HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2017 January 01; 74(1): 60–64. doi:10.1097/QAI.0000000000001168.

Factors associated with the selection of initial antiretroviral therapy from 2009 to 2012

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Abstract

We examined factors associated with selection of initial antiretroviral regimen in the CNICS cohort. Patients initiating antiretroviral therapy (ART) between July 2009 and Dec 2012 were classified as receiving an NNRTI, boosted-PI, or raltegravir-based regimen. Among 873 patients initiating ART, 488 regimens contained an NNRTI, 319 a boosted-PI, and 66 raltegravir. Patients with depression and women were less likely to receive an NNRTI, while those with underlying cardiovascular disease, liver disease, and those co-infected with hepatitis C were more likely to receive raltegravir. Those with baseline viral load > 100,000 c/ml and those with substance use were more likely to receive a boosted PI. Thus, in the 'real world' ARV regimen choices appear to take into account adverse effects and patient baseline characteristics. Factors that impact initial regimen selection will likely become more heterogeneous over time as more choices for HIV therapy become available.

Introduction

Over the last decade, antiretroviral (ARV) regimens have become more effective and better tolerated. As a result HIV disease has changed from a near-certain death sentence to a chronic manageable condition (1). Treatment regimens have also become more simplified, with several drugs being co-formulated into single tablet regimens that can be administered once daily. As a result of these therapeutic advancements, there are a number of regimen options for use in first line therapy for patients with HIV infection (2).

Clinical trials have characterized the relative efficacy and side effect profiles for available treatment regimens. Clinicians typically choose a regimen to use as initial therapy for a

given patient based on the patient's clinical presentation, including co-morbid conditions, interactions with other medications prescribed, and a regimen's side effect profile. There are few existing studies regarding clinician selection of regimens in 'real world' clinical practice during the integrase inhibitor era (3).

We examined factors associated with choice of the class of initial ARV regimen in the CNICS cohort at eight clinical sites throughout the United States. We sought to characterize the distribution of initial antiretroviral treatment (ART) regimens and clinical factors associated with selection of one type of regimen versus others among patients initiating ART in the modern treatment era.

Methods

Study Patients

The CFAR Network of Integrated Clinical Systems (CNICS) cohort includes >30,000 HIV-infected adults in care from 1995 to the present at eight HIV clinics at academic centers in the US, including the University of Alabama at Birmingham, University of Washington, University of California, San Francisco, University of California, San Diego, Case Western Reserve University, Harvard University / Fenway, Johns Hopkins University, and the University of North Carolina (4). Institutional review boards at each university have approved study protocols. All adult patients (> 18 years of age) initiating their first 3 (or more) drug regimen between July 2009 and December 2012 were included. Patients were excluded if they had documentation of receiving any ART (including use of one or two drug regimens), a viral load <200 c/ml any time prior to enrollment, had no viral load or CD4 count value within 12 months of study entry, or participated in a clinical trial for their initial antiretroviral therapy.

Data

The CNICS data repository integrates comprehensive clinical data that include demographic, medication, laboratory, and diagnosis information collected through point-of-care electronic medical records (EMR) and other institutional data systems at each site. Data quality assessment is conducted at the sites prior to data transmission and at the time of submission to the CNICS Data Management Core (DMC) at the University of Washington. After integration into the central repository, data undergo extensive quality assurance procedures and data issues are reported to CNICS sites to investigate and correct. Data are updated by each site, fully reviewed, and integrated into the repository quarterly. We examined baseline factors including demographic characteristics, risk factors for HIV transmission, type of ART, diagnoses (including AIDS-defining illnesses (ADIs), mental health and substance use disorders, hepatitis B and C virus infection, liver disease, diabetes mellitus, hypertension, cardiovascular and cerebrovascular disease, CD4 counts and viral load.

Statistical Analysis

We examined the association between baseline demographic characteristics and comorbid conditions diagnosed prior to initiation of a patient's first ARV regimen classified into three categories: NNRTI, boosted-PI (PI/r), and raltegravir-based, which was the only integrase

strand transfer inhibitor available for use in practice during the study period. The nucleoside/tide backbone component of the regimen was not evaluated. Factors suspected of being associated with regimen choice were explored using polytomous (multinomial) logistic regression models. All models included site as a stratification factor.

Results

Baseline characteristics of the 873 study patients at the time of ART initiation are shown in Table 1. The majority of patients were male (82%), most of whom (73%) had sex with men, between the 19 and 47 years of age (78%), Caucasian (56%), non-Hispanic (81%), non-IVDU (86%), and had public insurance (56%). The median viral load was 33,283 c/ml and median CD4 count was 351 cells/ul. Thirty four percent of patients had a diagnosis of depression, 33% had a substance use disorder, 26% had a psychiatric disorder other than depression, 16% had a diagnosis of liver disease / hepatitis C, 15% had a diagnosis of hypertension, 11% had a prior AIDS-defining illness, 5% had a diagnosis of diabetes, and 2% had a diagnosis of cardio-cerebrovascular disease.

Initial antiretroviral regimens were NNRTI-based (n=488; 56%), PI-based (n=319; 36%), or raltegravir-based (n=66; 8%) regimens. Multivariable models were fit. Of note, some variables were not included in the multivariable model because they either were not significant in univariate analyses ($p > 0.3$), had a significant degree of missing data, and/or there were concerns about collinearity. The variables not included were Hispanic ethnicity, baseline CD4 value, psychiatric or related disorder, history of an opportunistic infection, and presence of diabetes. In multivariable models, there was no significant difference in selection of NNRTI, PI, or raltegravir-based regimens based on age, race, risk factor, or diagnosis of hypertension (see Table 2). In contrast, individuals with higher viral load at baseline (> 100,000 c/ml) were more likely to receive a PI-based regimen than an NNRTI-based one (OR 1.8, 95% CI 1.3–2.5) as were women (OR 2.5, 95% CI 1.5–4.3). Those subjects with a history of depression were much more likely to start a raltegravir-based regimen than either an NNRTI (OR 3.5, 95% CI 1.9–6.4) or a PI-based regimen (OR 2.5, 95% CI 1.3–5.0). Similarly, patients with a diagnosis of HCV or liver disease were more likely to receive a raltegravir-based regimen (OR 3.3, 95% CI 1.4–7.8) than NNRTI-based one, although we found no significant selection preference for raltegravir over a PI-based regimen (OR 1.9, 95% CI 0.9–4.2). Those subjects with a diagnosis of cardiovascular or cerebrovascular disease were more likely to receive a raltegravir-based regimen than either an NNRTI (OR 4.7, 95% CI 1.3–17.0) or PI-based regimen (OR 4.9, 95% CI 1.2–19.2). Patients who reported active substance use were more likely to receive a PI-based regimen than an NNRTI (OR 1.7, 95% CI 1.2–2.5) or raltegravir-based regimen (OR 0.3, 95% CI 0.1–0.7).

Discussion

The remarkable advances in antiretroviral therapy have led to the development of a number of highly effective regimens available for clinicians to choose as initial treatment for their patients (5). Most of the regimens developed over the last decade have similar efficacy in clinical trials, but differ in their side effect profiles and potential for drug-drug interactions

(6–15). Clinical trial entry criteria often exclude patients who are not considered good candidates for some of the regimens used in the study, however in clinical practice clinicians select a regimen best suited for a particular patient. This study evaluated how antiretroviral agents are used in “real-world” clinical practice and types of regimens initiated among patients with different baseline laboratory or co-morbid conditions.

NNRTI-based regimens were the initial treatment in over half of the patients in our study. Although the most commonly employed regimen, we did not find demographic, laboratory, or co-morbid factors that favored selection of an NNRTI-based regimen over the other two regimen categories. In contrast, the use of PI-based or raltegravir-based regimens was selected over NNRTI-based regimens in the context of specific clinical scenarios. Taken together, NNRTI-based regimens seemed to be the ‘default’ regimen with clinicians opting for other regimens as indicated by the patient’s clinical presentation, likely due to co-formulation of efavirenz as the only single pill once daily regimen available during the time period of this study. This thesis is supported by prior reports that demonstrated high-uptake by efavirenz-based regimens, in particular, from 2000–2009 (16). By the end of the study period (2007) in the study by Willig, et al, over 80% of subjects were taking an efavirenz-based regimen (17).

A PI-based or raltegravir-based regimen was more likely to be selected than an NNRTI-based regimen among women, those who had a history of substance abuse, and those with higher viral load, liver disease, depression, cardiovascular disease, hepatitis C / liver disease, or a higher number of co-morbid conditions. More specifically, both raltegravir and PI-based regimens were more likely to be selected for women and patients with a number of co-morbid conditions in keeping with the relative contraindication of the use of efavirenz among women of child-bearing potential (during the time of the study) and the complexities of managing co-morbid conditions. Similarly, raltegravir-based regimens were preferred over both NNRTI- and PI-based regimens for those with depression or underlying cardiovascular disease. Likely due to an association between depression and the use of efavirenz, potential toxicity of nevirapine-based regimens in those with HCV or liver disease (6, 14) as well as potential drug-drug interactions for boosted PI regimens (15). In contrast, PI use was preferred over use of NNRTI regimens for those who had higher (> 100,000 c/ml) viral load values at baseline and preferred over both NNRTI- and raltegravir-based regimens for those patients with a history of substance abuse likely due to concerns regarding adherence and a higher barrier to resistance associated with PI-based therapies.

Our study has limitations. The number of patients studied limits the ability to detect differences. Although the time period evaluated (July 2009 – December 2012) represents fairly modern use of antiretroviral therapy, several newer therapies have been introduced over the last 2 years, in particular, two additional integrase inhibitor agents, elvitegravir and dolutegravir (7–9), which would require additional follow-up time to evaluate. The exclusion of patients who participated in clinical trials may have resulted in inclusion of individuals who had more co-morbidities or conditions that would not have allowed them to enter the clinical trial; however, the exclusion of these patients enables greater focus of real-world clinical practice where treatment is not driven by study protocol. This study focused on the ‘anchor’ drug of the regimen and did not examine patterns of use with regard to the

nucleoside/tide backbone. The majority of patients in the study were using tenofovir-based regimens and our ability to examine differences was limited by sample size. Future studies should address the impact of the newer integrase inhibitors and the role of nucleoside/tide backbone selection in combination with the anchor drugs of the regimen. Finally, our study cannot dissect the role patient preference plays in the selection of regimens (18).

To our knowledge, this study is the first to evaluate exclusively initial ART regimen selection by providers in a 'real-world' practice setting. The findings demonstrate that ARV regimen choices take into account adverse effects and patient baseline characteristics. As more choices for HIV therapy become available, factors that impact initial regimen selection will likely become more heterogeneous over time including drug-drug interaction considerations when treating patients co-infected with HCV, those with underlying kidney disease, and cost of therapy as more generic drug formulations become available.

Acknowledgments

Funding: UAB CFAR (5 P30-AI027767); CNICS R24 AI067039; and a grant from Merck Sharp & Dohme Corp.

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Table 1

Characteristics of naïve patients initiating HAART

	Total (N=873)		NNRTI (N=488)		PI/r (N=319)		Raltegravir (N=66)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Sex								
Female	154	17.6	61	12.5	75	23.5	18	27.3
Male	719	82.4	427	87.5	244	76.5	48	72.7
Age (years)								
19–36	429	49.1	246	50.4	157	49.2	26	39.4
37–47	250	28.6	137	28.1	89	27.9	24	36.4
48–75	194	22.2	105	21.5	73	22.9	16	24.2
Race								
Black	304	34.8	180	36.9	97	30.4	27	40.9
White	486	55.7	260	53.3	191	59.9	35	53.0
Other/Unknown	83	9.5	48	9.8	31	9.7	4	6.1
Hispanic								
Yes	155	18.8	81	17.7	65	21.3	9	14.3
No	671	81.2	377	82.3	240	78.7	54	85.7
Risk Factor								
IVDU	121	13.9	52	10.7	57	17.9	12	18.2
MSM	525	60.1	322	66.0	171	53.6	32	48.5
Heterosexual	227	26.0	114	23.4	91	28.5	22	33.3
Insurance								
Private	209	30.3	129	33.6	66	26.3	14	25.9
Public	385	55.9	201	52.3	152	60.6	32	59.3
Uninsured	95	13.8	54	14.1	33	13.1	8	14.8
Baseline[a] VL, copies/mL								
≤100,000	627	71.8	368	75.4	212	66.5	47	71.2
>100,000	246	28.2	120	24.6	107	33.5	19	28.8
Baseline[a] CD_4 count, cells/μL								

Characteristic	Total (N=873) N	%	NNRTI (N=488) N	%	PI/r (N=319) N	%	Raltegravir (N=66) N	%
<50	87	10.0	40	8.2	39	12.2	8	12.1
50–199	129	14.8	60	12.3	60	18.8	9	13.6
200–349	220	25.2	130	26.6	76	23.8	14	21.2
350–500	254	29.1	158	32.4	77	24.1	19	28.8
>500	183	21.0	100	20.5	67	21.0	16	24.2
Co-Morbid Conditions								
HCV+ or Liver Disease	136	15.6	53	10.9	63	19.7	20	30.3
Depression	295	33.8	135	27.7	122	38.2	38	57.6
Psych Other	230	26.3	115	23.6	90	28.2	25	37.9
Substance Use	284	32.5	134	27.5	127	39.8	23	34.8
Cardio/Cerebrovascular	20	2.3	8	1.6	6	1.9	6	9.1
Opportunistic Infection	95	10.9	51	10.5	36	11.3	8	12.1
Diabetes	27	3.1	15	3.1	7	2.2	5	7.6
Hypertension	131	15.0	69	14.1	46	14.4	16	24.2
Number of Comorbidities								
0	240	27.5	144	29.5	85	26.6	11	16.7
1–4	597	68.4	334	68.4	214	67.1	49	74.2
>4	36	4.1	10	2.0	20	6.3	6	9.1
Year started initial regimen (row percentages)								
2009	142	100	79	55.7	57	40.1	6	4.2
2010	277	100	145	52.3	112	40.4	20	7.3
2011	330	100	182	55.2	118	35.7	30	9.1
2012	124	100	82	66.1	32	25.8	10	8.1

[a]Baseline defined as value nearest antiretroviral therapy (ART) start date within a window of −180 to 14 days.

Missing values were observed in 47 regarding Hispanic ethnicity and 184 regarding insurance status.

Table 2

Multivariable polytomous regression model with site as stratification factor

	Raltegravir vs. NNRTI	Raltegravir vs. PI	PI/r vs. NNRTI
19–36 years old	1.00	1.00	1.00
37–47 years old	1.13 (0.58,2.22)	1.66 (0.83,3.34)	0.83 (0.58,1.20)
48–75 years old	0.74 (0.33,1.65)	1.11 (0.48,2.61)	0.84 (0.56,1.27)
White race	1.00	1.00	1.00
Black race	0.66 (0.33,1.31)	0.70 (0.34,1.47)	0.91 (0.61,1.37)
Other/unknown race	0.44 (0.13,1.52)	0.54 (0.15,1.86)	0.85 (0.49,1.47)
Male	1.00	1.00	1.00
Female	1.69 (0.71,3.99)	0.55 (0.21,1.42)	**2.53 (1.50,4.25)**
Heterosexual	1.00	1.00	1.00
IVDU	0.78 (0.25,2.39)	0.88 (0.31,2.53)	0.89 (0.49,1.62)
MSM	0.98 (0.43,2.26)	0.86 (0.34,2.16)	0.90 (0.56,1.45)
Baseline VL ≤100,000	1.00	1.00	1.00
Baseline VL >100,000	1.75 (0.92,3.34)	0.71 (0.36,1.41)	**1.77 (1.26,2.48)**
HCV+ or Liver Disease	**3.33 (1.42,7.79)**	1.91 (0.86,4.23)	1.36 (0.84,2.19)
Depression	**3.48 (1.90,6.36)**	**2.54 (1.28,5.03)**	1.34 (0.96,1.89)
Substance Use	0.62 (0.30,1.29)	**0.31 (0.14,0.68)**	**1.73 (1.19,2.51)**
Cardiovascular/Cerebrovascular	**4.70 (1.30,17.04)**	**4.86 (1.23,19.17)**	1.16 (0.36,3.70)
Hypertension	1.62 (0.76,3.45)	1.26 (0.58,2.73)	1.33 (0.84,2.11)