Once-daily Nevirapine dosing

**NVP QD:** pharmacokinetics, efficacy and safety

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**Clinical pharmacology of NVP**

In the context of attempts to simplify treatment regimens and enhance adherence, there is great interest in once-daily (QD) dosing regimens for the treatment of HIV-infected patients.

Nevirapine (NVP) has a long plasma half-life and high steady state plasma concentrations meaning that it may be a suitable candidate for once-daily use.

**Pharmacokinetics**

The pharmacokinetic data suggested that once-daily nevirapine dosing resulted in lower minimum nevirapine plasma concentrations compared with twice-daily treatment.

However these studies theoretically support once-daily dosing assuming that optimal adherence is maintained.

![Figure 1. Median steady-state plasma concentration vs time curves of nevirapine in 20 HIV-1-infected patients after administration of](image-url)
nevirapine 400 mg once-daily (solid circles) and 200 mg twice-daily (open circles).

[van Heeswijk RP et al. The steady-state pharmacokinetics of nevirapine during once daily and twice daily dosing in HIV-1-infected individuals. AIDS 2000; 14: F77–F82]

The median nevirapine plasma concentration at the end of the dosing interval (Cmin) was about 23% lower during once-daily dosing compared with twice-daily dosing [2.88 μg/mL (2.33–4.09 μg/mL) vs 3.73 μg/mL (3.20–5.08 μg/mL), respectively; P<0.01].

**2NN: efficacy**

The 2NN study compared the efficacy and safety of treatment with d4T and 3TC, and NVP once daily (QD), NVP twice daily (BID), EFV or the combination of NVP and EFV in 1216 ARV-naive HIV-1-infected patients at 48 weeks.

The primary endpoint of 2NN was the proportion of patients with treatment failure. Week 48 data showed no significant differences in treatment failure between regimens: the majority of patients in each arm had VLs <50 copies/mL: 65.4% in the NVP BID arm; 70% in the NVP QD arm; and 70% in the EFV arm.
2NN: side effects

The safety profiles of NVP and EFV differed in the 2NN study and authors advised this to be considered when selecting a treatment regimen.

One of the key findings showed a higher rate of hepatobiliary lab toxicity in the NVP once-daily compared to the twice-daily arm (13.2 vs 7.8, p=0.002), despite similar efficacy. The results, presented at the Retrovirus conference in February 2003, provided key comparative data for how NNRTIs have subsequently been used in clinical practice: research into the risk factors for serious rash-associated hepatic toxicity led to regulatory changes in the product labeling, with an indication to only prescribe NVP in treatment naïve patients with CD4 count <250 cells/mm³ in women and <400 cells/mm³ in men.

At the EACS meeting Dublin, 2005, Stephen Storfer from Boehringer Ingelheim presented an analysis of hepatic events based on Thai and non-Thai patients who started treatment based on these new CD4 guidelines that tied the higher rates seen in the once-daily nevirapine arm to a single site in Thailand.
2NN: 3 years later

Data collected retrospectively for almost 3 years confirmed no significant differences between the treatment regimens (2007, IAS meeting).

It only followed <50% of the original cohort with some disparities between the groups: 567 patients were followed out to week 144. During the interim period (week 49-144), there were more failures in the once daily arm (45% vs. 36%) though it didn’t reach statistical significance. It’s not certain if this is reflective of a trend, or simply a regression to the mean. There were slightly more failures in the twice daily arm for weeks 0-48.
Other clinical studies on NVP QD efficacy

**DAUFIN**

The DAUFIN study compared AZT/3TC 300 mg/150 mg plus NVP 200 mg twice daily with 3TC 300 mg, TDF 245 mg and NVP 400 mg once daily.

The study was stopped after early virological failure was observed in 8/36 (22.2%) once-daily patients.

Resistance mutations accumulated while on treatment; high rates of K65R mutations and severe NNRTI resistance profiles might be indicative of ongoing viral replication caused by suboptimal nevirapine plasma trough concentrations under non-adherence to the treatment regimen. Non-B-subtype infection (subtype A or C not stated) was observed in 4/10 patients with virological failure. The DAUFIN study was prematurely stopped without predetermined cessation criteria, presented data are not complete, and results should be interpreted with caution.

**ATHENA**

Analysis of 5,244 patients, including 4,471 patients receiving twice-daily NVP and 629 patients receiving once-daily NVP. They also looked at treatment responses to once- and twice-daily Viramune using three main study characteristics:
### Swiss HIV Cohort Study

1. those who used either dose upon starting HIV treatment for the first time,
2. those who switched to either dose after achieving an undetectable viral load with other antiretrovirals,
3. treatment-experienced patients with detectable viral loads who switched to either dose of NVP.

Among those starting treatment for the first time with a NVP regimen, 84% of the 82 patients on once-daily NVP and 84% of the 771 patients on twice-daily NVP had undetectable viral loads—below 50 copies—after two years of treatment, and it took longer for viral loads to go undetectable using once-daily NVP.

Among those who switched to NVP with an undetectable viral load, virologic responses were durable and comparable among the 1,507 using twice-daily NVP and the 193 patients using once-daily NVP for up to 96 weeks of follow-up.

Pretreated patients with detectable viral loads had better virologic outcomes with the use of once-daily, compared with twice-daily NVP. Time to viral load suppression was also shorter using once-daily NVP in this population of patients, and gains in CD4 cell counts were significantly better in the once-daily NVP group (an increase of 110 cells versus 80 cells in the twice-daily group).

“These data,” Dr. Calmy and her fellow authors suggest in the published study abstract, “suggest that once-daily NVP in clinical practice is at least as efficient as NVP prescribed twice a day. For patients with detectable [viral loads] who have been exposed to other antiretroviral drugs and [are] commencing a regimen including NVP, NVP once daily is associated with better and faster virologic suppression, as well as stronger immune restoration.”


### Transition from BID to QD: clinical data

**Whetham J.**

<table>
<thead>
<tr>
<th>Switching from NVP BID to NVP QD after risk period may be safe.</th>
</tr>
</thead>
<tbody>
<tr>
<td>110/284 NVP pts switch from BID to NVP QD.</td>
</tr>
<tr>
<td>Liver function tests at and since switch to QD were reviewed; viral control remained &lt;40 cp/ml.</td>
</tr>
</tbody>
</table>
Switching to NVP OD after the high risk period for adverse events results in no increased toxicity. High CD4 count at switch did not seem to be associated with a high rate of adverse events.

(Whetham J, et al., BHIVA 2006, Poster P11)

### Table 2. Comparison with 2NN data: Discontinuations for rash and hepatic adverse events

<table>
<thead>
<tr>
<th></th>
<th>2NN data NVP BD</th>
<th>2NN data NVP OD</th>
<th>Lawson Unit NVP BD</th>
<th>Lawson Unit after NVP OD switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation for Rash</td>
<td>6.5%</td>
<td>12.3%</td>
<td>4.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Discontinuation for abnormal LFT or clinical hepatitis</td>
<td>3.9%</td>
<td>7.7%</td>
<td>2.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>13.9%</td>
<td>6.7%</td>
<td>20.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>20.7%</td>
<td>20.7%</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Switching to NVP OD after the high risk period for adverse events results in no increased toxicity.

(Whetham J, et al., BHIVA 2006, Poster P11)

**Bruggeman R.**

The aim of this study was to determine if switching from NVP BID to QD has any hepatotoxic consequences. Twenty nine patients (3 females) took NVP BID for 6 months and achieved VLs <50 cp/mL. All patients had normal liver function test (LFT) values. Fourteen patients were randomised to switch to NVP QD. LFTs, CD4 cell count, VL and NVP serum levels were monitored at 1, 3 and 6 months. Viral control was maintained in both groups. There was no difference in ALT levels between the groups – indicating that there was no increase in hepatotoxicity due to switching to NVP QD.

(Bruggeman, R et al., ICAAC 2007, Chicago. Abs. A-1407)

**Benzie A.**

Prospective, single centre, cohort study that enrolled all ARV naïve patients starting NVP BID plus 3TC or FTC and 1 NRTI between January 2002 and January 2006 at St Mary’s Hospital, London. The total number of patients eligible for the analysis was 173. At Week 48, 85% of NVP patients had VL <50 cp/mL. Mean CD4 cell count had increased by 204 cells/mm3.

Twenty three subjects (13%) had switched to NVP QD by Week 48. The total number of patients who switched by Year 5 was 49. **No increased rates of hepatotoxicity** (increased ALT levels) were observed in patients who switched to NVP QD.

No significant differences in total or HDL cholesterol levels or in CD4 cell count or NRTI background were detected over the first 12 months of switching to NVP QD.

No patients taking NVP QD experienced treatment failure.

In this cohort, **switching to NVP QD within the first year of HAART was associated with high treatment success rates, irrespective of the NRTI backbone.**

(Benzie A, et. al., 11th EACS 2007, Madrid, Sp. Abs P7.9/02)

**NODY study**

This study compared the efficacy, hepatotoxicity and other safety parameters in HIV-1 infected patients who switched from NVP BID to NVP QD. It was a randomized, open label, multi centre, 12 month, Spanish study. A total of 298 patients were evaluable: 143 in the NVP QD...
arm; and 146 in the NVP BID arm. Virological success rates were similar in both arms (K-M estimate, ITT, \( p=0.673 \)). The time to Grade 3-4 hepatotoxicity was similar in both arms (K-M estimate, ITT, \( p=0.273 \)). Co-infection with hepatitis C (HCV+) and increased ALT levels at baseline were independently associated with hepatotoxicity in this study. Switching to NVP QD was associated with low frequency of hepatotoxicity and maintenance of viral suppression.


ATHEMA & Swiss SHCS

Data from 5244 patients in the ATHENA and Swiss SHCS cohorts who had taken NVP were included in the intent to treat (ITT) analysis. The majority of patients (85.2%) took NVP BID, while 12.2% had switched from BID to NVP QD and 12.0% had initiated NVP with QD dosing.

Patients who had discontinued NVP because of HSRs (rash and/or hepatotoxicity) within 18 weeks of starting NVP were identified. The median follow up was 4.6 years (2.4-6.7). HSRs occurred in 301/5244 (5.7%) of patients taking NVP for the first time. Stratification by dosing schedule showed:

- NVP BID: 201/4471 (4.5%)
- NVP QD: 41/629 (6.5%)
- During lead in dose: 59/144 (41.0%)

Hepatotoxicity occurred at similar rates in both QD (1.11%) and BID (1.12%) patients. Discontinuation of NVP due to rash was more common in QD (5.4%) than in BID (3.47%, \( p=0.016 \)) patients. In multivariate analysis, the dosing schedule remained significant (OR 1.69, \( p=0.008 \)).

A total of 641 patients switched from BID to NVP QD. Only 3/641 (0.47%) discontinued due to HSR (2 rashes, 1 hepatotoxicity). The ATHENA and Swiss Cohort Investigators concluded that it was safe to switch a stable NVP-based combination therapy from BID to QD.

(Calmy A, et. al., 11th EACS 2007, Madrid, Sp. Abs PS5/3)

The future

Boehringer-Ingelheim announced that it is beginning recruitment to an international study of an extended-release, once-daily formulation of its antiretroviral drug NVP.

The VERXVE study will compare twice daily dosing with once-daily dosing of a new, extended release formulation comprising one NVP tablet. All participants will receive TDF/FTC alongside NVP.

VERXVE is a 48-week study that will recruit around 1000 treatment-naive patients in North and South America, Europe, Australia and South Africa, and results are expected in 2010.
The study will also need to put to rest concerns regarding the efficacy of combinations which combine NVP and TDF. The DAUFIN study (Podzamczer, D, et al. 15th Conference on Retroviruses and Opportunistic Infections. 2008. Boston, USA. Abs 960) found a high risk of failure using the combination of tenofovir, 3TC and nevirapine, while an Italian study (Lapadula G et al, 11 European AIDS Conference, Madrid, abstract P7.3/10, 2007) found a high failure rate in recipients of Truvada (TDF/FTC) plus twice daily NVP who had high viral load.

The potential licensing of a new once-daily formulation will have an additional commercial advantage for Boehringer-Ingelheim: its patent exclusivity on the current formulation of NVP expires in Europe in 2010 and the United States in 2011, at which point generic manufacturers could begin to sell cheaper versions of the drug. A new extended release formulation of the drug would be patented as a new product, and so would be protected from generic competition.


Conclusions

- Once-daily nevirapine dosing results in lower Cmin levels compared with twice-daily treatment. However, these pharmacokinetic studies support once-daily dosing assuming that optimal adherence is maintained.

- Several clinical studies in antiretroviral-naïve HIV-1-infected patients suggest a similar virological and immunological response to nevirapine in a dose of 400 mg QD vs 200 mg BID. The frequency of hepatic abnormalities with once-daily nevirapine is dependent on gender, CD4 count and perhaps race. Severe rash was more common with once-daily dosing in the 2NN study. Although not observed in other nonrandomized studies of once-daily nevirapine, this and liver concerns remain significant obstacles to routine use of this dosing strategy.
When compared with NVP BID dosing, antiretroviral regimens in which NVP is dosed at 400 mg once-daily immediately after a 2-week lead-in period are associated with an increased risk of rash leading to treatment interruption or discontinuation. The risk of liver complications is another lingering concern. The pathophysiology of this increased adverse event rate is not fully understood. Although the increased Cmax with NVP QD has been proposed, little evidence to corroborate this can be found within published pharmacokinetic analyses. Risk factors other than high NVP exposure including sex, baseline CD4 count, hepatitis coinfection, race, and genetic profile appear to be important predictors of adverse events associated with nevirapine therapy.

Once-daily NVP dosing may still have a future. Results from clinical studies suggest that tolerance to high NVP concentrations may develop when a dose-escalation approach is used during the first weeks of therapy. It is theoretically possible that the benefits of QD dosing can be achieved without excess toxicity by switching to NVP QD only after several months of BID administration. Moreover Boehringer-Ingelheim is recruiting people for an international study of an extended-release, once-daily formulation NVP.

In conclusion, NVP is currently used twice a day, but the pharmacokinetics and now clinical trial data could indicate that QD dosing is possible and patients could be switched safely once the viral load has been suppressed. That would be anyway problematic in settings where there is no access to viral load.

Cooper CL, van Heeswijk RP. Once-daily nevirapine dosing: a pharmacokinetics, efficacy and safety review. HIV Med. 2007 Jan;8(1):1-7, also available in Medscape (registration free)

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