REVIEW ARTICLE

Antiretroviral therapy for drug users

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Summary: Injection drug use represents the primary risk factor for up to 40% of patients with HIV infection. Physicians are generally reluctant to prescribe antiretroviral therapy (ART) for these patients due to possible poor adherence, and the potential for complex drug interactions to occur. Providing daily observed ART in conjunction with methadone maintenance therapy (MMT) has significantly improved accessibility of ART for many drug users. Knowledge of potential drug interactions between methadone, ART, and both legally and illegally prescribed drugs has permitted such interactions to be anticipated and either avoided or treated appropriately. Optimizing ART for drug users therefore demands a multidisciplinary approach from medical, clinical pharmacology and psychiatric services.

Keywords: HIV, drug users, HAART, methadone

INTRODUCTION

Injection drug use is the most common risk factor for the acquisition of HIV infection in Ireland, with drug users representing 42% of the total HIV-positive cohort[1]. In the USA, injection drug use represents the primary risk factor for 22% of patients infected with HIV[2].

For many active drug users, periods of daily heroin use are punctuated by cycles of detoxification drug treatment, and incarceration for drug-related offences. Dependent heroin abusers are at an increased risk of premature death from drug overdose, violence, disseminated infections, sub-acute bacterial endocarditis, and infectious diseases, none more so than HIV infection[3]. Highly active antiretroviral therapy (HAART) is now the standard of care for all patients with HIV infection, however physicians may be less likely to provide such treatment to drug users because of the belief that they are less adherent to complex regimens[4]. What has become increasingly clear is that adherence is essential to therapeutic effectiveness, and that a multidisciplinary effort is needed to meet the adherence challenge[5]. A study conducted at the AIDS Clinic in the San Francisco General Hospital showed a highly significant association between self report of missed doses and detectable viraemia[6]. Drug use, both former and current, are associated with higher levels of non-adherence[7]. The adverse effect that drug use may have on daily life patterns probably accounts more for this association. Recent studies showed that compared with other risk groups, drug users were twice as likely not to be on HAART, and this increases to 3 times if they are not enrolled in a drug treatment unit[8]. Only 80% of drug users eligible for ART were receiving it, and only 37% of this group were 80% adherent with therapy[8].

Furthermore, clinical trials tend to under-repre-sent minority groups such as injection drug users (IDUs), and may exclude those with chronic hepatitis B or C infection. There are therefore little data available on the long-term efficacy and tolerability of HAART for these patients. A further cause for concern for IDUs receiving HAART is the potential for complex drug interactions to occur. There are known significant interactions between antiretrovirals and methadone[9], recreational drugs[10], antipsychotics[11], and other medications[12]. Such interactions must be clarified and their significance anticipated.

This paper reviews the active management of HIV infection in drug users, including linking HAART with MMT, suitable antiretroviral options and combinations, potential interactions between legally or illegally obtained drugs, potential interactions between methadone and antiretrovirals, and the role of co-infection with hepatitis C infection in these patients.

METHADONE MAINTENANCE THERAPY

Several studies have shown the efficacy of directly observed anti-tuberculosis therapy[13], and the application of this method to ART is an attractive option for IDUs. Most current or ex-IDUs attend methadone maintenance clinics on a daily basis. Methadone, a synthetic opioid was first reported as

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a treatment for opioid dependence by Dole and Nyswander in 1965[14]. The original model of high doses of methadone, long duration of treatment, and intensive rehabilitation services is still the most widely-used treatment for opioid dependence. Given in high doses, it reduces the craving for heroin/ and blocks the euphoric effects of injected heroin, thereby freeing the patient from the daily cycle of seeking out, buying, and using heroin. The exact daily dose of methadone is very variable, however a recent study shows that while both a moderate or high dose of methadone were effective in maintaining patients in treatment and substantially reducing rates of illicit opiate use, the high-dose group fared significantly better in all parameters[15].

DIRECTLY ADMINISTERED ANTIRETROVIRAL THERAPY (DAART)

Once IDUs are stabilized from their opioid dependence, and attending a drug treatment clinic regularly, this is an ideal opportunity to introduce ART. We have found that IDUs are generally the first to acknowledge the erratic nature of their lifestyles, and are more than willing to participate in any programme that will minimize the impact on their lives of starting therapy. Adherence is the major determinant of the success of drug treatment—adherence of the physician in prescribing the optimum appropriate regimen and monitoring it, and compliance of the patient in taking the medication as prescribed. One way to ensure patient compliance is 'directly observed therapy' (DOT), where the ingestion of every drug dose is witnessed. The World Health Organization (WHO) DOTS strategy advocates the use of DOT with a short-course drug regimen for the treatment of tuberculosis[16]. Cohort studies with historical controls receiving self administered therapy have shown improved cure rates from DOT in a number of centres[13,17]. In the UK DOT is recommended for patients who are unlikely to comply e.g. homeless, alcoholic or drug abusers, patients with multiple drug resistances, or those with a history of non-compliance with anti-tuberculous therapy[18], while in the USA, the Centers for Disease Control (CDC) recommends that DOT be considered for all patients[19]. Given the short- and long-term similarities between HIV and tuberculosis infection, with the association between inadequate compliance and the development of resistant strains, patients who are unlikely to adhere to ART should also be considered for DOT in the form of DAART. Such a programme of DAART linking MMT with HAART in the authors' clinic has proved very successful in enrolling patients, with 37 patients commencing therapy since September 1998. However, results show that after an initial period of success, with 70% below the level of detection at 6 months, many IDUs default from both drug treatment and HIV clinics, with 55% BLD (below the limit of detection: < 50 cpm Roche Ultrasensitive Assay) at one year, and only 25 of the original 37 patients still attending[20]. These figures are consistent with one year success rates of 53-62% from methadone clinics for opioid detoxification[21]. An improved liaison system between both HIV and drug treatment services, involving multidisciplinary specialized clinics, specially trained nursing staff, and additional paramedical training for carers in the units may help to improve this outcome.

HAART OPTIONS FOR IDUs

The current International AIDS Society 2000 Guidelines for the treatment of HIV infection recommend dual nucleoside reverse transcriptase inhibitors (NRTIs) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI)[22]. If possible, ART should be prescribed to drug users in the form of once-daily therapy. This permits optimal adherence whether a patient is self-medicating or participating in a programme of DAART. At least 2 of the NRTIs (didanosine [ddI], lamivudine [3TC]) can be given once daily. ddI is licensed for use in HIV-infected patients in a twice-daily regimen. However the long intracellular half-life of dideoxyadenosinetriphosphate (ddATP) (8-40 h in cell culture studies[23]), has been the basis of more formal studies showing that once-daily dosing of ddI leads to a similar exposure in plasma as twice-daily dosing[24]. The serum elimination half-life of lamivudine is approximately 2.5 h, and the *in vitro* intracellular half-life of its active 5-triphosphate anabolite is 11-14 h[25]. Therefore a once-daily dosing of 3TC is pharmacologically adequate. The other NRTIs require twice-daily dosing. The currently available PIs require either twice or three times daily dosing. The prolonged half-lives of nevirapine (NVP) and efavirenz (EFV) (25 and 45 h respectively) permit once-daily dosing[26,27].

Other drugs in early development e.g. MK944A, tenofovir, have long half-lives, which should permit once-daily dosing. A new PI, BMS232632, is currently in phase III trials and should acquire a license for once-daily dosing. The combination antiretroviral pill that includes zidovudine (AZT), 3TC, and abacavir (ABC) is also in phase III trials, and will allow a convenient one pill twice-daily dosing. Initial studies have shown comparable 48-week results for this combination to a dual nucleoside with indinavir regimen[28].

HAART AND PSYCHIATRIC MEDICATIONS

If psychiatric illness and drug addiction are uncontrolled, medication adherence may be compromised. Studies suggest a rate as high as 50% co-morbidity in HIV-positive patients in inner city clinics[29]. Co-morbid substance use is the most powerful predictor of psychiatric illness. Psycho-tropic medications, including anti-depressants, neuroleptics, and anti-convulsants are often pre-scribed for patients to manage drug or disease-related adverse events, for mood stabilizing effects, for concurrent psychiatric conditions. Such medications often have narrow therapeutic indices, and may be susceptible to interactions involving the cytochrome P450 enzyme system. Ritonavir (RTV) inhibits numerous CYP450 enzymes (3A4, 2D6, 2C9, 2C19, 2A6, 1A2, 2E1), and has the Greatest potential for significant interactions with psychotropic medications[30]. Such medications that are contraindicated with RTV include bupropion, clozapine, and pimozide[11]. RTV also has the potential to significantly increase serum concentrations of the tricyclic anti-depressants (TCADs), selective serotonin reuptake inhibitors (SSRIs), and the phenothiazines. It is recommended that the dose of such drugs is reduced by 50% with close monitoring of toxicity if they are co-prescribed[11]. Saquinavir (SQV), nelfinavir (NFV), indinavir and the NNRTIs are primarily CYP 3A4 inducers, and while their effect on psychotropic medications is less significant, they may still alter therapeutic levels.

Anti-convulsants are mainly CYP 3A4 inducers, and drugs such as carbamazepine, phenytoin, and phenobarbitone, should be avoided where possible[31], as they may lead to sub-therapeutic levels of antiretrovirals. Detailed tables outlining potential interactions are available and should be consulted prior to co-prescribing antiretrovirals and psycho-tropics[11,32].

HAART AND METHADONE: NNRTIs

Efavirenz and NVP are very useful drugs for the treatment of IDUs due to convenient once-daily dosing. Both drugs are potent inducers of the CYP 450 enzyme system, which is the primary pathway through which methadone is metabolized[26,27]. A significant interaction between these medications, with a mean reduction in AUCo-24h methadone of 60% has been demonstrated. During the initial period of treatment, there appears to be a process of 'induction-detoxification' whereby the increased dose of methadone required is not as great as might be expected from the PK data.

The mean dose required was 21.65%, with a mean time for symptoms of withdrawals of 7-10 days[9].

HAART AND METHADONE: PIs

The potential for an interaction between the PIs and methadone is less clear, with some conflicting reports. PIs in general inhibit CYP3A4, RTV most potently, IDV, NFV, SQV less intensely[12]. Initial studies suggested that RTV may retard methadone metabolism[33], however a further study, flawed due to the inclusion of patients not dependent on methadone, with patients receiving only 5-10 mg daily, did not show similar results[34]. There have been reports of both NFV-induced methadone withdrawal[35], and NFV-induced reduction in $AUC_{0\text{-}24h}$ methadone, but without inducing symptoms of methadone withdrawal[36]. Further studies are clearly needed to further define this interaction.

HAART AND METHADONE: NRTIs

There have been few studies looking at the interaction between methadone and the NRTIs. Methadone has been demonstrated to increase the AUC for AZT by approximately 40%[37]. To date there are no studies demonstrating an increased incidence of AZT-related toxicities in such patients i.e. myelosuppression, fatigue, myalgia. Another study has shown a mean reduction in the AUC for ddI of 60% when methadone was co-prescribed[38]. The aetiology of such an affect was hypothesized as altered gastrointestinal absorption. However, this study measured serum ddI levels and not the active triphosphate metabolite. More studies are needed to clearly define whether the dose of ddI needs to be increased in such patients receiving methadone and ddI.

OTHER DRUGS AND METHADONE

For patients on MMT receiving concurrent fluco-nazole, an inhibitor of CYP 450, a mean increase in the systemic methadone exposure of 34.8% has been demonstrated, however no signs or symptoms of methadone overdose were demonstrated during the study, and no patients complained of methadone withdrawal during the post-study period[39]. IDUs are at an increased risk of acquiring tuberculosis and the association between rifampi-cin and reduced effectiveness of methadone has been well described[40]. In a cohort of 30 patients receiving methadone and rifampicin 70% of patients required an increase in their methadone dose, with the onset of withdrawal symptoms from 1-33 days after the initiation of therapy[40]. There have been other similar reports of this interaction, and the requirement for additional methadone in such patients[41,42].

RECREATIONAL DRUGS

There are a wide range of recreational drugs used by drug users, including inhaled, injected, and orally taken substances. While there is a large database on the interactions between antiretrovirals and legally prescribed medications[12], there are little published data on interactions between antiretrovirals and illicit substances. Amphetamines are generally metabolized to active metabo-lites through the CYP 2D6 isoform of the CYP 450 system. There have been reports of a prolonged effect from a small dose of methylenedioxymetam-phetamine (MDMA or ecstasy), and a nearly fatal reaction to a small dose of *y*-Hydrobutyrate (GHB) in a patient receiving RTV and SQV[10]. This interaction is probably CYP 450 mediated, with RTV delaying the metabolism of both of these substances, prolonging their effect.

The benzodiazepines are primarily metabolized by CYP 3A4 and CYP 2C19. There is therefore a potential significant interaction with the PIs enhancing their effects via inihibition of these enzymes, and the NNRTIs reducing their effect via enzyme induction.

Cocaine is metabolized by hydrolysis by plasma cholinesterase and there is no interaction with antiretrovirals. Morphine, hydromorphine, and heroin are metabolized by glucuronidation, and there is a potential for induction of this process by PIs. Dextropropoxyphene and meperidine are metabolized by CYP450, and there is significant production of toxic metabolites if these are co-administered with PIs.

HEPATITIS C CO-INFECTION

The incidence of hepatitis C co-infection in IDUs is 80-90%[43]. Recent papers have demonstrated hepa-totoxicity associated with ART, especially RTV[44]. While this has been shown to be more common in patients with chronic hepatitis, the evidence to date does not support withholding PI therapy from persons co-infected with hepatitis B or C viruses. There have been no similar published data regarding the NNRTIs.

There have been numerous conflicting reports of both reduced and increased hepatitis C viral load during HAART therapy[45-48], and also of re-activation of hepatitis C infection during HAART therapy[49].

In conjunction with the improved outlook for HIV and hepatitis C co-infected patients, some of the emphasis of their management involves the active management of their hepatitis C infection. The long-term therapy of choice appears to involve combination therapy with ribavirin and interfer-on[50,51]. As ribavirin and the nucleoside analogues undergo intracellular activation to the active moiety, i.e. triphosphate, the potential for a drug interaction arises. Results published by our group have demonstrated the ability of ribavirin to influence the intracellular phosphorylation of the nucleosides AZT and ddI *in vitro*[52,53].

It is essential that the potential intracellular phosphorylation interaction involving ribavirin and the nucleoside analogues be determined prior to the introduction of hepatitis C therapy in the clinical setting, as this may have implications on the efficacy and the toxicity of these agents. If the *in vitro* inhibitory effect of ribavirin is significant, this could lead to a reduction in nucleoside analogue intracellular triphosphate resulting in reduced efficacy. This could be coupled with increased monophosphate drug levels, enhancing toxicity.

CONCLUSION

While combination ART has proven to be effective in slowing disease progression, the long-term benefits of these therapies can only be sustained if resistance strains of HIV do not emerge. Adherence to HAART is a critical component of such a successful outcome. IDUs are less likely to receive HAART than other risk groups and are less adherent with complex drug regimens. Strategies to improve this situation include novel ways of prescribing medications (i.e. DAART), choosing simple once- or twice-daily regimens, and anticipating, monitoring, and treating potential drug interactions.

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