LEADING ARTICLE

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The Emerging Roles of Non-Nucleoside Reverse Transcriptase Inhibitors in Antiretroviral Therapy

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Abstract

The availability of potent non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens for antiretroviral therapy and concerns regarding protease inhibitor (PI)-related metabolic disturbances have led to significant shifts in treatment practices in HIV infection. NNRTI-based regimens may have several advantages over PI-based therapy for initial or prolonged therapy, including more convenient administration regimens, lower tablet volume, fewer drug interactions, and central nervous system penetration. No data from prospective clinical trials currently exist comparing the 3 approved agents (efavirenz, nevirapine or delavirdine). Both efavirenz and nevirapine have been compared to triple therapy with the PI indinavir over 48 weeks as initial therapy, with similar responses being observed with nevirapine regimens and superiority observed with efavirenz. A smaller 24-week study has suggested nevirapine may be superior to the PI nelfinavir. Limited comparative data in patients with high viral loads treated with nevirapine- or delavirdine-based regimens currently exist. However, cohort data and selected patient data from clinical trials suggest comparable activity to PI-based regimens in these patients. The superiority of efavirenz over indinavir-based regimens has been observed in comparative data in a subset of patients with high viral loads. In treatment-experienced patients, available uncontrolled data suggest these agents contribute to regimen efficacy in NNRTI-naïve, treatment-experienced patients. Efavirenz has demonstrated superiority over nelfinavir in nucleoside-experienced patients, although combining these 2 agents may represent the best approach in these circumstances. The tolerability of NNRTIs appears generally good with few individuals discontinuing in clinical studies as a result of adverse drug events. The majority of adverse events with NNRTIs occur within the first month, and are predictable and manageable without therapy interruption.

The goal of all therapy is to improve length and quality of life. In HIV-1 infection the current best available route to this goal is to achieve both substantial and sustained suppression of viral replication in all cellular and body compartments.[1,2] Sustained viral suppression is associated with partial immune reconstitution and a marked reduction in risk of clinical events or death. Furthermore, arresting replication delays or prevents the emergence of drug-resistant virus, one of the principal reasons for loss of therapeutic benefit.[3]

The clinical value of triple combination antiretroviral therapy has been established by a number of large randomised controlled trials showing strik-

ing improvements in disease markers (e.g. viral load, CD4+ cell count), and improved survival and diminished disease progression relative to single and double agent therapy. Initiating treatment with 3 antiretroviral agents [2 nucleoside analogues (NA; nucleoside reverse transcriptase inhibitors) plus a third agent, a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or possibly a third NA] is now considered minimal standard-of-care for the clinical management of HIV infection.[1,2]

Metabolic toxicities associated with antiretroviral therapy have recently been recognised.[4] In particular, increases in cholesterol and triglyceride levels appear most common with PIs, and have caused a re-evaluation of the risk versus benefit of these agents, particularly in early disease.[5] These concerns and the need for more conveniently administered and better tolerated regimens has also led to the investigation of substitutes for the PI component of antiretroviral therapy.

NNRTIs are a chemically diverse group of compounds that are potent inhibitors of HIV-1 reverse transcriptase. HIV-2 possesses natural resistance to these agents. They act as competitive inhibitors of HIV-1 reverse transcriptase, binding to a hydrophobic pocket adjacent to the catalytic site.

NNRTI-containing regimens may have several advantages over PI-based therapy for initial or prolonged therapy. These advantages may include:

- more convenient, patient-friendly administration regimens (once or twice daily, non-food dependent)
- lower tablet volume
- fewer potentially serious drug interactions
- transient initial toxicities which do not generally overlap with or potentiate those associated with backbone NAs
- perceived (but not currently proven) lower risk of fat redistribution and metabolic problems
- maintenance of PIs as an option for second line therapy where PIs have established efficacy
- central nervous system penetration.

Although more data establishing equivalence of potency to PIs are required with some of these agents, issues requiring clarification with all PI-sparing regimens before full confidence with their use is established include durability of effect, virological benefits in non-plasma or so-called sanctuary sites such as lymph nodes, and if changes in immune function are similar (or better) than those observed with PIs. Further data on tolerability in specific populations, for example, patients with hepatitis B or C co-infection, would also be beneficial. Additionally, systematic evaluation of metabolic and body shape changes over prolonged follow-up are required to confirm the current perception that NNRTIs are associated with a diminished risk of these problems. Studies specifically addressing the potential for PI-based regimens to re-establish virological control in individuals after failure of an initial PI-sparing regimen are also required.

Three agents, efavirenz, nevirapine and delavirdine are the currently approved agents in this class. Delavirdine is not currently approved in the European Union.

1. Key Clinical Trials

Clinical studies support the use of NNRTI-based regimens for initial therapy. Additional data suggest some of these agents may meaningfully contribute to the activity of second-line or salvage therapy regimens, and may be used to improve the convenience of therapy regimens, or after toxicity, by substituting for PIs.

Analyses of key trials data have included 2 main statistical techniques: intent-to-treat non-completer = failure (ITT), and observed or on-treatment analysis (OT). These analyses provide different information regarding outcome. ITT is the most conservative analysis, it includes all patients who entered the study and treats all missing data as representing failure. Such an analysis will tend to underestimate the treatment effect in practice. Observed data provide results only on patients with available follow-up values; missing data are disregarded, thus, the denominator for analysis may not be the same as the number originally randomised. This type of analysis tends to overestimate the treatment effect observed in practice by ignoring patients who are

Table I. Outcomes [by conventional (OT) and conservative (ITT) analyses] in non-nucleoside reverse transcriptase inhibitor arms of key studies in treatment-naïve patients to week 24. Data from additional studies used for drug approval are included for comparative purposes

Trial	Therapy	No. of patients	Mean viral load at baseline (copies/ml)	<50 copies/ml at wk24 (ITT) [%]	<4-500 copies/ml at wk24 (OT) [%]
Atlantic[6]	d4T, ddI, NVP	68	4.19	67	89
DMP-006[7]	ZDV, 3TC, EFV	154	4.77	59	95
13C[8]	ZDV, mostly 3TC, DLV	168	4.8	29.3[a]	48.8
Incas[9]	ZDV, ddI, NVP	51	4.24	45	73
DMP-005[10]	ZDV, 3TC, EFV	34	4.72	49	88

a Naïve 3TC subset.

3TC = lamivudine; **d4t** = stavudine; **ddI** = didanosine; **EFV** = efavirenz; **ITT** = intent-to-treat non-completer = failure; **NVP** = nevirapine; **OT** = on-treatment analysis; **ZDV** = zidovudine.

unable to take or tolerate therapy or who change therapy because of insufficient response or toxicity.

Data from studies comparing these agents with PI therapy and key approval studies in treatment naive patients are included in table I. In several of the available comparative studies (DMP-006,[7] ACTG 364[11] and Atlantic[6]) twice daily NNRTI-based regimens have been compared with 3 times daily PI-based regimens (indeed, in Atlantic, because didanosine and indinavir administration should be separated, this arm is really a 4 doses per day regimen). Adherence studies have recognised that the middle dose is the most commonly missed, thus, poorly adherent patients in these studies were most likely to miss the PI rather than the other therapies. It may therefore be reasonable to expect that if a regimen is truly similar in potency to an PI-based regimen, it should demonstrate superiority under the bias of these designs. Superiority has only been observed in DMP-006.

2. Naïve Patient Studies

The key studies for efavirenz and nevirapine include direct comparison of these agents with PI-based regimens, for efavirenz against indinavir (DMP-006), with 72-week data reported, and for nevirapine against indinavir (Atlantic), with 48-week data available, and against nelfinavir (Combine),[12] with 24-week data only. Only in the Spanish Combine study is comparison made with a twice daily PI regimen. However, this study is small and differences appear to exist in the baseline characteristics of this study which hamper interpretation. The DMP-006 study also includes a 2-drug arm containing efavirenz and indinavir combined. This approach to the use of NNRTIs in a 'nucleoside sparing' regimen may attract further interest in the future if concerns regarding NA mitochondrial toxicity and the fat redistribution syndrome prove founded.

Results of the comparative studies support the use of efavirenz or nevirapine in first-line regimens with 2 NAs. In the 1266-patient DMP-006 study,[7] the proportion of patients with below 50 copies/ml (by ITT and OT analyses) and time to virological failure data indicate superiority for the efavirenz plus zidovudine/lamivudine regimen over indinavir plus zidovudine/lamivudine (and over efavirenz + indinavir). The ITT analysis is to some extent driven by the greater tolerability of efavirenz, a substantially higher proportion of participants randomised to indinavir + zidovudine/lamivudine had discontinued by 24 weeks (37.8%) compared with the indinavir + efavirenz (23.6%) or efavirenz + zidovudine/lamivudine groups (20.8%). The difference in discontinuations was largely secondary to a higher rate of adverse events, in particular nausea, in the zidovudine + lamivudine + indinavir group. Responses to efavirenz + zidovudine/lamivudine were similar in patients with baseline viral loads above and below 100 000 copies/ml and were significantly superior to the indinavir group in the those with above 100 000 copies/ml at baseline (by all analyses) at week 48.[7]

The 298 patient Atlantic study[6] is the first to directly compare the three leading treatment approaches to initial therapy: dual NA therapy with either NNRTI, PI or another NA. The dual NA base used in this study is stavudine plus didanosine with either the NNRTI nevirapine (400mg once daily), the PI indinavir (800mg three times daily) or the NA lamivudine (150mg twice daily). The low mean baseline viral load in this study (mean 4.18-4.22$\log_{10}$ copies/ml) means the efficacy of these regimens in patients with high viral loads is not adequately tested. At week 48, the ITT indicated that the proportion of participants with <50 copies/ml was 49, 49 and 40% for the nevirapine, indinavir and lamivudine groups, respectively, with no statistically significant differences. In patients with baseline viral loads >58 519 copies/ml (the upper quartile) the proportion of patients with a viral load <50 copies/ml at week 48 was 28, 48 and 26% for nevirapine, indinavir and lamivudine groups, respectively. Although these differences were not statistically significant they may be of practical importance when considering NNRTI choice in patients with higher viral loads. No differences in tolerability have been observed between groups. Table II include details of 48-week data from DMP-006 and Atlantic studies.

No data comparing delavirdine to standard-of-care regimens are available. Data from 2 completed 48-week studies (known as studies 21 part 2 and 13C) suggest inclusion of delavirdine with 2 NAs is superior to 2 NAs alone in treatment naïve patients. The proportion of people achieving an undetectable viral load response in 13C is lower than that reported in similar studies with efavirenz or nevirapine.[8]

3. Pretreated Patients

Differentiation of NNRTIs in treatment-experienced patients is challenged by the heterogeneity of patient experience and study designs reported. Broadly, all NNRTIs can draw on data which suggest activity in treatment experienced patients. However, information on efficacy in NA-pretreated patients is most complete for efavirenz. Efavirenz has been compared directly with the PI nelfinavir in NA experienced patients in ACTG 364.[11] The proportion of patients achieving viral suppression below 50 copies/ml at week 48 of this study significantly favoured efavirenz. However, an arm combining both efavirenz + nelfinavir was superior to efavirenz alone. Retrospective data from a 31-patient cohort suggest efavirenz has greater activity than nevirapine when combined with abacavir in PI-experienced patients.[13] However, despite efforts to ensure no differences existed in baseline characteristics, including geno- and phenotypic testing, the nonrandomised nature of this retrospective analysis limits the value of these observations.

Interest is growing in combining efavirenz and nevirapine in the salvage setting to get the maximal benefit from this drug class. Pharmacokinetic data indicate that the efavirenz dose may need to increase to 800mg in the evening to ensure adequate levels when combined with nevirapine. Studies prospectively assessing this approach are now ongoing.

Table II. Week 48 ITT data for percentage of patients with viral loads <50 copies/ml for the total population, and the number of patients with >100 000 copies/ml at baseline for key comparative studies (N)

Study	Analysis	N	<50 copies/ml (%)
Atlantic NVP[6]	All	71	49
Atlantic IDV	All	79	49
Atlantic 3TC	All	85	40
DMP-006 EFV[7]	All	154	65
DMP-006 IDV	All	152	43

3TC = lamivudine; **EFV** = efavirenz; **IDV** = indinavir; **ITT** = intent-to-treat non-completer = failure; **NVP** = nevirapine.

4. Other Considerations

Given that controlled trial data indicate initial PI-sparing therapy provides similar activity to PI-based approaches, the choice of initial therapy for HIV infection will relate to issues such as resistance profiles, tolerability, potential for drug interactions, convenience of administration, compartmental penetration, and potential for a second-line or salvage therapy to be effective. NNRTIs gener-

ally have advantages over PIs with regard to these characteristics. Differentiating NNRTIs for choice is challenged by the absence of comparative prospective data in all patient populations.

4.1 Resistance Profiles

The most common mechanism by which resistance develops is by a mutation in the *pol* gene leading to an amino acid substitution affecting the target enzyme. Darwinian selection processes lead to the selection of a viral variant containing mutations representing a balance between the benefit gained from reduced drug sensitivity against the partial loss of viral replication efficiency caused by mutation. For this process to occur, continued viral replication is necessary. Therefore, the only way to prevent the development of resistance is to fully switch off viral replication at all sites where drug is present, preventing the random generation of potentially resistant mutants.[3]

The key resistance mutations for efavirenz, nevirapine and delavirdine *in vivo* are K103N and Y181C, although other mutations may also affect sensitivity to all agents.[3,14,15] Other mutations associated with resistance to NNRTIs, generally in the *pol* gene codons 98-108 and 181-190, may further contribute to higher levels of resistance. Although some mutations or polymorphisms in these regions have been observed in those naïve to therapy, raising concerns about possible frequent transmission of NNRTI-resistant virus, the changes in sensitivity with most polymorphisms is a 2- to 4-fold shift in IC_{50} (50% inhibitory concentration) whereas these agents achieve trough exposure 10-fold or more above the IC_{95}. Thus, there is no reported impact from polymorphisms in these regions on treatment response in patients naïve to therapy. However, given the extent of cross-resistance within this class, sequential use of NNRTIs does not appear feasible.[3] New drugs in the NNRTI class which may possess activity against viruses resistant to the current NNRTIs are now entering clinical trials. NNRTIs do not exhibit cross-resistance with NA or PI classes.

4.2 Tolerability

The most common adverse events occurring with efavirenz have been CNS disturbances and skin rash, while rash and liver function test abnormalities are seen with nevirapine and delavirdine. NNRTI-related adverse events generally occur and resolve during the first month of therapy and infrequently lead to drug discontinuation. The overall frequency of CNS symptoms across studies with efavirenz is 54% compared with the rate in control patients of 27%. The majority of events are graded mild or moderate with only 2.7% leading to discontinuation.[16]

Hypersensitivity rashes associated with NNRTIs are generally of a maculopapular type and may be managed with antihistamines without treatment interruption. Stevens-Johnson syndrome has been reported; rarely with efavirenz and delavirdine and in 0.3% of patients with nevirapine. Rash (all grades, all types) is observed in a 10% excess to controls with efavirenz and a 15 to 17% excess with nevirapine and delavirdine. No risk factors for NNRTI-associated rash have been reported and cross-reaction is not the rule. The rash seen with nevirapine is less common if the drug is introduced gradually, allowing for hepatic induction. A regimen of 200mg once daily for 2 weeks followed by the full dose (200mg twice daily or 400mg once daily) is most commonly used. Antihistamines or prednisolone during the first weeks of nevirapine is used by some physicians, however available data suggest this may be of no benefit or indeed increase the risk of a severe reaction.

Raised levels of hepatic transaminases occur at a 7% excess to controls in nevirapine recipients. Approximately 1% of recipients discontinue nevirapine as a result of hepatitis. Clinically significant liver function abnormalities may be more common in individuals with hepatitis co-infection.[15] However, in some cases they may relate to the hypersensitivity reaction. Cautious monitoring of liver function tests during the first 8 weeks of nevirapine therapy is now recommended. Raised transaminase levels is a reported but infrequent reaction to delavirdine. Rates of increased transaminase levels

with efavirenz are similar to those in control arms of clinical studies.

Modest lipid elevations, both in cholesterol and triglycerides, have been observed in some efavirenz recipients. Increases in cholesterol levels with efavirenz, unlike those reported during PI therapy involve both high density lipoprotein and low density lipoprotein cholesterol and thus, may not increase risk of atherogenic diseases as much as has been suggested for PIs. Cross-sectional data on patients receiving initial therapy with 2 NAs and either efavirenz or nevirapine indicate no differences in the mean cholesterol or triglyceride values between NNRTI choices.[17]

4.3 Drug Interactions

Efavirenz, nevirapine and delavirdine are metabolised through the cytochrome P450 (CYP) system, predominately the CYP3A4 isozyme. Efavirenz acts as both an inhibitor and an inducer of this enzyme, while nevirapine is an inducer. Induction is associated with transient elevations in γ-glutamyl transferase levels. Relatively few drug interactions appear to require dosage adjustment, although co-administration with PIs (in the absence of ritonavir co-administration) may be contraindicated or require upward dosage adjustment.

Delavirdine is unique amongst available NNRTIs in acting exclusively as an inhibitor of CYP3A4 and other p450 cytochromes. Although this may lead to some clinically important drug interactions, for example with terfenadine, it may also be beneficially harnessed to improve PI pharmacology. The extent of increase in PI exposure by delavirdine varies between PIs but is in the 3- to 5-fold range with saquinavir (both hard and soft gel formulations), nelfinavir and indinavir. This interaction may enable greater drug exposure or allow for twice daily administration and/or lower PI pill numbers. The potential of these interactions have not been fully exploited to date, in part because of the absence of clinical efficacy data supporting the use of delavirdine or indeed this use of delavirdine.

4.4 Convenience of Administration

Issues which may influence convenience of administration include frequency, timing in relation to food, number of tablets, storage conditions and risk of medication unmasking HIV status to friends or colleagues. Administration of both efavirenz and nevirapine is independent of food and both agents may be taken once daily (although nevirapine is only approved for twice daily use). Delavirdine is approved for 3 times daily administration but is widely used as twice daily. An improved formulation enabling a dosage of 2 tablets twice daily should soon be available. Whereas efavirenz and nevirapine have long plasma half-lives (≈50 and ≈28 hours, respectively), delavirdine has a 4- to 6-hour plasma half-life. Although a long half-life may have advantages for flexible timing of doses, it does represent an obstacle to using these agents in 'structured treatment interruption' or 'pulse therapy' approaches.

4.5 Compartmental Penetration

Both nevirapine and efavirenz are also known to penetrate the CSF with free (non-protein bound) quantities of each agent being at least similar to free-plasma levels. Data on delavirdine are limited but this type of molecule is likely to penetrate the CNS.

Data on effects in lymph nodes of PI-sparing regimens have not been extensively examined. However, as the majority of plasma virus derives from lymphoid tissue, falls in plasma viral load with these regimens should represent control of virus in lymph nodes. Recent data with efavirenz suggest that clearance of viral activity from lymph nodes may be similar to that reported with protease inhibitors.[18]

5. Conclusions

NNRTI-based approaches to therapy appear attractive in terms of convenience of administration and long term tolerability, as well as offering CNS penetration and a diminished potential for clinically-important drug interactions relative to PIs.

Adverse effects with these agents do not extensively overlap with NAs and are generally observed only during the first month of therapy. Thus, once a patient is established on NNRTI therapy, tolerability is generally not a problem. Studies of similar design in treatment naïve patients have compared with a 3 times daily indinavir regimen to twice daily administration regimens with NNRTI-based approaches. Efavirenz provided superior efficacy to indinavir, whereas nevirapine regimens provided similar efficacy to indinavir but may be superior to nelfinavir. Comparative data with delavirdine are lacking, although older studies with this agent suggest activity in initial regimens superior to dual therapy. Data with efavirenz in patients with baseline viral loads $>10^5$ copies/ml suggest no diminution of activity. Data from comparative trials with nevirapine or delavirdine in these patients is currently lacking.

In treatment-experienced patients data are less clear. All agents may contribute to the efficacy of second-line regimens. Data from a small nonrandomised cohort of PI + NA-experienced patients suggested greater activity for efavirenz than nevirapine with abacavir. Interest in delavirdine in second-line therapy is currently focussed on its potential to act as a pharmacokinetic enhancer of PIs. The role of these agents in substituting for a PI in individuals fully suppressed on a PI-based regimen is currently under investigation. Sequencing of NNRTIs appears limited by a high level of cross-resistance between agents. Interest in combining NNRTIs to achieve additive or synergistic antiretroviral effects is growing and clinical trials evaluating the safety and efficacy of this approach are ongoing.

References

1. Gazzard BG, Moyle GJ, on behalf of the BHIVA Guideline Writing Committee. 1998 revision to the British HIV Association Guidelines for antiretroviral treatment of HIV seropositive individuals. Lancet 1998; 352: 314-6
2. Carpenter CJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998. JAMA 1998; 280: 78-86
3. Moyle GJ. Viral resistance patterns selected by antiretroviral drugs and their potential to guide treatment choice. Exp Opin Invest Drugs 1997; 6: 943-964
4. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998; 12: F51-8
5. Moyle G, Gazzard BG. Assessment of risk versus benefit for therapeutic intervention with HIV Protease inhibitors. Drug Saf 1999; 20: 299-321
6. Squires K. The Atlantic study: a randomized, open-label trial comparing two protease inhibitor (PI)-sparing anti-retroviral strategies versus a standard PI-containing regimen: final 48 week data [abstract LbPp7046]. XIII International AIDS conference; 2000 Jul 9-14, Durban
7. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N Engl J Med 1999; 341 (25): 1865-73
8. Wood R, Hawkins DA, Moyle G, et al. Second placebo-controlled study in naive individuals confirms the role of delavirdine in highly active antiretroviral, protease-sparing treatment [abstract no. 624]. 7th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4, Chicago: 185
9. Montaner JSG, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine in HIV-infected patients: the INCAS trial. JAMA 1998; 279: 930-7
10. Haas DW, Seekins D, Cooper R, et al. A phase II, double blind, placebo-controlled, dose ranging study to assess the antiretroviral activity and safety of efavirenz (EFV, Sustiva, DMP 266) in combination with open-label zidovudine (ZDV) and lamivudine (3TC) at 36 weeks (DMP 266-005) [abstract 22334]. 12th World AIDS Conference; 1998 Jun 28-Jul 3, Geneva
11. Albrecht M, Katzenstein D, Bosch R, et al. ACTG 364: virologic efficacy of nelfinavir (NFV) and/or efavirenz (EFZ) in combination with new nucleoside analogs in nucleoside experienced subjects [abstract no. 489]. 7th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4, Chicago: 159
12. Podzamczer D, Ferrer E, Consiglio E, et al. A randomized, open, multicenter trial comparing combivir plus nelfinavir or nevirapine in HIV-infected naive patients (the Combine Study) [abstract]. The 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC): 2000 Sep 17-20; Toronto (ON), 694
13. Moyle GJ, Wilkins E, Leen C, et al. Salvage therapy with abacavir plus efavirenz or nevirapine in HIV-1 infected persons with prior nucleoside analogue and protease inhibitor use. AIDS 2000. In press
14. Bachelor LT, Anton E, Baker D, et al. Impact of mutation, plasma protein binding and pharmacokinetics on clinical efficacy of the HIV-1 non nucleoside reverse transcriptase inhibitor, DMP 266 [abstract I-115]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 1997 Sep 28-Oct 1, Toronto (ON)
15. Murphy RL, Montaner J. Nevirapine: a review of its development, pharmacological profile and potential for clinical use. Exp Opin Invest Drugs 1996; 5: 1183-99

16. Moyle G. Efavirenz: shifting the HAART paradigm in adult HIV-1 infection. Exp Opin Invest Drugs 1999; 8: 473-86
17. Matthew G, Moyle G, Mandalia S, et al. Absence of association between individual thymidine analogues or nonnucleoside analogues and lipid abnormalities in HIV-1 infected persons on initial therapy. J Acquir Immune Defic Syndr 2000; 24 (4): 310-5
18. Dybul M, Chun TW, Ward DJ, et al. Evaluation of lymph node burden in HIV-infected individuals receiving an efavirenz-based protease-inhibitor sparing HAART regimen, abstract LB-15. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 1999 Sep 26-29, San Francisco (CA)

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