Efavirenz: a decade of clinical experience in the treatment of HIV

Franco Maggiolo*

Division of Infectious Diseases, Ospedali Riuniti, Largo Barozzi 1, Bergamo 24128, Italy

Efavirenz, a non-nucleoside reverse transcriptase inhibitor, has been an important component of the treatment of HIV infection for 10 years and has contributed significantly to the evolution of highly active antiretroviral therapy (HAART). The efficacy of efavirenz has been established in numerous randomized trials and observational studies in HAART-naive patients, including those with advanced infection. In the ACTG A5142 study, efavirenz showed greater virological efficacy than the boosted protease inhibitor (PI), lopinavir. Efavirenz is more effective as a third agent than unboosted PIs or the nucleoside analogue abacavir. Some, but not all, studies have suggested that efavirenz (added to two nucleoside reverse transcriptase inhibitors) is more effective than nevirapine. Virological and immunological responses achieved with efavirenz-based HAART have been maintained for 7 years. Dosing convenience predicts adherence, and studies have demonstrated that patients can be switched from PI-based therapy to simplified, once-daily efavirenz-based regimens without losing virological control. The one-pill, once-daily formulation of efavirenz plus tenofovir and emtricitabine offers a particular advantage in this regard. Efavirenz also retains a role after failure of a first PI-based regimen. Efavirenz is generally well tolerated: rash and neuropsychiatric disturbances are the most notable adverse events. Neuropsychiatric disturbances generally develop early in treatment and they tend to resolve with continued administration, but they are persistent and troubling in a minority of patients. Efavirenz has less effect on plasma lipid profiles than some boosted PIs. Lipodystrophy can occur under treatment with efavirenz but it may be reduced if the concurrent use of thymidine analogues is avoided. Efavirenz resistance mutations (especially K103N) can be selected during long-term treatment, underscoring the importance of good adherence. Recent data have confirmed that efavirenz is a cost-effective option for first-line HAART. In light of these features, efavirenz retains a key role in HIV treatment strategies and is the first-line agent recommended in some guidelines.

Keywords: HAART, treatment simplification, adherence, resistance

Introduction

The development and refinement of highly active antiretroviral therapy (HAART) during the last 10 years has dramatically prolonged the survival of HIV-infected individuals.1,2 In comparison with earlier combination regimens, current options are associated with greater viral suppression3,4 and lower discontinuation rates due to improved convenience and tolerability.5 According to current guidelines, HAART regimens for initial use should comprise two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI).3,4,6,7

The timing of HAART initiation is a controversial issue influenced by the relative benefit of treatment according to the disease stage, the impact of the therapy itself on the patient’s health and lifestyle, the need for long-term adherence and the risk of developing resistance. Other considerations that generally favour initiation of therapy include older age (the risk of progression to AIDS is higher in older patients), high cardiovascular risk and the presence of co-morbidities such as HIV-associated nephropathy. There is now a consensus that HAART should be initiated when the CD4 cell count falls to <350 cells/mm3.3,4,6,7 Accumulating evidence suggests that starting HAART at higher CD4 cell counts (i.e. earlier in the disease process) may further improve virological response, immunological recovery and disease prognosis.8 Thus, current recommendations state that HAART initiation be considered in some patients with CD4 counts of 350–500 cells/mm³ if they have risk factors for poor prognosis such as high viral...
load (VL), rapidly declining CD4 cell count or hepatitis co-infection. The earlier commencement of HAART, coupled with the longer survival of recipients, has increased the duration of antiretroviral drug exposure and prompted greater consideration of the long-term metabolic adverse effects of regimens and the durability of their efficacy.

Licensed in the EU in 1999, the NNRTI efavirenz has been an important component of the treatment of HIV infection for 10 years and has contributed significantly to the evolution of HAART. Currently efavirenz is a recommended option for initial therapy and is usually regarded as the preferred NNRTI. Indeed, the combination of efavirenz plus two NRTIs is recommended as the regimen of choice for initial therapy in the current UK guidelines. This article reviews the pharmacokinetics, long-term efficacy, resistance development, safety and cost-effectiveness of efavirenz.

Pharmacokinetics

Absorption

Peak efavirenz plasma concentrations are reached by 5 h following single oral doses in uninfected volunteers. The time to peak plasma concentrations is ~3–5 h and steady-state plasma concentrations of efavirenz are reached in 6–7 days. The bioavailability of a single 600 mg dose of efavirenz hard capsules in uninfected volunteers is increased by 17%–22% by food. Efavirenz is highly bound (~99.5%–99.75%) to human plasma proteins, predominantly albumin.

Biotransformation

Efavirenz is converted to inactive hydroxylated metabolites by the cytochrome P450 system. CYP2B6 is one of the major isozymes responsible for efavirenz metabolism. Efavirenz plasma exposure is increased in patients with the homozygous G516T genotype of CYP2B6. This is not associated with treatment failure, but it can lead to a higher rate of neuropsychiatric adverse events. In this situation, dose reduction is feasible and maintains virological suppression. The G516T genotype is more common in African Americans than in European Americans and has been reported to cause greater efavirenz exposure, although there is considerable overlap between racial/ethnic populations. The C1459T polymorphism has been reported not to affect efavirenz exposure. Other alleles of CYP2B6 may also influence efavirenz metabolism.

Elimination

Efavirenz has a terminal half-life of at least 52 h after single doses and 40–55 h after multiple doses. Approximately 14%–34% of a radiolabelled dose of efavirenz is recovered in the urine and <1% of the dose is excreted in urine as unchanged efavirenz. The half-life of efavirenz appears to be shorter (~24 h) when it is given in combination with didanosine and emtricitabine, but this combination is effective and well tolerated in long-term therapy.

The long half-life of efavirenz makes it suitable for once-daily dosing. The recommended dosage in adults is 600 mg once daily. Genotypic testing for variants of the CYP2B6 allele could detect individuals at increased risk of neuropsychiatric adverse events but this is not routine practice. There is no recommendation to adjust the dose of efavirenz according to race or sex.

Efficacy

Treatment-naive patients

The efficacy of efavirenz has been established in numerous trials in HAART-naive patients. Studies have compared efavirenz against PIs, other NNRTIs and triple NRTI regimens. In addition, efavirenz has been used as the common ‘third agent’ in evaluations of many NRTI combinations.

Comparison with PIs

The early randomized, open-label DMP 266-006 study showed that efavirenz was superior to unboosted indinavir when both were administered over 48 weeks with an NRTI backbone of zidovudine plus lamivudine. See Table 1.

In other studies, efavirenz was as effective as unboosted atazanavir and more effective than unboosted nelfinavir when all were combined with two NRTIs (Table 1). More recently, the AIDS Clinical Trial Group (ACTG) performed a landmark comparison of efavirenz versus ritonavir-boosted lopinavir. ACTG A5142 was a randomized, open-label, 96 week study of efavirenz versus boosted lopinavir—each administered with lamivudine plus zidovudine, stavudine or tenofovir—and efavirenz plus boosted lopinavir (an NRTI-sparing regimen). The primary endpoint analysis was the time to virological failure, defined as a lack of VL suppression by 1 log10 HIV RNA copies/mL or rebound before week 32, or a lack of VL suppression to <200 copies/mL or rebound after week 32. The efavirenz group showed a significantly longer time to this endpoint with a relative hazard ratio (HR) of 0.63 [95% confidence interval (CI) 0.45–0.87; P<0.006] (Figure 1). The time to regimen failure (defined as virological failure or toxicity-related discontinuation of any component of the randomized regimen) also showed a benefit for efavirenz over boosted lopinavir (HR 0.75; 95% CI 0.57–0.98; P=0.03), although this failed to reach the significance threshold adjusted for multiple comparisons (P=0.014). In terms of virological response, significantly more patients treated with efavirenz-based therapy achieved a VL of <200 copies/mL or <50 copies/mL at 96 weeks than did boosted lopinavir-treated patients, although the median increase in CD4 cell count was smallest in the efavirenz arm (Table 1). At 96 weeks, recurrent or new AIDS-defining conditions occurred in 4% of patients receiving efavirenz-based therapy versus 6% of those in the other arms.

Another, smaller study showed efavirenz to be superior to boosted lopinavir in patients with low CD4 cell counts, as discussed below. Observational cohort studies have also found that efavirenz has virological efficacy at least as high and durable as boosted lopinavir (and in some studies more so), including in patients with advanced disease. These studies include the Swiss HIV Cohort, EfavIP, MASTER, TEQUILA, SUSKA and Antiretroviral Therapy Cohort Collaboration (ART-CC) studies (Table 2).

The retrospective SUSKA study showed no difference between efavirenz (n=1159) and boosted lopinavir (n=391) in the
Table 1. Randomized studies that compared efavirenz with PIs, other NNRTIs or abacavir as third agents or which used efavirenz in evaluations of NRTI combinations in HIV-infected, treatment-naive patients (ITT analyses)

| Trial                  | Design | Treatment                     | n  | VL (copies/mL) | CD4 (cells/mm³) | Time | Percentage with VL: | Time to virological failure, HR (95% CI) | CD4 increase (cells/mm³) |
|------------------------|--------|-------------------------------|----|----------------|-----------------|------|---------------------|------------------------------------------|--------------------------|
| **Baseline**           |        |                               |    |                |                 |      | <400 copies/mL       | <50 copies/mL                           |                          |
| **EFV vs PI**          |        |                               |    |                |                 |      |                     |                                          |                          |
| DMP 266-006²³          | OL     | patients with ≥100 CD4 cells/mm³ |    |                |                 |      |                     |                                          |                          |
| EFV + ZDV + 3TC        | 361    | 4.70                          | 396.4 | 48 weeks       | 72.5 (P ≤ 0.05 vs IDV) | 66.6 (P ≤ 0.05 vs IDV) | NR | 200                   |
| IDV + ZDV + 3TC        | 357    | 4.70                          | 388.5 | 52.1           | 47.2            | 183 |
| EFV + IDV              | 356    | 4.71                          | 379.0 | 62.0 (P ≤ 0.05 vs IDV; P ≤ 0.05 vs CD4 < 100) | 56.1 (P ≤ 0.05 vs IDV; P ≤ 0.05 vs CD4 < 100) | 183 |
| patients with <100 CD4 cells/mm³ |       |                               |    |                |                 |      |                     |                                          |                          |
| EFV + ZDV + 3TC        | 46     | 5.28                          | 64.5 | 48 weeks       | 69.8            | 58.1 | NR                    | 184                                    |
| IDV + ZDV + 3TC        | 47     | 5.23                          | 61.3 | 50.0           | 40.9            | 177 |
| EFV + IDV              | 49     | 5.43                          | 65.6 | 38.1           | 23.8            | 118 |
| Maggiolo²⁴             | OL     | EFV + ddI + 3TC               | 34  | 5.21           | 184             | 52 weeks | 77.4 | NR                    | 194                                    |
| EFV + ZDV/3TC          | 34     | 5.22                          | 175 | 77.4           | NR              | 183 |
| NFV + ZDV/3TC          | 34     | 5.16                          | 169 | 50.0 (P = 0.02 vs EFV) | NR | 165 |
| ACTG A5142²⁵           | OL     | EFV + 2 NRTIs                 | 250 | 4.8⁴         | 195⁴           | 96 weeks | NR | 89 (P = 0.003 vs LPV/r) EFV vs LPV/r: 0.63 (0.45–0.87) (P = 0.006) | 230⁴                |
| LPV/r + 2 NRTIs        | 253    | 4.8                           | 190 | 77             | EFV vs EFV + LPV/r: 0.86 (0.61–1.21) | 287 (P < 0.01 vs EFV) |
| EFV + LPV/r            | 250    | 4.9                           | 189 | 83             | 273 (P < 0.01 vs EFV) |
| Sierra-Madero²⁶         | OL     | EFV + ZDV + 3TC               | 95  | NR             | 64⁴             | 48 weeks | 73 | 70 (P = 0.0141) | NR | 156.9 | 166.9 |
| LPV/r + ZDV + 3TC      | 94     | NR                            | 52  | 65             | 54             |
| **EFV vs NNRTI**       |        |                               |    |                |                 |      |                     |                                          |                          |
| 2NN²⁷                  | OL     | EFV + 3TC + d4T               | 400 | 4.7³         | 190³           | 48 weeks | NR | 70.0 | NR | 160³ |
| NVP QD                 | 220    | 4.7                           | 200 | 70.0           | 170             |
| NVP BID                | 387    | 4.7                           | 170 | 65.4           | 160             |
| EFV + NVP              | 209    | 4.7                           | 190 | 62.7           | 150             |
| FIRST²⁸                | NR     | EFV + 2 NRTIs                 | 111 | 5.0º            | 181º           | 5 years | NR | NR | NR | 172 |
| NVP + 2 NRTIs          | 117    | 5.1                           | 196 | NR             | NR | 153 |

Continued
| Trial | Design | Treatment | n | VL (copies/mL) | CD4 (cells/mm³) | Time | Percentage with VL: | Time to virological failure, HR (95% CI) | CD4 increase (cells/mm³) |
|-------|--------|-----------|---|----------------|----------------|------|-------------------|------------------------------------------|------------------------|
|       |        |           |   |                |                |      | <400 copies/mL | <50 copies/mL |                                      |                         |
| EFV vs triple NRTIs |        |           |   |                |                |      |                  |                           |                         |
| ACTG A5095²⁹  | DB     | EFV + ZDV/3TC±ABC/ABC+ZDV/3TC | 765 4.86 | 242 | 48 weeks | NR | 83 | NR⁴ | 173 |
|         |        |           | 382 4.85 | 234 |          | 61 | 61 |                         |                         |
| Evaluations of NRTIs |        |           |   |                |                |      |                  |                           |                         |
| EPV20001³⁰  | DB     | EFV + ZDV+3TC QD | 278 4.64a | 340a | 48 weeks | 59 | 64 | NR | 144a |
|         |        |           | 276 4.69 | 386 |          | 61 | 63 |                         |                         |
|         |        |           | 386 4.87 | 259 |          | 68 | 68 |                         |                         |
| CNA30021³¹  | DB     | EFV +3TC+ABC QD | 384 4.91a | 264a | 48 weeks | NR | 66 | NR | 188a |
|         |        |           | 386 4.87 | 259 |          | 68 | 68 |                         |                         |
|         |        |           | 324 4.81a | 267a | 48 weeks | 74 | 70 | NR | 209a |
|         |        |           | 325 4.81 | 258 |          | 71 | 69 |                         |                         |
| ACTG A5095³³  | DB     | EFV +ZDV/3TC | 382 4.87 | 238 | 192 weeks | NR | ~84 | 3 vs 4 drugs: 0.95 (0.69–1.33) | ~310 |
|         |        |           | 383 4.84 | 242 |          | NR | ~88 |                      |                         |
|         |        |           | 299 4.91 | 276 | 144 weeks | 70.6 | 67.9 | NR | 263 |
|         |        |           | 301 4.91 | 283 |          | 64.1 | 62.5 |                         |                         |
| GS934³⁶,³⁷ OL | EFV+TDF+FTC | 244 5.0a | 233a | 144 weeks | 64 | 71 | NR | 312a |
|         |        |           | 243 5.0 | 241 |          | 56 (P=0.08) | 58 (P=0.004) |                         | 271 |

ABC, abacavir; CI, confidence interval; DB, double blind; EFV, efavirenz; FTC, emtricitabine; HR, hazard ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; NR, not reported; NRTI, nucleoside reverse transcriptase inhibitor; OL, open-label; TDF, tenofovir; VL, viral load; vs, versus; ddl, didanosine; 3TC, lamivudine; d4T, stavudine; LPV/r, lopinavir/ritonavir; ZDV, zidovudine; IDV, indinavir; NFV, nelfinavir; NVP, nevirapine; QD, once daily; BID, twice daily.

Note: / indicates co-formulated drugs; + indicates components administered separately; ~ indicates value estimated from a graph.

¹Medians; other continuous data are means.

²There was no significant difference between groups in the proportion of patients who fulfilled the primary composite endpoint (VL ≥ 50 copies/mL at or after 8 months or death: HR 0.92; 95% CI 0.69–1.23), or in either component of this composite. However, patients randomized to EFV were significantly less likely to experience virological failure associated with NNRTI resistance (HR 0.65; 95% CI 0.41–1.01; P=0.05), NRTI resistance (HR 0.20; 95% CI 0.08–0.52; P<0.01) or any resistance (HR 0.60; 95% CI 0.39–0.93; P=0.02).

³The time to virological failure was significantly shorter with ABC-based therapy compared with EFV-based therapy (P<0.001).
adjusted HRs for virological failure (0.93; 95% CI 0.77–1.12; P=0.43), CD4 recovery (1.11; 95% CI 0.95–1.30; P=0.19) and clinical progression (0.71; 95% CI 0.39–1.31; P=0.27). However, recipients of boosted lopinavir were approximately twice as likely to discontinue treatment for any reason or for toxicity (HR 2.10; 95% CI 1.40–3.15; P=0.0003). The ART-CC study assessed virological failure (VL of <500 copies/mL) at 24 weeks and clinical outcomes within 2 years following the initiation of various third agents (each in combination with lamivudine and zidovudine) in a large cohort of 13546 patients from Europe, Canada and the USA. According to multivariate analysis, virological failure was less likely to occur with efavirenz than with any other third agent evaluated. Compared with efavirenz the adjusted odds ratio (OR) for the risk of failure ranged from 3.20 (95% CI 2.74–3.74) with nelfinavir to 1.32 (95% CI 1.12–1.57) with boosted lopinavir. The incidence of clinical AIDS events or death did not differ between efavirenz and these PIs; however, each regimen was associated with a 2 year AIDS-free survival rate of ~95% (Figure 2).

**Comparison with other NNRTIs**

Few randomized studies have compared efavirenz with nevirapine, the only other NNRTI currently licensed for use as first-line therapy (Table 1). In the 2NN study, nevirapine did not meet the criteria for non-inferiority as compared with efavirenz.

Recently, pertinent results were reported from the FIRST study, in which patients were randomized to one of three strategies: NNRTI plus NRTIs, PI plus NRTIs or a combination of all three classes (NNRTI plus PI plus NRTI). Patients randomized to receive an NNRTI plus NRTIs or the three-class strategy could choose their NNRTI or accept additional randomization to efavirenz or nevirapine. Among patients randomized in this NNRTI substudy (n=228), there was no significant difference between the efavirenz and nevirapine arms in the primary endpoint of the proportion of patients with a VL of ≥50 copies/mL (at or after 8 months) or death (HR 0.92; 95% CI 0.69–1.23). Similarly, there was no significant difference in rates of overall virological suppression or failure (although significant benefits for failure associated with resistance were reported for efavirenz, as discussed below), or in CD4 cell count recovery (Table 1). A similar pattern of results was observed in the total cohort comprising patients randomized to an NNRTI and those who had chosen their NNRTI. Randomized patients treated with efavirenz showed a significantly higher adjusted rate of disease progression events or death (HR 2.19; 95% CI 1.26–3.81; P=0.01), but the combined cohort did not show this finding and the substudy was not powered to evaluate events.

Large observational studies have reported superior virological, immunological and clinical outcomes with efavirenz over nevirapine (Table 2). In the ART-CC cohort, nevirapine initiation was associated with an adjusted OR for 24 week virological failure of 1.87 (95% CI 1.58–2.22) versus efavirenz. Furthermore, nevirapine use was associated with a significantly higher incidence of AIDS events or death over 2 years, compared with efavirenz (Figure 2).

**Comparison with triple NRTIs**

The use of the triple NNRTI combination of zidovudine plus lamivudine and abacavir in the randomized, double-blind ACTG A5095 study was halted when an interim analysis at 32 weeks revealed that virological failure had occurred in almost twice as many of the patients treated with the triple NNRTI regimen (21%) as in those treated with efavirenz plus either two or three NRTIs (11%; P<0.001). Efavirenz-based therapy maintained high levels of efficacy over 3 years, with abacavir adding no further benefit over efavirenz plus lamivudine and zidovudine.

In the observational ART-CC cohort, the use of abacavir rather than efavirenz as the third agent (added to zidovudine plus lamivudine) was more likely to be associated with virological failure (adjusted OR 2.13; 95% CI 1.82–2.50) and with the occurrence of an AIDS-defining event or death over 2 years (Figure 2).

**Comparisons with new classes of antiretroviral agent**

**CCR5 antagonists.** Maraviroc is a CCR5 antagonist that inhibits virus/cell binding via inhibition of the co-receptor target CCR5 on the surface of host CD4 cells. Maraviroc is not active against the CXCR4 co-receptor and an HIV tropism test, e.g. a Trofile™ assay, must be performed before treatment to ensure that patients are infected with the R5-using strain of the HIV-1 virus. The randomized, double-blind MERIT study compared the efficacy and tolerability of maraviroc (n=360) with efavirenz (n=361) in treatment-naive patients infected with R5 HIV-1, with both treatment groups also receiving Combivir (zidovudine/lamivudine). At 48 weeks, maraviroc did not show non-inferiority (margin 10%) compared with efavirenz for the primary endpoint of a VL <50 copies/mL (65.3% versus 69.3%; lower limit of one-sided 97.5% CI –10.9%). In addition, more
| Trial (reference)          | Design            | Treatment                                  | log₁₀ VL (copies/mL) | CD4 (cells/mm³) | Time to treatment failure, HR (95% CI)³ | VL < 50 copies/mL², HR (95% CI) or OR (95% CI) | CD4 recovery⁴, HR (95% CI) |
|---------------------------|-------------------|--------------------------------------------|----------------------|---------------|----------------------------------------|-----------------------------------------------|--------------------------|
| **EFV versus PI**         |                   |                                            |                      |               |                                        |                                               |                          |
| Swiss HIV Cohort ⁴⁰       | prospective       | EFV + 2 NRTIs                              | 89                   | 4.71          | 216                                    | 1.66 (1.11–2.49)⁵                      | 1.10 (0.80–1.52)⁵        |
|                           |                   | NFV or IDV or IDV/r or SQV/r + 2 NRTIs     | 183                  | 4.81          | 165                                    | 1                                    | 1                         |
| EfaVIP ²⁴¹                | retrospective      | EFV + 2 NRTIs                              | 92                   | 5.54          | 34                                     | 1¹                                    | 1                         |
|                           | (advanced disease) | NFV or IDV or RTV or IDV/r or SQV/r + 2 NRTIs | 218               | 5.40          | 38                                     | 4.91 (1.77–13.63)⁹               | 2.19 (1.23–3.89)⁹        |
| MASTER ⁴²                 | retrospective      | EFV + 2 NRTIs                              | 348                  | 4.8e          | 215f                                   | 1⁶                                    |                           |
|                           | longitudinal      | LPV/r + 2 NRTIs                            | 124                  | 4.9e          | 176f                                   | 0.40 (0.33–0.89)⁶                  |                           |
| TEQUILA ⁴³                | retrospective      | EFV + 2 NRTIs                              | 665                  | 5.26          | 37                                     | 1                                    | 1                         |
|                           | (advanced disease) | LPV/r + 2 NRTIs                            | 495                  | 5.30          | 35                                     | 1.19 (0.97–1.45)¹⁰                 | 1.17 (0.98–1.40)¹⁰        |
| SUSKA ⁴⁴                 | retrospective      | EFV + 2 NRTIs                              | 1159                 | 5.03          | 187                                    | 0.93 (0.77–1.12)⁸                  | 1.11 (0.95–1.30)⁸        |
|                           | longitudinal      | LPV/r                                     | 391                  | 5.16          | 120                                    | 1¹                                   | 1                         |
| **Evaluation of third drug** |                   |                                            |                      |               |                                        |                                               |                          |
| ART-CC ⁴⁵                |                   | EFV + ZDV + 3TC                            | 3788                 | 4.9           | 207                                    | 1⁶                                   |                           |
|                           |                   | NVP + ZDV + 3TC                            | 2151                 | 4.7           | 260                                    | 1.87 (1.58–2.22)³⁶                 |                           |
|                           |                   | LPV/r + ZDV + 3TC                          | 2875                 | 5.1           | 150                                    | 1.32 (1.12–1.57)²⁶                 |                           |
|                           |                   | NFV + ZDV + 3TC                            | 2217                 | 4.8           | 214                                    | 3.20 (2.74–3.74)³⁶                 |                           |
|                           |                   | ABC + ZDV + 3TC                            | 2515                 | 4.7           | 251                                    | 2.13 (1.82–2.50)³⁶                 |                           |

ABC, abacavir; EFV, efavirenz; HR, hazard ratio; LPV, lopinavir; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; OR, odds ratio; VF, virological failure; VL, viral load; /r, ritonavir-boosted; 3TC, lamivudine; ZDV, zidovudine; IDV, indinavir; RTV, ritonavir; SQV, saquinavir.

Note: + indicates components administered separately.

¹Hazard ratio (95% CI).
²Increase in CD4 count >50 cells/mm³.
³Treatment failure defined as: not achieving a VL of <400 copies/mL or having an increase above limit of quantification in two consecutive determinations after initial viral suppression; death; opportunistic infections; therapy discontinuations; or lost to follow-up.
⁴Probability of reaching a CD4 count of >200 cells/mm³.
⁵Mean values.
⁶Odds ratio (95% CI).
⁷Treatment failure defined as VF, death, opportunistic infection or treatment discontinuation.
⁸Time to CD4 count ≥200 cells/mm³ in patients who did not experience VF.
⁹CD4 recovery defined as >100 cells/mm³ gain from baseline.
¹⁰VF defined as a VL of >500 copies/mL at 24 weeks.
patients discontinued in the maraviroc compared with the efavirenz arm due to lack of efficacy (11.9% versus 4.2%). However, the mean change from baseline in CD4 cell count was greater for patients receiving maraviroc than efavirenz (+170 versus +144 cells/mm³), and fewer patients experienced grade 3/4 adverse events in the maraviroc than in the efavirenz arm. A recent re-analysis of the MERIT study found that maraviroc was non-inferior to efavirenz for a VL of <50 copies/mL if 15% (106/721) of patients originally classified as R5 HIV-1, but determined to have non-R5 HIV-1 using a more sensitive Trofile™ assay, were excluded.49

A Phase II dose-finding study of the CCR5 antagonist vicriviroc was discontinued because of a higher incidence of virological failure among patients randomized to vicriviroc 25 or 50 mg twice daily than with efavirenz-based therapy.50

**Integrase inhibitors.** Raltegravir is an integrase inhibitor which, following promising results in patients with highly resistant HIV,51,52 was compared with efavirenz in treatment-naive patients in the 004 and STARTMRK studies. The 004 study compared the efficacy and tolerability of raltegravir (n=160) against efavirenz (n=38), both combined with tenofovir and lamivudine.53,54 For the first 48 weeks patients receiving raltegravir were randomized to doses of 100, 200, 400 or 600 mg twice daily; all patients randomized to efavirenz received 600 mg once daily. At weeks 2, 4 and 8, more patients in each raltegravir dose group reached VL <50 copies/mL than those receiving efavirenz.55 These differences diminished with time; by week 24 (the primary endpoint) and week 48 (the secondary endpoint) ≥85% of patients reached VL <50 copies/mL in each treatment group. After 48 weeks, all raltegravir patients were given 400 mg twice daily and were analysed as a single group. At 96 weeks, the raltegravir and efavirenz groups exhibited similar rates of viral suppression, with 83% and 84% of patients, respectively, achieving VL <50 copies/mL by intent-to-treat (ITT) analysis.54 Increases in CD4 cell count were also similar for raltegravir and efavirenz (+221 versus +232 cells/mm³, respectively). Raltegravir was generally well tolerated, with drug-related adverse events less frequent in the raltegravir arm than in the efavirenz arm (51% versus 74%, respectively). Raltegravir was more lipid-neutral than efavirenz with respect to total cholesterol, low-density lipoprotein-cholesterol and triglycerides.55 The STARTMRK study reported 48 week data for treatment-naive patients (n=563) randomized to receive raltegravir or efavirenz, both combined with tenofovir and emtricitabine.56 At week 48, 86% of patients treated with raltegravir (n=281) and 82% with efavirenz (n=283) achieved a VL of <50 copies/mL, the primary study endpoint (P<0.001 for non-inferiority; non-completer=failure analysis), with the authors stating that raltegravir was non-inferior to efavirenz. Patients in the raltegravir arm had greater increases in CD4 cell count than those in the efavirenz arm (+189 versus +163 cells/mm³). Raltegravir was generally well tolerated, with drug-related adverse events significantly less frequent in the raltegravir arm than in the efavirenz arm (44% versus 77%; P=0.001).

Another integrase inhibitor, elvitegravir, reduces VL in treatment-experienced patients, but its effectiveness appears to depend on active background therapy.56 Elvitegravir has not been compared directly with efavirenz.

**Novel NNRTIs.** Novel NNRTIs, including rilpivirine (TMC278) and etravirine (TMC125), are under development. A dose-ranging study compared 25, 75 or 150 mg of rilpivirine once daily with 600 mg of efavirenz once daily (each added to two NRTIs) in 368 treatment-naive patients.57 The primary endpoint was the proportion of patients with a VL of <50 copies/mL at 48 weeks, which was reached by 80%, 80% and 77% of patients treated with rilpivirine 25, 75 and 150 mg, respectively, versus 81% of those receiving efavirenz. Both treatments were generally well tolerated; rash and nervous system disorders were less common with rilpivirine than with efavirenz. As discussed below, clinical trials indicate that etravirine is effective and generally well tolerated in patients with HIV resistant to efavirenz or nevirapine. A trial of 400 mg etravirine once daily versus 600 mg efavirenz once daily (each added to two NRTIs) in treatment-naive patients is in progress.58

**Conclusions.** At present there is no evidence that CCR5 antagonists, integrase inhibitors or novel NNRTIs are more effective than efavirenz in treatment-naive patients, but further studies are in progress. These new agents are generally well tolerated and may have an important role after the failure of initial therapy.

**Efavirenz in studies of NRTIs**

Many studies comparing different NRTI combinations have used efavirenz as the common third agent.31,32,34,35,37 In the Gilead Sciences (GS) 903 study, efavirenz-based regimens containing lamivudine plus either tenofovir or stavudine were similarly effective over 144 weeks of double-blind, randomized therapy (Table 1).34 Following a further 144 weeks of open-label treatment (total 288 weeks), 71 of 86 (83%) patients originally randomized to efavirenz plus tenofovir and lamivudine had a VL of <400 copies/mL and 69/86 (80%) had a VL of <50 copies/mL.59 Data confirming the maintenance of

---

**Figure 2.** Estimated AIDS-free survival among 13546 antiretroviral-naive HIV-infected patients in the Antiretroviral Therapy Cohort Collaboration study initiating antiretroviral therapy with zidovudine plus lamivudine stratified by the third drug in their regimen (2000–2005). Survival curves are estimated from a Weibull model with follow-up censored at 2 years, with covariates set at the average value across the population of patients and for the cohort with median survival. Efavirenz, continuous line; nevirapine, long dashed line; boosted lopinavir, widely spaced dashed line; nelfinavir, short dashed line; abacavir, dot plus dashed line. Corresponding adjusted HRs for the composite of incident AIDS event or death, compared with efavirenz, were: nevirapine, 1.20 (95% CI 0.95–1.50); boosted lopinavir, 1.08 (95% CI 0.89–1.32); nelfinavir, 0.95 (95% CI 0.77–1.18); and abacavir, 1.16 (95% CI 0.92–1.45). Reproduced with permission from Mugavero et al.45

---

**Table 1.** The GS 903 study compared the efficacy and tolerability of rilpivirine (TMC278) and etravirine (TMC125), are under development. A dose-ranging study compared 25, 75 or 150 mg of rilpivirine once daily with 600 mg of efavirenz once daily (each added to two NRTIs) in 368 treatment-naive patients. The primary endpoint was the proportion of patients with a VL of <50 copies/mL at 48 weeks, which was reached by 80%, 80% and 77% of patients treated with rilpivirine 25, 75 and 150 mg, respectively, versus 81% of those receiving efavirenz. Both treatments were generally well tolerated; rash and nervous system disorders were less common with rilpivirine than with efavirenz. As discussed below, clinical trials indicate that etravirine is effective and generally well tolerated in patients with HIV resistant to efavirenz or nevirapine. A trial of 400 mg etravirine once daily versus 600 mg efavirenz once daily (each added to two NRTIs) in treatment-naive patients is in progress.58

**Conclusions.** At present there is no evidence that CCR5 antagonists, integrase inhibitors or novel NNRTIs are more effective than efavirenz in treatment-naive patients, but further studies are in progress. These new agents are generally well tolerated and may have an important role after the failure of initial therapy.
virological and immunological responses at 7 years are available in abstract form.60 Following the randomized phase of GS903, patients switched from stavudine to tenofovir (plus efavirenz and lamivudine) also showed maintained virological suppression and continued CD4 cell counts increase over 144 weeks.61

In the GS934 study, the combination of efavirenz plus tenofovir and emtricitabine proved superior to efavirenz plus lamivudine and zidovudine for VL suppression and CD4 cell count recovery up to 144 weeks (Table 1).36,37,62 At 144 weeks, significantly more patients in the tenofovir/emtricitabine arm had a VL of <400 copies/mL (71% versus 58% on zidovudine/lamivudine; \( P = 0.004 \)). There were also trends favouring tenofovir/emtricitabine for virological suppression to <50 copies/mL (64 versus 56%; \( P = 0.08 \)) and for the increase in CD4 cell count (312 versus 271 cells/mm\(^3\); \( P = 0.09 \)).

Bartlett et al.63 systematically reviewed the results of seven trials that evaluated various NRTI regimens in combination with efavirenz in terms of the time to loss of virological response over 48 weeks (\( n = 3807 \) patients). Response rates were 65%–84% for VL <400 copies/mL and 61%–80% for a VL of <50 copies/mL, with regimens containing emtricitabine plus tenofovir, didanosine or stavudine showing the best efficacy (Figure 3).63 Virological failure occurred in 2%–8% of patients.

**Treatment-experienced patients**

**Treatment simplification**

Adherence is a major predictor of the success of HAART,64,65 with higher adherence rates leading to a lower risk of viral rebound and resistance development.65 The complexity of the treatment regimen is an important barrier to good adherence65,67 and patients generally prefer the simplicity of once-daily regimens.68,69 The use of once-daily agents and the co-formulation of multiple antiretrovirals in fixed-dose combinations have simplified HAART regimens in recent years. As well as providing simplified initial HAART regimens, these approaches have been used in switch strategies to improve convenience for patients stabilized on more complicated regimens.

In the GS934 study, patients who had received 96 weeks of treatment with efavirenz plus emtricitabine and tenofovir were switched to efavirenz plus a fixed-dose combination of tenofovir/emtricitabine and continued to show high rates of virological suppression.71 In the uncontrolled COMET study, virological suppression was also maintained when stable patients (VL <400 copies/mL) on efavirenz plus twice-daily zidovudine plus lamivudine had their NRTIs switched to once-daily fixed-dose tenofovir/emtricitabine.70 Of 402 patients, only 2% discontinued owing to adverse events and <1% discontinued for virological failure. At 24 weeks, 87% of patients had a VL of <400 copies/mL and 74% (versus 71% at baseline) had a VL of <50 copies/mL. Following the switch, patients reported increased satisfaction with treatment, fewer were bothered by adverse events and adherence rates were improved (as measured by the proportion who took ≥95% of doses). In the open-label Simplification With Easier Etricitabine and Tenofovir (SWEET) study, patients who were stabilized on efavirenz plus fixed-dose lamivudine/zidovudine (\( n = 250 \)) were randomized to remain on this regimen or to switch to fixed-dose efavirenz plus fixed-dose tenofovir/emtricitabine.71 At 48 weeks, the two arms showed similar virological responses, with 88% of the switch group and 85% of the continuation group achieving a VL of <50 copies/mL. Discontinuation rates because of adverse events were 3% and 5%, respectively. These data indicate that patients can be switched from PI-based HAART to simplified efavirenz-based regimens without loss of virological control.

The introduction of Atripla,68 a single-pill once-daily, fixed-dose formulation of efavirenz plus tenofovir and emtricitabine, has further reduced the pill burden of HAART. The Phase IV, open-label AI266073 study evaluated the effect of switching patients

| EPV-20001 | ZDV BID + 3TC BID | 63 | 65 | (n = 276) |
| EPV-20001 | ZDV BID + 3TC QD | 61 | 67 | (n = 278) |
| DMP-006 | ZDV BID + 3TC QD | 65 | 69 | (n = 422) |
| CNA-3021 | ABC QD + 3TC QD | 64 | 71 | (n = 384) |
| CNA-3024 | ZDV BID + 3TC QD | 69 | 71 | (n = 325) |
| CNA-3021 | ABC BID + 3TC QD | 65 | 72 | (n = 386) |
| CNA-3024 | ABC BID + 3TC QD | 69 | 73 | (n = 324) |
| GS934 | ZDV/3TC BID | 70 | 73 | (n = 243) |
| GS903 | TDF QD + 3TC BID | 76 | 79 | (n = 299) |
| FTC-301A | ddI QD + FTC QD | 78 | 81 | (n = 286) |
| GS903 | d4T BID + 3TC BID | 79 | 82 | (n = 301) |
| GS934 | TDF QD + FTC QD | 80 | 84 | (n = 244) |

**Figure 3.** Virological response using the time to loss of virological response rate (TLOVR) for HIV RNA <50 and <400 copies/mL thresholds at week 48 by study arm. The NRTI combination for each study is identified on the bars and the number of subjects in each arm is listed. The diamond shape indicates the TLOVR response rate at HIV RNA <50 copies/mL. ABC, abacavir; BID, twice daily; FTC, emtricitabine; QD, once daily; TDF, tenofovir; ZDV, zidovudine; 3TC, lamivudine; ddI, didanosine; d4T, stavudine. Reproduced with permission of Thomas Land Publishers from Bartlett et al.63 permission conveyed through Copyright Clearance Center, Inc.
stabilized on a conventional HAART regimen (n = 308) to fixed-dose efavirenz/emtricitabine/tenofovir.72 Most of the patients (87%) were treated with efavirenz or a boosted PI, plus two NRTIs. At 48 weeks, the rates of virological suppression with efavirenz/emtricitabine/tenofovir were non-inferior to those with the baseline regimen: respectively, 87% versus 85% had a VL of <50 copies/mL and 89% versus 88% of patients had a VL of <200 copies/mL. Among patients randomized to efavirenz/emtricitabine/tenofovir, 91% indicated a preference for this single-pill regimen.

Other data in treatment-experienced patients

Observational studies using the French Hospital HIV database have evaluated the efficacy of efavirenz-based regimens in patients who were stabilized or failing on their first PI-based regimens. In patients with an undetectable VL on their first PI regimen (n = 2462), the 12 month rates of virological rebound were 6.8%, 13.7% and 12.3% in patients switched to regimens based on efavirenz, nevirapine and abacavir, respectively.73 Compared with a switch to efavirenz, there were significant adjusted risks associated with a switch to nevirapine (HR 1.53; 95% CI 1.21–1.94) or abacavir (HR 1.53; 95% CI 1.12–2.08). Similarly, in patients with detectable VL switched from an initial PI regimen (n = 1140), 12 month probabilities of virological suppression were 73.6%, 53.9% and 66.1% among patients whose treatment was switched to efavirenz-, nevirapine- and abacavir-based HAART, respectively.74 Compared with patients switched to efavirenz, those switched to nevirapine were more likely to experience treatment failure (HR 0.63; 95% CI 0.54–0.74), while those switched to abacavir showed a trend for increased risk of failure (HR 0.84; 95% CI 0.68–1.04). The incidence of new AIDS-defining events did not differ significantly across the groups.

Other studies have not shown differences in outcome between efavirenz- and nevirapine-treated patients. In the NEFA randomized to switch from the PI to nevirapine, efavirenz or abacavir.75 At 12 months the likelihood of reaching the primary endpoint (death, progression to AIDS or an increase in HIV-1 RNA levels to ≥200 copies/mL) was 10% in the nevirapine group, 6% in the efavirenz group and 13% in the abacavir group (P = 0.10). The increases in CD4 cell count were similar in the three groups.75 At 3 year follow-up, the probability of virological failure was similar in the efavirenz and nevirapine arms, but higher in the abacavir arm.76 Retrospective, observational studies are vulnerable to selection bias and the conclusions drawn from the French HIV database have been questioned.77

The EuroSIDA observational study specifically compared virological outcome and genotypic resistance profiles in 759 patients starting NNRTI-based regimens, 87% of whom had received previous antiretrovirals.78 Overall, 74% of nevirapine recipients and 45% of efavirenz recipients experienced virological failure after treatment initiation (P < 0.001). After adjusting for confounding factors, the HR for virological failure with efavirenz versus nevirapine was 0.50 (95% CI 0.39–0.65; P < 0.001).

Thus, controlled clinical trials suggest that efavirenz provides similar virological outcomes to nevirapine in patients with experience of other antiretroviral drug classes. Some observational studies suggest superior outcomes with efavirenz but the limitations of such studies (e.g. the absence of randomization) should be kept in mind.

HIV subtypes

NNRTIs are highly selective for HIV-1 and do not inhibit HIV-2. Efavirenz treatment has predominantly been studied in patients with HIV-1 subtype B, the most prevalent form in developed countries.79 However, almost 90% of people infected with HIV worldwide do not carry subtype B virus,80 globally 50% are infected with subtype C.81 Studies have shown that subtypes B and C exhibit similar virological responses to efavirenz.80,82,83 Studies on the differences between subtypes B and C relating to genetic variations at NNRTI resistance-associated positions have shown that mutation at positions such as V106M and A98S is more common for patients with subtype C than B.82,83 However, Soares et al.80 have reported that there is no difference in the accumulation of NNRTI resistance mutations between subtypes B and C.

Safety and tolerability

Efavirenz has been generally well tolerated in clinical trials. According to the systematic review by Bartlett et al.,53 4%–16% of patients treated with efavirenz plus two NRTIs discontinued treatment due to adverse events; the NRTI combinations of lamivudine plus zidovudine or abacavir were associated with the higher end of this range.

The most notable adverse events associated with efavirenz are rash and central nervous system (CNS) symptoms. Rash is common, but led to discontinuation in <2% of patients and was severe in <1%.84 When efavirenz and nevirapine were directly compared (each plus lamivudine and stavudine) discontinuations due to adverse events or HIV events occurred in 15.8% of patients treated with efavirenz and 24.1% of patients treated with nevirapine once daily (P = 0.011).77 The difference between the groups in adverse event-related discontinuations was mainly due to a greater incidence of rash and hepatobiliary toxicity with nevirapine.77 In the FIRST study, grade 4 events were approximately half as common with efavirenz as with nevirapine (5.4 versus 10.2/100 person-years; P = 0.02).28

CNS or neuropsychiatric disturbances have been reported in ~25%–70% of patients receiving efavirenz.84–88 Symptoms include dizziness, headache, confusion, impaired concentration, agitation, amnesia, psychotic symptoms, sleep abnormalities, abnormal dreams and insomnia. These symptoms usually arise within the first few days of treatment and lead to early discontinuation of efavirenz in ~4%–10% of patients, although some investigators have reported higher discontinuation rates.89 The prevalence of most neuropsychiatric symptoms declines within a few weeks if therapy is continued.84,85,87,88,90 In a sub-study of the ACTG A5095 study, measures of neuropsychological performance revealed no significant difference between patients who did and did not receive efavirenz.91 While efavirenz recipients experienced more neurological symptoms at week 1 (P < 0.001), this was not the case at week 4, 12 or 24. Patients switched from another HAART regimen to efavirenz-based therapy in Study A1266073 showed an initial increase in light-headedness and dizziness, but these effects subsequently reduced to baseline levels.92

In a minority of patients, neuropsychiatric disturbances persist for several months or longer.89,90 or appear for the first time after several months of treatment with efavirenz.93 CNS
side-effects are an important risk factor for failure of therapy and for ‘blips’ in the HIV RNA level.33

The mechanism of neuropsychiatric disturbances is not fully understood. They may be partly related to previous psychiatric disturbances or to neuropsychiatric effects of HIV itself.33 Studies in animals have suggested that the effects of efavirenz on cytokines may play a role in depression associated with efavirenz.50 Sleep disturbances may play a role in the development of neuropsychiatric symptoms.33 Neuropsychiatric disturbances appear to be more common in African American patients than in European American or Hispanic patients. This may be a consequence of a higher prevalence of the CYP2B6 T/T genotype, resulting in slower metabolism of efavirenz and higher plasma exposure.16 Other studies have also given some (but not conclusive) evidence that a higher plasma level of efavirenz increases the risk of these problems.36,39,90 Plasma monitoring may be considered in patients with persistent symptoms. Nevirapine does not appear to be associated with a high level of neuropsychiatric events and it should be considered in patients at a high risk of these symptoms.27,86

Efavirenz-containing regimens may modestly increase plasma lipid levels compared with a triple NRTI regimen.94 The ACTG A5142 study showed no significant difference in the incidence of grade 3–4 elevations in low-density lipoprotein-cholesterol with efavirenz versus boosted lopinavir.25 However, grade 3–4 increases in triglyceride levels were significantly less common with efavirenz (2%) than with boosted lopinavir (6%; P < 0.05) or efavirenz plus boosted lopinavir (14%; P < 0.05). Other head-to-head comparisons of these agents have also shown a lesser effect of efavirenz on triglycerides.26 These findings also correspond with evidence that patients switched from PI-based to efavirenz-based therapy show significant improvements in triglyceride and high-density lipoprotein levels.72,96 Overall, efavirenz appears to have generally neutral effects on lipids, but this depends to a large extent on the accompanying NRTIs.96

Lipodystrophy can occur in patients receiving efavirenz-based HAART. It may result partly from effects on adipocytes including inhibition of lipogenesis and differentiation.97,98 Some in vitro studies have indicated that in contrast to efavirenz, nevirapine does not inhibit lipogenesis.99 Lipodystrophy is more common when thymidine analogues, particularly stavudine, are included in the NRTI backbone.56 In the GS903 study, treatment-naïve patients were randomized to receive stavudine or tenofovir in addition to efavirenz plus lamivudine.34 Through 144 weeks, investigator-reported lipodystrophy was significantly less common with tenofovir than with stavudine (3% versus 19% of patients). Limb fat increased from year 2 to year 7 in patients randomized to tenofovir during the extension phase of this study79,60 and in patients who switched from stavudine to tenofovir at 144 weeks.61 In GS934, treatment-naïve patients were randomized to receive efavirenz in combination with zidovudine/lamivudine or tenofovir plus emtricitabine.57,62 Limb fat was significantly (P < 0.001) greater in the tenofovir plus emtricitabine arm. Similarly, efavirenz recipients switched from fixed-dose zidovudine/lamivudine to fixed-dose tenofovir/emtricitabine in the SWEET study showed significant (P = 0.025) increases in limb fat compared with those who were not switched.79

In the A5005S trial, patients were randomized to receive efavirenz, neflunavir or both, combined with zidovudine plus lamivudine or didanosine plus stavudine.100 At 144 weeks, zidovudine plus lamivudine was superior to didanosine plus stavudine with respect to limb fat loss, and the presence of nelfinavir (with or without efavirenz) was associated with additional loss compared with efavirenz. In a 48 week study, efavirenz and atazanavir (each added to zidovudine plus lamivudine) were associated with similar increases in limb fat in treatment-naïve patients.101 In the ACTG 5142 study, the incidence of lipodystrophy (defined as >20% loss of limb fat) was 32% with efavirenz, 17% with lopinavir and 9% with efavirenz plus lopinavir (the NRTI-sparing arm).102 This result is difficult to interpret because the definition of lipodystrophy differs from that in other studies and the choice of NNRTI backbone (lamivudine in all patients with the addition of tenofovir, stavudine or zidovudine at the investigators’ discretion) was not randomized. One study showed that patients switching from a PI- to an efavirenz-based HAART regimen did not exhibit changes in fat distribution.103 A recent review concluded that efavirenz may produce a modest gain in limb fat that is greater than that with nelfinavir, similar to that with atazanavir and less than that with lopinavir.96

Lipodystrophy associated with NRTIs is believed to occur through mitochondrial toxicity. NRTIs can alter mitochondrial function by inhibiting mitochondrial DNA polymerase —the enzyme responsible for replication of mitochondrial DNA.104,105 This leads to reduced energy production and cellular damage, resulting ultimately in lipodystrophy.

While exposure to HAART increases the risk of myocardial infarction,106 this appears to be due to PIs and not to NNRTIs.107 Renal toxicity has been reported, albeit rarely, with tenofovir administration.108 Although small differences in glomerular filtration rate have occurred over time when tenofovir was combined with efavirenz over 144 weeks in HAART-naïve patients, no clinically relevant renal disease or adverse events were observed.109

Use of efavirenz in special patient populations

Recent statistics from the Antiretroviral Pregnancy Registry showed no increase in the risk of overall birth defects associated with drugs having sufficient reports of first-trimester exposure to detect at least a 2-fold increase in risk.110 Despite these observations, efavirenz should not be used in pregnant women unless there are no other appropriate treatment options, and pregnancy should be avoided in women receiving efavirenz.9

Generally, guidelines do not make specific recommendations for the selection of therapy in late-presenting HIV-infected patients, i.e. those with low CD4 cell counts or high VL. Several studies have demonstrated that efavirenz is similarly effective regardless of the baseline CD4 count. In DMP 266-006, efavirenz (plus zidovudine and lamivudine) showed virological response rates in both patients with CD4 counts <100 cells/mm³ and those with counts of ≥100 cells/mm³.23 In GS934, efavirenz-containing regimens gave similar virological responses in the overall population and in patients with baseline CD4 cell counts <200 cells/mm³ or <50 cells/mm³.111

Clinical trials have demonstrated that a regimen of efavirenz plus two NRTIs has similar efficacy in patients with a VL of >100000 copies/mL or <100000 copies/mL.30,30–32,35 Similarly, a post hoc analysis of ACTG 5095 revealed that rates of virological failure following 3 years of treatment with efavirenz plus zidovudine and lamivudine were not significantly affected by baseline VL (even up to ≥300000 copies/mL) or CD4 cell counts (down to <50 cells/mm³).47

919
In the ACTG A5142 study, efavirenz-based therapy was associated with a significantly longer time to virological failure than lopinavir-based therapy \( (P=0.01) \) in patients with a VL of \( \geq 100000 \text{ copies/mL} \). In a prospective, open-label study in patients with baseline CD4 counts of \( <200 \text{ cells/mm}^3 \), efavirenz was significantly more effective than boosted lopinavir \( (P=0.0141) \) in terms of the proportion of patients who reached a VL of \( <50 \text{ copies/mL} \) at 48 weeks (Table 1). Efavirenz showed most benefit over boosted lopinavir in patients with a baseline CD4 count of \( \leq 50 \text{ cells/mm}^3 \) (79% versus 49% with a VL of \( <50 \text{ copies/mL} \); \( P=0.012 \)). Immune reconstitution was similar between the groups. These results suggest that efavirenz may be preferable to boosted lopinavir for initial therapy in patients with advanced disease.

In the USA, the recommended therapy for children with HIV depends on age, symptoms and immune status. Efavirenz (plus two NRTIs) is a recommended agent for the treatment of children aged \( >3 \) years and weighing \( >10 \text{ kg} \); it is not recommended for children \( <3 \) years of age or those who cannot swallow capsules (efavirenz being available only in tablet or capsule form in the USA).

**Hepatitis B/C co-infection**

Patients with HIV co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) have a significantly worse prognosis than those infected with HIV alone, and guidelines now recommend early treatment of both conditions. The choice between a PI- or NNRTI-based regimen is determined using similar criteria to those for patients without HBV/HCV co-infection. In patients with HBV co-infection the NRTI backbone should include tenofovir or tenofovir plus lamivudine or emtricitabine because these agents have activity against both HIV and HBV. All antiretroviral agents have the potential for hepatotoxicity, which is increased in the presence of HBV/HCV co-infection. Increased hepatotoxicity, including elevated liver enzymes, has been seen in patients co-infected with HBV/HCV (particularly HCV) receiving efavirenz-based regimens. It has been postulated that HBV/HCV co-infection results in higher exposure to efavirenz, leading to the hepatic side-effects observed. However, recent studies in patients with HIV have found no significant differences in efavirenz plasma levels between those with and without HBV/HCV co-infection. The cause of the increased risk of liver toxicity remains to be determined. One study suggested that nevirapine was associated with increased progression of liver fibrosis in patients co-infected with HCV, but a more recent investigation found that exposure to NNRTIs was associated with reduction of fibrosis and that this effect was more consistent with nevirapine than with efavirenz. Overall, the results suggest that NNRTIs have an important role in the management of HBV/HCV co-infected patients, with vigilant monitoring of hepatic function. The data are insufficient to indicate whether efavirenz or nevirapine should be preferred.

**Resistance**

**Resistance and drug class**

Despite high levels of treatment success, resistance to efavirenz can develop. Efavirenz resistance mutations developed in 6%–8% of patients treated with efavirenz plus two NRTIs for 2–3 years, with the K103N reverse transcriptase mutation being by far the most common single mutation. In the FIRST study, efavirenz was associated with a significantly lower rate of virological failure in conjunction with NNRTI resistance (12.9 versus 20.6 person-years; \( P=0.05 \)) or any type of antiretroviral resistance (13.3 versus 22.7/100 person-years; \( P=0.02 \)), compared with nevirapine. At the time of virological failure, rates of resistance in the observational EuroSIDA study were similar for efavirenz and nevirapine.

In ACTG A5142, resistance mutations were present in 48% of efavirenz-treated patients with virological failure and an available genotype compared with 21% of those treated with boosted lopinavir (\( P=0.002 \)). Efavirenz was also associated with more mutations associated with resistance to two drug classes and more K65R mutations than boosted lopinavir. However, there was no significant difference between efavirenz- and lopinavir-based therapy in the proportions of patients with virological failure and at least one resistance mutation (9% versus 6%, respectively).

**Drug interactions**

Knowledge of drug–drug interactions enables efavirenz-treated patients with HIV to undergo therapy for other conditions while maintaining viral suppression. Efavirenz is an inducer of cytochrome P (CYP)3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4, and compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Patients co-infected with HIV and *Mycobacterium tuberculosis* are an important subgroup and interactions occur between efavirenz and rifampicin and rifabutin, antibiotics used for the treatment of tuberculosis. Co-administration of rifampicin and efavirenz results in decreased efavirenz exposure and it is advised that the efavirenz dose should be increased from 600 to 800 mg once daily when taken with rifampicin. Co-administration of rifabutin with efavirenz results in reduced rifabutin exposure, and the daily dose of rifabutin should be increased by 50% when administered with efavirenz, while twice-weekly doses should be doubled. Caution should be exercised when prescribing efavirenz for patients who also need treatment for malaria, for example amodiaquine is contraindicated as it results in elevations of liver transaminases. Several antimalarial drugs are metabolized by CYP3A4, e.g. halofantrine, lumefantrine, the artemisinins and quinine, and co-administration with efavirenz can result in increased/decreased exposure to these drugs. Another subpopulation of patients with HIV affected by efavirenz drug–drug interactions are those with opioid dependence. Methadone concentrations are reduced when co-administered with efavirenz, which leads to patients reporting opioid withdrawal. An alternative drug for the treatment of opioid dependence is buprenorphine. Buprenorphine has a pharmacokinetic but not a pharmacodynamic interaction with efavirenz, and consequently co-administration with efavirenz does not result in opioid withdrawal.

Lipid-lowering agents are commonly used in patients with HIV to counteract metabolic disorders associated with HAART. Efavirenz may interact with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, such as atorvastatin, pravastatin and simvastatin, that are metabolized primarily via CYP3A4.
CYP3A4. Co-administration of efavirenz results in decreased exposure to these agents, thus dosage adjustments may be required.128

Herbal preparations containing St John’s wort (Hypericum perforatum) should not be used while taking efavirenz due to the risk of decreased plasma concentrations and thus reduced clinical effects of efavirenz.84 Efavirenz must also not be co-administered with the antihistamines terfenadine and astemizole, the gastrointestinal agent cisapride, the sedatives midazolam129 and triazolam, the antipsychotic pimozide, the arrhythmia drug bepridil or ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine) used as antimigraine agents.84 These agents compete with efavirenz for CYP3A4, which could result in inhibition of metabolism and create the potential for serious and/or life-threatening events such as cardiac arrhythmias, prolonged sedation or respiratory depression.84 Efavirenz has also been shown to interact with the ethinylestradiol component of oral contraceptives, with the concentration of ethinylestradiol increasing when co-administered with efavirenz.130 As the clinical significance of this effect is unknown, a reliable barrier method of contraception should be used by patients receiving efavirenz in addition to oral contraceptives.84

Co-administration of efavirenz with other HAART agents including PIs, boosted PIs and NRTIs is generally acceptable. Exceptions are: boosted atazanavir,131 which is not recommended; boosted lopinavir, for which dose increases are recommended;132 and low-dose ritonavir, which may lead to an increased incidence of efavirenz-associated adverse events.84,133

Implications of genotype

Efavirenz is principally metabolized by CYP2B6 and the 516G>T single nucleotide polymorphism is associated with elevated efavirenz levels.13 The TT genotype is more common in black and Hispanic than white populations12 and may be a challenge in regions with a high prevalence of tuberculosis, as efavirenz levels are increased in such patients receiving concomitant rifampicin.134 It has been reported that in patients with the TT genotype, reduction of the efavirenz dose can maintain virological suppression and alleviate CNS symptoms.17 Patients with the 983T>C polymorphism at position CYP2B6 also have increased levels of efavirenz.135

Resistance and future NNRTI therapy

The introduction of new NNRTIs (e.g. etravirine) necessitates a consideration of how the selection of efavirenz-resistant mutants might affect subsequent therapy with this drug class. A recent genotypic analysis of 1586 HIV isolates with NNRTI resistance mutations revealed that 8.2% had three or more mutations associated with efavirenz resistance (e.g. G190A, Y181C and K101E) while only 1.1% had four or more such mutations.136 Mutational patterns associated with intermediate efavirenz resistance occurred in 26.2% of the samples, while high-degree resistance occurred in 4.9%. A separate analysis of 248 HIV isolates from patients on stable NNRTI therapy in Italy revealed that 35.5% carried one efavirenz resistance mutation, 21.4% had two mutations and 4.8% had three mutations.137 Thus, while low to intermediate efavirenz resistance may be relatively common in NNRTI-resistant HIV, high-level efavirenz resistance appears uncommon.

Efavirenz resistance mutations were significantly more common in stably treated patients receiving nevirapine than for efavirenz (OR 2.73; 95% CI 1.62–4.62; P<0.001).137 The principal mutation selected by efavirenz—K103M—does not confer resistance to efavirenz, while the primary mutation selected during nevirapine therapy (Y181C) does confer efavirenz resistance.138 These data suggest that efavirenz is more likely to be effective in patients previously treated with efavirenz than with nevirapine.

In the DUET-1 and DUET-2 studies, etravirine showed efficacy versus placebo when used together with darunavir, NRTIs and optional enfuvirtide, after the failure of antiretroviral therapy in patients with genotypic evidence of resistance to currently available NNRTIs and PIs.139,140 However, other data indicate that a PI may be more effective than etravirine in PI-naive patients after failure of an NNRTI-based regimen.141

Adherence

Adherence is a major determinant of virological failure and may lead to the emergence of resistance in patients with HIV, but the relationships between resistance development, rebound and adherence differ between antiretroviral drug classes.142,143 A recent study involving 1191 patients initiating HAART based on NNRTIs (efavirenz 59% and nevirapine 41%) or PIs.66 The rate of rebound (VL >50 copies/mL) was >10% in patients treated with PIs (14.7%) or boosted PIs (11.7%) at an adherence level of 76%–95%, and ~30%–50% at the lowest adherence rates (<55%). For NNRTIs, adherence of <55% was needed to observe a similar rebound rate (17.6%) (Figure 4).66 By contrast, resistance selection decreased with increasing adherence for NNRTIs, while the converse was true for unboosted PIs. The risk of selecting NNRTI resistance mutations was estimated to be 4.9% in NNRTI recipients at adherence rates of <75% and 4.2% in single-PI recipients with >95% adherence. Boosted PI-treated patients showed an intermediate pattern and a lower level of resistance risk (1.3% resistance for adherence of 75%–95%).66 In the HOMER cohort study (n = 1634), the risk of virological breakthrough (defined as two consecutive measurements of VL >1000 copies/mL) was strongly associated with <95% adherence to the PI (HR 1.66; 95% CI 1.38–2.01) and NNRTI (HR 1.47; 95% CI 1.01–2.14), but not the boosted PI (HR 1.05; 95% CI 0.46–2.42) treatments.144 A smaller REACH cohort study (n = 268) examining viral suppression (VL<50 copies/mL) found that NNRTI- and boosted PI-based regimens were comparable and better than PI regimens at achieving viral suppression at levels of adherence of <95%.145

A recent study involving 1191 patients initiating HAART found that those with <95% adherence to NNRTIs were significantly more likely to accumulate resistance mutations than those with >95% adherence (HR 7.0; 95% CI 3.4–14.5; P = 0.0001), while adherence rates had little effect on resistance for PIs and NRTIs.146 Previously, Bangsberg et al.147 compared the prevalence of resistance mutations according to the adherence levels in patients (n = 108) stably treated with NNRTIs (35% efavirenz and 65% nevirapine) or PIs. NNRTI-treated patients were more
likely to show viral suppression to <50 copies/mL than PI-treated patients (50% versus 22%, respectively; \( P = 0.005 \)). Higher levels of adherence were significantly associated with improved viral suppression with each class. At low adherence levels (0%–48%), NNRTI resistance was more common than PI resistance (69% versus 23%; \( P = 0.01 \)). The frequency of NNRTI resistance decreased as adherence increased, from 69% in patients with 0%–48% adherence to 13% in those with 95%–100% adherence (\( P = 0.01 \)). On multivariate analysis, each 10% improvement in adherence decreased the risk of NNRTI resistance by 25% (\( P = 0.04 \)). In contrast, the risk of PI resistance increased by 41% (\( P = 0.03 \)) with each 10% improvement in adherence.

A prospective study of 543 virologically suppressed patients found that the rate of self-reported adherence was slightly, but significantly, higher with NNRTI-based HAART than with PI-based HAART (mean 93.6% versus 89.9%, respectively; \( P = 0.018 \)).148 PI recipients with a self-reported adherence rate of ≥85% had a virological failure rate of >20% over 6 months. In contrast, virological failure rates in NNRTI recipients (of whom 57% were taking efavirenz and 43% were taking nevirapine) exceeded 10% only when their adherence rate was ≤75%. In patients with an adherence rate of >75%, virological failure was less likely with NNRTIs than with PIs.

These differences between classes have been explained by differences in the relative replicative fitness of resistant viruses (versus susceptible strains) in the presence of the drugs147 as well as the pharmacokinetic and pharmacodynamic differences between the classes.66 Other recent data suggest that the spacing of missed doses is also important to resistance risk with NNRTIs. Thus, in patients with low-to-moderate adherence (<80%), the duration of sustained treatment interruption was linked to virological rebound, while average adherence (i.e. interspersed missed doses as a percentage of total doses) was not.149

One of the most important factors in the level of adherence is the number of pills that must be taken per day,150 with patients preferring once-daily regimens.68,72,151 Preliminary patient-reported outcomes in the ADONE study suggested that patients found a single-dose efavirenz/tenofovir/emtricitabine treatment highly preferable in terms of simplicity, convenience, tolerability and potency, and more patients reported being without HIV-related symptoms.151

**Quality of life**

A substudy of the 2NN trial reported that efavirenz or nevirapine improved health-related quality of life in treatment-naive patients.152 In the randomized INITO trial, efavirenz-based or nelfinavir-based therapy improved physical and mental health scores during 3 year follow-up.153 In the VESD study over two-thirds of patients receiving once-daily efavirenz/didanosine/lamivudine considered their quality of life ‘good’ or ‘very good’ at 6 and 12 months.154 In the AI266073 study, patients who switched to a single-dose efavirenz/emtricitabine/tenofovir treatment reported improvements in HIV-related symptoms such as diarrhoea, bloating, pain, gas, change in the way their body looked and problems having sex, although they also experienced transient worsening of CNS symptoms at week 4.92 Other studies have also reported improved treatment satisfaction after switching to the fixed-dose regimen.70

Neuropsychiatric symptoms with efavirenz impair quality of life in some patients, especially at the start of therapy.86,89,90 This is important because lower quality of life during treatment with efavirenz is a predictor of virological failure.155 Depression
is important because it is commonly overlooked in patients with HIV infection. However, one report suggests that if patients are able to continue long-term efavirenz-based therapy, their quality of life can be good despite persisting neuropsychiatric symptoms.

Cost-effectiveness

Few pharmacoeconomic studies have compared recommended options for HIV treatment. Basu et al. used pooled data from clinical trials to compare the costs of reaching and maintaining an undetectable VL in HAART-naive patients using each of the nine NNRTI- and PI-based regimens recommended in 2005. Efavirenz- and boosted lopinavir-based regimens were the most effective in terms of virological suppression rates. Efavirenz was consistently the third agent associated with the lowest cost per patient with undetectable VL across time periods ranging from 30 to 96 weeks.

More recently, a study in the UK compared the cost-effectiveness of various initial HAART regimens, taking into account the annual costs of inpatient and outpatient visits, day ward visits, HAART, other drugs, tests and procedures, together with effectiveness measured as time to treatment failure. First-line use of an NNRTI plus two NRTIs was calculated to be cost-effective or cost-saving compared with boosted PI-containing regimens.

Conclusions

Numerous clinical trials performed over the last 10 years have established the effectiveness of efavirenz-based HAART in the initial treatment of HIV-infected individuals. Efavirenz has shown potent and durable virological suppression in this setting, with efficacy demonstrated over 7 years. Recent data also confirm that efavirenz is a cost-effective option for first-line therapy.

The once-daily dosing schedule of efavirenz has enabled its inclusion in the first one-tablet once-a-day regimen alongside two widely used NRTIs. The convenience of this regimen may aid long-term adherence and perhaps increase the durability of treatment responses. Several studies have shown that patients stable on PI-based HAART requiring multiple daily doses and pills can be switched to simplified efavirenz-based regimens without loss of virological control. Efavirenz also retains a role in the management of patients after failure of a first-line PI-based regimen.

Efavirenz is generally well tolerated during prolonged therapy, although neuropsychiatric symptoms are common in the first few weeks of treatment and lead to discontinuation in a relatively small proportion of patients. Efavirenz appears to be generally neutral on lipids. Efavirenz-based regimens can be associated with lipodystrophy but the use of newer NRTI backbones (e.g. tenofovir and emtricitabine) appears to reduce this problem. The potential for resistance selection by efavirenz underscores the need for high levels of treatment adherence. Evidence suggests that efavirenz is unlikely to compromise the efficacy of the newer NNRTIs, such as etravirine.

In light of these features, efavirenz retains a key role in the recommended HIV treatment strategies and is recommended as the first-line agent in some guidelines.

Funding

This review was made possible by funding from Bristol-Myers Squibb, EMEA Paris, who provided funding for the editorial and writing aspects of the paper.

Transparency declarations

F. M. has served as a consultant on advisory boards for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche and Tibotec. He has received lecture fees from Abbott, Bayer, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp and Dohme, Pfizer and Roche; and has received research and educational grants from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag and Roche.

Richard Murphy of Adelphi Communications Ltd, UK, provided editorial assistance to Professor Maggiolo in the preparation of this review, funded by Bristol-Myers Squibb, EMEA Paris.

References

1. Bhaskaran K, Hamouda O, Sannes M et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. JAMA 2008; 300: 51–9.
2. Lohse N, Hansen AB, Pedersen G et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. Ann Intern Med 2007; 146: 87–95.
3. Gazzard BG. British HIV Association Guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. HIV Med 2008; 9: 563–608.
4. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2008; 1–146. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (13 August 2009, date last accessed).
5. Willig JH, Abroms S, Westfall AO et al. Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. AIDS 2008; 22: 1951–60.
6. Cline N, Pozniak A, Raffi F. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. HIV Med 2008; 9: 65–71.
7. Hammer SM, Eron J Jr, Reiss P et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society—USA panel. JAMA 2008; 300: 555–70.
8. Gallant JE. Should antiretroviral therapy be started earlier? Curr HIV/AIDS Rep 2007; 4: 53–9.
9. Bristol-Myers Squibb Pharmaceuticals Ltd. Efavirenz: Summary of Product Characteristics. European Medicines Evaluation Agency, 2009. http://emc.medicines.org.uk/medicine/11284/SPC/Sustiva+600+mg+Film-Coated+Tablets/ (13 August 2009, date last accessed).
10. Almond LM, Hoggard PG, Edirisinghe D et al. Intracellular and plasma pharmacokinetics of efavirenz in HIV-infected individuals. J Antimicrob Chemother 2005; 56: 738–44.
11. Ward BA, Gorski JC, Jones DR et al. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther 2003; 306: 287–300.
12. Haas DW, Smeaton LM, Shafer RW et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir: an Adult Aids Clinical Trials Group Study. J Infect Dis 2005; 192: 1931–42.
13. Rodríguez-Novoa S, Barreiro P, Rendon A et al. Influence of 516G→T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. Clin Infect Dis 2005; 40: 1358–61.
14. Gutierrez F, Navarro A, Padilla S et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. Clin Infect Dis 2005; 41: 1648–53.
15. Rotger M, Colombo S, Furrer H et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenet Genomics 2005; 15: 1–5.
16. Haas DW, Ribaudo HJ, Kim RB et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 2004; 18: 2391–400.
17. Gatanaga H, Hayashida T, Tsuchiya K et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. Clin Infect Dis 2007; 45: 1230–7.
18. Burger D, van der Heiden I, la Porte C et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol 2006; 61: 148–54.
19. Rotger M, Tegude H, Colombo S et al. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. Clin Pharmacol Ther 2007; 81: 557–66.
20. Wang J, Sonnerborg A, Rane A et al. Identification of a novel specific CYP2B6 allele in Africans causing impaired metabolism of the HIV drug efavirenz. Pharmacogenet Genomics 2006; 16: 191–8.
21. Molina JM, Peytavin G, Perusat S et al. Pharmacokinetics of emtricitabine, didanosine and efavirenz administered once-daily for the treatment of HIV-infected adults (pharmacokinetic substudy of the Montana ANRS 091 trial). HIV Med 2004; 5: 99–104.
22. Molina JM, Journot V, Furco A et al. Five-year follow up of once-daily therapy with emtricitabine, didanosine and efavirenz (Montana ANRS 091 trial). Antivir Ther 2007; 12: 417–22.
23. Nelson M, Staszewski S, Morales-Ramirez JO et al. Successful virologic suppression with efavirenz in HIV-infected patients with low baseline CD4 cell counts: post hoc results from study 006. In: Abstracts of the Tenth European Congress of Clinical Microbiology and Infectious Diseases, Stockholm, Sweden, 2000. Abstract 3-349.
24. Maggiolo F, Ripamonti D, Gregis G et al. Once-a-day therapy for HIV infection: a controlled, randomized study in antiretroviral-naive HIV-1-infected patients. Antivir Ther 2003; 8: 339–46.
25. Riddler SA, Haubrich DR, DiRienzo AG et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2008; 358: 2095–106.
26. Sierra-Madero J, Villasis-Keever A, Mendez P et al. A prospective, randomized, open label trial of efavirenz vs lopinavir/ritonavir based HAART, among HIV infected naive individuals presenting for care with CD4+ cell counts <200 cell/mm³ in Mexico. In: Abstracts of the Seventeenth International AIDS Conference, Mexico City, Mexico, 2008. Abstract TUA0104.
27. van Leth F, Phanuphak P, Ruxrungtham K et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet 2004; 363: 1253–63.
28. van den Berg-Wolf M, Hullsie KH, Peng G et al. Virologic, immunologic, clinical, safety, and resistance outcomes from a long-term comparison of efavirenz-based versus nevirapine-based antiretroviral regimens as initial therapy in HIV-1-infected persons. HIV Clin Trials 2008; 9: 324–36.
29. Gulick RM, Ribaudo HJ, Shikuma CM et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med 2004; 350: 1850–61.
30. DeJesus E, McCarty D, Farning CF et al. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naive adults with HIV infection: a randomized equivalence trial. Clin Infect Dis 2004; 39: 411–8.
31. Moyle GJ, DeJesus E, Cahn P et al. Abacavir once or twice daily combined with once-daily lamivudine and efavirenz for the treatment of antiretroviral-naive HIV-infected adults: results of the Ziagen Once Daily in Antiretroviral Combination Study. J Acquir Immune Defic Syndr 2005; 38: 417–25.
Review

45. Mugavero MJ, May M, Harris R et al. Does short-term virologic failure translate to clinical events in antiretroviral-naive patients initiating antiretroviral therapy in clinical practice? AIDS 2008; 22: 2481–92.

46. Keiser P, Nassar N, White C et al. Comparison of nevirapine- and efavirenz-containing antiretroviral regimens in antiretroviral-naive patients: a cohort study. HIV Clin Trials 2002; 3: 296–303.

47. Ribaudo H, Kuritzkes DR, Lalam CA et al. Efavirenz-based regimens in treatment-naive patients with a range of pretreatment HIV-1 RNA levels and CD4 cell counts. J Infect Dis 2008; 197: 1006–10.

48. Saag M, Ives P, Heera J et al. A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc versus efavirenz, both in combination with Comvirib (zidovudine/lamivudine), for the treatment of antiretroviral-naive subjects infected with R5 HIV-1: week 48 results of the MERIT study. In: Abstracts of the Fourth IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 2007. Abstract WESS104.

49. Saag M, Heera J, Goodrich J et al. Reanalysis of the MERIT study with the enhanced Trifile™ assay. In: Abstracts of the Forty-eighth Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, USA, 2008. Abstract H-1232. American Society for Microbiology, Washington, DC, USA.

50. Landovitz RJ, Angel JB, Hoffmann C et al. Phase II study of vicriviroc versus efavirenz (both with zidovudine/lamivudine) in treatment-naive subjects with HIV-1 infection. J Infect Dis 2008; 198: 1113–22.

51. Steigbigel R, Kumar P, Eron J et al. 48-week results from BENCMRKR-2, a phase III study of raltegravir (RAL) in patients failing antiretroviral therapy (ART) with triple-class resistant HIV-1. In: Abstracts of the Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, 2008. Abstract 789. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

52. Cooper DA, Gatell J, Rockstroh JK et al. 48-week results from BENCMRKR-1, a phase III study of raltegravir (RAL) in patients failing antiretroviral therapy (ART) with triple-class resistant HIV-1. In: Abstracts of the Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, 2008. Abstract 788. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

53. Markowitz M, Nguyen BY, Gotuzzo E et al. Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: results of a 48-week controlled study. J Acquir Immune Defic Syndr 2007; 46: 125–33.

54. Markowitz M, Nguyen B-Y, Gotuzzo E et al. Sustained antiretroviral efficacy of raltegravir as part of combination ART in treatment-naive HIV-1-infected patients: 96-week data. In: Abstracts of the Seventeenth International AIDS Conference, Mexico City, Mexico, 2008. Abstract TUAB0102.

55. Lennox J, DeJesus E, Lazzarin A. STARTMRK, a phase III study of the safety and efficacy of raltegravir (RAL)-based vs efavirenz (EFV)-based combination therapy in treatment-naive HIV-infected patients. In: Abstracts of the Forty-eighth Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, USA, 2008. Abstract H-896a. American Society for Microbiology, Washington, DC, USA.

56. Zolopa AR, Lampiris H, Blick G et al. The HIV integrase inhibitor elvitegravir (EVI/7) has potent and durable antiretroviral activity in treatment-experienced patients with active optimized background therapy (OBT). In: Abstracts of the Forty-seventh Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, USA, 2007. Abstract 143LB. American Society for Microbiology, Washington, DC, USA.

57. Santoscoy M, Cahn P, Gonzalez C et al. TMC278 (rilpivirine), an investigational next-generation NNRTI, demonstrates long-term efficacy and tolerability in ARV-naive patients: 96-week results of study C204. In: Abstracts of the Seventeenth International AIDS Conference, Mexico City, Mexico, 2008. Abstract TUAB0103.

58. US National Institutes of Health. A Clinical Trial Comparing Etravirine to Efavirenz in Combination with 2 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors in Treatment-naive HIV-1 Infected Patients. http://clinicaltrials.gov/ct2/show/NCT0100903682 (13 August 2009, date last accessed).

59. Cassetti I, Madruga JV, Suleiman JM et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naive HIV-1-infected patients. HIV Clin Trials 2007; 8: 164–72.

60. Cassetti I, Madruga JV, Etze A et al. The safety and efficacy of tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naive patients through seven years. In: Abstracts of the Seventeenth International AIDS Conference, Mexico City, Mexico, 2008. Abstract TUPE0557.

61. Madruga JR, Cassetti I, Suleiman JM et al. The safety and efficacy of switching stavudine to tenofovir DF in combination with lamivudine and efavirenz in HIV-1-infected patients: three-year follow-up after switching therapy. HIV Clin Trials 2007; 8: 381–90.

62. Pozniak AL, Gallant JE, DeJesus E et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes—a 96-week analysis. J Acquir Immune Defic Syndr 2006; 43: 535–40.

63. Bartlett JA, Chen SS, Quinn JB. Comparative efficacy of nucleoside/nucleotide reverse transcriptase inhibitors in combination with efavirenz: results of a systematic overview. HIV Clin Trials 2007; 8: 221–6.

64. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. J Infect Dis 2008; 197 Suppl 3: S272–S278.

65. Mills EJ, Nachega JB, Bangsberg DR et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med 2006; 3: e438.

66. Maggiolo F, Airoldi M, Kleinloog HD et al. Effect of adherence to HAART on virologic outcome and on the selection of resistance-conferring mutations in NNRTI- or PI-treated patients. HIV Clin Trials 2007; 8: 282–92.

67. Maggiolo F, Ripamonti D, Arici C et al. Simpler regimes may enhance adherence to antiretrovirals in HIV-infected patients. HIV Clin Trials 2002; 3: 371–8.

68. Moyle G. The assessing patients’ preferred treatments (APPT-1) study. Int J STD AIDS 2003; 14 Suppl 1: 34–6.

69. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimes and medication compliance. Clin Ther 2001; 23: 1296–310.

70. DeJesus E, Ruane P, McDonald C et al. Impact of switching virologically suppressed, HIV-1-infected patients from twice-daily fixed-dose zidovudine/lamivudine to once-daily fixed-dose tenofovir disoproxil fumarate/efavirenz. HIV Clin Trials 2008; 9: 103–14.

71. Fisher M, Moyle GJ, Shahmanesh M et al. A randomized comparative trial of continued zidovudine/lamivudine or replacement with tenofovir disoproxil fumarate/efavirenz in efavirenz-treated HIV-1-infected individuals. J Acquir Immune Defic Syndr 2009; 51: 562–8.

72. DeJesus E, Young B, Flaherty J et al. Simplification of antiretroviral therapy with efavirenz/efavirenz/tenofovir DF single tablet regimen unmodified antiretroviral therapy in virologically suppressed, HIV-1 infected patients. In: Abstracts of the Forty-eighth Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, USA, 2008. Abstract H-1234. American Society for Microbiology, Washington, DC, USA.
73. Abgrall S, Yeni PG, Bouchaud O et al. Switch from a first virologically effective protease inhibitor-containing regimen to a regimen containing efavirenz, nevirapine or abacavir. AIDS 2006; 20: 2999–106.

74. Abgrall S, Yeni PG, Bouchaud O et al. Comparative biological and clinical outcomes after a switch from a virologically unsuccessful first protease inhibitor-containing antiretroviral combination to a 3-drug regimen containing efavirenz, nevirapine, or abacavir. Clin Infect Dis 2007; 44: 120–7.

75. Martínez E, Arnaiz JA, Podzamczer D et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. N Engl J Med 2003; 349: 1036–46.

76. Martínez E, Arnaiz JA, Podzamczer D et al. Three-year follow-up of protease inhibitor-based regimen simplification in HIV-infected patients. AIDS 2007; 21: 367–9.

77. Martínez E, Gatell JM. Considerations on the effectiveness of nevirapine in protease inhibitor-based regimen simplification. AIDS 2007; 21: 1829–30.

78. Bannister WP, Ruiz L, Cozzi-Lepri A et al. Comparison of genotypic resistance profiles and virological response between patients starting nevirapine and efavirenz in EuroSIDA. AIDS 2008; 22: 367–76.

79. Thomson MM, Nájera R. Increasing HIV-1 genetic diversity in Europe. J Infect Dis 2007; 196: 1120–4.

80. Soares EA, Santos AF, Sousa TM et al. Differential drug resistance acquisition in HIV-1 of subtypes B and C. PLoS ONE 2007; 2: e730.

81. Hemelaar J, Gouws E, Gyhs PD et al. Global and regional distribution of HIV-1 genetic subtypes and recombinants in 2004. AIDS 2006; 20: W13–W23.

82. Grossman Z, Istomin V, Averbuch D et al. Genetic variation at NNRTI resistance-associated positions in patients infected with HIV-1 subtype C. AIDS 2004; 18: 909–15.

83. Brenner B, Turner D, Oliveira M et al. A V106M mutation in HIV-1 clade C viruses exposed to efavirenz confers cross-resistance to non-nucleoside reverse transcriptase inhibitors. AIDS 2003; 17: F1–F5.

84. European Medicines Agency. EPARs for Authorised Medicinal Products for Human Use: Susvira SmPC. http://www.emea.europa.eu/human-docs/Humans/EPAR/susvira/susvira.htm (13 August 2009, date last accessed).

85. Fumaz CR, Tuldra A, Ferrer MJ et al. Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens. J Acquir Immune Defic Syndr 2002; 29: 244–53.

86. Hawkins T, Geist C, Young B et al. Comparison of neuropsychiatric side effects in an observational cohort of efavirenz- and protease inhibitor-treated patients. HIV Clin Trials 2005; 6: 187–96.

87. 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. Study 006 Team. N Engl J Med 1999; 341: 1865–73.

88. Perez-Molina JA, Fumaz CR, Ferrer MJ et al. Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates, management. A neurobehavioral review. AIDS Rev 2009; 11: 103–9.

89. Arendt G, de Nocker D, von Giesen HJ et al. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf 2007; 6: 147–54.

90. Clifford DB, Evans S, Yang Y et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med 2005; 143: 714–21.

91. Hodder S, Mouzner K, DeJesus E et al. Patient-reported outcomes after simplification to a single tablet regimen of efavirenz (EFV)/lamivudine (FTC)/tenofovir DF (TDF). In: Abstracts of the Ninth International Congress on Drug Therapy on HIV infection, Glasgow, UK, 2008. Abstract P63.

92. Zaccarelli M, Soldani F, Luzzi G et al. CNS side effects as main risk factor for efavirenz failure and transient HIV-RNA elevation. In: Abstracts of the Ninth Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA, 2002. Abstract 720-T. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

93. Shikuma CM, Yang Y, Glesby MJ et al. Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 infection (AIDS Clinical Trials Group Study A5095). J Acquir Immune Defic Syndr 2007; 44: 540–50.

94. Fisac C, Fumero E, Crespo M et al. Metabolic benefits 24 months after replacing a protease inhibitor with abacavir, efavirenz or nevirapine. AIDS 2005; 19: 917–25.

95. Perez-Molina JA, Domingo P, Martinez E et al. The role of efavirenz compared with protease inhibitors in the body fat changes associated with highly active antiretroviral therapy. J Antimicrob Chemother 2008; 62: 234–45.

96. El Hadri K, Glorian M, Monsenpes C et al. In vitro suppression of the lipogenic pathway by the nonnucleoside reverse transcriptase inhibitor efavirenz in 3T3 and human preadipocytes or adipocytes. J Biol Chem 2004; 279: 15130–41.

97. Diaz-Delfín J, Gallego-Escuredo JM, Milanski M et al. Comparison of the effects of nevirapine with respect to efavirenz on differentiating and mature human adipocytes in culture. In: Abstracts of the Tenth International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, London, UK, 2008. Abstract P-01.

98. Fisher M, Moyle G, Ebrahimh R et al. Switching from Combivir (CBV, AZT/3TC) to Truvada (TVD, TDF/FTC) maintains viral suppression, prevents and reverses limb fat loss, and improves biochemical parameters: results of a 48 week randomised study. In: Abstracts of the Eleventh European AIDS Conference, 2007. Abstract PSS7.

99. Dube MP, Komarow L, Mulligan K et al. Long-term body fat outcomes in antiretroviral-naive participants randomized to nevirapine or efavirenz or both plus dual nucleosides. Dual X-ray absorptiometry results from A5005s, a substudy of Adult Clinical Trials Group 384. J Acquir Immune Defic Syndr 2007; 45: 508–14.

100. Jemsek JG, Arthoorn E, Arlotti M et al. Body fat and other metabolic effects of atazanavir and efavirenz, each administered in antiretroviral-naive HIV-infected patients. Clin Infect Dis 2008; 42: 273–80.

101. Haubrich RH, Riddler SA, DiRienzo AG et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. AIDS 2009; 23: 1109–18.

102. Estrada V, De Villar NG, Larrad MT et al. Long-term metabolic consequences of switching from protease inhibitors to efavirenz in therapy for human immunodeficiency virus-infected patients with lipodystrophy. Clin Infect Dis 2002; 35: 69–76.

103. Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. Nat Med 1995; 1: 417–22.

104. Pinti M, Salomoni P, Cossarizza A. Anti-HIV drugs and the mitochondria. Biochim Biophys Acta 2006; 1757: 700–7.

105. Friis-Møller N, Sabin CA, Weber R et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 2003; 349: 1993–2003.
HIV-infected patients with and without viral hepatitis. *Br J Clin Pharmacol* 2003; 22: 2155–63.

110. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989–31 January 2008. http://www.apregistry.com/forms/exec-summary.pdf (13 August 2009, date last accessed).

111. Pozniak AL, Gallant JE, Staszewski S et al. Similar 96-week efficacy profile regardless of baseline characteristic variable for tenofovir disoproxil fumarate (TDF) versus stavudine (D4T) when used in combination with lamivudine and efavirenz in antiretroviral naïve patients. In: Abstracts of the IAS Conference on HIV Pathogenesis and Treatment, Paris, France, 2003. Abstract 559.

112. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*. 2009. http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf (13 August 2009, date last accessed).

113. Kontonis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis* 2003; 23: 173–82.

114. Sulkowski MS, Thomas DL, Mehta SH et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002; 35: 182–9.

115. Brück S, Witte S, Brust J et al. Hepatotoxicity in patients prescribed efavirenz or nevirapine. *Eur J Med Res* 2008; 13: 343–8.

116. Ena J, Amador C, Benito C et al. Risk and determinants of developing severe liver toxicity during therapy with nevirapine- and efavirenz-containing regimens in HIV-infected patients. *Int J STD AIDS* 2003; 14: 776–81.

117. Katsounas A, Frank A, Klinker H et al. Efavirenz-therapy in HIV-patients with underlying liver disease: importance of continuous TDM of EFV. *Eur J Med Res* 2007; 12: 331–6.

118. Pereira SA, Caixas U, Branco T et al. Efavirenz concentrations in HIV-infected patients with and without viral hepatitis. *Br J Clin Pharmacol* 2008; 66: 551–5.

119. Macias J, Castellano V, Merchante N et al. Effect of antiretroviral drugs on liver fibrosis in HIV-infected patients with chronic hepatitis C: harmful impact of nevirapine. *AIDS* 2004; 18: 767–74.

120. Berenguer J, Bellon JM, Miralles P et al. Association between exposure to nevirapine and reduced liver fibrosis progression in patients with HIV and hepatitis C virus coinfection. *Clin Infect Dis* 2008; 46: 137–43.

121. Margot NA, Lu B, Cheng A et al. Resistance development over 144 weeks in treatment-naive patients receiving tenofovir disoproxil fumarate or stavudine with lamivudine and efavirenz in Study 903. *HIV Med* 2006; 7: 442–50.

122. Breun RA, Swaden L, Ballinger J et al. Tuberculosis and HIV co-infection: a practical therapeutic approach. *Drugs* 2006; 66: 2299–308.

123. Matteieli A, Regazzi M, Villani P et al. Multiple-dose pharmacokinetics of efavirenz with and without the use of rifampicin in HIV-positive patients. *Curr HIV Res* 2007; 5: 349–53.

124. Hollender E, Stambaugh J, Ashkin D et al. The concomitant use of rifabutin and efavirenz in HIV/TB co-infected patients. In: *Abstracts of the Tenth Conference on Retroviruses and Opportunistic Infections*, Boston, MA, USA, 2003. Abstract 785. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

125. German P, Greenhouse B, Coates C et al. Drug interaction between antimalarial drugs and efavirenz. In: *Abstracts of the Fourteenth Conference on Retroviruses and Opportunistic Infections*, Los Angeles, CA, USA, 2007. Abstract 577. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

126. Bruce RD, McCance-Katz E, Kharasch ED et al. Pharmacokinetic interactions between buprenorphine and antiretroviral medications. *Clin Infect Dis* 2006; 43 Suppl 4: S216–S223.

127. McCance-Katz EF. Treatment of opioid dependence and co-infection with HIV and hepatitis C virus in opioid-dependent patients: the importance of drug interactions between opioids and antiretroviral agents. *Clin Infect Dis* 2005; 41 Suppl 1: S89–S95.

128. Gerber JG, Rosenkranz SL, Fichtenbaum CJ et al. Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* 2005; 39: 307–12.

129. Fellay J, Marzolini C, Decosterd L et al. Variations of CYP3A activity induced by antiretroviral treatment in HIV-1 infected patients. *Eur J Clin Pharmacol* 2005; 60: 865–73.

130. Joshi AS, Fiske WD, Benedek IH et al. Lack of a pharmacokinetic interaction between efavirenz and ethinyl estradiol in healthy female volunteers. In: *Abstracts of the Fifth Conference on Retroviruses and Opportunistic Infections*, Chicago, IL, USA, 1998. Abstract 348. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

131. Poirier JM, Giuaid-Schmid JB, Meynard JL et al. Critical drug interaction between ritonavir-boosted atazanavir regimen and non-nucleoside reverse transcriptase inhibitors. *AIDS* 2006; 20: 1087–9.

132. Klein CE, Cai Y, Chiu YL et al. Pharmacokinetics of lopinavir and ritonavir after multiple dose administration of lopinavir/ritonavir tablet coadministered with efavirenz. In: *Eighth International Conference on Drug Therapy of HIV Infection*, Glasgow, UK, 2006. Poster #366.

133. Faroux S, Berhoune M, Sauvageon-Martre H et al. Therapeutic drug monitoring of efavirenz in HIV-infected patients treated by Sustiva associated or not with ritonavir. In: *Abstracts of the Fourth International Workshop on Clinical Pharmacology of HIV Therapy*, Cannes, France, 2003. Abstract 5.12.

134. Kwara A, Larney M, Sagoe KW et al. Pharmacokinetics of efavirenz when co-administered with rifampin in TB/HIV co-infected patients: pharmacogenetic effect of CYP2B6 variation. *J Clin Pharmacol* 2008; 48: 1032–40.

135. Wyen C, Hendra H, Vogel M et al. Impact of CYP2B6 983T>C polymorphism on non-nucleoside reverse transcriptase inhibitor plasma concentrations in HIV-infected patients. *Antimicrob Chemother* 2008; 61: 914–8.

136. Llibre JM, Santos JR, Puig T et al. Prevalence of etravirine-associated mutations in clinical samples with resistance to nevirapine and efavirenz. *J Antimicrob Chemother* 2008; 62: 909–13.

137. Lapadula G, Calabresi A, Castelnovo F et al. Prevalence and risk factors for etravirine resistance among patients failing on non-nucleoside reverse transcriptase inhibitors. *Antivir Ther* 2008; 13: 601–5.

138. Vingerhoets J, Peeters M, Azjin H et al. An update of the list of NNRTI mutations associated with decreased virological response to etravirine (ETR): multivariate analysis on the pooled DUET-1 and DUET-2 clinical trial data. In: *Abstracts of the Seventeenth International HIV Drug Resistance Workshop*, Sitges, Spain, 2008. Abstract 24.

139. Lazzarin A, Campbell T, Cotlet B et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; 370: 39–48.
140. Madruga JV, Cahn P, Grinsztejn B et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007; 370: 29–38.

141. Ruxungham K, Pedro RJ, Latiff GH et al. Impact of reverse transcriptase resistance on the efficacy of TMC125 (etravirine) with two nucleoside reverse transcriptase inhibitors in protease inhibitor-naive, nonnucleoside reverse transcriptase inhibitor-experienced patients: study TMC125-C227. HIV Med 2008; 9: 883–96.

142. Bangsberg DR, Kroetz DL, Deeks SG. Adherence-resistance relationships to combination HIV antiretroviral therapy. Curr HIV/AIDS Rep 2007; 4: 65–72.

143. Bangsberg DR, Moss AR, Deeks SG. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. J Antimicrob Chemother 2004; 53: 696–9.

144. Gross R, Yip B, Wood E et al. Boosted PI are more forgiving of suboptimal adherence than non-boosted PI or NNRTI. In: Abstracts of the Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, CO, USA, 2006. Abstract 533. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

145. Bangsberg D, Hahn J, Weiser S et al. Less than 95% adherence to ritonavir-boosted protease inhibitors leads to viral suppression: an update to address currently prescribed antiretroviral regimens. In: Abstracts of the Fourth IAS Conference, Sydney, Australia, 2007. Abstract WEPEB111.

146. Tam LW, Chui CK, Brumme CJ et al. The relationship between resistance and adherence in drug-naive individuals initiating HAART is specific to individual drug classes. J Acquir Immune Defic Syndr 2008; 49: 266–71.

147. Bangsberg DR, Acosta EP, Gupta R et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. AIDS 2006; 20: 223–31.

148. Maggiolo F, Ravasio L, Ripamonti D et al. Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. Clin Infect Dis 2005; 40: 158–63.

149. Parienti JJ, Das-Douglas M, Massari V et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. PLoS ONE 2008; 3: e2783.

150. Stone VE, Jordan J, Tolson J et al. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. J Acquir Immune Defic Syndr 2004; 36: 808–16.

151. Maggiolo F, Airoldi M, Trotta MP et al. Effect of a fixed-dose combination of emtricitabine, tenofovir and efavirenz on adherence and treatment acceptability (ADONE study). In: Ninth International Conference on Drug Therapy in HIV Infection, 2008. Poster 167.

152. van Leth F, Conway B, Laplume H et al. Quality of life in patients treated with first-line antiretroviral therapy containing nevirapine and/or efavirenz. Antivir Ther 2004; 9: 721–8.

153. Bucciardini R, Fraga V, Massella M et al. Health-related quality of life outcomes in HIV-infected patients starting different combination regimens in a randomized multinational trial: the INITIO-QoL substudy. AIDS Res Hum Retroviruses 2007; 23: 1215–22.

154. Santos J, Palacios R, López M et al. Simplicity and efficacy of a once-daily antiretroviral regimen with didanosine, lamivudine, and efavirenz in naive patients: the VESD study. HIV Clin Trials 2005; 6: 320–8.

155. Schackman BR, Ribaudo HJ, Krambrink A et al. Racial differences in virologic failure associated with adherence and quality of life on efavirenz-containing regimens for initial HIV therapy: results of ACTG A5095. J Acquir Immune Defic Syndr 2007; 46: 547–54.

156. Asch SM, Kilbourne AM, Gifford AL et al. Underdiagnosis of depression in HIV: who are we missing? J Gen Intern Med 2003; 18: 450–60.

157. Fumaz CR, Munoz-Moreno JA, Molto J et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. J Acquir Immune Defic Syndr 2005; 38: 560–5.

158. Basu RP, Grimes RM, Helmy AF. Cost to achieve an undetectable viral load using recommended antiretroviral regimens. HIV Clin Trials 2006; 7: 309–18.

159. Beck EJ, Mandalia S, Youle M et al. Treatment outcome and cost-effectiveness of different highly active antiretroviral therapy regimens in the UK (1996–2002). Int J STD AIDS 2008; 19: 297–304.