

Efavirenz therapy in drug users

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Introduction

Adherence to antiretroviral therapy is known to influence the efficacy of therapy, those patients with greatest adherence achieving greatest suppression of viral replication [1,2]. To realistically achieve optimal adherence, the ideal patient would be emotionally mature, motivated, educated, literate, financially secure, able to afford comfortable housing, excellent at time management, a team player, and would have absolute trust and faith in the medical staff. Many injection drug users (IDUs) do not fulfil most of these criteria. In an internal audit of IDUs attending the Department of Genitourinary Medicine in St James's Hospital, 30% of the drug-using cohort were homeless, 86% were unemployed and 10% illiterate. The management of HIV infection in these patients is therefore both complex and challenging.

Treatment choices for IDUs

The BHIVA treatment guidelines and those of the US panel of the International AIDS society are based on the results of randomized clinical trials [3,4]. However, it is questionable whether those results apply in the management of HIV infection in drug users. First, such large cohort studies rarely include a significant proportion of drug users. Secondly, those participants with injection drug use as their primary risk factor for the acquisition of HIV by inclusion criteria have, inevitably, been stable in respect to this for a number of years. As a result, physicians are often reluctant to prescribe highly active antiretroviral therapy (HAART) to drug users [5], with drug users twice as likely to be without antiretroviral treatment compared with other risk groups. This probability increases further if a drug user is not attending a drug treatment unit [6]. Prescribers are therefore often left to fall back on their own experience when selecting treatment options for these patients. This includes both simple, once- or twice-daily regimens to optimize adherence and, as previously described, a programme of directly administered antiretroviral therapy (DAART) [7], in which antiretroviral therapy is provided daily in conjunction with methadone maintenance therapy.

Role of efavirenz

Efavirenz (EFV) is prescribed as a once-daily preparation, taken either in the morning or at night-time to reduce neurological side effects. With convenient once-daily dosing and a low pill burden of three pills daily, EFV is a useful component of antiretroviral therapy for many patients (Fig. 1) [8]. Its efficacy in IDUs has been seen in a cohort of patients attending our unit ($n = 46$), receiving EFV as part of combination antiretroviral therapy. Two-thirds of this cohort is antiretroviral-experienced, and one-third is naïve to treatment. The mean baseline CD4 count for the cohort was 190 cells/ μ L, and the mean baseline viral load was 5.23 logs. By an intent-to-treat analysis, 44% of this group were below the level of detection (< 50 HIV-1 RNA copies/mL Roche ultrasensitive assay) after 48 weeks of therapy. Early neurological symptoms were identified in 15 patients, including dizziness and altered sleeping habits. The symptoms occurred in the first 1–5 days of treatment, and resolved spontaneously in all patients within 5–7 days. Since all patients were on methadone, we hypothesize that this drug may have helped to reduce the severity of the central nervous system effects.

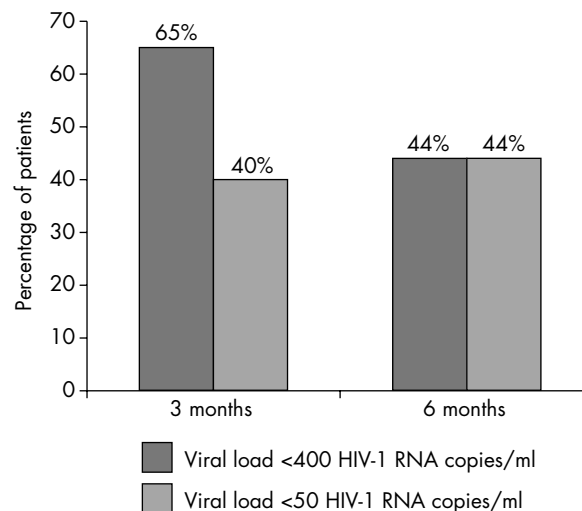


Fig. 1 Efavirenz efficacy, as shown by the percentage of patients with a viral load below the limit of detection (< 400 and < 50 copies/ml) at 3 and 6 months.

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Problems with the use of methadone

Forty of 46 patients complained of symptoms consistent with methadone withdrawal from days 7–10 onwards. The concern about these symptoms is that, first, patients may return to using illicit drugs to counteract their withdrawal symptoms and, secondly, they may discontinue their antiretrovirals once a direct relationship is appreciated between the new medications and withdrawal symptoms. The effectiveness of methadone maintenance therapy for opiate addiction has been well established, and one study has shown that patients given this treatment are able to function well during therapy, and may even become productive members of their communities [9]. Its complex metabolic pathway, however, creates many potential problems when other medications are concurrently prescribed.

Pharmacology of methadone

Methadone exists in two stereo isomeric forms [10]. *In vitro* binding experiments have shown that the necessary concentration of (R)-MET [or l(-)-methadone] to inhibit by 50% the binding of (H)-naloxone to rat brain homogenate is 10 times less than that of (S)-MET or d-(+)-methadone. In humans (R)-MET is about 50 times as potent an analgesic as the (S) form [11], so that 7.5 mg oral R-MET and 15 mg (R,S)-MET induce intense and sustained respiratory depression and meiosis [10,11].

Methadone [6-(dimethylamino)-4,4-diphenyl-3-heptanone] is mainly *N*-demethylated *in vitro* by cytochrome P450, specifically isoenzymes 2C8, 2C18 and 2D6 [12]. The urinary ratio of methadone to its pyrrolidine metabolite is between 1/1 and 1/5, demonstrating an extensive metabolism [13]. The metabolites are free from pharmacological effect. However, previous studies and case reports have demonstrated that drugs which are inhibitors or inducers of CYP450 may alter the metabolism of methadone, producing symptoms of narcotic overdose (inhibition) or precipitating symptoms of methadone withdrawal (induction) when given to patients receiving stable methadone maintenance therapy [14–20].

Interactions between methadone and antiretrovirals

Injection drug users have an increased risk of acquiring tuberculosis and the association between rifampicin and reduced effectiveness of methadone has been well described [17–20]. In a cohort of 30 patients receiving methadone and rifampicin, 70% required an increase in their methadone dose, with the onset of withdrawal

symptoms ranging from 1 to 33 days after the initiation of therapy [18]. There have been other similar reports of this interaction, and the requirement for additional methadone in such patients.

Methadone and EFV interactions

Study of patients and methods

To quantify the extent of methadone metabolism induced by EFV, a study was set up to enrol patients who fulfilled standard criteria to commence antiretroviral therapy on a methadone maintenance therapy. Fourteen patients on a methadone dose of 35–100 mg daily were recruited into the study, and commenced antiretroviral therapy with dual nucleoside analogues and EFV. As well as EFV, five patients received combination zidovudine and lamivudine, five received stavudine and didanosine, and four received stavudine and lamivudine. The patients were reviewed daily in a methadone maintenance clinic, any symptoms or signs of methadone withdrawal were documented, and a daily diary of neurological or withdrawal symptoms was requested from each subject. Methadone pharmacokinetics before and 2–3 weeks after initiating EFV at 600 mg daily were determined. Blood samples were obtained 0, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h post-dose. Following centrifugation, separated plasma was inactivated and stored at –80 °C until analysis.

Results to date

During the initial period of EFV therapy, we found a significant induction of hepatic enzymes, with symptoms of methadone withdrawal occurring from days 7 to 10 [21]. However, the mean increase in methadone dose required was not as great as might have been expected from the pharmacokinetic data. We also found a significant correlation between baseline area under the curve for 0–24 h (AUC_{0-24h}) for methadone (i.e. before EFV) and the percentage reduction in AUC_{0-24h} for methadone after 2–3 weeks of EFV treatment [21]. The mean reduction in AUC_{0-24h} for methadone, when given with 600 mg EFV, was 60% when assessed in 11 patients. These findings are consistent with the fact that methadone is a low-clearance drug. Thus initially high levels indicate a low degree of clearance and drug effects will be greater at this time than for other drugs [22,23]. Half of the patients complained of early neurological symptoms during the study period. These symptoms occurred from days 1 to 5 and resolved spontaneously in all patients. It seems, therefore, that such symptoms may be confused with those of methadone withdrawal, and patients should be counselled in this regard before commencing therapy [21].

Conclusions

EFV has proved its efficacy in large, randomized cohort studies, and this appears to translate into good patient outcome in minority groups in clinical practice. When EFV is used as part of combination antiretroviral therapy for IDUs, early neurological symptoms must not be confused with symptoms of methadone withdrawal, which symptoms will not occur until days 7–10 of therapy.

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