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Responses to First-Line Antiretroviral Therapy in Patients with Isolated NNRTI Transmitted Drug Resistance

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Background

Nonnucleoside reverse-transcriptase inhibitor (NNRTI)-associated transmitted drug resistance (TDR) is the most common type of TDR. Few data guide the selection of antiretroviral therapy (ART) for patients with such resistance. Boosted protease inhibitors have been used historically, but because NNRTI TDR may be a proxy for additional minority variant TDR, it is uncertain whether regimens with lower genetic barriers to resistance would be effective.

Methods

Patient population

The cohort included **HIV-1 infected, ART-naïve** adult patients in the Kaiser-Permanente Medical Care Program – Northern California (KPNC) undergoing SGRT prior to ART initiation between April 2002 and May 2014 who had **isolated NNRTI TDR**.

Isolated NNRTI TDR was ≥ 1 NNRTI surveillance drug resistance mutation (SDRM) with no NRTI or PI SDRMs (Bennett et. al., PLoS One, 2009). Standard ART regimens were those used in more than one patient and composed of a dual NRTI backbone plus one agent from the following base-drug classes: integrase inhibitor (INSTI); boosted protease inhibitor (bPI); and NNRTI. Patients initiating non-standard ART regimens were excluded due to regimen heterogeneity.

Analysis

Medical and pharmacy records were reviewed to retrospectively characterize responses to therapy up to two years following ART initiation.

Definitions:

Virological Suppression (VS): HIV-1 RNA level <75 copies per ml.
Virological Failure (VF): (i) failing to achieve VS by 24 weeks of ART, (ii) rebounding with ≥2 consecutive HIV-1 RNA levels ≥200 copies/ml following VS, or (iii) changing therapy with an elevated virus load.

Statistical analysis:

The effect of the base-drug class on clinical outcomes in patients with isolated NNRTI TDR was evaluated with two analyses:
As-Treated: Patients developing VF were considered as failure events.
Intention to treat (ITT): Patients developing VF, lost to follow up (LTFU), or change of therapy at any point were considered failure events.

Demographic and clinical characteristics were compared between base-drug classes using Kruskall-Wallis, Wilcox rank sum, and Fisher exact tests. Univariate and multivariate Cox regression analyses were used to evaluate the effect of base-drug class on failure outcomes. Multivariate analysis included variables with p ≤ 0.05 in univariate analysis in addition to base-drug class. Kaplan-Meier analyses generated survival curves.

Results

Cohort Description

Of 3,245 ART-naïve patients undergoing SGRT prior to ART initiation, 131 (4.0%) had isolated NNRTI-associated TDR. Nine of these were excluded for a non-standard ART regimen.

The remaining 122 patients included in our analysis were treated with:
- bPIs (54): atazanavir/r (25), darunavir/r (20), lopinavir/r (9)
- INSTIs (52): raltegravir (31), elvitegravir (21)
- NNRTIs (16): efavirenz (5), etravirine (2), and rilpivirine (9)

NNRTI SDRMs occurred in the following patterns:

Single SDRMs N(%)
- K103N 94 (77)
- Y188L 9 (7)
- Y181C 6 (5)
- G190A 5 (4)
- K101E 3 (2)
- K101P 1 (1)
- Y188C 1 (1)
- V179F 1 (1)

Multiple SDRMs N (%)
- Y181C + K101E + V179F 1 (1)
- K103N + P225H 1 (1)

Table 1. Patient Characteristics by Base-Drug Class

Characteristic	bPIs n = 54	INSTIs n = 52	NNRTIs n = 16	All Classes n = 122	*P* Value
Female	8 (15)	5 (10)	3 (19)	16 (13)	0.49[a]
Age (years)	41 (33-49)	40 (30-48)	34 (28-44)	39 (31-48)	0.21[b]
Race					0.02[a]
White	24 (44)	24 (46)	7 (44)	55 (45)	
Black	14 (26)	6 (12)	1 (6)	21 (17)	
Hispanic	11 (20)	14 (27)	2 (13)	27 (22)	
Other	5 (9)	2 (4)	3 (19)	10 (8)	
Unknown	0	6 (12)	3 (19)	10 (8)	
CD4 count (cells/μL)	283 (248-398)	401 (265-525)	357 (145-458)	343 (248-477)	0.02[b]
HIV-1 RNA load (log copies/mL)	4.6 (3.9-5.2)	4.5 (4.1-4.8)	4.6 (3.9-4.9)	4.5 (4.0-5.0)	0.82[b]
NRTI backbone					0.07[a]
TDF/FTC	47 (87)	51 (98)	16 (100)	114 (93)	
ABC/3TC	1 (2)	1 (2)	0	2 (2)	
AZT/3TC	6 (11)	0	0	6 (5)	
Year of ART initiation	2009 (2007-2010)	2012 (2011-2014)	2012 (2012-2013)	2011 (2009-2013)	<0.001 [b]
HIV-1 RNA monitoring interval (wks)	12 (10-15)	15 (11-20)	14 (8-18)	13 (10-17)	0.14[b]

Abbreviations: bPI, boosted protease inhibitor; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; TDF, tenofovir; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; AZT, zidovudine. Data are presented as No. (%) or median (range). [a]Fisher exact test. [b]Kruskal-Wallis test.

Patient and Treatment Characteristics

Our patients were predominantly male (87%) and had a median age of 39 years (Table 1). Forty-five percent were Caucasian, 22% were Hispanic, 17% were Black, and 8% were other races. Races differed between groups, seemingly due to more back patients in the bPI group.

The median baseline CD4 count was 343 cells/mm^3, and the baseline Log_{10} HIV-1 RNA was 4.5 copies/mL (Table 1). CD4 counts in the bPI group were lower than other groups. The year of initiation in the bPI group (2009), was also earlier that the other groups (2012). Ninety-three percent of patients received the dual NRTI backbone TDF/FTC. Viral loads were monitored a median of every 13 weeks.

Table 2. Univariate As-Treated and ITT Analyses

	As-Treated		ITT	
Explanatory Variable	**HR (95% CI)**	***P* value[a]**	**HR (95% CI)**	***P* value[a]**
CD4 count[b]	0.90 (0.78-1.05)	0.17	0.93 (0.85-1.00)	0.06
HIV-1 RNA load[c]	1.8 (0.85-3.8)	0.12	1.29 (0.87-1.92)	0.20
Year of ART initiation[d]	1.02 (0.36-2.9)	0.96	1.0 (0.56-1.70)	1.00
Race:				
White	1	NA	1	NA
Black	2.5 (0.73-8.8)	0.14	1.6 (0.7-3.5)	0.25
Hispanic	0.0 (0.0-inf)	1.00	1.3 (0.6-2.9)	0.48
Other	2.0 (0.39-10.3)	0.41	1.3 (0.4-3.8)	0.66
Unknown	2.6 (0.29-23.9)	0.39	1.6 (0.4-7.2)	0.52
Age[e]	0.64 (0.38-1.09)	0.10	0.65 (0.49-0.87)	0.004
Female gender[f]	3.4 (1.03-10.9)	0.05	1.5 (0.7-3.4)	0.33
Base-drug class:				
bPI	1	NA	1	NA
INSTI	0.15 (0.02-1.2)	0.07	0.4 (0.2-0.9)	0.03
NNRTI	2.7 (0.8-9.0)	0.11	1.7 (0.8-3.9)	0.18

Abbreviations: ITT, intention-to-treat; HR, hazard ratio; ART, antiretroviral therapy; bPI, boosted protease inhibitor; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor. [a]Univariate Cox proportional hazards model. [b]Per 50 cells/mm^3 increase. [c]Per 1 log copies/ml increase. [d]Per 5 year increase. [e]Per 10 year increase. [f]Relative to male gender.

Patient Outcomes According to Base-Drug Class

The median duration of follow-up period was 100 weeks (bPIs 104; INSTIs 72; and NNRTIs 65 weeks). Eleven patients were LTFU (bPIs 8; INSTIs 2; and NNRTIs 1).

In the **As-Treated** analysis, 13 patients (11%) developed failure events overall: **bPIs 8 (15%); INSTIs 1 (2%); and NNRTIs 4 patients (25%)**. INSTIs had a lower risk of failure and NNRTIs higher relative to bPIs in univariate analysis, but differences were not statistically significant (Table 2).

In the **ITT** analysis, 42 patients (34%) developed failure events**: bPIs 25 (46%); INSTIs 9 (17%); NNRTI 8 patients (50%)**. Treatment with INSTIs relative to bPIs were associated with a statistically significant lower risk of a failure event in univariate analysis. NNRTIs had a higher risk of failure, but this was not statistically significant, likely due to low numbers in the group (Table 2).

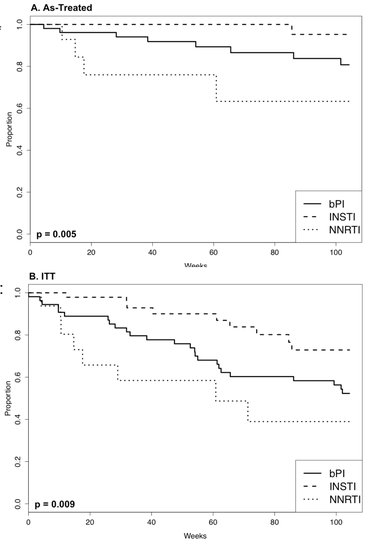

Figure 1. Kaplan-Meier plots show the cumulative incidence of patients free of failure events according to the base-drug class. *A* The as-treated analysis failure outcome was virological failure (VF), defined as not reaching an undetectable HIV-1 RNA level by 24 weeks, virological rebound, and regimen switching during viremia. *B* The intention-to-treat (ITT) failure outcome was a broader definition of failure, including VF, loss to follow-up, and regimen switching during virological suppression. *P* values were calculated by the log-rank test.

Multivariate analysis:

As Treated Hazard Ratios:
- **bPI – 1 (reference)**
  INSTI – 0.15
  (0.02-1.2) p = 0.07
  NNRTI – 2.7
  (0.8-9.0) p = 0.11

ITT Hazard Ratios:
- **bPI – 1 (reference)**
  INSTI – 0.4
  (0.2-0.9) p = 0.03
  NNRTI – 1.7
  (0.8-3.9) p = 0.18

Conclusion

Patients with isolated NNRTI TDR experienced low VF rates with INSTIs and bPIs. INSTIs were non-inferior to bPIs in an analysis of VF (powered to detect a 1.2% margin of inferiority), but superior to bPIs when frequency of switching and LTFU were also considered. NNRTIs showed higher risk of failure in both analysis, but small numbers allowed detection of only a 44% margin of inferiority. Despite their lower genetic barrier to resistance, INSTIs now appear to be a safe choice in this population.

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