

Analysis of Neuropsychiatric Adverse Events During Clinical Trials of Efavirenz in Antiretroviral-Naive Patients: A Systematic Review

Brian Gazzard¹, Andrew Balkin² and Andrew Hill³

¹Chelsea and Westminster Hospital, London, UK; ²AmberMed Ltd, London, UK; ³Pharmacology Research Laboratories, University of Liverpool, Liverpool, UK

Abstract

People with HIV infection have several risk factors for developing neuropsychiatric adverse events: preexisting conditions, HIV disease stage, and antiretroviral treatment. The most widely used system for assessing neuropsychiatric adverse events in clinical trials is the US Division of AIDS severity grading scale, from Grade 1 (mild) to Grade 4 (life-threatening). First-line treatment with efavirenz has been associated with higher rates of neuropsychiatric adverse events than several other antiretrovirals.

A MEDLINE search identified 17 randomized clinical trials of first-line HAART with two nucleoside analogs plus efavirenz, of which 13 reported neuropsychiatric adverse events using the Grade 1-4 system. The percentage of patients with graded neuropsychiatric adverse events, and the system used for analysis, was compared across the trials.

Of the 13 trials identified, there were five different methods used to report neuropsychiatric adverse events: Grade 1-4 all, Grade 1-4 drug related, Grade 2-4 all, Grade 2-4 drug related, Grade 3-4 all, Grade 3-4 drug related, and adverse events leading to discontinuation. In addition, three trials used questionnaire-based methods instead of the Division of AIDS grading system. There were a significantly higher percentage of patients with Grade 1-4 neurological or psychiatric adverse events in the efavirenz versus comparator arms in the DMP-006, TMC278-C204, and STARTMRK trials. There were generally too few patients with each individual neuropsychiatric adverse event to allow meaningful comparisons of treatment arms. There were no significant differences in Grade 3 or 4 neuropsychiatric adverse events between the treatment arms in the ACTG 5142 or 2NN trials.

In summary, there is a wide range of different systems used to report neuropsychiatric adverse events in HIV clinical trials. Use of a standardized endpoint would improve the interpretability of results across clinical trials. (AIDS Rev. 2010;12:67-75)

Corresponding author: Andrew Hill, microhaart@aol.com

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Correspondence to:

Andrew Hill
Pharmacology Research Laboratories
University of Liverpool
70 Pembroke Place
Liverpool L69 3GF, UK
E-mail: microhaart@aol.com

Introduction

There is a high prevalence of reported neurological and psychiatric symptoms among people with HIV infection^{1,2}, linked to three main factors: preexisting conditions, HIV disease progression, and antiretroviral treatment.

Preexisting conditions, such as depression, drug abuse, or alcoholism, may lead to psychological problems, independent of HIV disease stage or treatment received³. Among people with HIV, depression is more common for people with high alcohol consumption or previous diagnosis of psychiatric disorders^{3,4}. Depression may lead to poorer adherence to antiretroviral treatment⁵.

The three main effects of HIV infection on central nervous system (CNS) or psychiatric symptoms is HIV dementia, also known as AIDS dementia complex (ADC) or HIV-associated dementia (HAD)⁶. This syndrome is characterized by impaired short-term memory coupled with a reduced ability in mental concentration. This may be manifested in the misplacing of objects and a lack of coordination, and an inability to perform previously learned tasks.

The rates of reported HIV-associated CNS complications have declined since the advent of combination antiretroviral therapy⁷. However, neurocognitive disturbances can still be detected for a subset of patients receiving antiretroviral treatment and with undetectable HIV RNA levels^{8,9}.

Treatment with the nonnucleoside efavirenz is associated with a well characterized set of neuropsychiatric adverse events, including insomnia, dizziness, balance problems, and vivid dreams¹⁰. These adverse events are most common in the first month of treatment, and tend to be more common for patients with higher plasma levels of efavirenz¹¹. Patients with depressive symptoms before starting efavirenz are more likely to show neuropsychiatric adverse events during treatment¹². A minority of patients show longer-term problems, including suicidal ideation, and have to discontinue treatment. Despite these issues, efavirenz has shown consistently high levels of efficacy in randomized clinical trials and is recommended for first-line use, combined with two nucleoside analogs, in international HIV treatment guidelines^{13,14}.

Given the high prevalence of neuropsychiatric adverse events among people with HIV infection and the influence of antiretroviral treatment, it is important to assess whether improvements in treatment could improve this situation. Many randomized clinical trials have evaluated the efficacy and safety of efavirenz

versus other antiretrovirals, but the trials have been analyzed using a wide range of endpoints.

In most clinical trials, adverse events are collected prospectively at each study visit. Adverse events are graded in severity, and The Division of AIDS (DAIDS) 2007 system¹⁵ of classifying clinical and laboratory adverse events is used widely to classify both clinical and laboratory events as either Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening). In addition, investigators judge how strongly these adverse events are associated with study medication.

Adverse events collected during a trial are then coded using a dictionary of predefined terms (e.g. MEDRA). The adverse events are then grouped under System Organ Classes: in the MEDRA dictionary, there are System Organ Classes of "psychiatric" and "central nervous system" adverse events. One way to analyze neuropsychiatric adverse events is to compare the number of patients in each arm who have any adverse event in these two System Organ Classes. Other trials have analyzed these events by "preferred term" – these are more specific adverse events, such as dizziness, insomnia, or headache. The number of patients with each individual adverse event is compared between treatment arms. In several clinical trials, patients have completed questionnaires on their personal experience of neuropsychiatric adverse events and their effects on quality of life.

However, in publications of clinical trials, there are many different methods for reporting these adverse events, ranging from all Grade 1-4 adverse events, regardless of the relationship to study drug, to only adverse events leading to study drug discontinuation, or results from quality of life questionnaires. A systematic review of randomized clinical trials of first-line use of efavirenz was therefore conducted to assess the incidence of neuropsychiatric adverse events measured using different methods and endpoints.

Methods

A systematic MEDLINE review was conducted for prospective clinical trials of HAART regimens containing efavirenz-based HAART in antiretroviral-naive HIV-infected individuals published between January 1, 1999 and March 1, 2010. This search used the generic names of each antiretroviral, followed by "clinical trial" and "naive".

This search was further extended by a review of the proceedings and abstract books of the following international scientific conferences, organized during the

abovementioned index period: the Conference on Retroviruses and Opportunistic Infections (CROI), the Inter-science Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Conference on Clinical Aspects and Treatment of HIV Infection (EACS), the International AIDS Conference (also known as the World AIDS Conference), the International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment, the International Conference on Drug Therapy in HIV Infection (ICDT) and the Annual Meeting of the Infectious Diseases Society of America (IDSA).

Finally, the latest US Food and Drug Administration (FDA)-approved package inserts for each protease inhibitor currently licensed for the treatment of HIV infection in treatment-naïve, HIV-infected adults were examined and listed trials were reviewed.

Trials derived from this systematic review of public domain data and conference presentations were included in this analysis if they met all of the following eligibility criteria:

- They had to include at least 100 chronically infected, treatment-naïve, HIV-infected individuals aged 16 years or above at any stage of HIV infection.
- The minimum duration of follow-up reported for these trials at the moment of inclusion in the systematic review had to be 48 weeks.
- Safety data had to be reported for the 48 week time point or later, using the Division of AIDS 2007 grading system for neuropsychiatric adverse events¹⁵, or a questionnaire on quality of life, including neuropsychiatric symptoms.
- They had to evaluate, in at least one treatment arm, HAART regimens comprising efavirenz and a combination of two nucleoside analogs. Treatment arms which evaluated other combinations (for example, protease inhibitor plus nonnucleoside reverse transcriptase inhibitor only) were not included.

This search generated 13 clinical trials with data available on neuropsychiatric adverse events by treatment arm during first-line treatment with two nucleoside analogs plus efavirenz.

There were eight trials which directly compared efavirenz with other antiretrovirals. In order of publication, these were (i) the DMP-006 trial, which compared zidovudine/lamivudine/indinavir with zidovudine/lamivudine/efavirenz¹⁶; (ii) the 2NN trial (stavudine/lamivudine plus efavirenz or nevirapine¹⁷; (iii) the BMS-034 trial (zidovudine/lamivudine plus efavirenz or atazanavir)¹⁸; (iv) the ACTG 5142 trial (two nucleoside analogs plus efavirenz or lopinavir/ritonavir)¹⁹; (v) the MERIT trial (zidovudine/lamivudine plus efavirenz or maraviroc)²⁰;

(vi) the Abbott M03-613 trial (zidovudine/lamivudine plus either lopinavir/ritonavir or efavirenz²¹; (vii) the STARTMRK trial (tenofovir/emtricitabine plus efavirenz or raltegravir)^{22,23}; (viii) the TMC278-C204 trial (two nucleoside analogs plus efavirenz or rilpivirine)²⁴.

In addition, there were five trials which evaluated different nucleoside analogs in combination with efavirenz. These were (i) EPV20001 (zidovudine/lamivudine plus efavirenz, comparing once vs. twice-daily lamivudine)²⁵; (ii) CNA30021 (abacavir/lamivudine plus efavirenz, comparing once vs. twice-daily abacavir)²⁶; (iii) CNA30024 (abacavir/lamivudine plus efavirenz vs. zidovudine/lamivudine plus efavirenz)²⁷; (iv) Gilead 903 (stavudine/lamivudine plus efavirenz vs. tenofovir/lamivudine plus efavirenz)²⁸; (v) Gilead 934 (tenofovir/emtricitabine plus efavirenz vs. zidovudine/lamivudine plus efavirenz)²⁹.

There were four clinical trials with neuropsychiatric adverse events not reported by the DAIDS system: ALTAIR³⁰, ACTG 5095³¹, the stepped-dose study³², and the Spanish first-line study³³. However, there was a detailed neurological sub-study of the ACTG 5095 trial (A5097S)³⁴, which is described in: CES-D and Z-scores, ACTG 5095 Trial. Neuropsychiatric adverse events in the stepped-dose trial of efavirenz and the Spanish first-line study were assessed by questionnaire, and the results are also discussed in: The Medical Outcomes Study Questionnaire (Spanish Trial)^{32,33}.

For each clinical trial, the percentage of patients with neuropsychiatric adverse events in each treatment arm was recorded. The system for reporting these adverse events was also recorded for each trial. We used the longest-term data available for each clinical trial. The neuropsychiatric adverse events from the TMC278-C204 trial were reported in the greatest detail using the DAIDS 2007 system²⁴, and are summarized in table 1.

The percentage of patients with each type of neurological or psychiatric adverse event was then tabulated, with clinical trials grouped by the reporting system used. The mean incidence of neuropsychiatric adverse events for patients treated with efavirenz versus other antiretrovirals was shown. For all neuropsychiatric adverse events reported in randomized clinical trials of efavirenz versus other antiretrovirals, chi-square tests were used to determine whether there was a significant difference between treatment arms at the 5% significance level.

Where other systems were used to report neuropsychiatric adverse events (for example quality of life questionnaires), these results were summarized by treatment arm.

Table 1. Methods of reporting neuropsychiatric adverse events in randomized clinical trials of antiretroviral-naive patients

Neuropsychiatric endpoint	Clinical trials
DAIDS-graded adverse events:	
Grade 1-4, all cause, all neuropsychiatric AE	TMC278-C204 ²⁴ DMP-006 ¹⁶ STARTMRK ²²
Grade 1-4, all cause, individual AE	MERIT ²⁰ CNA30021 ²⁷ EPV20001 ²⁵
Grade 2-4, all cause, individual AE	CNA30024 ²⁶ Gilead 934 ²⁹
Grade 2-4, drug-related, individual AE	TMC278-C204 ²⁴ BMS-034 ¹⁸ Abbott M03-613 ²¹
Grade 3-4, all cause, individual AE	ACTG 5142 ¹⁹ 2NN ¹⁷ Gilead 903 ²⁸
Neuropsychiatric AE not reported:	ALTAIR ³⁰
Quality of life questionnaires	
Neuropsychological Z-score	ACTG 5095 ³¹
Profile of mood state questionnaire	Spanish naive trial ³³
Medical Outcomes Study questionnaire	Spanish naive trial ³²
Oviedo University questionnaire	Stepped-dose trial ³²

DAIDS: Division of AIDS; AE: adverse events.

Results

Reporting systems for grade 1-4 neuropsychiatric adverse events

Table 1 shows the different methods used to report neuropsychiatric adverse events in clinical trials of first-line antiretroviral treatment including efavirenz. Some of the trials used more than one system of reporting. The endpoints used differed in four ways:

- Either all neurological and psychiatric adverse events were reported, or individual events (e.g. dizziness, insomnia, abnormal dreams).
- The grade reported: some trials reported Grade 1-4 events, others Grade 2-4 or Grade 3-4 events.
- Drug-related versus all-cause: some trials reported adverse events judged to be least possibly related to trial medication by the investigators, while other trials reported adverse events with any cause.
- The cut-off used to report individual adverse events. Some trials reported adverse events seen

in at least 5% of patients in either arm (e.g. MERIT trial), while others reported those seen in at least 2% of patients (TMC278-C204 trial), or 1% of patients (2NN trial) in either arm.

There were 13 randomized clinical trials of first-line efavirenz with neuropsychiatric adverse events reported by the Grade 1-4 DAIDS 2007 system. The neuropsychiatric adverse events from the TMC278-C204 trial were reported in the greatest detail and are summarized in table 2. Results from the eight comparative trials of efavirenz compared head-to-head with other antiretrovirals are shown in table 3. Table 4 shows the results from five clinical trials where all patients received efavirenz, but were randomized to different nucleoside analogs.

In the TMC278-C204 trial²⁴, data was available for several different grading systems. Table 2 shows how most of the observed Grade 1-4 neuropsychiatric events were Grade 1 or 2. This is one of a small number of trials which reported the overall incidence of nervous system and psychiatric adverse events by

Table 2. Number and percentage of patients with treatment-emergent neurological or psychiatric adverse events (all cause) by week 96 in the TMC278-C204 trial²⁴

Treatment arm (n)	Neuropsychiatric adverse events	
	Efavirenz n = 89	Combined TMC278 n = 279
Grade 1-4 neurological*	53 (59.6%)	91 (32.6%)
All cause		
Grade 1	40 (44.9%)	73 (26.2%)
Grade 2	12 (13.5)	18 (6.5%)
Grade 3	1 (1.1%)	0
Grade 4	0	0
Grade 1-4 psychiatric†	19 (21.3%)	45 (16.1%)
All cause		
Grade 1	9 (10.1%)	23 (8.2%)
Grade 2	9 (10.1%)	17 (6.1%)
Grade 3	1 (1.1)	3 (1.1%)
Grade 4	0	2 (0.7%)

*Neurological adverse events of interest: cluster headache, cranial neuropath disturbance in attention, dizziness, facial palsy, headache, lethargy, memory impairment, mononeuropathy, circumoral paresthesia, photophobia, restlessness, sensation of pressure in ear, somnolence, uveitis, vertigo, blurred vision.

†Psychiatric adverse events of interest: abnormal dreams, affective disorder, aggression, agitation, anxiety, confusional state, depressed mood, homicidal ideation, insomnia, irritability, decreased libido, major depression, mood swings, nervousness, nightmare, panic attack, phobia, posttraumatic stress disorder, sleep disorder, social phobia, spoor, stress symptoms, suicide attempt.

treatment arm. Table 2 shows analysis of Grade 2-4 drug-related individual neuropsychiatric adverse events occurring in at least 2% of patients in one arm. The four most common adverse events were dizziness, abnormal dreams, somnolence, and vertigo, which were reported in 2-3% of patients in the efavirenz arm versus 0.4-1% in the rilpivirine arm. The percentage of patients with these Grade 2-4 drug-related neuropsychiatric events was small compared to the number with Grade 1-4 adverse events of any cause.

Among the other clinical trials shown in tables 3 and 4, the percentage of patients with neuropsychiatric adverse events was fairly consistent when measured using the same endpoint. For example, the percentage of patients receiving efavirenz who had at least one Grade 1-4 neurological adverse event of any type was 58% in DMP-006, 60% in TMC278-C204, and 60% in STARTMRK. By contrast, the percentage of patients with each individual adverse event differed widely if a range of reporting systems was used. For example the percentage of patients with dizziness while taking efavirenz was 31% in the MERIT trial (Grade 1-4 all cause) versus 3.4 to 12% in three other trials where the endpoint of Grade 2-4 drug-related adverse events was used (Tables 3 and 4).

Across the eight randomized comparative trials summarized in table 3, there was an overall trend for more

neuropsychiatric adverse events in the efavirenz arms compared with the comparator arms. This higher incidence was seen for the analysis of all neurological and psychiatric adverse events in the TMC278-C204, STARTMRK, and MERIT trials. Looking at individual adverse events, there were higher percentages of patients with dizziness, abnormal dreams, insomnia, somnolence, and vertigo in the efavirenz arms relative to the comparator arms. There was no consistent difference in the incidence of headache between efavirenz and comparator treatments. In the analysis of the five trials in table 4, there was no consistent difference in the incidence or severity of neuropsychiatric adverse events between nucleoside analogs (results not shown).

There were a significantly higher percentage of patients with Grade 1-4 neurological or psychiatric adverse events in the efavirenz versus comparator arms in the DMP-006, TMC278-C204, and STARTMRK trials (Table 3). Analysis of individual Grade 1-4 adverse events showed a more mixed picture. For example, in the MERIT trial there was a significantly higher percentage of patients with dizziness in the efavirenz arm, but not headache.

Looking at only Grade 2-4 drug-related adverse events, there were generally too few patients with each individual neuropsychiatric adverse event to allow meaningful comparisons of treatment arms. Even so,

Table 3. Percentage of patients with neuropsychiatric adverse events in randomized clinical trials of first-line antiretrovirals versus efavirenz

Trial (duration)	Design	Total (n)	Endpoint used	Percent with adverse events		
				Efavirenz arm	Comparator arm	Reporting cut-off
DMP-006 ¹⁶ (48 weeks)	ZDV/3TC/EFV vs. ZDV/3TC/IDV	450	Grade 1-4 all: nervous	58%*	26%	All events
TMC278-C204 ²⁴ (96 weeks)	2 NRTI/TMC278 vs. 2 NRTI/EFV	279	Grade 1-4 all: nervous Grade 1-4 all: psychiatric	60%* 21%	33% 16%	All events
STARTMRK ²³ (96 weeks)	TDF/FTC/RAL vs. TDF/FTC/EFV	563	Grade 1-4 all: nervous Grade 1-4 all: psychiatric	60%* 37%*	38% 29%	All events
MERIT ²⁰ (48 weeks)	ZDV/3TC/MVC vs. ZDV/3TC/EFV	561	Grade 1-4 all: dizziness Grade 1-4 all: headache	31%* 23%	13% 23%	At least 5% in either arm
TMC278-C204 ²⁴ (96 weeks)	2 NRTI/TMC278 vs. 2 NRTI/EFV	279	Grade 2-4 DR: dizziness Grade 2-4 DR: abnormal dreams Grade 2-4 DR: somnolence Grade 2-4 DR: vertigo	3.4% 3.4% 2.2% 2.2%	1.1% 0.7% 0.4% 0.4%	At least 2% in either arm
BMS-034 ¹⁸ (48 weeks)	ZDV/3TC/ATV vs. ZDV/3TC/EFV	810	Grade 2-4 DR: dizziness Grade 2-4 DR: headache	6%* 6%	2% 6%	At least 1 patient
Abbott M03-613 ²¹ (96 weeks)	ZDV/3TC/LPV/r vs. ZDV/3TC/EFV	159	Grade 2-4 DR: dizziness Grade 2-4 DR: insomnia	12% 12%	<5% <5%	At least 5% in either arm
ACTG 5142 ¹⁹ (112 weeks)	2 NRTI + LPV/r vs. 2 NRTI + EFV	757	Grade 3 or 4 all: headache	2%	4%	At least 2% in either arm
2NN ¹⁷ (48 weeks)	d4T/3TC/NVP vs. d4T/3TC/EFV	1,216	Grade 3 or 4 all: CNS/psychiatric Grade 3 or 4 all: depression Grade 3 or 4 all: insomnia	5.5% 1.5% 1.5%	3.6% 0.3% 0%	At least 2% in either arm More than 1% overall

*p < 0.05 for comparison of efavirenz versus comparator arm.

ZDV: zidovudine; 3TC: lamivudine; EFV: efavirenz; IDV: indinavir; NRTI: nucleoside reverse transcriptase inhibitor; TDF: tenofovir; FTC: emtricitabine; RAL: raltegravir; MVC: maraviroc; ATV: atazanavir; LPV: lopinavir; d4T: stavudine; DR: drug related.

in the BMS-034 trial the percentage of patients with Grade 2-4 drug-related dizziness was significantly higher for patients using efavirenz than the comparator arm (atazanavir). There were no significant differences in Grade 3 or 4 neuropsychiatric adverse events between the treatment arms in the ACTG 5142 or 2NN trials (Table 3).

Quality of life questionnaires for neuropsychiatric adverse events

Several different questionnaires have been used to assess patient quality of life during HIV clinical trials of efavirenz. Some of these are general quality of life questionnaires, which include a component for nervous system or psychiatric issues; others assess only these symptoms.

CES-D and Z-scores (ACTG 5095 trial)

CES-D is a validated, self-reported questionnaire containing 20 items that represent major components of depression: a score < 16 is indicative of depression. This questionnaire was used as part of a battery of tests in a sub-study of the ACTG 5095 trial. This trial compared three first-line combinations in treatment-naïve patients: (i) zidovudine/lamivudine/abacavir, (ii) zidovudine/lamivudine/efavirenz, and (iii) zidovudine/lamivudine/abacavir/efavirenz. The ACTG 5097 sub-study assessed the impact of efavirenz on neuropsychological performance, mood, and sleep behavior among people with HIV in 303 patients³⁴.

The patients were assessed over the initial 24 weeks of antiretroviral therapy, including neuropsychological

Table 4. Percentage of patients with neuropsychiatric adverse events in non-comparative clinical trials of efavirenz

Trial (duration)	Design	Total (n)	Endpoint used	Percent with AE	Reporting cut-off
CNA3002127 (48 weeks)	ABC/3TC/EFV (ABC OD vs. BID)	770	Grade 1-4 all: dizziness Grade 1-4 all: headache Grade 1-4 all: abnormal dreams Grade 1-4 all: depression	22% 17% 16% 12%	At least 10% in either arm
EPV200125 (48 weeks)	ZDV/3TC/EFV (3TC OD vs. BID)	545	Grade 1-4 all: dizziness Grade 1-4 all: abnormal dreams Grade 1-4 all: headache Grade 1-4 all: mood disorder	30.5% 24% 16% 9.5%	At least 10% in either arm
CNA3002426 (48 weeks)	ABC/3TC/EFV vs. ZDV/3TC/EFV	649	Grade 2-4 all: depression: Grade 2-4 all: abnormal dreams	6% 6%	At least 5% in either arm
Gilead 93429 (48 weeks)	TDF/FTC/EFV vs. ZDV/3TC/EFV	511	Grade 2-4 all: dizziness Grade 2-4 all: depression Grade 2-4 all: insomnia Grade 2-4 all: headache	8% 5.5% 4.5% 4.5%	At least 5% in either arm
Gilead 90328 (144 weeks)	TDF/3TC/EFV vs. d4T/3TC/EFV	600	Grade 3/4 all: depression	1.5%	At least 2% in either arm

AE: adverse events; ABC: abacavir; 3TC: lamivudine; EFV: efavirenz; ZDV: zidovudine; TDF: tenofovir; FTC: emtricitabine; OD: once daily; BID: twice daily.

performance (Z-scores of Digit Symbol Substitution and Trailmaking A and B – NPZ-3), Pittsburgh Sleep Quality Index (PSQI), Centre for Epidemiologic Studies – Depression (CES-D), Spielberger State-Trait Anxiety Inventory (STAI), symptom questionnaires designed to incorporate efavirenz-specific adverse events, and efavirenz serum level assays. Patients were tested at baseline and weeks 1, 4, 12, and 24 of therapy.

No significant differences in depressed mood (CES-D) or anxiety (STAI) between patients receiving or not receiving efavirenz were observed at any time. There were no significant differences in changes in neuropsychological testing at any time among any of the patients, regardless of whether their regimen included efavirenz. However, the symptom questionnaire (specifically designed to detect efavirenz-related adverse events) identified a significant increase in neurological symptoms at week 1, but not at any time point thereafter. A similar pattern was seen with the PSQI, with more bad dreams detected at week 1, but no differences between the groups in later weeks.

The medical outcomes study questionnaire (Spanish trial)

The Medical Outcomes Study – HIV Health Survey (MOS-HIV) is sometimes used to measure quality of life, although many of the studies noting CNS adverse events did not actually conduct quality of life studies.

MOS-HIV consists of 35 questions assessing various health aspects over the past four weeks. Each domain is scored, along with a physical health summary score (PHSS) and mental health summary score (MHSS); the higher the score, the better the patient’s quality of life.

In a randomized study, the MOS-HIV questionnaire was used together with a Profile of Mood questionnaire to assess the quality of life for patients given HAART including either efavirenz or a protease inhibitor³³. Patients treated with efavirenz reported a higher incidence of dizziness, abnormal dreams, insomnia, and nervousness compared with the protease inhibitor-treated group. However, the overall quality of life measured by MOS-HIV was significantly higher in the efavirenz arm compared to the protease inhibitor arm, mainly because the patients reported improved simplicity for the efavirenz dosing. This example shows the importance of assessing overall quality of life as well as focusing on adverse events of interest in a trial.

Spanish questionnaire (Stepped-dose study)

In this randomized trial, 114 patients started two nucleoside analogs plus efavirenz, either at the full 600 mg once-daily dose, or they raised their dose from 200 mg once daily in days 1-6, to 400 mg once daily for days 7-13, then full dose from day 14 onwards. Patients completed a questionnaire recording the incidence and severity of neuropsychiatric adverse

events during the first two weeks. Using this methodology, stepped-dose efavirenz was found to lower the incidence of neuropsychiatric adverse events³².

Conclusions

The Division of AIDS 2007 grading scale¹⁵ remains the most common system to assess neuropsychiatric adverse events during HIV clinical trials. This standardized system allows comparison of the prevalence of adverse events between clinical trials. However, many different endpoints have been used from the DAIDS grading system to analyze neuropsychiatric adverse events in clinical trials.

Using an endpoint of all Grade 1-4 clinical neuropsychiatric adverse events, efavirenz has shown a significantly higher prevalence than comparator treatments. Using other endpoints, such as Grade 3 or 4 (severe or life-threatening) adverse events, no significant differences have been seen between efavirenz and other first-line antiretrovirals.

We cannot expect the primary publications of all randomized clinical trials to include a detailed or standardized analysis of neuropsychiatric endpoints. However, given the importance of these symptoms for patient quality of life, it would be helpful to introduce more standardized methods of reporting in the future. In addition, if all trials could be reanalyzed by a common endpoint (for example the percentage of patients with Grade 2-4 drug-related neuropsychiatric adverse events), it may be easier to interpret the safety results across a range of clinical trials. The percentage of patients with any neurological or psychiatric adverse event is a more comprehensive measure of safety. New treatments may show an unexpected profile of neuropsychiatric adverse events, and so analysis of the data using the whole system organ class is more likely to detect these new adverse events.

Discontinuation for adverse events has been used as an endpoint in other studies. However, the implications of discontinuing trials could differ widely between countries, making this endpoint difficult to compare across studies. For example, a patient in a developing country may have few treatment options outside a clinical trial, and may therefore be more willing to tolerate a drug despite moderate or severe neuropsychiatric adverse events. By contrast, a European patient with access to free healthcare outside the trial could be more confident of discontinuing trial medication with few or no long-term implications.

It is very important to check the mental health of patients and baseline, and to check whether there is a

prior psychiatric history and/or use of recreational drugs. This baseline assessment can be used to assess whether adverse events occurring during a trial are preexisting or treatment emergent. In addition, it is important that the patient visit is conducted carefully because the decisions on whether adverse events are new and/or drug-related can be complex and subjective. When analyzing data on neuropsychiatric adverse events from clinical trials, it is important to assess the severity and duration of these events – many can be mild, transient, and preexisting. In future, switch studies could help to assess what proportion of neuropsychiatric adverse events could be resolved by stopping efavirenz and using alternative antiretrovirals.

Analyses of neuropsychiatric adverse events also need to account for the use of antidepressants, sleeping tablets, and other medications which might confound the analysis. In addition, double-blinding of clinical trials can reduce the chance for investigator and patient bias in reporting adverse events.

Many different questionnaires have been used to assess the patient experience of antiretroviral treatment. It is very difficult to compare the results from these questionnaires between clinical trials. A new questionnaire has been developed to assess patient symptoms during antiretroviral treatment. The HIV Patient Symptoms Profile questionnaire is a patient-reported outcome questionnaire developed to capture the tolerability of HIV treatment from the subject's perspective. It is a multi-item questionnaire measuring 14 domains: digestion, mood, sleep, body shape changes, skin, vision, tiredness, attention and memory, pain, body temperature changes, respiratory problems, dizziness/vertigo, sexual or reproductive health, and problems with taking medications. This is a new questionnaire, focused on adverse events of treatment, which is being used for the first time in the SENSE trial of first-line treatment with two nucleoside analogs plus either efavirenz or etravirine in 150 treatment-naïve patients.

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