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Prevalence and Outcomes of Recycling NNRTIs Despite Documented NNRTI Resistance in HIV-Infected Children and Youth

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Abstract

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are commonly used in pediatric patients; however, rapid development of resistance, due to non-adherence and cross-resistance, results in their discontinuation and limits their recycling. We evaluated the clinical experience of recycling NNRTIs despite documented NNRTI resistance (NNRTI-R), and examined virologic and CD4 cell count outcomes among participants enrolled in Longitudinal Epidemiologic Study to Gain Insight into HIV/AIDS in Children and Youth (LEGACY), a national HIV-infected pediatric cohort. We conducted a retrospective analysis of LEGACY participants with major NNRTI-R. Using chi-square analyses and logistic regression, we examined demographic and clinical factors associated with prescription of NNRTIs despite documented NNRTI-R, and associated changes in plasma HIV RNA viral load and CD4 cell counts. Sixteen of 133 (12%) participants with documented NNRTI-R re-started NNRTIs for a median of 370 days (IQR 105–919) with a median 402 days (IQR 70–841) between documentation of NNRTI-R to NNRTI recycling. Participants recycling NNRTIs were less likely to have documented past non-adherence (40.0% vs. 69.2%; $p=0.02$). Among twelve patients with virologic data at 24 (± 8) weeks; seven (58.3%) experienced virologic suppression while on the recycled NNRTI-based regimens. Of the five who failed to suppress, three with subsequent genotyping developed additional NNRTI-R mutations compromising higher generation NNRTIs. While NNRTI's were recycled in only a small fraction of LEGACY participants harboring NNRTI-R mutations, such recycling increased the risk of inducing further resistance mutations that compromised use of higher generation NNRTIs.

Introduction

The use of genotypic resistance testing at initiation and subsequent changes in antiretroviral treatment regimens, as recommended in HIV management guidelines,[1,2] can guide selection of optimal regimens to maximally suppress viral replication and promote successful treatment of HIV. However, fewer antiretroviral agents are available for treatment of pediatric HIV infection due to a paucity of pediatric pharmacokinetic data, and limited availability and palatability of liquid formulations.[3] The number of available agents is decreased further for those whose virus has developed resistance, particularly to non-nucleoside reverse transcriptase inhibitors (NNRTI). NNRTIs have a half-life of 40–55 h, which is longer than protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) that, in general, have half-lives of less than 10 h.[4–6] When coupled with incomplete adherence to a prescribed antiretroviral regimen, the longer half-life of NNRTIs may lead to periods where NNRTIs may be present in the bloodstream in the absence of other drugs in the regimen, effectively simulating NNRTI monotherapy.[4] The combination of continued virologic replication and suboptimal drug levels promotes the selection of drug-resistant variants. Cross-resistance among the NNRTIs nevirapine and efavirenz limits the use of other agents in the class with the exception of the newer generation of NNRTIs currently consisting of etravirine and rilpivirine.[7] Both of these agents were specifically designed to be effective despite the presence of the K103N mutation; however, non-K103N mutations such as G190A/S, Y181C/I, V179D/F, L100I, K101E/P, and V106I can still compromise their efficacy.[7]

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In pediatric patients, the use of NNRTI-based regimens is often preferred due to their tolerability and the availability of once-daily combination pills such as Atripla® that simplify dosing and pill burden. However, once NNRTIs have been used, providers hesitate to reinitiate them, particularly in patients with documented adherence problems during NNRTI use, or whose virus displays even minor NNRTI resistance (NNRTI-R) mutations. There is concern for additional undetected resistance that has faded from virus in the blood plasma compartment, but is retained in a latent undetectable reservoir that would render the regimen less effective if an NNRTI were restarted (i.e., recycled).[8–10] Given the limitations of ARV use in children, some providers may seek to reinitiate or recycle NNRTIs even in the setting of documented clinically relevant resistance that may compromise their effectiveness; however, there are no data on this practice in the United States. We evaluated the clinical experience of NNRTI recycling in the setting of documented NNRTI-R and examined outcomes in plasma HIV RNA viral load (HIV VL) and CD4+ T-lymphocyte (CD4 cell) outcomes in those patients recycling NNRTIs in a national domestic cohort of HIV-infected children.

Methods

We conducted a retrospective analysis of 133 pediatric participants enrolled in the Longitudinal Epidemiologic Study to Gain Insight into HIV/AIDS in Children and Youth (LEGACY) cohort study for whom genotypic antiretroviral resistance testing of plasma-derived HIV indicated the presence of any major mutation associated with NNRTI-R (per International AIDS Society Guidelines).[16] Mutations to etravirine or rilpivirine were not studied as these antiretrovirals were not FDA-approved and licensed prior to the completion of data entry for this study. The LEGACY study is a Centers for Disease Control and Prevention (CDC)-funded, observational, retrospective, and prospective cohort study of 2039 HIV-infected children and adolescents enrolled between birth and 24 years of age from 22 HIV specialty clinics across the U.S. and Puerto Rico. This study population was selected using a three-stage cluster probability-proportional-to-size sampling of HIV-infected infants, children, and adolescents receiving care in 22 geographically diverse small, intermediate, and large-sized facilities. The study was approved by the Institutional Review Board (IRB) of the CDC and the IRBs of all local study sites. Between November 2005 and June 2007, at least 80% of eligible HIV-infected youth presenting for care at LEGACY clinic sites were offered enrollment. Participation was voluntary. Written informed consent and, where appropriate, assent were obtained. The medical records of participants were reviewed and data abstracted by specially-trained personnel. Data collected included demographics, mode of HIV infection, clinical diagnoses, antiretroviral (ARV) and non-ARV medications, laboratory test results, including CD4 cell counts, HIV VL determinations, and genotype and phenotype drug resistance test results, adherence, and mortality data.

Participants enrolled in the LEGACY cohort with documented HIV infection, and at least one genotype showing NNRTI-R were eligible for inclusion in this analysis. We defined baseline NNRTI-R by the presence of any major mutation associated with NNRTI-R (per International AIDS Society Guidelines),[11] specifically the following mutations: L100I, K101P, K103N, V106M, V108I, Y181C, Y188C/L/H, G190A, and P225H. Participants who re-initiated NNRTIs despite evidence of NNRTI-R were defined as recyclers. We abstracted information from the medical charts regarding provider knowledge of NNRTI-R and the reason for NNRTI recycling. We did not retrospectively interview the providers. For those patients who were prescribed regimens with recycled NNRTIs, we examined CD4 count and HIV VL data 24 weeks ± 8 weeks after the restart of an NNRTI-based regimen and where available, all subsequent genotyping after initiation of the regimen containing a recycled NNRTI.

Statistical analysis

The outcome of interest was NNRTI recycling. Pearson chi-squared and Fisher's Exact tests were used to determine factors (e.g., age, race/ethnicity, CD4 count, HIV VL, HIV acquisition risk, history of nonadherence, type of NNRTI-R) associated with recycling of NNRTIs in the setting of documented NNRTI-R. We also used descriptive statistics and Wald Z tests, assuming equal proportions to examine the HIV VL and CD4 cell changes among patients who subsequently recycled NNRTIs. The Wilcoxon Z test was used to examine the elapsed time between documentation of resistance and NNRTI recycling. SAS software (SAS Institute, Inc., Version 9.2, Cary, NC) was used for the analyses. All statistical tests are two-sided and based on a 5% level of significance.

Results

Sixteen of 133 (12%) participants with NNRTI-R were prescribed recycled NNRTIs a median of 401.5 days (IQR 70–841 days) after documentation of NNRTI-R and continued such therapy for a median duration of 370 days (IQR 105–919). There was evidence of laboratory-documented NNRTI-R present prior to re-starting NNRTIs. The reasons for recycling NNRTIs included avoiding side effects of protease inhibitors (PIs) (3/16), highly resistant virus with an attempt to partially suppress (2/16), phenotypic testing suggesting NNRTI activity (2/16), regimen simplification (1/16), NNRTI-R not present on subsequent genotype (1/16), or no reason provided (7/16). There were no significant demographic differences between participants who were prescribed recycled NNRTIs and those who were not (Table 1). Participants who were prescribed recycled NNRTIs were less likely to have a documented problem with adherence in the past (40.0% vs. 69.2%; $p = 0.02$) (Table 1). Additionally, although a higher proportion of participants who were prescribed recycled NNRTIs compared to those not prescribed recycled NNRTIS had CD4 < 200 cells/mm^3, this difference was not statistically significant (37.5% vs. 20.0%; $p = 0.12$; Table 1).

NNRTI mutations

The most commonly identified NNRTI mutations are presented in Table 2. Participants who were prescribed recycled NNRTIs were less likely to have the K103N mutation than non-recyclers (18.7% vs. 61.5%; $p = 0.002$).

Outcomes for participants who recycled NNRTI-based regimens despite NNRTI-R

Only 12 of 16 participants had virologic data at 24 (±8) weeks after recycling NNRTIs. Seven of 12 participants

Table 1. Demographic Characteristics of HIV-1 Infected Children with Documented NNRTI-R Mutations Who Did or Did Not Recycle NNRTI-Based Regimens[a] LEGACY Cohort, United States, 2001–2006

	Did not initiate NNRTI-based regimen N = *117* n *(%)*	*Initiated NNRTI-based regimen* N = *16* n *(%)*	p *Value*
Age, years (median)	10.1	11.8	0.17
Race/ethnicity			0.16
White, non-Hispanic	3 (2.6)	2 (12.5)	
Black, non-Hispanic	84 (71.8)	9 (56.3)	
Hispanic	27 (23.1)	5 (31.3)	
Other/unknown	3 (2.6)	0 (0)	
Gender			0.14
Male	50 (42.7)	10 (62.5)	
Female	67 (57.3)	6 (37.5)	
Mode of HIV infection			0.62
Perinatal	95 (81.2)	12 (75)	
Breastfeeding only	1 (0.9)	0 (0)	
Blood transfusion, blood products only	3 (2.6)	0 (0)	
Behavioral—consensual sexual activity only	3 (2.6)	0 (0)	
Sexual abuse only	2 (1.7)	1 (6.3)	
Other only	2 (1.7)	0 (0)	
Multiple risks	9 (7.7)	3 (18.8)	
Unknown transmission	1 (0.9)	0 (0)	
Men who have sex with men	1 (0.9)	0 (0)	
Injection drug use	0 (0.0)	0 (0.0)	
Adherence after mutation detected			0.02
No documented adherence problem	36 (30.8)	10 (62.5)	
Documented adherence problem	81 (69.2)	6 (37.5)	
Poor clinic attendance			0.051
Yes	23 (19.7)	7 (43.8)	
No	94 (80.3)	9 (56.2)	
Immunologic stage when mutation detected			0.12
CD4 $\geq$200 cells/mL (CD4% $\geq$14%)	84 (80.0)	10 (62.5)	
CD4 $<$200 cells/mL (CD4% $<$14%)	21 (20.0)	6 (37.5)	

[a]105 individuals had available CD4 testing at the time NNRTI mutation detected.

(58%) demonstrated virologic suppression at VL $<$400 copies/mL) at 24 weeks while prescribed NNRTI-based regimens. Of the seven ARV regimens, four excluded PIs and none included etravirine. Of note, three participants demonstrated virologic suppression while prescribed nevirapine or efavirenz despite previously documented presence of the K103N mutation. Being virologically suppressed either at a VL $\leq$400 copies/mL at 24 weeks after NNRTI recycling compared to not being virologically suppressed was associated with having a CD4 cell count $\geq$200 cells/mL [7/7(100%) vs. 1/5(20%)]; $p = 0.01$; percentages and p values the same for both levels of virologic detection) but not to having a longer elapsed time from NNRTI-R detection to NNRTI recycling (Wilcoxon $Z = -0.16$, $p = 0.87$). Participants achieving virologic suppression remained suppressed for a median of 9 months (range 2–38 months) with a median change in CD4 of +60.5 cells/mm^3 (range, 209–814 cells/mm^3) during that period. Of five participants who did not achieve plasma virologic suppression at 24 weeks, among three who had results available from subsequent genotyping, all demonstrated evidence of having accumulated additional NNRTI-R mutations (G190S, V118I, K103N in one, G190S, Y181C, L100I, and V108I in a second, and V118I in the third patient).

Discussion

The recycling of non-etravirine NNRTIs, despite the presence of documented NNRTI-R, occurred in 12% of patients in the LEGACY cohort. Although some participants who were prescribed recycled NNRTIs achieved virologic suppression, a substantial proportion did not and also developed additional genotypic resistance mutations that would have compromised the use of newer generation NNRTIs. Fewer providers prescribed recycled NNRTIs in participants whose virus exhibited the K103N mutation compared with participants whose virus did not. It appears that providers were not as concerned about the presence of non-K103N mutations or chose to recycle because the absence of K103N would increase the likelihood of success suppressing viral replication with efavirenz or nevirapine. Non-K103N mutations have a greater impact on the newer generation NNRTIs (i.e., etravirine and rilpivirine),[7] and further accumulation of these mutations resulting from reintroduction of efavirenz or

Table 2. Distribution of NNRTI Resistance Mutations,[a] LEGACY Cohort, United States, 2001–2006

	Did not recycle NNRTI-based regimen N = *117* n *(%)*	*Recycled NNRTI-based regimen* N = *16* n *(%)*	p *Value*
Major NNRTI mutations			
L100I	9 (7.7)	0 (0)	0.60
K101E	10 (8.6)	5 (31.3)	0.02
K103N	72 (61.5)	3 (18.8)	< 0.01
V106A	3 (2.6)	0 (0)	1.00
V106M	1 (0.9)	0 (0)	1.00
V108I	15 (12.8)	3 (18.8)	0.45
Y181C	30 (25.6)	8 (50.0)	0.07
Y181I	0 (0)	1 (6.3)	0.12
Y188C	3 (2.6)	0 (0)	1.00
188H	3 (2.6)	1 (6.3)	0.40
Y188L	10 (8.6)	1 (6.3)	1.00
G190A	16 (13.7)	5 (31.3)	(0.13)
P225H	10 (8.6)	0 (0)	0.61
Minor NNRTI mutations			
K103S	1 (0.9)	0 (0)	1.00
V179D	6 (5.1)	0 (0)	1.00
V179E	1 (0.9)	0 (0)	1.00
G190E	1 (0.9)	0 (0)	1.00
G190S	3 (2.6)	1 (6.3)	0.40
G190A/E	16 (13.7)	5 (31.3)	0.13

[a]Resistance mutations not mutually exclusive.

nevirapine would likely compromise the future utility of the newer agents in these patients.

Even though some individuals recycling NNRTIs achieved virologic suppression, particularly those who had lower levels of viremia on a prior regimen before recycling of the NNRTI-based regimen, they were equally as likely to not achieve virologic suppression. It is probable that the NNRTI was not the most active component of the new regimen and the greatest effect on viral load was due to other ARVs, such as NRTIs, in the regimen. Residual viral suppression by NRTIs even in the setting of documented NRTI resistance has been reported;[17] this phenomenon is less likely to occur with NNRTIs in the setting of NNRTI resistance.[7]

The presence of NNRTI-R predicts NNRTI failure.[18] Using protease inhibitors in participants with documented NNRTI-R may be superior in terms of achieving virologic suppression and improved CD4 cell count outcomes. In crafting a salvage regimen, providers would ideally like to use at least two new active agents.[1] In clinical practice, due to the limited number of agents available for pediatric patients, the challenges of nonpalatable ARV formulations, and nonadherence, pediatric providers are constantly struggling to find regimens that will not only work for recycling but that their patients will take, as evidenced by the reasons cited by the providers of the participants. Often regimens can contain agents that balance expected activity (i.e., will be less likely to achieve suppression) with what patients will agree to take, with the goal of providing a regimen that will achieve some virologic suppression and provide some immunologic support while continuing to encourage adherence or wait for newer available agents. These issues in managing pediatric HIV-infected patients underscore the importance of pharmaceutical companies to continue to expand their research into pediatric-friendly formulations and doses and into other treatment strategies (e.g., de-intensification, bridging, monotherapy studies) that will provide immunologic support, but not lead to accumulation of resistance while addressing issues with adherence. Additionally, it is critical for pediatric practitioners to continue to re-evaluate antiretroviral drug regimens, particularly as newer agents become available.[16]

Our study has a number of strengths and limitations. Strengths include the fact that we evaluated data from a sample of diverse pediatric HIV care sites both geographically and in terms of the size of the patient population. Because LEGACY is an observational study and not a clinical trial with strict eligibility criteria, we were able to include a broader range of patients than those included in randomized trials; however, our findings may be subject to bias, and not be generalizable to all U.S. pediatric HIV clinic sites. Additional limitations include the fact that the reasons for recycling NNRTIs were abstracted from the medical record and not from interviews with providers. Finally, the small sample size and retrospective nature of this study limit our ability to conduct more in depth analyses, such as multivariable analyses of predictors for successful viral suppression when recycling NNRTs in persons with NNRTI-R.

When faced with limited treatment options due to intolerance of PIs or poor adherence, even in the setting of documented NNRTI-R, some pediatric providers recycle NNRTIs. Recycling NNRTIs despite documented NNRTI-R may be successful in some patients who have previously achieved virologic suppression and who have experienced longer duration of time from identification of NNRTI-R to initiation of recycling. Our small study raises concerns about the risk of inducing resistance that would have compromised the effectiveness of newer generation NNRTIs in the context of recycling NNRTIs among patients who failed to suppress viral load. Although the limited number of available pediatric formulations and the challenges of treatment in this population often create a need to utilize nontraditional strategies, recycling NNRTIs in the setting of documented resistance is an approach that generally cannot be recommended. However, as it may potentially be a viable option in very select patient populations, (e.g., highly adherent, low level viremia, intolerance of other agents, lack of other options), providers choosing to proceed should do so with a high degree of caution.

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Author Disclosure Statement

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