Commentary
Continuing HIV therapy in the ICU
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Abstract
The widespread introduction of highly active antiretroviral therapy (HAART) in 1996 has revolutionised the prognosis of HIV disease [1–3]. The incidence of death from AIDS has fallen markedly and many opportunistic infections have become relatively rare. Consequently, the pattern of referrals to the intensive care unit (ICU) has altered. It is important to appreciate, however, that in spite of advances in treatment, 30% of new HIV diagnoses are made when patients are already severely immunocompromised; the patient may be presenting with AIDS for the first time [4]. A dilemma arises when a patient on HAART is admitted to the ICU. Unless the admission is directly related to HAART, there is little consensus on what to do in terms of continuing treatment.

HAART enables the immune system to function relatively normally and has demonstrable benefit in at least two areas impinging on ICU. Viral load is suppressed in patients on haemodialysis, and morbidity and mortality is considerably reduced [5]. Similarly the incidence of both community- and hospital-acquired pneumonia is reduced in patients on HAART [6]. There are little data showing how HAART patients respond to treatment of non-HIV related conditions. However, the impact on immunity, the reduction in morbidity from dialysis, and the reduction in pneumonia are all circumstantial evidence that patients on HAART are more resilient and therefore potentially more responsive, at least to infective problems.

The second group of patients with HIV may have developed resistance to some or all of their antiretroviral therapy. These patients continue to have poorly controlled viral replication, and are at risk of opportunistic infection as their immune suppression continues.

The third group of patients with HIV may have an acute illness that is immunosuppressive in nature. If HAART is discontinued on admission to ICU, the risk of further opportunistic infections for these patients will increase dramatically [7].

The fourth and final group may be presenting with complications directly related to their antiretroviral therapy, such as lactic acidosis and pancreatitis [8,9]. Nucleoside analogues such as zidovudine or stavudine have been associated with the development of mitochondrial dysfunction [10,11]. The drugs can inhibit mitochondrial DNA polymerase gamma, causing abnormalities in the respiratory chain and life-threatening lactic acidosis. Pancreatitis may be

HAART = highly active antiretroviral therapy; ICU = intensive care unit.
part of this syndrome but is also related to the use of specific antiretroviral drugs, such as didanosine. Some protease inhibitors may cause large increases in cholesterol, triglycerides, and glucose, which can lead to severe acute metabolic complications.

Non-nucleosides, such as Nevaripine, have been associated with hepatic failure. Other, more rare, syndromes, such as uncontrolled fits in neonates and severe hypotension, have been reported with other HIV drugs. Liver toxicity is a major concern with HAART, in its own right and in combination with certain other agents used in ICU, especially in patients with chronic viral hepatitis.

**Resistance, absorption, and interactions**

The critically ill patient on antiretroviral drugs is a challenge. Much of what is done is based on physician experience rather than data from controlled studies. Clearly, if the presenting condition is related to the HIV therapy, the drugs must be stopped. It is often difficult to substitute with alternative regimes because of overlapping toxicities, previous drug resistance, or difficulties in administrating the drug. When patients are nil by mouth abruptly stopping antiretroviral therapy may cause a sudden fall in CD4+ cell count and a rise in viral load. Some patients may even develop an acute seco-convulsison illness. Interestingly, however, stopping and starting HAART is a strategy used for trying to enhance immune responses to HIV in asymptomatic patients [12].

Discontinuing some drugs, such as the non-nucleosides, may even lead to drug resistance. Once they are stopped, some drugs exist in the plasma and cells for several days at sub-therapeutic levels because their half-lives are 3–5 days. Once the drugs are discontinued, the virus replicates and re-emerges in the plasma. This may enable the virus to develop resistance to the drug.

Resistance may also occur because of poor drug absorption. If plasma and cellular levels of some of the compounds are not adequate then resistance can occur after relatively few doses of the non-nucleosides or lamivudine.

Unfortunately, most antiretroviral drugs can only be given in patients with a normally functioning gut and who can be fed orally or through a nasogastric tube. Zidovudine is the only drug that can be given intravenously. There are few data on the absorption and pharmacokinetics of any of the antiretrovirals when given through a gastric or jejunal feeding tube. Drug levels can be measured for protease inhibitors [13] and non-nucleosides but plasma levels are not reliable for nucleosides, which are activated by intracellular phosphorylation.

Drug interactions are important, especially when enzymes inducers, such as phenytoin and rifampicin, are used. There are still relatively few data on the interactions between many of the drugs used in the ICU and those used in HIV therapy. The protease inhibitors and the non-nucleosides can act as cytochrome P450 3A4 inhibitors, and affect the metabolism of many of the drugs used in ICU, such as midazolam or opiates.

In practical terms it makes sense to continue HIV treatment where possible. The consequences of stopping treatment may be serious, and research is needed on drug absorption and stopping-and-starting therapy in the ICU, as well as drug interactions. The effect of HAART on ICU outcomes, either directly or indirectly through its effect on viral load and CD4+ cells, needs to be explored.

**Competing interests**

None declared.

**References**

1. Mcrobart A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, Chiesi A, Phillips AN, Kirk O, Lundgren JD: AIDS across Europe, 1994–98: the EuroSIDA study. Lancet 2000, 356:291–296.
2. Mcrobart A, Vella S, Benfield TL, Chiesi A, Miller V, Gargaliansos P, d’Ambrimo Montforte A, Yust J, Bruun JN, Phillips AN, Lundgren JD: Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998, 352: 1725–1730.
3. Miller V, Staszewski S, Naizius G, Cozzi Lepri A, Sabin CA, Phillips AN: Risk of new AIDS diseases in people on triple therapy. Lancet 1999, 353:463.
4. Gupta SB, Gilbert RL, Brady AR, Livingstone SJ, Evans BG: CD4 cell counts in adults with newly diagnosed HIV infection: results of surveillance in England and Wales, 1990–1998. CD4 Surveillance Scheme Advisory Group. AIDS 2000, 14:853–861.
5. Ahuja TS, Borucki M, Grady J: Highly active antiretroviral therapy improves survival of HIV-infected hemodialysis patients. Am J Kidney Dis 2000, 36:574-580.
6. de Gaetano Donati K, Bertagnolio S, Tumbarello M, Tacconelli E, Cataldo M, Longo B, Casini R: Effect of highly active antiretroviral therapy on the incidence of bacterial pneumonia in HIV-infected subjects. Int J Antimicrob Agents 2000, 16:357-360.
7. Deeks S, Barbour J, Grant R, Martin J: Incidence and predictors of clinical progression among HIV-infected patients experiencing virologic failure of protease inhibitor-based regimens. VIII Conference on Retroviruses and opportunistic Infections. Chicago, IL: February 2001 [abstract 428].
8. Chatta G, Anell AI, Cummings C, Tierney LM Jr: Lactic acidosis complicating the acquired immunodeficiency syndrome. Ann Intern Med 1993, 118:37–39.
9. Lonergan JT, Behling C, Fanger H, Hassanein TI, Mathews WC: Hyperlactatemia and hepatic abnormalities in 10 immunodeficiency virus infected patients receiving nucleoside analogue combination regimens. Clin Infect Dis 2000, 31:162–166.
10. John M, Moore CB, James IR, Nolan D, Upton RP, McKinnon EJ, Mallal SA: Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. AIDS 2001, 15:717-23.
11. Kakuda TN: Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. Clin Ther 2000, 22:685-708.
12. Fagard C, Lebraz M, Gunthard H, Tortajada C, Garcia F, Battegay M, Furrer H J, Vernazza P, a Bencs K, Chiesi A, Phillips AN, Lundgren JD: AIDS across Europe, 1994–98: the EuroSIDA study. Lancet 2000, 356:291–296.
13. Burger DM, Hugen PW, Droste J, Huisman DR, for the ATHENA study group: A randomised controlled clinical trial to evaluate whether therapeutic drug monitoring (TDM) contributes to reduced HIV related mortality. 1st International Workshop on Clinical Pharmacology. Nordwijk, The Netherlands, 30–31 March 2000 [abstract 6.6].