correspondence: F. van Leth, IATEC, room T0-122, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands, f.vanleth@iatec.com

2981

Nevirapine and efavirenz have a comparable viral decay rate, which is not associated with virologic failure.

F. van Leth [1], C. Huisamen [2], R. Badaro [3], B. Vandercam [4], J. de Wet [5], J. Montaner [6], D. Hall [7], F.W. Wit [1], and J.M.A. Lange [1,8] for the 2NN study group.

[1] IATEC, Amsterdam, The Netherlands; [2] Molteno Road Practice, Cape Town, South Africa; [3] Hospital Universitario Professor E. Santos, Salvador, Brazil; [4] Cliniques Universitaires St. Luc, Brussels, Belgium; [5] Virion Clinical Sciences, Vancouver, Canada; [6] St. Pauls's Hospital, Vancouver, Canada; [7] Boehringer-Ingelheim, Ridgefield, USA; [8] University of Amsterdam, The Netherlands.

1: Introduction

The rate of decline in plasma HIV-1 RNA concentration after start of antiretroviral therapy is expressed by the Viral Decay Rate (VDR). This VDR is considered to be bi-phasic, whereby the first phase is assumed to be an indicator of the potency of the antiretroviral treatment.

The main objective of the 2NN study was to compare the efficacy and safety of nevirapine (NVP) and/or efavirenz (EFV) in combination with stavudine (d4T) and lamivudine (3TC), in antiretroviral therapy naive patients infected with HIV-1. There were no significant differences between NVP and EFV regarding efficacy parameters after 48 weeks of treatment, although equivalence within the 10% limit could not be established between the two drugs.

This study examined the early efficacy of NVP and EFV in terms of viral kinetics within the first 2 weeks of treatment.

2: Methods

The 2NN is a 48-weeks international, multicenter study that enrolled 1,216 adult ART-naive patients infected with HIV-1, without restrictions on CDC-class or CD4+ T-cell count. Patients were allocated to a combination of d4T and 3TC with either NVP-once daily, NVP-twice daily, EFV, or NVP+EFV.

Plasma HIV-1 RNA concentrations (pVL) were measured at day 0, 3, 7, and 14 after start of allocated treatment. Of patients remaining on allocated treatment during the first week (n=1106) and the second week (n=1038), the rate of pVL decline was calculated using the non linear function $V_{(t)}=V_{(0)} * e^{(-kt)}$, where $V_{(t)}$ denotes the pVL at time=t, $V_{(0)}$ the pVL at baseline, and k=viral decay constant (VDR).
The two NVP-only arms were combined since these patients used the same dosing scheme in the first two weeks of treatment (200mg once daily).

Multivariate analyses identified factors associated with a high VDR (75th percentile). A 'Cox proportional hazard' analysis assessed the association between VDR and virologic failure while on allocated treatment (never a pVL < 50 c/mL, or 2 consecutive pVL > 50 c/mL after having had a pVL < 50 c/mL; censoring at change of allocated treatment). A two sided p-value < 0.05 was considered statistically significant.

3: Baseline characteristics

	NVP n=556	EFV n=362	NVP+EFV n=188	TOTAL n=1106
Sex, % male	61.7	62.7	69.2	63.3
Age, median (iqr)	34 (29-41)	34 (30-39)	32 (29-39)	34 (29-40)
CD4 cells, cells/mm^3, median (iqr)	180 (70-330)	180 (70-340)	190 (90-330)	180 (70-330)
HIV-1 RNA, $\log_{10}$, median (iqr)	4.7 (4.4-5.5)	4.7 (4.4-5.5)	4.7 (4.4-5.4)	4.7 (4.4-5.5)
Baseline pVL > 100,000 c/mL, (%)	30.9	34.5	30.3	32.0
CDC-class C, %	21.0	21.0	18.6	20.6
Risk behaviour, %				
heterosexual	59.7	57.7	52.7	57.9
homosexual	26.1	29.0	34.6	28.5
IVD	3.2	3.6	5.3	3.7
other/unknown	11.0	9.7	7.4	9.9

There were no significant differences in baseline characteristics between the study arms. The baseline characteristics of the present study group were comparable with the characteristics of all patients enrolled in the 2NN study.

4: Viral Decay Rates

The plots depicting the $\log_{10}$ transformed pVL concentrations at baseline, day 3, 7, and 14, indicate a faster decline in pVL during the first week of treatment, compared to the second week (Figure 1). The VDR for week 1 and week 2 by treatment arm are therefore summarised separately in the table below

Proportion virus cleared per day median (IQR)	NVP n=556	EFV n=362	NVP+EFV n=188	p-value
Week 1	0.47 (0.37-0.59)	0.51 (0.43-0.60)	0.49 (0.39-0.59)	0.002
Week 2	0.15 (0.09-0.23)	0.13 (0.07-0.21)	0.15 (0.10-0.21)	0.036

5: Factors associated with a high Viral Decay Rate

Factors associated with a VDR above the 75th percentile were identical for week 1 and week 2, with the exception of region, which was associated with a higher VDR in week 1 but not in week 2. The factors that were associated with VDR in this univariate analysis were, together with the variable arm, included in a multivariate analysis. In week 1, only baseline pVL was independently associated with a higher VDR (the effect of region disappeared), while in week 2, also baseline CD4 count was independently associated.

Odds Ratio from multivariate analyses	Week 1	Week 2
Baseline pVL (c/mL)		
≤ 100, 000	1	1
> 100,000	8.5 (6.1-12.0)	1.8 (1.3-2.5)
Baseline CD4 (cell/mm^3)		
< 50	1.0 (0.6-1.5)	2.2 (1.4-3.5)
50-200	0.8 (0.5-1.3)	1.0 (0.7-1.4)
>200	1	1

The adjusted VDR for each of the treatment arms by week is reported below. In week 1, the value is adjusted for baseline pVL. For week 2, the value is adjusted for baseline pVL and baseline CD4 count.

Proportion virus cleared per day median (IQR)	NVP n=556	EFV n=362	NVP+EFV n=188	p-value
Week 1	0.47 (0.44-0.56)	0.47 (0.44-0.57)	0.47 (0.44-0.55)	0.741
Week 2	0.15 (0.14-0.17)	0.15 (0.14-0.17)	0.15 (0.14-0.16)	0.833

6: VDR and virologic failure

Patients with a VDR > 75th percentile for week 1 were slightly less likely to have a virologic failure while on treatment (HR=0.95, 95% CI: 0.7-1.3, p=0.095), compared to patients with a lower VDR in week 1. For week 2 this estimate was 1.2 (0.9-1.6). Over the full 2-week period, the association of high VDR and virologic failure was non-significant (HR=1.0, 95% CI: 0.7-1.14, p=0.996)

Figure 1

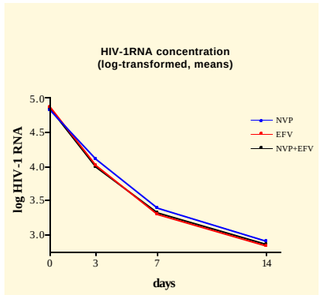
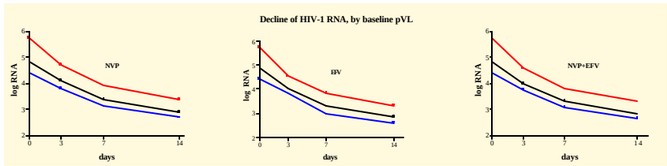


Figure 2



7: Conclusions

- **The VDR was higher in week 1 than in week 2 in each of the treatment arms.**
- **The VDR was significantly higher in patients with a baseline HIV-1 RNA concentration > 100,000 copies/mL, both in week 1 and week 2.**
- **The VDR in week 2 was significantly higher in patients with low baseline CD4 count.**
- **Adjusted for differences in baseline viral load and CD4 count, the VDR was comparable in all treatment arms, both in the 1st and 2nd week of treatment.**
- **The VDR was not predictive for virologic failure on or before week 48 while remaining on allocated treatment.**

8: 2NN collaborators

Site investigators: *Argentina:* P. Cahn, J. Cassetti, H. Laplumé, M.B. Lasala, M.H. Losso, G. Reboredo; *Australia:* M. Bloch, O. Russell; *Belgium:* J. Demonty, R. Peleman, B. Vandercam; *Brazil:* R. Badaro, B. Grinsztejn, G.C. Levi, B.R. Santos, M. Schechter, D. Ulp; *Canada:* B. Conway, J.J. de Wet, J.S.G Montaner; *France:* C. Katlama, J.M. Livrozet, F. Raffi, W. Rozenbaum, D. Sereni; *Germany:* S. Staszewski; *Greece:* M. Lazanas, N. Stavrianeas; *Ireland:* F. Mulcahy; *Italy:* A. Chirianni, F. Leoncini, F. Montella; *Poland:* M. Beniowski, A. Boron-Kaczmarska, W. Halota, A. Horban, D. Prokopowicz; *Portugal:* F. Antunes, R.S.E. Sarmento; *South Africa:* S. Andrews, E. Baraldi, C.B. Huisamen, D. Johnson, U.G. Lalloo, D.R. Malan, O.Martin, S. Miller, D. Petit, I. van der Westhuizen, R. Wood; *Switzerland:* E. Bernasconi; *Thailand:* P. Phanuphak; *United Kingdom:* M. Fisher, B. Gazzard, M.A. Johnson, E.G.L. Wilkins; *USA:* S. Becker, H. Katner, R.L. Murphy, D. Rimland, M.S. Saag, K. Squires, M. Thompson, M. Witt.
Project management: J.P.M. Dam, A. Potarca, M. Cronenberg, L. Kreekel
Data management: R. Meester, J. Khodabaks, H-J Boima, K. Jansen, M. Mulder, G. Ruiter, I. Farida, N. Esrhir, M. Feenstra, A. Klotz,
Monitoring: Quintiles, Boehringer-Ingelheim.
Laboratory: C.B. Bass, E. Pluymers, E. de Vlegelaer (projectmanagers Labcorp), R. Leeneman (study manager VCL)
Boehringer Ingelheim: P. Robinson, H. Carlier, E. van Steenberghe

The 2NN study was conducted by IATEC and financially supported by Boehringer-Ingelheim