

## Has the time come to abandon efavirenz for first-line antiretroviral therapy?

Francois Raffi<sup>1\*</sup>, Anton L. Pozniak<sup>2</sup> and Mark A. Wainberg<sup>3</sup>

<sup>1</sup>Division of Infectious Diseases, Nantes University Hospital, Nantes, France; <sup>2</sup>HIV Department, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK; <sup>3</sup>Departments of Medicine and of Microbiology, Jewish General Hospital, McGill University, Montreal, Canada

\*Corresponding author. Tel: +33-240-083-372; E-mail: francois.raffi@wanadoo.fr

Efavirenz has been recommended as a preferred third agent together with two nucleos(t)ides for first-line combination antiretroviral therapy (ART) for >15 years. The availability of efavirenz in a fixed-dose combination makes it very attractive. However, because of (i) adverse events associated with efavirenz, (ii) a poorer overall efficacy of efavirenz compared with newer antiretrovirals, (iii) the ranking of efavirenz as FDA Pregnancy Category D and (iv) the relatively high prevalence of transmitted drug-resistance mutations, there is a need to reconsider the role of efavirenz in first-line ART. We review the available evidence that challenges efavirenz's current position in first-line HIV treatment guidelines. Apart from its animal teratogenic potential, and moderate neuropsychiatric adverse events associated with its use, efavirenz has recently been associated with an increased risk of suicidality when compared with other antiretroviral drugs. Most importantly, efavirenz has demonstrated overall inferior efficacy to various comparator drugs, which include rilpivirine, raltegravir and dolutegravir, in antiretroviral-naïve patients. Furthermore, epidemiological data indicate that the prevalence of non-nucleoside reverse transcriptase inhibitor resistance has reached 5%–8% in various parts of the world, and minority transmitted non-nucleoside reverse transcriptase inhibitor resistance-associated mutations can have a negative impact on the outcome of first-line efavirenz-based ART. Based on considerations of efficacy, toxicity and resistance, it is time to reconsider the routine use of efavirenz in ART. This, of course, presupposes that other antiretrovirals will be available in place of efavirenz, and may not be applicable in certain developing country settings where this is not the case.

**Keywords:** HIV type 1, non-nucleoside reverse transcriptase inhibitors, drug resistance, suicide, neuropsychiatric adverse events, HIV clinical trials

### Background

One of the major goals of antiretroviral therapy (ART) is the use of effective well-tolerated regimens that require little long-term monitoring. We need to continually re-evaluate what we consider to be a preferred regimen in the light of new data. Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1, has been recommended as a preferred third agent together with two nucleos(t)ides for first-line combination ART for >15 years. This choice has been based on the virological and pharmacological properties of efavirenz, such as its high *in vitro* potency, forgiveness in regard to missed doses, simplicity of dosing and consistent data from multiple randomized clinical studies that have demonstrated that efavirenz-containing regimens were 'unbeaten' in terms of rates of virological suppression.<sup>1</sup> Indeed, large randomized controlled trials and cohort studies of treatment-naïve patients have demonstrated potent viral suppression in efavirenz-treated patients, with a substantial proportion having HIV-1 RNA levels <50 copies/mL with up to 6 years of follow-up.<sup>2,3</sup> In head-to-head randomized comparative studies, regimens containing efavirenz plus two nucleoside reverse transcriptase inhibitors were superior virologically to several protease

inhibitor-based regimens, including indinavir,<sup>4</sup> lopinavir/ritonavir<sup>5</sup> and nelfinavir,<sup>6</sup> and to triple nucleoside reverse transcriptase inhibitor-based regimens.<sup>7</sup> In addition, efavirenz has been shown to possess comparable anti-HIV activity to nevirapine,<sup>8</sup> rilpivirine<sup>9,10</sup> and atazanavir-based regimens.<sup>11</sup> Until the spring of 2012, treatment guidelines routinely emphasized that 'To date, no regimen has proven superior to efavirenz-based regimens with respect to virologic responses.'<sup>1</sup> In all recent guideline recommendations issued by national and international agencies as of late 2013, efavirenz-based regimens remain among the preferred options for the treatment of ART-naïve patients<sup>12–15</sup> and, in the latest WHO guidelines, as the preferred option for the initiation of ART.<sup>16</sup> A major advantage of efavirenz is its pharmacokinetic profile, which allows it to be successfully incorporated into a once-daily, one-pill regimen with tenofovir and emtricitabine. Indeed, the availability of a once-daily, single-tablet regimen represents an important milestone with regard to convenience and potential for improved patient adherence, a factor that is the most important in ultimately determining the success or failure of any ART regimen. Three different once-daily single-tablet regimens are now available and others will soon follow.

## The need for a reappraisal of efavirenz

Despite its virological potency and efficacy, it has long been recognized that efavirenz has important limitations. One of these is potential teratogenicity, while the second, more serious, limitation involves CNS and psychiatric side effects, which may commonly resolve within several weeks. First, efavirenz was found to cause major CNS congenital abnormalities in a number of non-human primates, an unfortunate occurrence of possibly limited significance, since most other antiretroviral drugs have not been tested in monkeys.<sup>1</sup> Despite the fact that new meta-analyses of the use of efavirenz during pregnancy are reassuring,<sup>17</sup> the data cannot exclude a potential 2-fold to 3-fold increase in the rates of neural tube birth defects as a result of first-trimester exposure to efavirenz. Indeed, several cases of neural tube defects in the newborns of mothers exposed to efavirenz during the first trimester of pregnancy have been reported.<sup>18,19</sup> A recent 16 year retrospective analysis of the French perinatal cohort showed that first-trimester exposure of pregnant women to efavirenz was associated with an adjusted OR of CNS birth defects of 3.2 (95% CI: 1.1–9.1;  $P=0.03$ ).<sup>20</sup> However the overall risk–benefit profile has led the British HIV Association 2012 guidelines committee to recommend that efavirenz, if initiated in women of childbearing potential, be continued in the event that conception occurs while on the drug,<sup>21</sup> and the WHO 2013 guidelines give the same recommendation.<sup>16</sup> Because efavirenz is classified as FDA Pregnancy Category D, meaning the evidence is based on studies in primates and observations in humans, the US Department of Health and Human Services guidelines advocate that alternative treatment options that do not include efavirenz should be strongly considered in sexually active women who are not taking effective contraception.<sup>15</sup> As the risk of neural tube defects is restricted to the first 6 weeks of pregnancy, i.e. before pregnancy is usually recognized, there is still a debate on the use of efavirenz in women of childbearing potential.

The most important clinical issue with efavirenz is that it frequently causes CNS side effects, including dizziness, abnormal dreams, headaches and depression. Although these adverse events can sometimes lead to treatment discontinuation, they are often self-limited and resolve spontaneously after a few days to weeks. Even in people who have tolerated efavirenz for years, changing to other drugs results in improvements in mood.<sup>22</sup> A recent meta-analysis of four large randomized clinical studies in ART-naïve patients, of which one was double-blinded, suggested that the adjusted risk of suicidality (tendency to commit suicide) was significantly higher in efavirenz than non-efavirenz recipients, with a hazard ratio of 2.28.<sup>23</sup> These data, if confirmed, raise the question of the risk–benefit profile of efavirenz, taking also into account the fact that neurocognitive function improves less in people taking efavirenz.<sup>24</sup>

### Phase 3 studies

In addition to the foregoing, three independent randomized clinical studies have shown that efavirenz is not non-inferior to comparator agents that have been used in first-line therapy (Table 1).<sup>25–27</sup> The STaR study was a multicentre, international, randomized, open-label phase 3b 96 week study that evaluated two single-tablet regimens, tenofovir/emtricitabine/efavirenz and tenofovir/emtricitabine/rilpivirine, in first-line ART in 786 HIV-1

antiretroviral-naïve adults. Randomization involved stratification on the basis of baseline HIV-1 RNA ( $\leq$  or  $>100\,000$  copies/mL). The proportions of patients achieving virological suppression by time to loss of virological response (in a missing-equals-failure analysis) were 80% and 85% at week 48 and 73% and 79% at week 96 for the efavirenz-based regimen and rilpivirine-based regimen, respectively.<sup>27,28</sup> The 95% CIs for the differences were 0.6%–11.2% at week 48 ( $P=0.03$ ) and 0.7%–12.6% at week 96 ( $P=0.03$ ) and indicated the superiority of tenofovir/emtricitabine/rilpivirine compared with tenofovir/emtricitabine/efavirenz. In the subgroup of patients with baseline HIV-1 RNA  $\leq 100\,000$  copies/mL (65% of the total study population), there was a statistically significant difference in virological suppression at week 96 favouring tenofovir/emtricitabine/rilpivirine (79% versus 71%, 95% CI for difference: 0.2%–15.1%;  $P=0.048$  by snapshot analysis).<sup>27</sup> In the subgroup of patients with a baseline HIV-1 RNA  $\geq 100\,000$  copies/mL, tenofovir/emtricitabine/rilpivirine was non-inferior to tenofovir/emtricitabine/efavirenz (76% versus 75%, 95% CI for difference: –8.7% to 11.6%;  $P=0.78$  by snapshot analysis).<sup>27</sup> Tenofovir/emtricitabine/rilpivirine was also better tolerated than tenofovir/emtricitabine/efavirenz with significantly fewer nervous system and psychiatric adverse events ( $P<0.001$ ) and significantly fewer discontinuations due to adverse events (3% versus 11%, respectively; Table 2).

The STARTMRK trial was a randomized double-blind study comparing the use of tenofovir plus emtricitabine plus either raltegravir or efavirenz in 566 treatment-naïve patients. Raltegravir was dosed twice daily, while patients on the efavirenz arm of the study received active efavirenz as part of their night-time regimen and a placebo in the morning.<sup>26</sup> Raltegravir was shown to be superior to efavirenz at week 192 of treatment, despite the fact that efavirenz possesses a far longer plasma half-life than raltegravir. Thus, it can be argued that any degree of non-adherence in the STARTMRK trial should have favoured the efavirenz arm and the demonstrated superiority of raltegravir over efavirenz could be seen as more impressive than the data of the intent-to-treat analysis would seem to indicate [proportions with HIV RNA  $<50$  copies/mL at week 240 were 71% and 61% for raltegravir and efavirenz, respectively (95% CI: 1.7%–17.3%)].<sup>26</sup> Significantly fewer drug-related clinical adverse events occurred in patients on raltegravir ( $P<0.0001$ ),<sup>30–33</sup> and there was a benefit of raltegravir over efavirenz in regard to lipid profile.<sup>26</sup>

The SINGLE study was a multicentre, international, randomized, double-blind phase 3 96 week study that evaluated two once-daily regimens, i.e. a tenofovir/emtricitabine/efavirenz single-tablet regimen versus abacavir/lamivudine/dolutegravir in 833 HIV-1 ART-naïve adults. At weeks 48 and 96, the proportion of patients having HIV-1 RNA  $<50$  copies/mL was significantly higher in the abacavir/lamivudine/dolutegravir group than in the tenofovir/emtricitabine/efavirenz group (88% versus 81%;  $P=0.003$ ). Rates of discontinuation for adverse events were also lower in the abacavir/lamivudine/dolutegravir group than in the tenofovir/emtricitabine/efavirenz arm (2% versus 10%).<sup>25</sup>

### Epidemiological data on resistance

A major disadvantage of currently available NNRTIs is the prevalence of NNRTI resistance mutations in antiretroviral-naïve patients and the low genetic barrier of NNRTIs for the development of drug resistance.<sup>34</sup> Indeed, treatment failure of first-line

**Table 1.** Randomized clinical trials in antiretroviral-naïve patients with virological response to efavirenz-based regimens that were not non-inferior to comparators

	ECHO	THRIVE	STaR	STARTMRK	SINGLE
Design	double-blind	double-blind	open-label	double-blind	double-blind
Duration (years)	2	2	2	5	2
Efavirenz comparator	RPV	RPV	RPV	RAL	DTG
Nucleotide/nucleoside backbone	TDF/FTC <sup>a</sup>	TDF/FTC <sup>a</sup> 60% <sup>b</sup>	TDF/FTC <sup>c</sup>	TDF+FTC	ABC/3TC <sup>c</sup>
<i>n</i> , total	690	680	786	563	833
Female (%)	21	27	7	19	16
Median baseline HIV-1 RNA (log <sub>10</sub> copies/mL)	5	5	4.8 (mean)	5	4.68
Median baseline CD4 (cells/mm <sup>3</sup> )	248	263	390 (mean)	208	338
Primary endpoint	ITT-TLOVR at week 48	ITT-TLOVR at week 48	ITT-FDA snapshot	per protocol, non-completer = failure	ITT-FDA snapshot
Non-inferiority margin	12%	12%	12%	12%	10%
Week 48 outcome [reference(s)]	<b>9,29</b>	<b>10,29</b>	<b>28</b>	<b>30</b>	<b>25</b>
HIV-1 RNA <50 copies/mL (comparator versus efavirenz)	83% versus 83%	86% versus 82%	86% versus 82%	86.1% versus 81.9%	88% versus 81%
difference in virological success (95% CI)	-0.4% (-5.9% to 5.2%)	3.5% (-1.7% to 8.8%)	4.1% (-1.1% to 9.2%)	4.2% (-1.9% to 10.3%)	7% (2% to 12%) <sup>d</sup>
discontinuation for AE (comparator versus efavirenz)	2.3% versus 8%	4% versus 7%	2.5% versus 8.7%	2.8% versus 6%	2.4% versus 10%
response rate, baseline HIV-1 RNA <100000 copies/mL (comparator versus efavirenz); difference (95% CI)	90% versus 83%; 6.1% (-1.1% to 13.3%)	91% versus 84%; 7.1 (0.2% to 13.9%) <sup>d</sup>	89% versus 82%; 7.2% (1.1% to 13.4%) <sup>d</sup>	92.5% versus 89.1%; 3.4% (-4.1% to 11.0%)	90.4% versus 82.6%; 7.7% (2% to 13%) <sup>d</sup>
Week 96 outcome [reference(s)]		<b>31,32</b>	<b>27</b>	<b>33</b>	NA
HIV-1 RNA <50 copies/mL (comparator versus efavirenz)		78% versus 78%	78% versus 72%	81% versus 79%	
difference in virological success (95% CI)		-0.4% (-4.6% to 3.8%)	5.5% (-0.6% to 11.5%)	2% (-4% to 9%)	
discontinuation for AE (comparator versus efavirenz)		4% versus 9%	3% versus 11%	3.6% versus 6.7%	
response rate, baseline HIV-1 RNA <100000 copies/mL (comparator versus efavirenz); difference (95% CI)		84% versus 80%; 4.0% (-1.7% to 9.7%)	79% versus 71%; 7.6% (0.2% to 15.1%) <sup>d</sup>	NA	
Long-term outcome (HIV-1 RNA <50 copies/mL at week 240); difference in virological success (95% CI) <sup>26</sup>		NA	NA	71% versus 61.3%; 9.5% (1.7% to 17.3%) <sup>d</sup>	NA

RPV, rilpivirine; RAL, raltegravir; DTG, dolutegravir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; ITT, intent-to-treat; TLOVR, time to loss of virological response; AE, adverse event; NA, not available.

<sup>a</sup>As fixed-drug combination, in addition to third agent.

<sup>b</sup>30% Zidovudine/3TC; 10% ABC/3TC.

<sup>c</sup>As single-tablet regimen.

<sup>d</sup>Significant superiority.

**Table 2.** Neurological, psychiatric and cutaneous adverse events by week 48 in selected efavirenz-based randomized clinical trials performed in antiretroviral-naïve patients

		ECHO <sup>9</sup>	THRIVE <sup>10</sup>	STaR <sup>28</sup>	STARTMRK <sup>30</sup>	SINGLE <sup>25</sup>
Neurological	comparator	16%	18%	30%	26% <sup>a</sup>	22%
	efavirenz	37%	39%	51%	59% <sup>a</sup>	47%
Psychiatric	comparator	15%	15%	16%	—	29%
	efavirenz	25%	20%	38%	—	38%
Rash	comparator	4%	3%	8% <sup>b</sup>	0% <sup>c</sup>	3%
	efavirenz	15%	13%	13% <sup>b</sup>	7% <sup>c</sup>	14%

For comparator, see Table 1.

<sup>a</sup>CNS (neuropsychiatric) events.

<sup>b</sup>Through week 96.

<sup>c</sup>Of moderate to severe intensity through week 96.

NNRTI-based regimens can have serious consequences, including a further accumulation of NNRTI and nucleoside reverse transcriptase inhibitor resistance mutations, which can result in cross-resistance to second-generation NNRTIs (e.g. etravirine and rilpivirine) and diminished effectiveness of the nucleoside 'backbone' of subsequent treatment regimens, respectively. Other potential consequences are suboptimal immunological recovery and increased morbidity and mortality associated with lack of virological control, especially in patients presenting with advanced HIV infection. In randomized first-line clinical studies conducted in 2001–2004 in the USA, in which efavirenz-containing regimens were compared with a non-efavirenz-containing regimen, the prevalence of baseline NNRTI resistance was 5% and the risk of virological failure for subjects with baseline NNRTI resistance was higher than for subjects without such resistance (hazard ratio=2.27, 95% CI: 1.15–4.49;  $P=0.018$ ).<sup>35</sup> Detection of low-level NNRTI resistance by either bulk sequencing or more ultrasensitive analyses is significantly associated with the likelihood of virological failure involving first-line efavirenz- or nevirapine-based therapy.<sup>36</sup> In the EuroCoord-CHAIN joint project, the risk of virological failure was doubled in patients with transmitted NNRTI drug resistance.<sup>37</sup> More recently, a meta-analysis of 985 participants from 10 studies showed that the presence of a minority HIV-1 NNRTI drug resistance mutation before starting ART was associated with a 2-fold to 3-fold higher risk of virological failure in treatment-naïve patients initiating an NNRTI-based regimen.<sup>38</sup> In a European case-control study of 260 patients, minority NNRTI resistance mutations at baseline were associated with an adjusted 2.4-fold (95% CI: 1.12–5.18;  $P=0.024$ ) increased risk of virological rebound of HIV-1 RNA to >200 copies/mL in patients on first-line NNRTI-based regimens.<sup>39</sup> This concern in regard to an increased prevalence of transmitted drug resistance to NNRTIs has led to the recommendation in high-income countries that HIV genotypic resistance testing be performed before initiating therapy with an NNRTI, a practice which may not always be possible in low-income countries where resources for resistance testing are limited. Although the prevalence of detectable NNRTI resistance mutations in ART-naïve patients is stable or declining in most regions of the world (i.e. 5%–8%)<sup>40,41</sup> these numbers do not take into consideration

the presence of minority NNRTI resistance mutations.<sup>39,42</sup> These considerations all suggest that the use of either nevirapine or efavirenz in first-line therapy may no longer be a preferred therapeutic option, either in high- or low-income countries. Of course, however, a decision no longer to recommend efavirenz in resource-limited settings will only be ethical if safer and more effective antiretrovirals are available for use as third agents in combination ART.

## Summary

In conclusion, efavirenz today remains one of the commonly used components of prescribed antiretroviral regimens. We acknowledge that cost, availability and acceptability are issues that drive much antiretroviral use, but we should continually re-evaluate what we recommend and challenge current paradigms. Treatment advances have now resulted in safer and even superior alternatives to efavirenz. Considerations of efficacy, toxicity and resistance suggest that efavirenz should be reconsidered for use in first-line therapy, as has already happened for multiple other drugs, e.g. stavudine, zalcitabine and nelfinavir. This should not only happen in high-income countries but ideally also in low-income settings, if alternative drugs are available, and this recommendation should be reflected in the treatment guidelines of the WHO and both governmental and non-governmental organizations, especially since the monitoring of drug toxicities and transmitted resistance is often not practicable in resource-limited areas. In order for the success of ART to become a reality in all countries, we need always to use the safest and most effective antiretroviral combinations. Assuming that alternative therapies are available, this means that the risk-benefit profile of efavirenz as a first-line agent should now be reconsidered by guidelines committees.

## Transparency declarations

F. R., A. L. P. and M. A. W. have received research grant support and/or honoraria from each of ViiV Healthcare, Merck Inc., Bristol-Myers Squibb, Gilead Sciences, Abbvie and Janssen Pharmaceuticals.

## References

- 1 Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. March 27, 2012 Update. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL003093.pdf> (16 January 2014, date last accessed).
- 2 Gulick RM, Ribaud HJ, Shikuma CM *et al*. AIDS Clinical Trials Group (ACTG) A5095 Study Team. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. *JAMA* 2006; **296**: 769–81.
- 3 Casseti I, Madruga JV, Suleiman JM *et al*. Study 903E Team. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naïve HIV-1-infected patients. *HIV Clin Trials* 2007; **8**: 164–72.
- 4 Staszewski S, Morales-Ramirez J, Tashima KT *et al*. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999; **341**: 1865–73.
- 5 Riddler SA, Haubrich R, DiRienzo AG *et al*. AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; **358**: 2095–106.
- 6 Robbins GK, De Gruttola V, Shafer RW *et al*. AIDS Clinical Trials Group 384 Team. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; **349**: 2293–303.
- 7 Gulick RM, Ribaud HJ, Shikuma CM *et al*. AIDS Clinical Trials Group Study A5095 Team. Triple-nucleoside regimens versus efavirenz containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004; **350**: 1850–61.
- 8 van Leth F, Phanuphak P, Ruxrungtham K *et al*. 2NN Study Team. 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.
- 9 Molina JM, Cahn P, Grinsztejn B *et al*. ECHO Study Group. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naïve adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 2011; **378**: 238–46.
- 10 Cohen CJ, Andrade-Villanueva J, Clotet B *et al*. THRIVE Study Group. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011; **378**: 229–37.
- 11 Daar ES, Tierney C, Fischl MA *et al*. AIDS Clinical Trials Group Study A5202 Team. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med* 2011; **154**: 445–56.
- 12 Ministère des Affaires Sociales et de la Santé, Conseil National du Sida, Agence Nationale de Recherches sur le Sida et les Hépatites Virales. *Prise en Charge Médicale des Personnes Vivant Avec le VIH, Recommandations du Groupe d'Experts, Rapport 2013*. [http://www.sante.gouv.fr/IMG/pdf/Rapport\\_Morlat\\_2013\\_Mise\\_en\\_ligne.pdf](http://www.sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf) (26 December 2013, date last accessed).
- 13 European AIDS Clinical Society. *Guidelines, Version 7.0, October 2013*. [http://www.eacsociety.org/Portals/0/Guidelines\\_Online\\_131014.pdf](http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf) (12 January 2014, date last accessed).
- 14 Williams I, Churchill D, Anderson J *et al*. BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012. *HIV Med* 2012; **13** Suppl 2: 1–85.
- 15 Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. February 12, 2013 Update. <http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf> (12 January 2014, date last accessed).
- 16 WHO HIV/AIDS Programme. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Summary of Key Features and Recommendations*. June 2013. [http://apps.who.int/iris/bitstream/10665/85322/1/WHO\\_HIV\\_2013.7\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/85322/1/WHO_HIV_2013.7_eng.pdf) (12 January 2014, date last accessed).
- 17 Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS* 2011; **25**: 2301–4.
- 18 Fundaro C, Genovese O, Rendeli C *et al*. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS* 2002; **16**: 299–300.
- 19 Antiretroviral Pregnancy Registry Steering Committee. *The Antiretroviral Pregnancy Registry Interim Report, 1 January 1989 Through 31 January 2013*. [http://www.apregistry.com/forms/interim\\_report.pdf](http://www.apregistry.com/forms/interim_report.pdf) (12 January 2014, date last accessed).
- 20 Sibiude J, Mandelbrot L, Blanche S *et al*. Birth defects and ART in the French perinatal cohort, a prospective exhaustive study among 13,124 live births from 1994 to 2010. In: *Abstracts of the Twentieth Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, USA, 2013*. Abstract 81. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.
- 21 Hsu H, Rydzak C, Cotich KL *et al*. CEPAC Investigators. Quantifying the risks and benefits of efavirenz use in HIV-infected women of childbearing age in the USA. *HIV Med* 2011; **12**: 97–108.
- 22 Nguyen A, Calmy A, Delhumeau C *et al*. A randomized cross-over study to compare raltegravir and efavirenz (SWITCH-ER study). *AIDS* 2001; **25**: 1481–7.
- 23 Mollan K, Smurzynski M, Na L *et al*. Hazard of suicidality in patients randomly assigned to efavirenz for initial treatment of HIV-1: a cross-study analysis. In: *Abstracts of IDWeek 2013, San Francisco, CA, USA, 2013*. Abstract 670.
- 24 Winston A, Puls R, Kerr SJ *et al*. Dynamics of cognitive change in HIV-infected individuals commencing three different initial antiretroviral regimens: a randomized, controlled study. *HIV Med* 2012; **13**: 245–51.
- 25 Walmsley SL, Antela A, Clumeck N *et al*. SINGLE Investigators. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; **369**: 1807–18.
- 26 Rockstroh JK, DeJesus E, Lennox JL *et al*. STARTMRK Investigators. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr* 2013; **63**: 77–85.
- 27 Cohen C, Wohl D, Arribas J *et al*. STaR study: single tablet regimen rilpivirine/emtricitabine/tenofovir DF maintains non-inferiority to efavirenz/emtricitabine/tenofovir DF in ART-naïve adults through week 96. In: *Abstracts of the Fourteenth European AIDS Conference, Brussels, Belgium, 2013*. Abstract LBPE7/17. European AIDS Clinical Society.
- 28 Cohen C, Wohl D, Arribas J *et al*. STaR study: single-tablet regimen emtricitabine/rilpivirine/tenofovir DF is non-inferior to efavirenz/emtricitabine/tenofovir DF in ART-naïve adults. Week 48 results. In: *Abstracts of the Eleventh International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, 2012*. Abstract O425.
- 29 Molina JM, Clumeck N, Redant K *et al*. Rilpivirine vs. efavirenz in HIV-1 patients with baseline viral load 100,000 copies/mL or less: week 48 phase III analysis. *AIDS* 2013; **27**: 889–97.
- 30 Lennox JL, DeJesus E, Lazzarin A *et al*. STARTMRK Investigators. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; **374**: 796–806.

- 31** Cohen CJ, Molina JM, Cassetti I *et al.* ECHO and THRIVE Study Groups. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS* 2013; **27**: 939–50.
- 32** Molina JM, Clumeck N, Orkin C *et al.* ECHO and THRIVE Study Groups. Week 96 analysis of rilpivirine or efavirenz in HIV-1-infected patients with baseline viral load  $\leq 100\,000$  copies/mL in the pooled ECHO and THRIVE phase 3, randomized, double-blind trials. *HIV Med* 2014; **15**: 57–62.
- 33** Lennox JL, Dejesus E, Berger DS *et al.* STARTMRK Investigators. Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. *J Acquir Immune Defic Syndr* 2010; **55**: 39–48.
- 34** Wensing AM, van de Vijver DA, Angarano G *et al.* Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis* 2005; **192**: 958–66.
- 35** Kuritzkes DR, Lalama CM, Ribaudo HJ *et al.* Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis* 2008; **197**: 867–70.
- 36** Geretti AM, Fox ZV, Booth CL *et al.* Low-frequency K103N strengthens the impact of transmitted drug resistance on virologic responses to first-line efavirenz or nevirapine-based highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2009; **52**: 569–73.
- 37** Wittkop L, Günthard HF, de Wolf F *et al.* EuroCoord-CHAIN Study Group. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. *Lancet Infect Dis* 2011; **11**: 363–71.
- 38** Li JZ, Paredes R, Ribaudo HJ *et al.* Low-frequency HIV-1 drug resistance mutations and risk of NNRTI-based antiretroviral treatment failure: a systematic review and pooled analysis. *JAMA* 2011; **305**: 1327–35.
- 39** Cozzi-Lepri A, Noguera-Julian M, Di Giallonardo F *et al.* Low-frequency drug-resistant HIV-1 and risk of virological failure to first-line NNRTI-based ART: a multi-cohort European case-control study using centralized ultrasensitive 454 sequencing. *Antivir Ther* 2013; **18** Suppl 1: A41.
- 40** Frentz D, Boucher CA, van de Vijver DA. Temporal changes in the epidemiology of transmission of drug-resistant HIV-1 across the world. *AIDS Rev* 2012; **14**: 17–27.
- 41** Parikh UM, Kiepiela P, Ganesh S *et al.* IPTc Taskforce. Prevalence of HIV-1 drug resistance among women screening for HIV prevention trials in KwaZulu-Natal, South Africa (MTN-009). *PLoS One* 2013; **8**: e59787.
- 42** Li JZ, Paredes R, Ribaudo HJ *et al.* Impact of minority nonnucleoside reverse transcriptase inhibitor resistance mutations on resistance genotype after virologic failure. *J Infect Dis* 2013; **207**: 893–7.