regimen. Twenty-six (17%) initiated a PI-based regimen, of which 15 initiated an atazanavir-based regimen, 5 initiated darunavir, and 6 initiated lopinavir/ritonavir. Patients on INSTI-based regimens had higher median pre-ART initiation VL (109,000 copies/mL) compared with the PI (55,000 copies/mL) and NNRTI (56,000 copies/mL) regimens ($P = .03$).

3.4. Virologic suppression rates

In total 112 (72%) achieved virologic suppression <50 copies/mL within 1 year of initiating ART; 139 (90%) achieved DHHS goal of <200 copies/mL. The median time to virologic suppression was 105 days (IQR 50–164). Patients on INSTI-based regimens were more likely to achieve virologic suppression at 3, 6, and 12 months, and had a lower median time to suppression of 60 days compared to 137 days on NNRTI regimens and 147 days on PI regimens ($P < .01$; Table 1). On Kaplan-Meier analysis, time-to-virologic suppression was significantly lower in INSTI-based regimens than PI- or NNRTI-based regimens ($P < .01$; Fig. 1). On multivariate analysis, although age at ART initiation, race/ethnicity, and BMI were not significantly associated with virologic suppression at 12 weeks, regimen type (INSTI vs PI vs NNRTI) was ($P < .001$). No incidences of immune reconstitution inflammatory syndrome occurred in this cohort.

4. Discussion

INSTI-based regimens are now the recommended and preferred first-line ART for the treatment of HIV-1 infection in ART-naïve patients due to their favorable side effect profile, limited drug-drug interactions, and virologic potency.[10] Accordingly, among our cohort, INSTI-based regimens were the most frequently initiated ART regimen class.

In this real world analysis, patients on INSTI-based ART regimens experienced higher rates of virologic suppression at 3, 6, and 12 months, and shorter median time from ART initiation to virologic suppression compared to patients on other ARV regimens. Furthermore, in our cohort, the observation that patients taking INSTI-based regimens had higher initial VLs, makes this finding even more significant. Our findings are consistent with previous studies that have similarly documented faster time to virologic suppression on INSTI-based ART regimens compared with NNRTI- and PI-based regimens.[10,11] Indeed, in clinical trials, majority of patients on INSTI-based ART achieve full virologic suppression at 12 to 16 weeks of therapy.[12–14] This occurrence may attributable to where INSTIs act in the viral life cycle and how they affects viral decay dynamics preintegration particularly among different T-cell populations.[15,16] Models show that INSTI-based regimens may decrease the slope of and lengthen the first phase (rapid phase) of virologic decay, potentially explaining the faster virologic suppression observed in our and other studies.[16–18]

For individuals who have achieved full virologic suppression, the first evidence of HIV treatment failure, preceding immunologic decline and the development of opportunistic infections, is virologic rebound. Therefore, routine VL monitoring may allow for earlier detection of treatment failure. Current DHHS guidelines define virologic failure as inability to achieve or maintain an HIV VL < 200 copies/mL, typically expected after 24 to 48 weeks on ART,[6] but our findings suggest that patients on INSTI-based ART regimens should be evaluated for treatment failure if they have not achieved virologic suppression as early as 12 weeks after ART initiation. This has important implications for clinical practice, particularly in situations in which patients would particularly benefit from shorter time to virologic

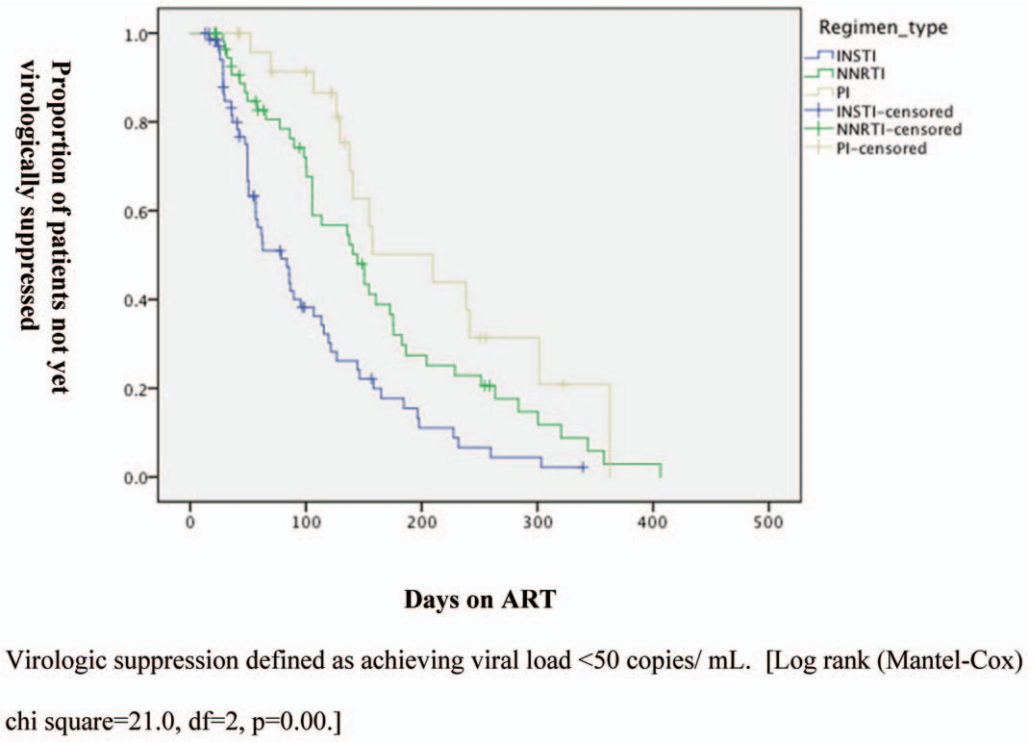

Figure 1. Kaplan Meier analysis of time from ART initiation to virologic suppression. The proportion of patients on antiretroviral therapy (ART) who had not yet achieved virologic suppression declined faster in the integrase inhibitor (INSTI) group compared with the protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) group.

suppression, for example, in pregnancy and among serodifferent couples where transmission is a concern.

In our study, patients on PI-based regimens were more likely to be women. This is most likely due to provider selection of a PI-based regimen for women of childbearing age, given the paucity of data on safety of INSTI use in pregnancy at the start of the study period and the concern for efavirenz-associated teratogenicity. In addition, it is plausible that patients suspected to be at higher risk of nonadherence were preferentially placed on PI-based regimens due to the higher barrier for resistance. In our cohort, women were more likely to have injection drug use (IDU) as their primary risk factor for acquiring HIV, and as IDU is a risk for nonadherence, this may explain both the preponderance of women and comparatively lower rates of virologic decline noted in the PI-based regimen group. However, we did exclude patients with documented poor adherence from the analysis to minimize its effect on study results. In addition, multivariate analysis did not find that sex was associated with virologic suppression at 12 weeks, although the study was not powered to detect differences stratified by sex.

Finally, we analyzed rates of viral suppression based on current DHHS guidelines using cutoff of HIV RNA <200 copies/mL as indicative of virologic suppression and the more contemporary definition of virologic suppression as <50 copies/mL as is currently accepted in clinical practice. Notably, there was a large difference in time to virologic suppression according to these 2 cutoffs. Guidelines should be updated to reflect current clinical practice and further studies should base outcome definitions on up-to-date practices.

Limitations of this study include small sample size, slight differences in clinical parameters between groups as it was a retrospective study, and nonuniform timing of VL measurements after ART initiation. Nonuniform frequency of VL monitoring may have skewed data, but this is expected in a real world study. Resistance profiles of patients were not analyzed as reasons for nonsuppression. We did not account for the impact of regimen tolerability that may have led patients to have poor adherence or change regimens, and thus were not analyzed in our data. Excluding patients with suspected nonadherence may limit generalizability to real-world clinic populations. We did not assess the impact of rapid virologic suppression on CD4 count recovery due to limited available data owing to differential practice of our clinic providers. Furthermore, we relied on chart documentation of medication adherence instead of more objective measurements such as pill count and pharmacy refill data, and changes in adherence would certainly impact VL decay. However, we believe that despite these limitations, these data contribute to understanding of ART-associated virologic decay patterns over time in a real-world clinical setting and is valuable to clinicians caring for patients living with HIV infection.

5. Conclusions

INSTI-based ART regimens resulted in faster time to virologic suppression compared to NNRTI- and PI-based regimens in this real-world cohort of HIV-infected treatment-naïve patients initiating ART. Patients on INSTI-based ART regimens should be evaluated for poor adherence and other causes of treatment failure if they have not achieved virologic suppression by 12 to 24 weeks, rather than 24 to 48 weeks as currently dictated by national guidelines.

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