



# Safety and Efficacy of NRTI-only Antiretroviral Regimens in HIV-infected Children

Neely M<sup>1</sup>, Rutstein R<sup>2</sup>, del Bianco G<sup>3</sup>, Heresi G<sup>3</sup>, Barton T<sup>4</sup>, Wheeling J<sup>5</sup>, Wiegand R<sup>6</sup>, Bohannon B<sup>6</sup>, Dominguez K<sup>6</sup>, Wiznia A.<sup>7</sup> and the LEGACY Consortium<sup>6</sup>

(1) Keck Sch. of Medicine, Dept. of Pediatrics, Univ. of So. California, Los Angeles, CA, USA; (2) Children's Hospital of Philadelphia, Philadelphia, PA, USA; (3) Univ. Texas Hlth. Sci. Ctr. at Houston, Houston, TX, USA;

(4) Univ. Texas Southwestern Med. Ctr., Dallas, TX, USA; (5) Northrup Grummon, Inc., Atlanta, GA, USA; (6) CDC, Atlanta, GA, USA; and (7) Jacobi Medical Center, Bronx, NY, USA



Michael Neely, MD  
1640 Marengo St., #300  
Los Angeles, CA 90033  
Tel: (323) 226-2330  
Fax: (323) 226-2505  
E-mail: mneely@usc.edu

## Abstract

**Background:** In adults, NOARs (i.e., ≥3 NRTIs) are less potent than regimens combining multiple antiretroviral classes. Published experience with NOARs in children is more limited.

**Methods:** We analyzed demographic and clinical data from NOAR-treated patients in LEGACY, a multicenter observational cohort study of HIV-infected children and adolescents. We defined NOAR duration based on prescribed start and stop dates. We applied US Department of Health and Human Services criteria for virologic failure (VF), immunologic decline (ID) and adverse event (AE) grading. NRTI mutations were defined according to the Stanford database. Multivariate logistic regression was used to analyze factors associated with week 48 viral load (VL) >400 copies/mL.

**Results:** Of 575 patients with data from time of HIV diagnosis through 2006, 92 (16%) received NOARs in 25 different NRTI combinations; most (46%) received the fixed dose combination of zidovudine (AZT), lamivudine (3TC) and abacavir (ABV). NOAR use peaked in 2001-2002. Patients starting NOARs had a median age of 15 years (interquartile range [IQR] 11-19); were 57% female, 61% black, 28% Hispanic, and 53% treatment-naïve. Neither race nor gender differed significantly compared with children who did not receive NOARs. Median NOAR duration was 2.0 years (IQR 0.9-4.4). After week 12, only 10 (14%) of 73 had <1 log<sub>10</sub> decrease in VL; by week 48, 47 (69%) of 68 had VF (>400 copies/mL), and 8 (11%) of 70 with immunologic data had ID (≥ 5% CD4 cell count decline from baseline). VF and ID prevalences did not differ significantly among pre-NOAR treatment-naïve or -experienced patients. In multivariate analysis, baseline VL and Hispanic ethnicity were significantly associated with increased odds of week 48 VL >400 copies/mL, and NOARs with AZT/3TC/ABV with decreased odds of VL >400 copies/mL. AEs (all grades) occurred in 65 (71%) patients, including anemia (59%), leukopenia (43%), hepatitis (18%), rash (10%) and pancreatitis (9%). Among 49 patients who were treatment-naïve at NOAR initiation, we detected NRTI mutations in 21 (95%) of 22 tested after VF.

**Conclusions:** In LEGACY, NOAR users experienced high rates of VF, adverse events, and NRTI mutations. VF was notably associated with use of TDF-based NOARs. Immunologic decline was more moderate. NOARs should be avoided, when possible, in HIV-infected children and adolescents.

## Introduction

•NRTI-only regimens (NOARs, with 3 or more NRTIs) suppress virologic replication less well than NRTI plus NNRTI and/or PI combinations in HIV-infected adult patients, especially with baseline viral loads of >100,000 copies/mL.<sup>1</sup>

•Nonetheless, NOARs are simple and generally well tolerated, and there may still be a role in patients for whom adherence is a significant concern or as “maintenance” therapy after a period of complete virologic suppression on a more burdensome antiretroviral regimen.

• Pediatric experience with NOARs is far more limited and they are only recommended for use in special circumstances.<sup>2</sup> There are no published pediatric data on NOARs used as initial therapy

•In one study, 20 children with undetectable viral loads were switched to a triple NRTI regimen consisting of AZT or d4T plus 3TC and ABC, after a mean follow up of 108 weeks, all but one remained on therapy with VL < 50 and normal CD4. There were no serious adverse effects.<sup>3</sup>

•Since the existing data are so sparse, the LEGACY cohort presented a unique opportunity to gather information on the use of NOARs in children and adolescents.

## References

- Vibhagoool A, Cahn P, Schechter M, et al. Triple nucleoside treatment with abacavir plus the lamivudine/zidovudine combination tablet (COM) compared to indinavir/COM in antiretroviral therapy-naïve adults: results of a 48-week open-label, equivalence trial (CNA3014). *Curr Med Res Opin.* 2004;20(7):1103-14
- Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2009. <http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf>
- Palma P, Romiti ML, Cancrini C, et al. Successful simplification of protease inhibitor-based HAART with triple nucleoside regimens in children vertically infected with HIV. *AIDS.* 2007;21(18):2465-72

## Methods

### DEFINITIONS

**NOAR = Three or more NRTIs without any concurrent PI or NNRTI.**

**Baseline = Values closest to, but not after the NOAR start date.**

**Virologic failure (VF)**

**Early: VL >400 copies/mL and <1 log<sub>10</sub> drop in VL after at least 90 days of therapy**

**Late: >400 copies/mL after at least 6 months of therapy, when compared to baseline**

**Immunologic decline (ID) = Drop in CD4+ percentage of >5 points after at least 6 months of therapy, compared to baseline.**

**NRTI mutations = According to Stanford Database.**

**STUDY DESIGN:** Retrospective analysis of the LEGACY cohort with complete data through December 2006 (N=575). LEGACY is a multi-site, U.S. based cohort of HIV-infected children and adolescents from birth through 24 years of age.

**INCLUSION CRITERION:** All HIV-infected children and adolescents who were treated with a NOAR.

**ABSTRACTED DATA:** The following data were recorded at baseline and until the NOAR stop date. For any patient with more than one NOAR, only the first NOAR was included.

- Demographic – weight, height, age, date of birth, race/ethnicity
- Virologic – Viral Load (VL) in RNA copies/mL
- Immunologic – CD4+ lymphocyte counts and percentages
- Toxicologic – Nausea, vomiting, diarrhea, anorexia, weight loss, anemia, pancreatitis, rash, lactic acidosis, lipodystrophy, hepatitis, AIDS-defining conditions. These items were recorded from the medical records if described by medical providers as such.
- HIV genotypic NRTI resistance mutations

### STATISTICAL ANALYSIS

•Continuous variables were compared by Student's T-test.

•Categorical variables were compared using Chi-Square or Fisher's Exact tests.

•Early and Late VF were calculated as defined above using the VL closest to, but not before, 12 and 24 weeks of therapy, respectively.

•Analysis of factors associated with VL < 400 copies/mL after at least 48 weeks of NOAR treatment was by logistic regression. All factors were initially included in the multivariate model, and retained during backwards elimination if significant.

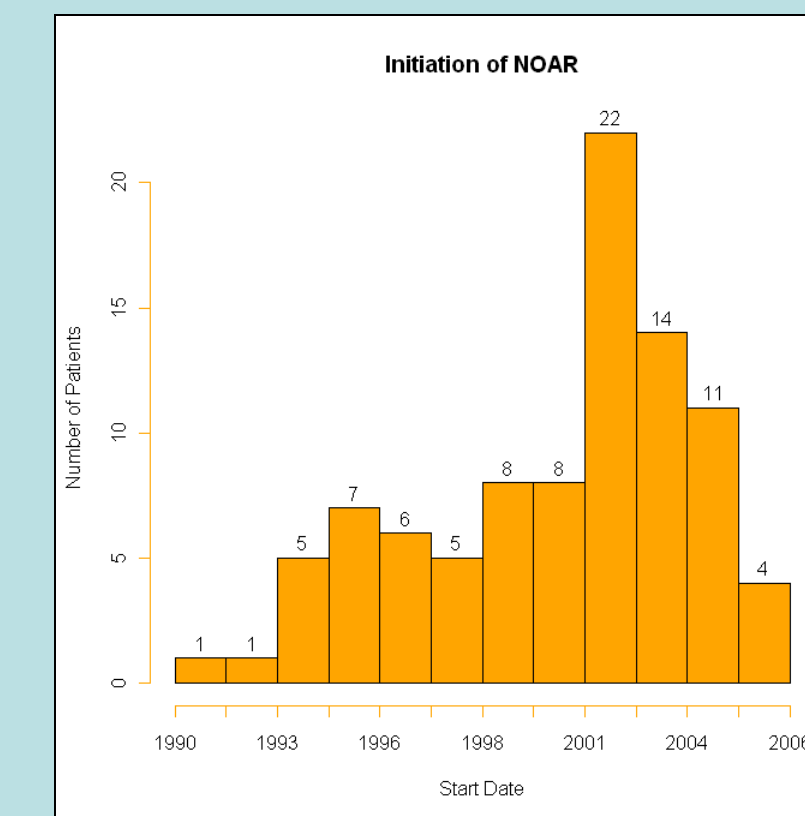
## Results

	N=92
<b>Age at NOAR start</b>	15.0 y (5.0 – 23.0)
<b>Female</b>	52 (54%)
<b>Race/Ethnicity</b>	
Black	56 (61%)
Hispanic	26 (28%)
White/Other	10 (11%)
<b>Treatment history</b>	
Treatment naïve	49 (53%)
Prior regimens in non-naïve	3 (2 – 16)
<b>NOAR Duration</b>	2.0 y (1 d – 8.2 y)
<b>NRTI frequency</b>	
Lamivudine	85 (92%)
Zidovudine	79 (86%)
Abacavir	69 (75%)
Didanosine	22 (24%)
Stavudine	15 (16%)
Tenofovir	9 (10%)
Emtricitabine	1 (1%)
Adefovir	1 (1%)
<b>VL Samples/subject</b>	9 (1 – 40)
<b>CD4 Samples/subject</b>	9 (1 – 24)
<b>Any reported toxicity</b>	65 (71%)
<b>≥1 NRTI mutation after VF in previously treatment-naïve patients</b>	21 (95%) of 22 tested

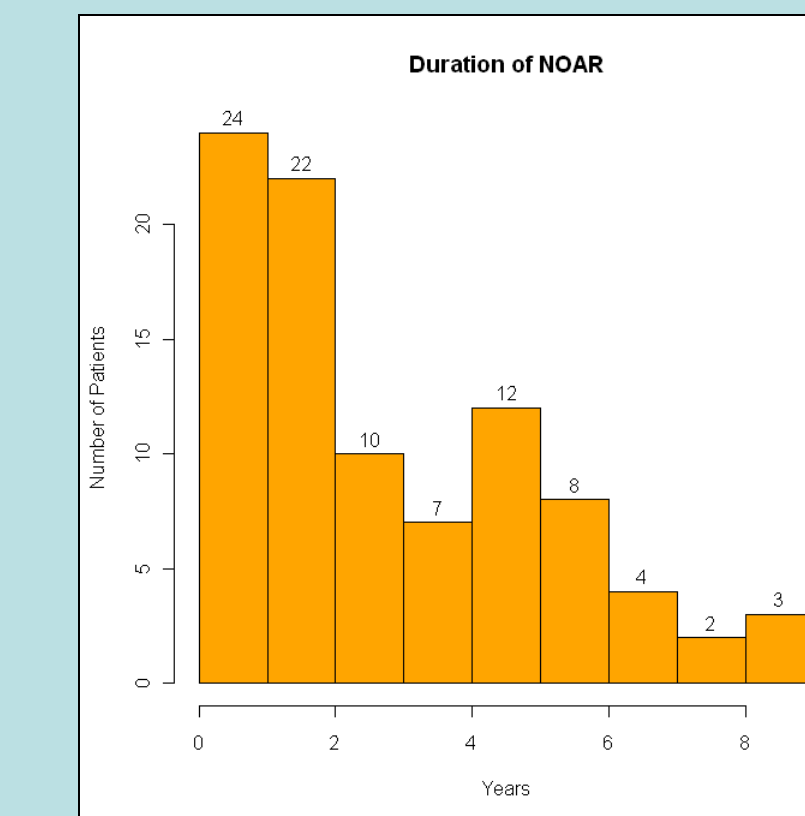
**Table 1 – Population characteristics. Data are median (range) or number (%).**

	Baseline	>Week 48	P-value
<b>Viral load Experienced</b>	3.8 log <sub>10</sub> (3.0 – 5.9)	3.5 log <sub>10</sub> (2.6 – 5.9)	0.30
<b>Naïve</b>	3.8 log <sub>10</sub> (1.7 – 5.8)	3.5 log <sub>10</sub> (1.7 – 5.6)	0.54
<b>CD4% Experienced</b>	22.0 (0 – 58.8)	24.0 (1.0 – 47.8)	0.63
<b>Naïve</b>	26.8 (2.0 – 51.7)	28.0 (13.0– 51.0)	0.67

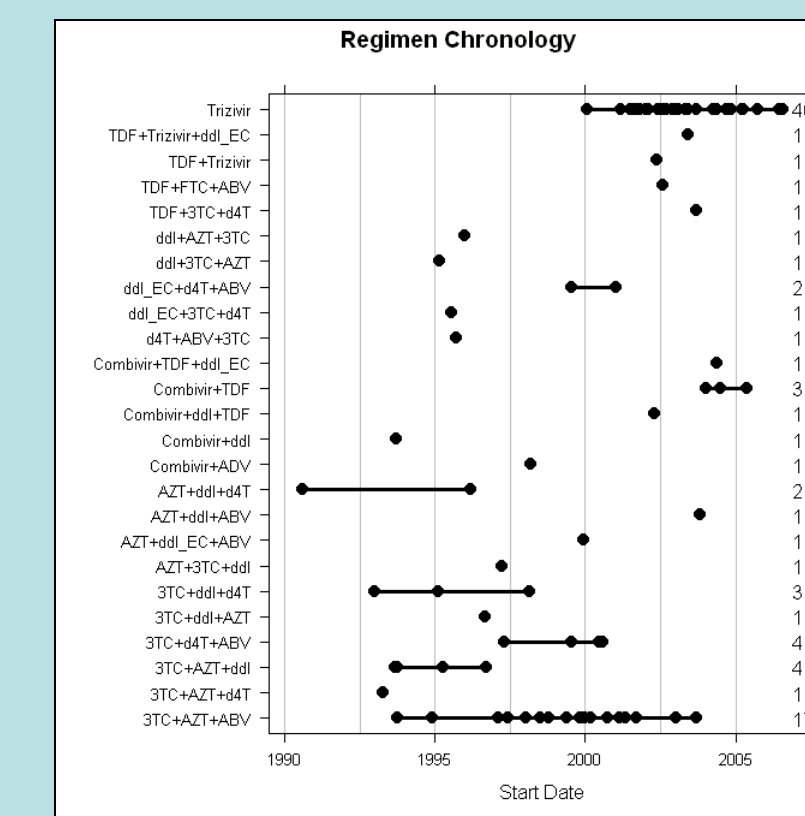
**Table 2 – Median (range) viral load and CD4% at baseline and after at least 48 weeks of NOAR therapy. Overall, 8 (11%) had a decline of >5% in CD4%.**



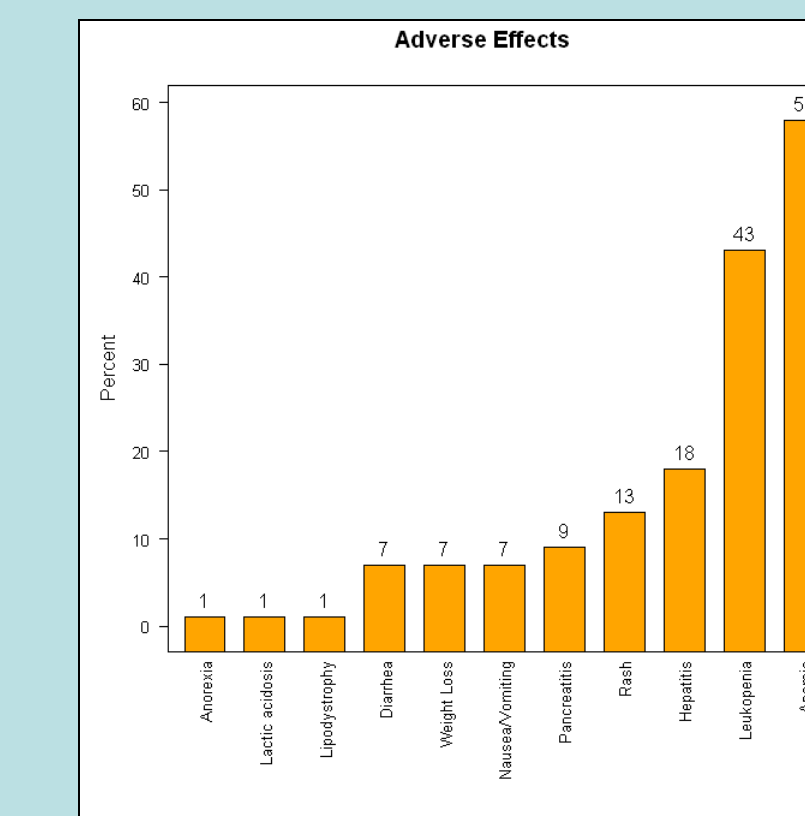
**Figure 1 – Initiation of NOARs by year.**



**Figure 2 – Duration of NOARs.**



**Figure 3 – Composition of NOARs by year. Each dot represents one patient. Total number of each combination are shown along the right axis.**



**Figure 4 – Percent of patients with adverse effects recorded in medical record.**

	Late Failure	No Late Failure	
<b>Early Failure</b>	30	33	63
<b>No Early Failure</b>	2	8	10
	32	41	73

**Table 3 – Virologic failures according to early or late criteria.**

	Baseline		
>Week 48	<400	>400	
<400	6	15	21
>400	6	41	47
	12	56	68

**Table 4 – Numbers of patients with virologic suppression at baseline (18%) and after at least 48 weeks of NOAR therapy (31%), which was not significantly different (P=0.17).**

	Week 48 VL <400 N=21	Week 48 VL >400 N=47	Univariate OR [95% CI] P-value	Multivariate OR [95% CI] P-value
<b>Mean (SD) [range] Age (years)</b>	14.61 (5.73) [6-23]	13.98 (5.57) [5-23]	1.00 (0.89-1.07), P=0.66	
<b>Female</b>	12 (57%)	25 (53%)	0.85 (0.30-2.40), P=0.76	
<b>Race</b>				
Black	14 (66%)	31 (66%)	3.69 (0.80-20.11), P=0.10	1.50 (0.25-9.69), P=0.66
Hispanic	2 (10%)	13 (28%)	10.83 (1.56-109.77), P=0.02	14.78 (1.63-191.79), P=0.02
Other	5 (24%)	3 (6%)	Ref	Ref
<b>Mean (SD) Baseline VL (log<sub>10</sub> copies/mL)</b>	3.43 (1.18)	4.12 (1.12)	1.72 (1.09-2.88), P=0.03	2.24 (1.24-4.46), P=0.01
<b>Baseline log<sub>10</sub> VL &lt; 5</b>	19 (90%)	32 (68%)	0.22 (0.03-0.91), P=0.06	
<b>Any reported toxicity</b>	20 (95%)	37 (79%)	0.19 (0.01-1.07), P=0.12	0.57 (0.35-0.87), P=0.01
<b>Treatment naïve at start of NOAR</b>	8 (38%)	21 (45%)	1.31 (0.46-3.87), P=0.61	
<b>TDF/other/other AZT/3TC/ABV</b>	2 (10%) 18 (86%)	7 (15%) 32 (68%)	1.66 (0.36-11.88), P=0.55 0.36 (0.08-1.26), P=0.14	0.14 (0.02-0.74), P=0.04

**Table 5 – Univariate and multivariate analysis of factors associated with virologic suppression after at least 48 weeks of NOAR therapy. OR > 1 indicate increased odds of VL > 400 copies/mL, i.e. incomplete suppression of viral replication. Percentages are columnar.**

## Conclusions

1. In children and adolescents, NOARs were associated with delayed virologic control (<1 log<sub>10</sub> drop in VL after 12 weeks of therapy in 86%) and poor longer term virologic control (>400 copies/mL in 44% after 24 weeks of therapy and in 69% after 48 weeks of therapy).
2. Higher baseline VL, particularly >100,000 copies/mL, and Hispanic ethnicity were significantly associated with increased odds of VL >400 copies/mL at 48 weeks in univariate and multivariate models.
3. Adjusted for baseline VL and race/ethnicity, NOAR regimens containing AZT/3TC/ABV were significantly associated with reduced odds of VL >400 copies/mL at 48 weeks, and appeared to be better choices than TDF-based NOAR.
4. Mean CD4% did not differ significantly between baseline and week 48, and 11% of patients experienced a decline in CD4% of more than 5 percentage points.
5. Toxicity was common, reported in 71% overall, with anemia most frequently in 56%.
6. In previously treatment-naïve patients, NRTI mutations emerged during NOAR therapy in 95% of those tested.

## Acknowledgements and Disclaimer

We thank the participants and their families for consenting to participate in this CDC-sponsored longitudinal cohort study and thank Westat, Inc. for serving as the monitoring contractor for this project and for developing the remote data capture software used to abstract the data. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.