

Low level HIV-1 viremia in Thai women 24 weeks after treatment initiation with NNRTI-based antiretroviral therapy (ART) was not associated with prior single-dose nevirapine (SDNVP) exposure or viral resistance mutations

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Background

- Studies of response to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based highly active antiretroviral therapy (ART) after SDNVP have indicated:
 - If treated within 6 months of SDNVP - poorer virologic response
 - If treated >6-12 months after SDNVP - adequate virologic response

Objective

- To assess the association of low level viremia (viral load 40 – 399 copies/ml) at 24 weeks after NNRTI-based ART initiation with prior SDNVP exposure and viral resistance mutations

The NNRTI Response Study

(Stringer, et al. PLoS Medicine, in press)

- The NNRTI Response Study enrolled 878 single-dose NVP exposed (n = 355) and non-exposed (n = 523) women in Zambia (n=509), Thailand (n=217), and Kenya (n=152) to determine virologic response to NNRTI-based ART
- We report on the 217 women who commenced ART in Thailand

Enrollment

- Inclusion Criteria
 - Women, age ≥ 18 years old, ART naïve
 - Qualify to start NNRTI-based HAART according to national guidelines
- Comparison groups
 - NVP-unexposed women: No receipt of SDNVP in pregnancy
 - NVP-exposed women: Prior receipt of SDNVP in pregnancy
 - All women in Thailand got PMTCT regimen of zidovudine + SDNVP
- NVP-unexposed women were frequency matched to NVP-exposed women by CD4 cell count and WHO stage in a ratio of 1.5 to 1

Medical Care

- Antiretroviral therapy
 - Stavudine
 - Lamivudine
 - Nevirapine (or efavirenz if on TB treatment)
- Study visits at week 0, 2, 4, 8, 16, 24, 36, 48 after initiating HAART
 - Viral load and CD4 cell counts at weeks 0, 24, 48
 - Clinical management directed locally by providers
 - Research staff provided adherence support and outreach to maintain women in care

Methods

- Definitions
 - Low level viremia: VL at 24 weeks = 40-399 copies/ml
 - Viral suppression: VL at 24 weeks <40 copies/ml
- Laboratory testing for viral load
 - COBAS Taqman or Roche Amplicor assays
- Resistance testing on baseline plasma specimens before starting ART
 - A broadly-sensitive in-house sequencing-based genotyping assay was used to genotype the reverse transcriptase gene encompassing codons 1-251
 - Allele-specific Real-Time PCR assays were used to screen for minor strains of NNRTI-associated drug resistance mutations including K103N, V106M/I, Y181C and G190A
 - Subtype classification was determined by phylogenetic analysis using MEGA 4 software
 - Abstract T-172, Poster 192 (*Yang, et al*) has more details on the prevalence of resistance mutations detected in this study
- Statistical analysis
 - Backwards stepwise regression was conducted to assess factors associated with low level viremia

Baseline characteristics

Baseline cohort characteristics	N = 217 (%)
SDNVP exposure *	
Exposed	87 (40.1)
Unexposed	130 (59.9)
Baseline VL	
<100,000 copies/ml	104 (47.9)
≥100,000 copies/ml	113 (52.1)
Baseline CD4	
0-49 cells/ul	54 (24.9)
50-199 cell/ul	94 (43.3)
≥200 cells/ul	69 (31.8)
Viral subtype	
CRF01_AE	201 (92.6)
B	14 (6.5)
Unclassified	2 (0.9)
Baseline viral resistance mutations (PCR) **	
Any	13 (6.2)
K103N	5
V106I	4
Y181C	4
G190A	2
K103T	1

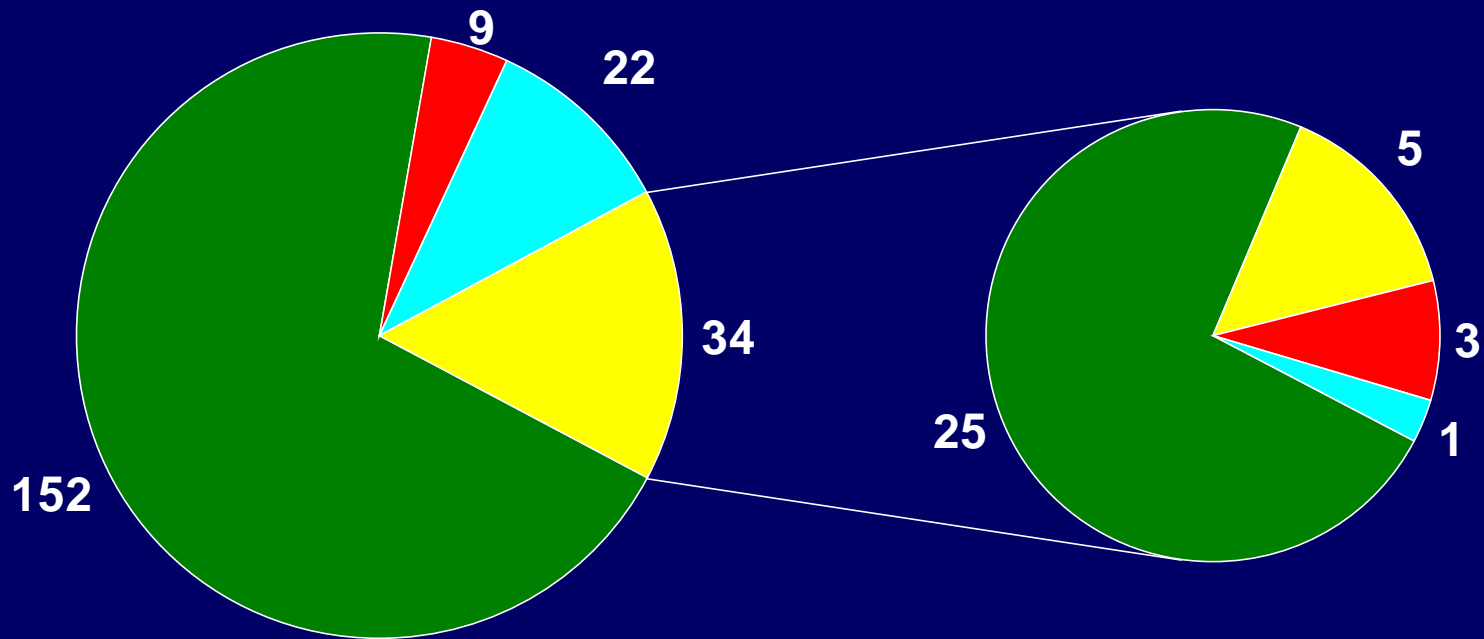
Table Legend

- * Women exposed to SDNVP were exposed a median of 24.2 months prior to ART initiation (inter-quartile range = 12.3, 45.9)
- **4 of 13 women had the same mutations detected by allele-specific Real-Time PCR assays and a sequencing-based genotyping assay

Viral load outcomes at 24 and 48 weeks

24 weeks

48 weeks



■ VL < 40 ■ VL > 400 ■ Died or stopped ART ■ VL 40-399

Figure legend

- At 24 weeks, 152 had viral load <40 copies/ml, 34 had 40-399 copies/ml, 9 had >400 copies/ml and 22 had died/discontinued the study or NNRTI-based treatment
- Of women with viral load <40 copies/ml at 24 weeks who remained on NNRTI-based ART all had viral load <40 copies/ml at 48 weeks
- Thirty-three of 34 women with viral load 40-399 copies/ml at 24 weeks continued NNRTI-based ART until week 48 (1 discontinued ART); 25 (73.5%) of 33 women had viral load <40 copies/ml at 48 weeks, 5 (14.7%) had 40-399 copies/ml, and 3 (8.8%) had \geq 400 copies/ml

Factors associated with low level viremia at 24 weeks

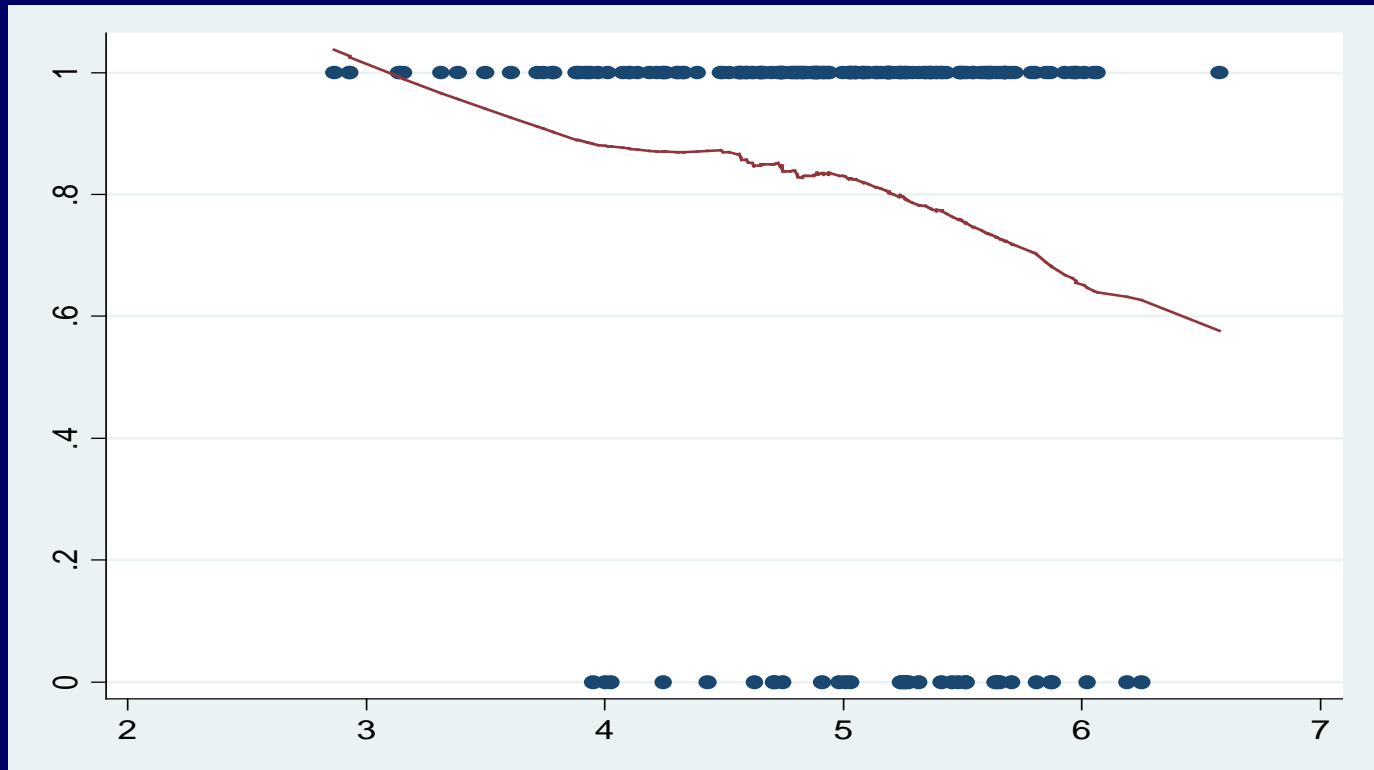
Factor	VL <40 (n=152)	VL 40-399 (n=34)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age				
<30 years	52	6	1	1
≥30 years	100	28	2.43 (0.95-6.23)	3.26 (1.15-9.24)
SDNVP exposure				
Exposed	92	19	1	
Unexposed	60	15	1.21 (0.57-2.57)	
Baseline VL				
<100,000 copies/ml	80	11	1	
≥100,000 copies/ml	72	23	2.32 (1.06-5.10)	2.51 (1.10-5.73)
Baseline mutations				
No	145	32	1	
Yes	7	2	1.30 (0.26-6.53)	
Viral strain				
CRF01_AE	146	29	1	1
B	5	4	4.03 (1.02-15.91)	6.32 (1.35-29.72)
Unclassified	1	1		

Table legend

- The odds of having low level viremia (VL 40-399 copies/ml) as compared to having an undetectable viral load (VL<40 copies/ml)

Association between baseline viral load and low level viremia versus viral suppression at 24 weeks

Probability of viral suppression



Viral load result at baseline (log₁₀ copies/ml)

Figure legend

- Locally-weighted regression (LOESS) model of the risk of having a viral load <40 copies/ml versus 40 – 399 copies/ml at 24 weeks as a function of the viral load prior to starting NNRTI-based treatment
 - The individual dots represent individual patients who either had viral load 40 – 399 copies/ml (bottom) or <40 copies/ml (top)
- The strength of the association is provided by the logistic regression slope treating log₁₀ viral load as continuous variable
 - For a 1-unit decrease in log₁₀ baseline VL there is 0.46 decrease in the odds of viral suppression at 24 weeks (95% CI 0.25,0.86 p=0.013)

Summary

- Low level viremia of 40-399 copies/ml versus viral load <40 copies/ml was associated with higher baseline viral load and viral subtype , but not with prior SDNVP exposure or the presence of baseline resistance mutations
- Patients with viral subtype B were significantly more likely than those with CRF01_AE to have low level viremia, as were patients with a high baseline viral load
- Almost all patients with low level viremia at 24 weeks had viral load <40 copies/ml at 48 weeks while continuing on an NNRTI regimen

Conclusions

- Viral load of 40-399 copies/ml at 24 weeks of NNRTI-based ART does not predict virologic failure at 48 weeks
- Patients with low level viremia at 24 weeks and prior SDNVP exposure or baseline viral resistance mutations associated with SDNVP exposure are not associated with virologic failure if maintained on their current ART regimen
- Patients with viral load of 40–399 copies/ml after 24 weeks of NNRTI-based ART should be continued on their current regimen regardless of prior exposure to SDNVP or presence of mutations at baseline