

Contemporary Role of Nevirapine in HIV Treatment

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Abstract

Nevirapine was the first nonnucleoside reverse transcriptase inhibitor that was approved for treatment of HIV infection and quickly became an important component of HAART. As experience with this drug grew, potential toxicities and significant clinical benefits became apparent. With the development of new patient criteria based on CD4⁺ cell counts, new treatment initiation guidelines were developed. Incorporation of these criteria has reduced the incidence of rare but significant toxicities associated with nevirapine therapy to levels seen with other drugs. For treatment-naive patients who meet established starting criteria, or for patients switching from other nonnucleoside reverse transcriptase inhibitor- or protease inhibitor-based regimens, nevirapine can offer potent and durable viral suppression with significant clinical benefits. These benefits include the absence of central nervous system effects in patients who are at risk for depression, minimal untoward effects on serum lipid profiles, which is especially important for patients who have other cardiovascular disease risk factors, and relative safety during pregnancy for women of childbearing age. Patients who should avoid nevirapine include those with prior hypersensitivity reactions, those who do not meet treatment initiation criteria, those who experience adverse reactions during induction, and those with existing hepatotoxicity. This review focuses on current information regarding the role of nevirapine in HAART and defines patient groups whose clinical profiles may warrant consideration of nevirapine. (AIDS Rev. 2012;14:132-44)

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Key words

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Introduction

Since its approval in 1996 as the first nonnucleoside reverse transcriptase inhibitor (NNRTI), nevirapine (NVP) has been well established as an efficacious and durable component of antiretroviral (ARV) therapy. While it is no longer a component of US Department of Health and Human Services (DHHS) recommended first-line regimens, NVP is included as a component of acceptable regimens in the current US DHHS guidelines for naive patients (March 2012)¹. Because there are newer members of the NNRTI class that do not

have some of the risks that have been associated with NVP, particularly before the establishment of the CD4⁺ cell count-based initiation criteria, the current role of NVP in clinical practice has become an important question.

The role of NVP in current practice can be understood in the context of its unique pharmacologic properties, which confer important clinical advantages in treating patients with particular comorbidities. These clinical benefits must be weighed against several important limitations of NVP therapy in individualized patient care. When treatment is initiated in accordance with current recommendations (CD4⁺ cell counts < 400 cells/mm³ in men and < 250 cells/mm³ in women) when initiating NVP therapy, the risk of hepatotoxic events is reduced (US prescribing information)². The most recent (October 2011) European AIDS Clinical Society (EACS) guidelines recommend NVP in combination with a backbone regimen of tenofovir/emtricitabine (TDF/FTC) in treatment-naive patients³. However, they also note that NVP should be used with extreme caution in treatment-naive patients with elevated CD4⁺ cell counts

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(women with CD4⁺ cell counts > 250, and men with CD4⁺ cell counts > 400 μ l)³.

Based on a recent study by Kesselring, et al.⁴, the European NVP prescribing information also recognizes these CD4⁺ cell counts (< 400 cells/mm³ in men and < 250 cells/mm³ in women when initiating NVP therapy), but additionally consider detectable HCV RNA levels (> 50 copies/ml)⁵. It is also important to note that both the European guidelines³ and the latest DHHS guidelines¹ recommend that patients with a well-suppressed viral load can be switched to NVP-containing regimens, regardless of the CD4⁺ cell count, based on the De Lazzari study (2008)⁶.

Nevirapine can be a good choice for (1) treatment-naïve patients with an elevated cardiovascular risk profile, (2) patients with a history of mental illness, especially depression or substance abuse, and (3) women who are pregnant or planning to become pregnant^{2,7}. Regarding use of this agent in pregnant women, years of clinical experience and extensive surveillance via national registries⁷ have demonstrated NVP to be among the safest ARV available for use during pregnancy; it has recently been upgraded to a pregnancy schedule B drug by the US Food and Drug Administration (FDA)².

For patients already on a stable and efficacious NVP-based regimen, data support the continued use of NVP for as long as four years of treatment⁸. In cases of untoward side effects from efavirenz (EFV) or protease inhibitor (PI)-based regimens, switch studies have provided safety and efficacy outcomes data applicable in clinical scenarios, where a switch to a NVP-based regimen may be desirable⁹.

For which groups of treatment-naïve patients might nevirapine be considered?

Use of nevirapine in HIV-infected antiretroviral-naïve patients

Current DHHS guidelines¹ recommend EFV plus TDF plus FTC as the preferred NNRTI-based regimen. Nevirapine was found to be comparable to EFV in antiviral efficacy and immune reconstitution as measured by increases in CD4⁺ counts in treatment-naïve patients in both the large prospective randomized 2NN study¹⁰ and in the smaller FIRST study¹¹. However, the incidence of rare but life-threatening grade 4 toxicities (severe rash and hepatotoxicity) in patients with high CD4⁺ counts and treated with NVP (which were often observed before the institution of starting guidelines

based on CD4⁺ cell counts²), coupled with some reports of increased virologic failure associated with resistance in NVP-treatment arms compared with EFV-treatment arms¹¹⁻¹³, supported the use of EFV as the preferred NNRTI for the initiation of therapy in treatment-naïve patients.

However, when the randomized and “NNRTI-selected by choice” cohorts in the FIRST study were combined (n = 915), the immunologic and clinical outcomes were similar in both treatment groups, despite an increase in the incidence of virologic failure, with or without resistance, with NVP. A *post hoc* analysis of the randomized 2NN study demonstrated no difference in antiviral efficacy or viral failure between the NVP and EFV treatment arms, but did show an increase in the incidence of rash in women with higher CD4⁺ cell counts at the beginning of therapy¹⁴. Taken together, these studies demonstrated the need to consider guidelines for initiation of NVP based on CD4⁺ cell count and to analyze potential baseline resistance prior to initiation of NVP when deciding on an ARV treatment regimen.

Changes in the most recent DHHS guidelines for treatment-naïve adults and adolescents have upgraded NVP and the most commonly used double NRTI combinations regimens to be CI or CIII acceptable in terms of safety and efficacy. Based on the ARTEN study, which well illustrated the non-inferiority of NVP versus boosted atazanavir (ATV) with a TDF/FTC backbone¹⁵, the 2012 DHHS guidelines now recognize the combination of NVP with TDF/FTC as an acceptable (CI) regimen¹. In previous DHHS guidelines, NVP and Truvada[®] were to be used with caution based on small studies, which had found unexpectedly high virologic failure rates resulting from the emergence of viral resistance in patients taking NVP/TDF/FTC or lamivudine (3TC) regimens^{12-13,16}.

The combination of NVP plus zidovudine/lamivudine (ZDV/3TC) continues as an acceptable alternative regimen (CI) in naïve adult patients in the DHHS 2012 adult guidelines and remains as a preferred regimen in the DHHS 2011 perinatal guidelines. Also updated in 2012, NVP in combination with abacavir plus 3TC is now recognized as a CIII regimen by the DHHS guidelines, given that HLA-B*5701 screening greatly reduces the risk for abacavir hypersensitivity¹.

A recent Cochrane review analyzed data from seven randomized controlled clinical trials, with a total enrollment of 1,688 patients, comparing the efficacy of NVP with EFV. The authors found no critical differences between NVP and EFV when each was a part of an

ARV regimen that included two nucleoside reverse transcriptase inhibitors (NRTI) as the backbone therapy¹⁷. However, EFV and NVP did differ in their toxicity profiles, with NVP being more likely to lead to elevated transaminases and neutropenia, whereas EFV was more likely to cause central nervous system (CNS) side effects¹⁷. A higher mortality rate was reported in NVP 400 once-daily treatment groups (a non-approved use of the immediate release formulation) compared to Efavirenz based regimens in the Cochrane review. However, in the 2NN study (which accounted for the majority of patients analyzed in the Cochrane analysis), none of the deaths in the 400 mg qd arm were directly related to NVP. Two of the 25 deaths in the 2NN study were attributed directly to NVP, and both of these deaths occurred in patients receiving NVP twice-daily¹⁰. The quality of the literature studied in this meta-analysis to support these conclusions was considered moderate to high. The duration of follow-up, clinical settings, and NRTI backbones all varied greatly between studies¹⁷. The results of this analysis support the use of both agents in well-considered patient populations.

The advantages of NVP include the absence of untoward effects on serum lipids (in contrast to agents such as EFV and certain PI that can significantly alter serum lipid profiles), which is a serious consideration for patients with preexisting cardiovascular disease (CVD) risk factors¹⁸. Of the recommended NNRTI, NVP is preferred over EFV in: (1) patients with underlying psychiatric risk factors because of significant CNS effects by EFV, or (2) women who are or may become pregnant since EFV is a pregnancy schedule D drug.

The EuroSIDA study compared the durability of NVP, EFV, and lopinavir (LPV)-based regimens in patients who achieved viral load suppression to < 500 copies/ml after three months on treatment¹⁹. Kaplan-Meier analysis revealed that after a median of 2.6 years, the three regimens demonstrated equivalent durability¹⁹. Analysis of specific reasons for treatment discontinuation revealed that compared with patients on NVP, those receiving EFV or LPV had higher rates of discontinuation: 31% ($p = 0.01$) and 66% ($p < 0.0001$) higher risk, respectively, caused by toxicities or patient/physician choice¹⁹. However, the rate of virologic failure was higher for patients receiving NVP, since patients receiving EFV or LPV had a 48% ($p = 0.0002$) and 63% ($p < 0.0001$) lower risk, respectively, of discontinuation because of reported treatment failure, including virologic, immunologic, and clinical failure¹⁹. Increased virologic failure with NVP was seen primarily in patients who were treatment-experienced prior to

initiating NVP, since virologic failure after viral suppression was a very rare cause of treatment failure for patients on NVP who were ARV-naive at baseline. The study authors concluded that in treatment-naive patients, if NVP is tolerated with viral suppression in the first three months, then it can be the basis for a very durable regimen. This study underscores the necessity of resistance testing prior to initiation of ARV regimens.

Recent trials: nevirapine and emtricitabine plus tenofovir

Several recent studies with large patient populations have shown beneficial outcomes with the combination of NVP plus FTC and TDF. The ARTEN study¹⁵ was the first large study ($n = 569$) to test directly the non-inferiority of NVP ($n = 376$) and ritonavir-boosted atazanavir (ATV/r; $n = 193$), each in combination with TDF/FTC in ARV-naive patients. In this direct comparison of two regimens with favorable effects on serum lipid profiles, no significant difference in viral efficacy was seen between the two groups; 67% of patients receiving NVP compared with 65% receiving ATV/r ($p = 0.63$) achieved a treatment response, defined as a viral load < 50 copies/ml at two consecutive visits (weeks 24 and 36), without subsequent rebound or change in regimen prior to week 48. When stratified by baseline HIV RNA > or < 100,000 copies/ml, there were no statistical differences in efficacy between the NVP or ATV/r groups¹⁵. The smaller US-based NEWART study ($n = 152$) compared NVP twice daily to ATV/r, both on a TDF/FTC backbone, and reported similar efficacy in each arm, with 61.3 vs. 64.9% of patients with < 50 HIV RNA copies/ml at 48 weeks (NVP vs. ATV/r, respectively)²⁰.

A notable disadvantage of NVP in the ARTEN study was that patients in the NVP arm had a fourfold higher discontinuation rate caused by adverse events compared with patients in the ATV/r arm (13.6 vs. 3.6%). The majority of adverse events in the NVP arm were mild to moderate rashes that occurred during the 14-day lead-in period¹⁵. In this first large study where CD4⁺ T-cell restrictions for NVP were implemented, no cases of Steven-Johnsons syndrome or any cases of life-threatening hepatic toxicity were reported. Although the NEWART study was smaller, discontinuation caused by adverse events was comparable between the NVP and ATV/r groups²⁰.

Another shortcoming of NVP in the ARTEN study was the development of viral resistance during 48 weeks: virologic resistance occurred in 29/44 (66%) of patients

who failed either twice-daily or once-daily NVP therapy, but not in any of the 28 patients who failed ATV/r therapy¹⁵. Overall, selection of drug-resistant mutations occurred in 30/374 (7.9%) of patients on the NVP regimen¹⁵. Notably, 11/188 (5.9%) of the once-daily vs. 21/188 (11.2%) of the patients in the twice-daily NVP group experienced virologic failure, perhaps reflecting increased adherence with daily dosing¹⁵. However, it is important to note that all patients in both NVP arms in the ARTEN study were receiving the NVP immediate-release formulation (200 mg tablets)¹⁵, since this trial did not include the newer NVP extended-release formulation, so no direct comparisons can be made to trials using the newer NVP extended-release once-daily formulation.

In the TENOR trial²¹, a prospective and nonrandomized study, 70 patients who were either treatment-naïve or needed to be switched from their current ARV regimen were treated with TDF, FTC, and once-daily NVP. Of the 52 (74.3%) patients who remained on the regimen after 72 weeks, 44 patients (84.6%) had a viral load below the limit of detection. The regimen demonstrated good efficacy, with a 2.5 log₁₀ decrease in the median viral load and a 44.8% increase in the median CD4⁺ count.

In the large OCTANE-2 study²² of 500 treatment-naïve African women with CD4⁺ counts < 200, NVP plus TDF plus FTC was found to be equivalent to lopinavir/ritonavir (LPV/r) plus TDF plus FTC. At 48 weeks, 85.6 and 86.3% of women in the NVP and LPV/r groups, respectively, achieved viral suppression to < 400 copies/ml. The results of this study are in contrast to OCTANE-1²³, where the same NVP-based regimen was inferior to LPV/r in women who had previously been exposed to single doses of NVP to prevent vertical transmission. Although no significant differences were seen between severe grade 3 or 4 adverse events or laboratory abnormalities, early NVP discontinuations because of side effects were significantly more common than in the LPV/r group of the OCTANE-2 study²².

Once-daily nevirapine dosing with extended-release formulation

Convenience is an important factor to consider when choosing an ARV regimen, especially with regard to patient adherence. The NVP immediate-release formulation is approved only for twice-daily dosing to maintain appropriate serum concentrations of NVP; however, a new once-daily NVP extended-release formulation was approved by the US FDA in March 2011, based on the safety and efficacy data from two key trials demonstrating the non-inferiority of the extended-release

formulation compared with current twice-daily formulation in treatment-naïve (VERxVE study)²⁴ and in treatment-experienced patients (TRANxITION study)²⁵. Historically, significantly higher liver toxicities in the once-daily as compared to the twice-daily dosing of the 2NN study led to avoidance of once-daily dosing for treatment-naïve patients. However, this study was prior to incorporation of the CD4 count limitations and the NVP extended-release formulation¹⁰.

VERxVE was a large international study (n = 1,013) comparing safety and efficacy in treatment-naïve subjects randomized to receive either NVP immediate-release (200 mg) twice daily or 400 mg once daily of the NVP extended-release formulation, both on a backbone of TDF/FTC²⁴. The two formulations demonstrated equivalent virologic efficacy and safety, with 80% of patients in the extended-release arm and 75% in the immediate-release arm achieving the primary endpoint of an HIV viral load < 50 copies/ml at 48 weeks²⁴. Of concern, severe or life-threatening rashes occurred in 2% of the subjects, evenly split between the 14-day lead-in period and early post-randomization period²⁴. Five cases of Steven-Johnsons syndrome occurred in VERxVE: three in the pre-randomized period and two in post-randomized immediate-release patients²⁴. Rates of grade 3 or 4 hepatotoxicity were similar between the extended-release (6%) and immediate-release (7%) arms in this study²⁴. While there were 10 fatalities during the course of the trial, it should be noted that none of these were considered by the investigators to be related to study medication²⁴.

The TRANxITION study confirmed the safety and efficacy of switching from a twice-daily NVP immediate-release regimen to a once-daily extended-release regimen in patients who were virologically suppressed on a twice-daily NVP immediate-release regimen²⁵. The majority of patients in this US-based study had CD4⁺ T-cell counts > 500 cells/mm³ and were male. The rate of drug-related grade 2 or 4 adverse events was equivalent between the extended-release and immediate-release treatment arms at 0.3 and 1.4%, respectively²⁵. Efficacy was comparable, with 93.6% in the extended-release arm and 92.6% in the immediate-release arm remaining virologically suppressed with HIV-1 RNA levels < 50 copies/ml at 24 weeks²⁵.

Nevirapine in patients at risk for cardiovascular disease

Unlike other ARV drugs/classes, NVP demonstrates minimal disruption to serum lipids, and in several studies

has actually been reported to exert a presumptive beneficial effect on serum lipids. Importantly, NVP increases high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-1 (ApoA1) levels; although the phenomenon is not fully understood, studies suggest that NVP stimulates ApoA1 synthesis²⁶. In combination, higher HDL-C and ApoA1 levels are expected to have significant anti-atherogenic effects^{26,27}. Although not proven, the reported increase in HDL-C with NVP may be protective against coronary arterial disease, given that in a large prospective study of non-HIV-infected individuals, even a small increase of 0.025 mmol/l in HDL-C translates into a risk reduction of 2-5%²⁷. Another distinguishing characteristic of NVP is the minimal effect it has on serum triglycerides¹⁵ compared with ritonavir-containing regimens. This is significant for patients with CVD, since both elevated plasma triglyceride levels and low HDL-C levels are risk factors, independent of low-density lipoprotein cholesterol (LDL-C) plasma levels associated with CVD risk^{15,28}.

Evaluation of the lipid parameters in the ARTEN study suggests that NVP may have a more favorable lipid profile than ATV/r²⁹. This is especially noteworthy as ATV has been reported to have the least impact on serum lipids amongst the PI²⁹. In the ARTEN study, the NVP plus TDF/FTC treated group had significantly higher elevations in the anti-atherogenic lipids HDL-C and ApoA1 compared with the ATV/r plus TDF/FTC arm at 48 weeks²⁹. The NVP arm also had a significantly higher increase in LDL-C, but lower triglyceride levels compared with the ATV/r arm²⁹. Increased levels of both HDL-C and Apo-A are considered to be protective against coronary disease in the general population. The authors also noted that the Apo B:Apo A ratio, a strong indicator of decreased cardiovascular risk in the general population, was significantly decreased in the NVP vs. ATV/r group, again suggestive of a reduced cardiac risk²⁹.

Multiple studies have reported that NVP has fewer untoward effects on serum lipid profiles than other ARVs. In a small subanalysis of the Atlantic Study, NVP treatment was associated with a sustained and significant increase in HDL-C when compared with the serum lipid changes seen in the PI and triple NRTI therapy groups³⁰. In the 2NN study, patients in the NVP arm experienced significantly increased HDL-C levels and a significantly decreased total cholesterol/HDL-C ratio over a 48-week period when compared with patients receiving EFV³¹.

Historically, atherogenic effects of ARV therapy have been associated with the PI class of agents³²,

including increases in total LDL-C, total cholesterol, and triglycerides³³⁻³⁵. Metabolic syndrome observed in HIV-treated individuals, characterized by abdominal obesity, hypertension, dyslipidemia, and insulin resistance, causes an increase in CVD risk³⁶ and is associated with the use of PI^{37,38}.

In the prospective observational analysis of 23,437 HIV-positive patients in the D:A:D study³⁹ after adjusting for serum lipid profiles, the relative rate of myocardial infarction for patients in the PI group was greater than in the NNRTI group (RR: 1.1; 95% CI: 1.04-1.18 vs. RR: 1.00; 95% CI: 0.93-1.09). Observations like this contributed to studies where patients were switched from PI- or EFV-based regimens to regimens based on NVP, with correspondingly fewer untoward effects on serum lipid parameters.

Addressing patients with clinical lipodystrophy or fat redistribution, an open-label study by Ruiz, et al. found that switching to NVP led to significantly decreased total cholesterol and triglycerides, increased HDL-C, and lower C-reactive protein levels compared with patients who remained on a PI-containing regimen. However, there were no obvious differences in lipodystrophy in the NVP-switched group at 48 weeks⁴⁰. In another study looking at patients with lipodystrophy who were switched from PI to NVP, similar reversals of their atherogenic profiles were reported⁴¹. The 12-month results from the Barcelona PI Switch Study indicated that a switch to NVP significantly decreased total cholesterol, LDL-C, and triglyceride levels compared with a switch to EFV or remaining on a PI regimen. In this study of Spanish HIV-positive patients, there was no significant increase in serum HDL-C levels⁴².

Two more recent switch studies demonstrated the presumptive cardiovascular benefits of switching from an EFV-based regimen to a NVP-based regimen. These include changes in patient serum lipid profiles, which are associated with lower CVD risks in non-HIV-infected patients. In a small randomized trial, LDL-C levels were found to be significantly decreased in patients who were switched to NVP from EFV⁴³. Additionally, in a small retrospective analysis total cholesterol, LDL-C, and triglyceride levels decreased significantly, with a significant increase in HDL-C in patients who were switched from EFV to NVP⁴⁴.

Given these effects on serum lipid profiles, NVP is worthy of consideration for patients who are at higher risk for CVD with multiple risk factors (i.e. diabetes, body mass index > 35 kg/m², hypertension, older

age, smoking, and a family history of myocardial infarction)^{18,26,45}. Older age is of special concern given that patients with HIV are living longer (~ 20% of current patients are aged > 50 years^{46,47}), with predictions that this age group will increase to 50% by 2015⁴⁸. Of significance, older patients typically have plasma lipid profiles that are associated with higher risk for CVD, including increased LDL-C, decreased HDL-C, and increased total cholesterol/HDL-C ratios and triglycerides⁴⁹.

Mental health concerns in the setting of HIV infection

Overall, HIV-infected patients have an around four- to fivefold higher rate of depression than seronegative individuals⁵⁰. Depression in HIV has the potential to adversely affect not only quality of life but compliance with ongoing treatment and disease management⁵¹. It has been repeatedly demonstrated that NVP has minimal, if any, untoward CNS effects or exacerbated or emergent depression, despite extensive trials and clinical experience in varied patient populations, including those with mental health issues⁵², and thus NVP may be a good option for those with depression. In contradistinction to EFV, NVP has few if any CNS-related side effects, including vivid dreams, hallucinations, or dysphoria, which may exacerbate depression⁵³. In fact, in a small retrospective study, patients who were switched from EFV to NVP because of neuropsychiatric symptoms had a significant reduction of these symptoms after the switch⁴⁴. Improved neuropsychiatric scores were reported in patients only 12 weeks after switching from EFV to NVP⁴³. Despite its lack of neuropsychiatric effects, NVP demonstrates excellent CNS penetration, which has been correlated with positive cognitive improvement on neuropsychological screening⁵². Thus, this NNRTI may be a good choice for patients who are at risk for or exhibit signs of cognitive impairment because of HIV disease or other CNS pathology.

While not considered a major issue warranting sweeping changes in the treatment guidelines, a few published reports have demonstrated that drug metabolism may be impaired in patients with the 2B-6 genotype 516 (more common in African Americans), which is a single-nucleotide polymorphism in the CYP enzyme system⁵⁴. This pathway is involved in EFV metabolism, and reports have indicated that EFV-related CNS effects may be exacerbated in patients who have this genetic polymorphism, thus leading to

intolerance or potential nonadherence to the drug⁵⁵. Although NVP utilizes the same metabolic pathway as EFV and modest increases in NVP plasma concentrations have been associated with different 516 genotypes, no ill effects have been reported in patients with the 2B-6 genotype 516 who are receiving NVP therapy⁵⁶. Regardless of causality, intolerance to EFV may be another rationale for NVP use, especially in those cases where staying within the NNRTI class is a therapeutic goal.

Pregnancy and postpartum therapy

The Centers for Disease Control and Prevention estimates that 280,000 women are living with HIV/AIDS in the USA, with > 80% of them being of childbearing age (aged 13-49 years)⁵⁷. Because of the lack of teratogenic effects reported with NVP use during pregnancy, the DHHS guidelines recommend NVP as an option for women who are pregnant or plan to become pregnant¹. Extensive surveillance via national registries⁷ has demonstrated NVP to be among the safest ARV available for use during pregnancy; it has recently been upgraded to a pregnancy schedule B drug² by the FDA. In addition, according to the Public Health Service Task Force Perinatal Guidelines⁵⁸, women who are stable receiving NVP when they become pregnant should remain on NVP regardless of their CD4⁺ cell count as they are not at an increased risk for hepatotoxicity if stable on their current regimen. Women who are pregnant or who wish to become pregnant but are not receiving ARV therapy, with CD4⁺ counts < 250 cells/mm³ and who do not have risk factors for hepatotoxicity, might consider NVP as a first-line NNRTI with AZT and 3TC, the recommended backbone NRTI therapy for pregnant women⁵⁹. Studies of NVP-related fatal rash (Steven-Johnsons syndrome or toxic epidermal necrolysis) or hepatotoxicity have shown no increased risk with NVP use during pregnancy⁷.

Nevirapine effectively crosses the placenta⁵⁸. In HIV-positive women who are ARV-naïve at delivery, one option is to give continuous AZT during labor along with a single dose of NVP. Because of potential resistance, given the long half-life of NVP, it is recommended that 3TC be added during labor and that AZT/3TC be given for seven days post labor⁷. Women who are pregnant but not receiving NVP, with CD4⁺ counts > 250 cells/mm³, should only start receiving NVP if the benefits outweigh the risks⁵⁸.

See the summary assessment guidelines (Fig. 1).

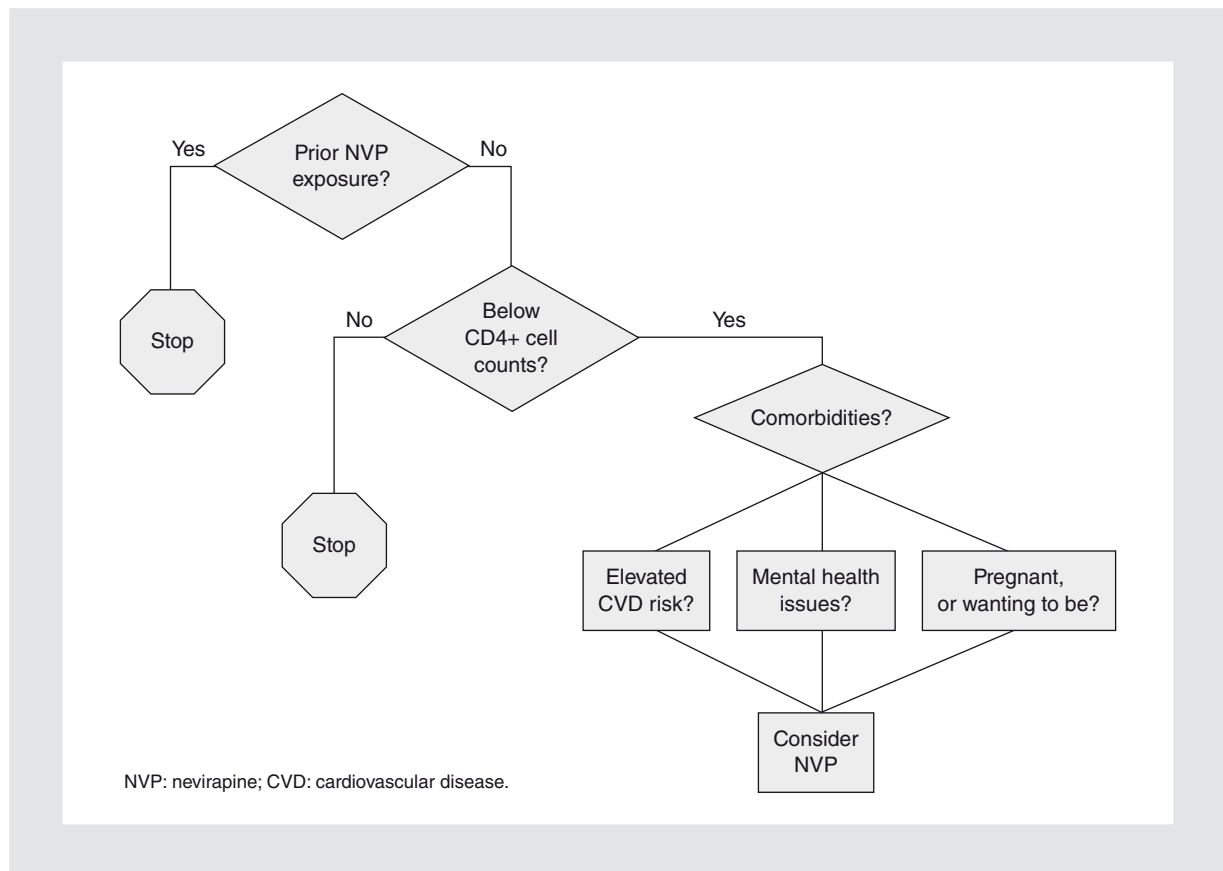


Figure 1. Flowchart for consideration of nevirapine in treatment-naive patients.

Patient groups for whom nevirapine should be avoided

The prescribing information for NVP presents specific guidelines for treatment initiation, including key parameters for CD4⁺ cell counts at baseline: < 400 cells/mm³ in men; < 250 cells/mm³ in women². Patients whose CD4⁺ cell counts are higher than these values at baseline have a greater risk of developing certain adverse events (e.g. hepatotoxicity) and thus should not start NVP therapy². In the 2NN study comparing the efficacy of EFV vs. NVP in treatment-naive patients, elevated CD4⁺ cell counts at baseline was a risk factor for severe reactions with NVP; otherwise, both drugs demonstrated equivalent efficacies after one year¹⁰.

Initiation of nevirapine treatment

It is important to note that the CD4⁺-based criteria are for NVP initiation only. Once patients are virologically suppressed on NVP with good tolerability, CD4⁺ count increases are to be expected and indicate a

positive immunologic response generally associated with effective ARV therapy⁶⁰. Likewise, switching treatment-experienced patients, regardless of their CD4⁺ counts at time of switch, from a previous suppressive ARV regimen to one that includes NVP (e.g. for tolerability) appears to be safe and not associated with the same degree of risk for NVP hypersensitivity reactions as would be seen in treatment-naive patients⁶¹. In a meta-analysis of risk factors for NVP toxicity in cohort studies, treatment-experienced patients with high CD4⁺ cell counts and viral load > 400 copies/ml were at significantly increased risk for hypersensitivity when compared with ARV-naive patients with a low CD4⁺ count⁴.

Because of the higher risk for toxic epidermal necrolysis or Steven-Johnsons syndrome, patients with a history of drug-induced rashes or those who develop severe rashes or a rash with increased transaminases or constitutional symptoms should not reinstate or continue with NVP treatment². In Thai patients, the HLA-Cw*04⁶² and HLA-B3505-^{63,64} alleles are strongly associated with a NVP-induced rash. In the future, HLA

subtyping, comparable to HLA-B5701 screening prior to the initiation of abacavir treatment⁶⁵, may make it possible to identify patients at high risk for adverse reactions prior to the initiation of NVP treatment.

Because of hepatotoxicity concerns, patients who meet the criteria for Child-Pugh grade B or C or have ever had a severe adverse reaction to NVP upon prior administration should not consider NVP. In the eight HIV-NAT randomized controlled trials in Thailand, severe hepatotoxicity (defined as an increase in alanine aminotransferase level to five times the upper limit of normal and an increase of at least 100 IU from baseline) was associated by multivariate analysis with HBV or HCV co-infection and NNRTI exposure⁶⁶. In addition, there may be a genetic component to this phenomenon⁶⁷. More recent reports have associated NVP treatment-related hepatotoxicity with HCV coinfection; however, hepatotoxicity can be improved with successful treatment of the HCV infection^{22,68}. Although NVP-associated severe hepatotoxicity is increased in patients with HBV or HCV coinfection⁶⁹, multiple studies concurred that NVP therapy can be safely used in patients coinfecting with HIV and HBV or HCV^{70,71}. A complete understanding of the full scope of the various risk factors for NNRTI treatment-related hepatotoxicity will require further study.

With regard to the impact of ARV therapy on the progression of liver fibrosis because of HCV coinfection, the limited data available are not in agreement. In a cross-sectional study of 152 HIV/HCV-coinfecting patients, NVP-based HAART was associated with faster progression of fibrosis⁷². More recently, in a similar patient population in Spain, chronic NVP exposure has been associated with reduced liver fibrosis progression in an analysis of 201 liver biopsies and other clinical data from HIV/HCV-coinfecting patients⁷³. These conflicting data from cross-sectional studies indicate the need for a definitive prospective study to address this important clinical question.

In terms of ARV drug interaction, NVP should not be coadministered with atazanavir (ATV) because it will lead to decreased ATV levels and an increase for risk of NVP-associated toxicity because of elevated levels of NVP⁷⁴. Although not a contraindication for coadministration, the LPV/r dose must be increased when given with NVP. For patients who are on methadone maintenance, NVP increases the risk for methadone toxicity or withdrawal since NVP can alter methadone kinetics⁷⁵. Buprenorphine, a partial opioid agonist also used in opioid addiction therapy, however, has no significant interactions with NVP⁷⁶, with which it can be safely used.

It should be noted that since 2001, the Centers for Disease Control has issued warnings against the use of NVP for postexposure prophylaxis because of the risk for severe hepatotoxicity.

Resistance: the “Achilles heel” of nonnucleoside reverse transcriptase inhibitors

Nonnucleoside reverse transcriptase inhibitors bind to an allosteric side pocket on the HIV-1 reverse transcriptase enzyme. While NNRTI are very potent and selective inhibitors of HIV-1 reverse transcriptase, as a class they do have significant limitations. Because of a low genetic barrier for resistance to these drugs, NNRTI resistance can emerge with one or two key mutations⁷⁷, which can translate into significant cross-resistance across the class, even with point mutations. Once drug-resistant strains have been selected for NNRTI (mainly K103N for EFV and Y181C for NVP)^{77,78}, they can limit the efficacy of those agents. For example, in the OCTANE-1 study, mothers given NVP peripartum monotherapy had an increased risk of subsequent NVP resistance²². Therefore, an additional consideration for the initiation of NVP treatment, especially in patients who have failed prior NNRTI-containing regimens, would be predicted resistance by genotypic or phenotypic testing⁷⁹.

In the patients who developed resistance while taking NVP in the ARTEN study, Y181 C/I/V/S were the most common NNRTI resistance mutations identified, followed by K103N/S/T, V106A/M, V108I/M/V, and K101E/R mutations¹⁵. In addition, NRTI resistance mutations 184V/I and K65R were reported in patients receiving NVP, whereas no NRTI mutations were identified in patients receiving ATV/r with virologic failure¹⁵.

In the ARTEN study there was a slight trend for increased drug resistance for patients in the NVP arms with higher HIV-RNA load and lower CD4⁺ T-cell counts compared with those in the NVP arms with a lower HIV-RNA load, although this difference was not significant¹⁵. In a small pilot study where a high level of resistance was seen in patients randomized to NVP plus TDF/FTC, resistance was most marked in the groups where initial viral load was high and CD4⁺ T-cell counts were low¹³.

In a large meta-analysis of 20 clinical trial reports that included 7,970 patients, no significant difference was seen in the rates of virologic failure at 48 weeks between patients on NNRTI (4.9%) vs. patients on a boosted PI (5.3%; $p = 0.50$). Of the virologic failures

genotyped, the reverse transcriptase M184V mutation was reported in 35.3% of patients on NNRTI-based regimens vs. 21.0% of patients receiving a boosted PI-based regimen ($p < 0.001$)⁸⁰.

A second-line NNRTI, etravirine (ETR), was approved in 2009. Resistance to this drug can emerge, but there is less cross-resistance with first-line NNRTI (EFV and NVP). Ongoing analysis of the phase III DUET-I and DUET-II trials documented a number of ETR resistance-associated mutations, including L100I, K101E/P, V179D/F, Y181C/I/V, and G190A/S⁸¹. Additional resistance-associated mutations continue to be identified, and this growing data collection assists with the refinement of drug-resistance algorithms. An analysis of viral resistance mutations identified in samples from 1,343 patients who had previously failed either NVP or EFV treatment in the resistance database of the Spanish AIDS Research Network showed that both groups of patients were at equal risk (~ 19%) of subsequent ETR failure, indicating that ETR rescue therapy might be available to ~ 80% of patients with prior NVP or EFV failure⁸¹.

Because the genetic pathways of resistance for NNRTI are different from other ARV classes such as NRTI or PI⁷⁸, these may still be effective if NVP fails. However, it is important to keep in mind that for all patients whose regimen is failing, the sooner a new potent regimen is identified and initiated, the better, as resistance to all agents can accumulate quickly in the setting of partially suppressive therapy. Consistent with current clinical guidelines, resistance testing can help guide informed therapeutic decision making.

Switching to nevirapine from other antiretroviral agents

A number of clinical trials have examined the efficacy, safety, and durability of NVP-based regimens after patients were switched from PI or other ARV therapy options. In the ATHENA study ($n = 2,470$), 775 patients with HIV-1 RNA ≤ 500 copies/ml switched to another regimen from an initial PI-containing regimen. At year 1, the rate of switching related to drug toxicity from the second regimen was 24% (95% CI: 21-28%), primarily because of neuropathies and gastrointestinal toxicities. In patients who switched to a PI, the risk of a second switch was increased (RR: 2.5; 95% CI: 1.7-3.5). However, switching to NVP from the original PI, while maintaining the rest of the regimen, was protective against a second switch as opposed to substituting a different PI (RR: 0.2; 95% CI: 0.1-0.6)^{9,82}.

The DHHS guidelines indicate that patients with a well-suppressed viral load who have achieved an increase in CD4 counts can be safely switched to NVP-containing regimens, no matter what their CD4⁺ cell count is^{1,6}. In the Kesselring study, women with a plasma HIV-1 viral load ≥ 50 copies/ml and CD4 counts > 250 cells/mm³ had a higher risk of symptomatic hepatic adverse events compared with women with CD4⁺ cell counts < 250 cells/mm³ (11.0 vs. 0.9%, respectively)⁴. A similar trend was noted in men with detectable HIV-1 RNA (> 50 copies/ml) and CD4 counts > 400 cells/mm³ compared with men with CD4 counts < 400 cells/mm³ (6.3 vs. 1.2%, respectively)⁴. Patients with undetectable plasma viral loads (i.e. < 50 copies/ml) did not display an increase in toxicity risk based on CD4⁺ cell thresholds⁴.

In the NEFA study, 460 HIV-positive, treatment-experienced adults were randomized to replace a current PI with NVP twice daily ($n = 155$), EFV once daily ($n = 156$), or abacavir twice daily ($n = 149$)⁸³. Intent-to-treat analysis of the patients originally randomized showed 93.5% of NVP-treated patients, 92.9% of EFV-treated patients, and 80.5% of abacavir-treated patients achieved virologic success after three years⁸³. In contrast, patients who remained on the initial drug maintained viral control at 75%. Importantly, in the NEFA study, patients with a high CD4⁺ count and viral loads < 50 copies/ml who were switched to NVP had no significant increases in hepatotoxicity compared with EFV or abacavir⁸⁴.

The most recent DHHS guidelines recommend a switch to NVP or ETR if patients have EFV-related toxicities such as CNS side effects¹. In a recently published clinical trial AIDS Clinical Trial Group A5095 subanalysis for the 9% of patients with an adverse event related to EFV who switched to NVP⁸⁵, the switch was generally safe, with resolution of all EFV-associated CNS symptoms and the majority of EFV-related rashes. This *post hoc* analysis found NVP to be efficacious, although it was not powered to analyze efficacy⁸⁵. In this study, grade 3 or 4 hepatotoxicity was observed in 14% of patients receiving NVP therapy vs. 6% in patients who continued receiving EFV; although controlled for NVP CD4⁺ restrictions, the viral loads were not suppressed prior to starting.

An analysis of Spanish patients who were switched from a PI-containing regimen to an NNRTI regimen (NVP or EFV) found that after 48 weeks of follow-up, both NNRTI were equally effective if initiated in patients with undetectable viremia. However, EFV was more effective than NVP in patients with PI failure. The tolerability

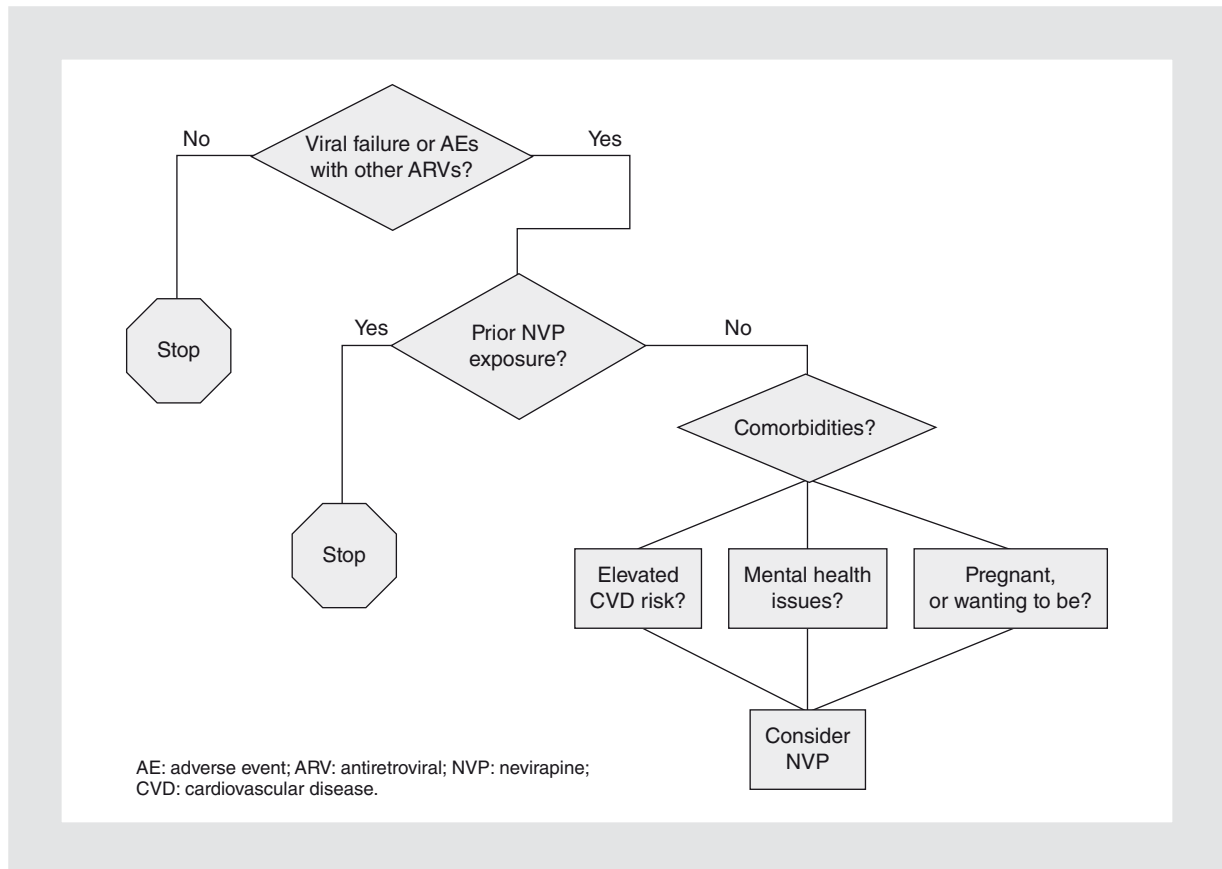


Figure 2. Flowchart for consideration of nevirapine in treatment-experienced patients.

of EFV and NVP was equivalent to the majority of EFV discontinuations from CNS toxicity and NVP discontinuations from hepatotoxicity⁸⁶.

See the summary assessment guidelines (Fig. 2).

**Executive summary:
The role of nevirapine in today’s
antiretroviral landscape**

As the first NNRTI to be approved for the treatment of HIV-infection, with unique pharmacodynamic properties, the clinical profile of NVP has been studied extensively. A recent Cochrane review found no critical differences between NVP and EFV in efficacy, but did note that the two NNRTI were distinguished by their toxicity profiles, which help to define the populations that would benefit most from either drug¹⁷.

Recently, the international ARTEN clinical trial¹⁵ and the US-based companion NEwArT trial²⁰ demonstrated the non-inferior efficacy and equivalent safety of NVP vs. ATV/r when both were administered on a TDF/FTC

backbone in ARV treatment-naive HIV-infected patients. Both of these lipid-sparing regimens were potent and durable, and each had minimal untoward effects on serum lipids, which can be an important component of the management of the dyslipidemias that are common in HIV-infected patients.

Once-daily regimens have been shown to improve treatment adherence. The VERxVE trial demonstrated the non-inferior efficacy of a new NVP extended-release formulation vs. the NVP immediate-release formulation in treatment-naive patients²⁴. The TRANxITION trial demonstrated the non-inferiority of the extended-release formulation versus the immediate-release formulation in treatment-experienced patients who switched to the extended-release formulation for once-daily dosing convenience²⁵.

Patients who should avoid NVP include those who do not meet the CD4⁺ T-cell count treatment initiation criteria, patients who develop unresolved rashes or elevated transaminases during the 14 to 28 day lead-in period, or patients with Child-Pugh grade B or C hepatic impairment².

The emergence of resistance mutations is a well-characterized phenomenon with NNRTI regimens. As with all ARV, pretreatment resistance testing is important to confirm the potential efficacy of all regimens under consideration. With the development of second-line NNRTI such as ETR, which demonstrate different resistance profiles, substitution with ETR will allow rescue therapy in up to 80% of patients who experience virologic failure on either NVP- or EFV-based regimens⁸¹.

Early administration of NVP preserves novel class agents for later use. For patients who are experiencing stable virologic suppression on a NVP-containing regimen, studies have demonstrated long-term efficacy and tolerability^{87,88}. Patients experiencing drug-related adverse events while on a PI- or EFV-based regimen can successfully switch to a NVP-based regimen, especially when significant dyslipidemias or mental health concerns are apparent. For these patient populations, NVP remains an important option.

Analysis of recent and ongoing studies will provide further clarification of the effectiveness and safety of once-daily NVP extended-release and NVP-containing regimens with a TDF/FTC backbone. Future studies are needed to evaluate if the effects of NVP on lipid profiles have a clinical impact in decreasing cardiovascular events.

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