



The Effect of Different HAART Regimens on Slope of Viral Rebound in HIV-Infected Patients Failing Therapy

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Background:

Highly-active antiretroviral therapy (HAART) leading to undetectable levels of plasma HIV-1 RNA (viral load) has led to sustained decreases in AIDS-related morbidity and mortality. However, viral load often rebounds to detectable levels while patients are taking therapy. Over the short term, slope of viral rebound may vary between different HAART regimens.

Objectives:

To compare viral rebound in HIV-1 infected patients on three distinct kinds of HAART regimens, with respect to:

- Predictors of viral rebound
- Time to rebound
- Slope of rebound

Methods:

Individual patient data were compared from the triple regimen arms of 4 completed clinical trials:

Trial	Triple Regimen
INCAS:	Nevirapine (NVP)/Zidovudine (ZDV)/Didanosine (ddl)
AVANTI-2:	Indinavir (IND)/ZDV/Lamivudine (3TC)
AVANTI-3:	Nelfinavir (NFV)/ZDV/3TC
CNAAB3005:	Abacavir (ABC)/ZDV/3TC

HIV RNA levels were performed in prospectively collected samples after completion of each trial, and thus were not available for use in patient management. Rebound was defined as two consecutive viral load values above the lower limit of quantification (LLOQ) after achieving ≥ 1 viral load below LLOQ. Different values for LLOQ were used in each trial. In order to standardize this, statistical analysis was also done using 400 copies/ml as the LLOQ for all trials.

The different triple regimens were compared for predictors of rebound, time to rebound and slope of rebound, using a logistic regression model, Cox proportional-hazards model and linear regression model respectively. Slope of rebound was determined using 3 points: the ultimate value below the LLOQ and the first 2 values above the LLOQ. Subjects were considered non-adherent if they reported taking <75% of any of the study medications between visits (AVANTI), or if they failed to take study medications for >28 days within the first year of follow-up (INCAS).

Results:

Table 1: Baseline characteristics of patients in the triple therapy arms of INCAS, AVANTI-2, AVANTI-3, and CNAAB3005 (ABC-arm)

Clinical Trial	INCAS	AVANTI-2	AVANTI-3	CNAAB3005
	NVP/ddI/ZDV	IND/3TC/ZDV	NFV/3TC/ZDV	ABC/3TC/ZDV
Number of patients in triple therapy arm	51	52	53	262
Patients with:				
viral suppression < 400 c/mL(n)	46	49	50	222
blip (%)	17	16	6	25
viral rebound > 400 c/mL (%)	52	24	26	25
CD4 at baseline ($\times 10^6$, med)	395	281	295	359
HIV RNA at baseline (log c/mL, med)	4.25	4.7	5.0	4.85

Table 2:

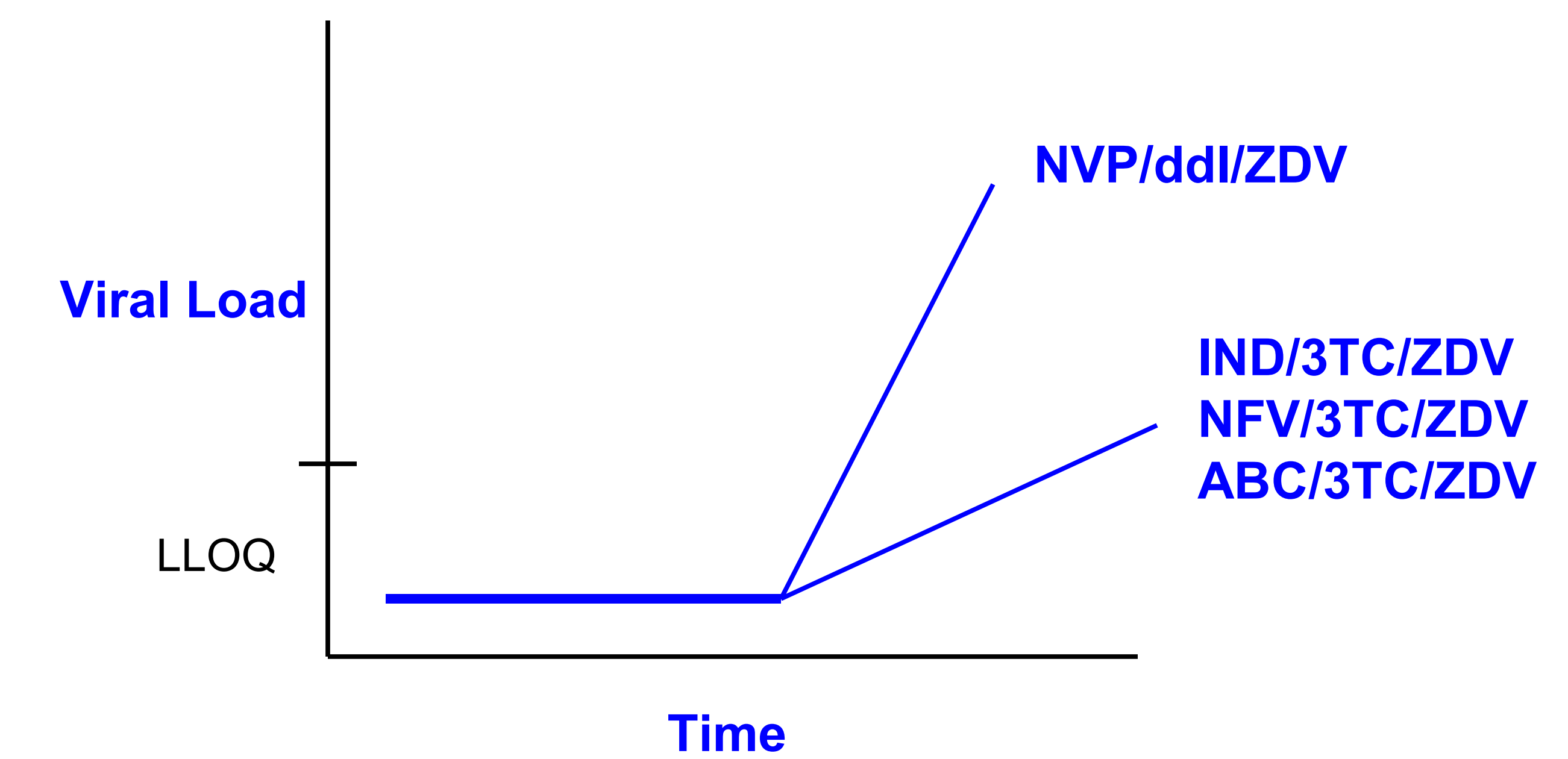
Multivariate analysis of predictors of viral rebound >400 copies/ml

Factor	Predictor of viral rebound (OR)	(p value)	Time to rebound (RR)	(p value)	Slope of rebound (p value)
Incomplete-adherence	2.87*	0.0001	2.95*	0.0001	0.57
NVP/ddI/ZDV-regimen	2.81*	0.002	1.51	0.11	0.066
Baseline CD4	1.0	0.87	1.0	0.70	0.91
Baseline VL	1.3	0.08	1.27	0.08	0.29
Blip	0.89	0.70	0.62	0.06	0.09

* statistically significant

Figure 1:

Slope of rebound was steeper for the NVP/ddI/ZDV-regimen than the IND/3TC/ZDV or NFV/3TC/ZDV or ABC/3TC/ZDV regimens (not to scale)



The NVP-regimen had the steepest slope of viral rebound ($p=0.006$) using the LLOQ of each trial. Even when 400 c/ml was used as the LLOQ for all the trials, the NVP-regimen maintained a trend for steepest slope of rebound ($p=0.066$).

Conclusions:

- Incomplete adherence was a predictor of viral rebound and a shorter time to rebound.
- Occurrence of a single detectable HIV RNA (blip), baseline CD4 count and baseline viral load were not predictive of rate of viral rebound or slope of rebound.
- When only adherent patients were included in the analysis, baseline viral load was the only predictor of shorter time to rebound (RR 1.48).
- Patients taking the NVP-regimen had a steeper slope of rebound than patients taking PI or ABC-containing regimens ($p=0.006$).
- When 400 c/mL was used as the LLOQ for all the trials, the NVP-regimen maintained a trend for steepest slope of rebound ($p=0.066$).
- The non-NVP regimens all contained 3TC, hence differences in early virologic rebound could be related to the emergence of the M184V mutation versus the K103N or Y181C mutation in the NVP regimen.