

Discontinuation of Atripla as first-line therapy in HIV-1 infected individuals

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Background: Central nervous system (CNS) adverse events are common with initiation of efavirenz, but these are often described as transient. We aimed to describe the outcomes of individuals commencing Atripla (Gilead Sciences Inc, Foster City, California; Bristol-Myers Squibb Co, Princeton, New Jersey, USA) as a first-line regimen.

Methods: We performed a retrospective case-based analysis of all individuals within our HIV cohort who had received Atripla as their first antiretroviral combination. In individuals who discontinued Atripla data was collected on evolution of adverse events.

Results: Four hundred and seventy-two individuals commenced Atripla as first-line therapy at 12 months, 383 individuals (81%) remained on Atripla with 98% achieving HIV-1 RNA less than 50 copies/ml (on treatment analysis). CNS toxicity was the commonest reason for switching therapy in 63 (71%) cases. The median duration of first reported CNS toxicity was 27 days (IQR 7–104 days) and the commonest reported symptoms were nightmares or vivid dreams in 28 (44%), insomnia in 27 (43%) and depression in 22 (35%). In those with CNS toxicity, six (10%) switched at 0–4 weeks, four (6%) at 4–12 weeks, 30 (48%) at 12–52 weeks and 23 (36%) changed regimen 52–96 weeks after commencing Atripla. Among those with available documentation 25 of 63 (40%) had reported improvement or resolution of their CNS side effects.

Discussion: One-fifth of all individuals commencing Atripla will need to switch therapy, often for adverse events. The commonest reason for switch in our cohort was CNS toxicity, which although it may develop shortly after initiation may persist, ultimately leading to discontinuation of Atripla months or years later.

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Background

Atripla is a once daily, single pill, fixed dose combination of tenofovir (tenofovir disoproxil fumarate), emtricitabine

(FTC) and efavirenz. Longitudinal cohort data examining the adverse event profile of Atripla in the modern antiretroviral era are lacking. Central nervous system (CNS) adverse events are common with initiation of

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efavirenz, but these are often described as transient [1]. However, the Study of Efavirenz Neuropsychiatric Events Versus Etravirine (SENSE) compared etravirine with efavirenz (each with two nucleoside reverse transcriptase inhibitor) and revealed that after 2 weeks, the prevalence of grade 1–4 neuropsychiatric adverse events in the efavirenz arm was 39.7% and remained high at 48 weeks (21.5% of individuals) [2]. Studies have demonstrated the benefit of switching from efavirenz to an alternative agent in those with ongoing CNS toxicity [3,4]. We aimed to describe the outcomes of individuals commencing Atripla as a first-line regimen.

Methods

We performed a retrospective analysis of all individuals within our HIV patient cohort who had received Atripla as their first antiretroviral combination; those who commenced separate components prior to switch were excluded. A case notes review was performed for each individual to assess demographics and pathology results (CD4, HIV-1 RNA, total cholesterol) at baseline and 12 months after commencing Atripla. In individuals who discontinued Atripla data was collected on nature and duration of adverse events, reason for switching therapy, alternative antiretroviral regimen and, wherein available, evolution of adverse events after regimen change.

Results

Four hundred and seventy-two individuals commenced Atripla as first-line therapy, 442 (94%) were men with a median age of 37 years (IQR 31–43). Ethnicities were documented as follows; white British 199 (42%), white Irish 18 (4%), other white 137 (29%), white and black Caribbean eight (2%), white and black African four (1%), any other mixed background nine (2%), Indian four (1%), any other Asian 13 (3%), Caribbean six (1%), black African 29 (6%), Chinese three (1%) and any other ethnic group 22 (5%); for 20 (4%) ethnicity was not documented. Median CD4 cell count at initiation of Atripla was 285 cells/ μ l (IQR 208–362 cells/ μ l), median HIV-1 RNA 16 000 copies/ml (IQR 708–54 000 copies/ml) and median total cholesterol 4.3 mmol/l (IQR 3.8–5 mmol/l). At month 12, 383 individuals (81%) remained on Atripla with 98% achieving HIV-1 RNA less than 50 copies/ml (on treatment analysis). In these patients the median CD4 cell count increased to 449 cells/ μ l (IQR 327–536 cells/ μ l) and median total cholesterol also increased to 4.8 mmol/l (IQR 4.2–5.5 mmol/l).

Eighty nine (19%) people discontinued Atripla after a median duration of 294 days (IQR 108–495 days). CNS toxicity was the commonest reason for switching therapy

Table 1. Demographics and baseline results of individuals discontinuing Atripla for central nervous system toxicity only (n = 63).

Sex	Male 60 (95%) Female 3 (5%)	
Age	Median 39 years IQR (33–43 years)	
Ethnicity	White British	28 (44%)
	White Irish	3 (5%)
	Other white	17 (27%)
	White and black Caribbean	2 (3%)
	Any other mixed background	3 (5%)
	Indian	1 (2%)
	Any other Asian	1 (2%)
	Black African	3 (5%)
	Any other ethnic group	3 (5%)
	Not collected	2 (3%)
CD4 (IQR)	278 cells/ μ l (207–336 cells/ μ l)	
HIV-1 RNA (IQR)	30 000 copies/ml (4000–90 000 copies/ml)	

in 63 (71%) cases, other causes included hepatotoxicity in seven (8%), rash in six (7%), virological failure and/or resistance in six (7%), pregnancy in three (3%), nontoxicity switch research trial two (2%), lifestyle (drug and alcohol) in two (2%), gastrointestinal toxicity in one (1%) and drug–drug interaction in one (1%). Demographics of those with reported CNS toxicity and reported findings are shown in Table 1.

Table 2 describes the characteristics and development of CNS toxicities in those discontinuing Atripla and the antiretroviral regimen patients were switched to.

Among those with available documentation, 25 of 63 (40%) had reported improvement or resolution of their CNS side effects.

Discussion

Atripla is an efficacious first-line antiretroviral therapy, but approximately one in five of all individuals commencing Atripla will need to switch therapy, often for adverse events. The commonest reason for switch in our cohort was CNS toxicity and our data, consistent with the SENSE study [2], demonstrate a high proportion of individuals develop CNS adverse events within a month but these are persistent for many. Consequently, discontinuation of Atripla may occur months or years later. Six individuals (10%) with CNS toxicity had a prior documented history of depression with two of these (3%) on antidepressant medication. Higher rates of CNS toxicity have been reported in those with African ancestry due to polymorphisms of cytochrome P450 2B6 (CYP2B6) [5,6], however, our data showed no increased prevalence of CNS toxicity in this ethnic group and no association with nadir CD4 cell count. It is noteworthy that three individuals discontinued antiretroviral therapy without consultation due to CNS side

Table 2. Evolution and nature of central nervous system adverse events ($n = 63$).

Duration of Atripla before first CNS AE reported (IQR; data available for $n = 53$)	27 days (IQR 7–104 days)	
Reported CNS adverse events and frequency (some individuals reported multiple events; $n = 63$)	Nightmares/vivid dreams 28 (44%)	
	Insomnia 27 (43%)	
	Depression 22 (35%)	
	Dizziness 12 (19%)	
	Fatigue 9 (14%)	
	Anxiety 8 (13%)	
	Nausea 6 (10%)	
	Headache 6 (10%)	
	Poor concentration 6 (10%)	
	Suicidal thoughts 5 (10%)	
	Hot flushes 4 (6%)	
	Mania 3 (5%)	
	Painful paraesthesia 3 (5%)	
	Other CNS adverse event 3 (5%)	
	Paranoia 2 (3%)	
Time to switch in those with CNS toxicity (weeks) [$n=63$]	0–4	6 (10%)
	>4–12	4 (6%)
	>12–52	30 (48%)
	>52–96	
Switch regimen ($n = 63$)	TDF/FTC etravirine 39 (62%)	
	TDF/FTC atazanavir/r 15 (24%)	
	TDF/FTC darunavir/r 6 (10%)	
	TDF/FTC lopinavir/r 1 (2%)	
	TDF/FTC raltegravir 1 (2%)	
	TDF/3TC nevirapine 1 (2%)	

3TC, lamivudine; AE, adverse event; CNS, central nervous system; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

effects, one of these presented with *Pneumocystis carinii* pneumonia and one with detectable resistance mutations. Another three individuals took deliberate overdoses in suicide attempts that they directly attributed to their CNS toxicity (one of these was on treatment for hepatitis C). With the advent of new combination tablets and treatment strategies, physicians should elucidate whether individuals have continuing CNS toxicity on Atripla as this group may benefit from alternative agents.

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Conflicts of interest

There are no conflicts of interest.

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