

To initiate or not to initiate antiretroviral therapy in the critically ill?

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Introduction

The use of highly active antiretroviral therapy (HAART) in people infected with the human immunodeficiency virus (HIV) has resulted in a significant increase in life expectancy since the roll-out programmes were initiated in 1996.¹ Increased life expectancy has resulted in increasing optimism and the aggressive management of these patients. Thus, admissions to the intensive care unit (ICU) are increasing, with better outcomes than those achieved in the pre-antiretroviral therapy (ART) era.² Although, the reasons for critical illness have shifted from acquired immune deficiency syndrome (AIDS)-related opportunistic infections to chronic non-AIDS co-morbidities, opportunistic infections still contribute significantly to the HIV-related ICU morbidity burden in developing countries.³

Despite worldwide progress in improving accessibility to HAART, only half of patients eligible for immediate ART are receiving it, according to the World Health Organization (WHO) criteria.⁴ This might be owing to poor healthcare access, stigmatisation and low voluntary testing rates. As a result, HIV status is unknown in up to 40% of cases at ICU admission.² Thus, intensivists have to diagnose and make decisions regarding ART initiation in the critically ill.

The lack of good-quality evidence from prospective randomised controlled trials means that there is no immediate answer to the question on the benefit and safety of ART initiation in critically patients. Guidance is obtained mainly from expert opinion and retrospective studies which are not specific to critical illness. In support of initiation, three retrospective studies are widely cited.⁵⁻⁷ Improved ICU survival in patients on ART was demonstrated following a chart review of patients at San Francisco general hospital from 1996-1999. In this study, 25% of the patients had been initiated on ART prior to ICU admission. Non-AIDS ICU diagnoses were made for 63%, which makes it difficult to generalise the findings to patients with opportunistic infections whose ART was initiated in the ICU. In the second study on a retrospective cohort of HIV-infected patients admitted to the ICU with *Pneumocystis carinii* pneumonia, significantly reduced mortality was found in those on HAART started before or during hospitalisation. In a third study from Mexico, a retrospective chart review of ICU patients, there was increased ICU survival in those on HAART, although also not specific to those in whom HAART was initiated in the ICU.

Likewise, no survival benefit with ART initiation in ICU has been shown in some studies. These were retrospective chart reviews^{8,9} not specific to those in which ART was initiated during the ICU stay. In another study, the benefits of HAART initiation in the ICU were found to be long term on slowing progression to AIDS, rather than in the immediate ICU stay.¹⁰

The move towards earlier ART initiation, as reflected in the 2013 WHO guidelines, suggests that there is merit in its initiation in the ICU. The WHO recommends the initiation of ART at a CD4 count of < 500 cells/ μ l,¹¹ a strong recommendation based on moderate-quality evidence.¹² The reasons for improved outcomes include optimisation of the immunological response to ART and a reduction in morbidity from immune reconstitution inflammatory syndrome (IRIS) that is likely to occur if ART is started at a CD4 count < 50 cells/ μ l. These benefits are likely to be realised in critically ill immunocompromised patients with a prolonged ICU stay for sepsis and inflammation since they undergo a switch to immune suppression, with decreased monocyte function and enhanced anti-inflammatory cytokines.¹³ Theoretically, this can result in HIV clinical progression, although this has not been documented in the literature.

The ICU admission diagnosis should also be considered when making the decision. Patients with AIDS-associated neoplasms, such as Kaposi's sarcoma and progressive multifocal leukoencephalopathy, are likely to benefit from the initiation of ART in the ICU since ART,¹⁴ in combination with chemotherapy, is the only effective treatment. IRIS can complicate the treatment of AIDS-associated neoplasms, although this is uncommon. Opportunistic infections are also likely to benefit from ART initiation, although the likelihood of IRIS occurrence is higher. Starting ART within two weeks of initiating treatment for opportunistic infection has been shown to have a survival benefit, except in cryptococcal and tuberculosis meningitis.¹⁵ Poor outcomes have been shown with early ART within four weeks of starting the treatment for meningitis.¹⁶ These studies were not in the ICU setting.

IRIS is a significant problem in the South African setting. An incidence of 22.9% and mortality of 24%¹⁷ was described in a study in KwaZulu-Natal, typically in patients with a very low CD4 count of < 100 cells/ μ l and a high viral burden. The specific incidence of IRIS in the ICU is undefined. The clinical presentation is that of an exaggerated inflammatory response to an infectious

or non-infectious insult that occurs in the first days to weeks after the initiation of ART, owing to the recovery of pathogen-specific T-cell responses. Fever, pneumonitis, pericarditis, hepatitis, retinitis, distributive shock and meningitis are indistinguishable from many ICU diagnoses and drug toxicities. It is a diagnosis of exclusion since there are no definitive laboratory confirmatory tests. This poses a further challenge with misguided anti-infective therapy use in the ICU where antibiotic stewardship principles are advisable.

Considering the mortality of IRIS in our setting, studies that propose the initiation of ART within two weeks of treatment of opportunistic infections in the ICU setting are difficult to generalise as they do not include critically ill patients with multi-organ failure on mechanical ventilation.

The concerns around drug pharmacokinetics, toxicities and interactions in the setting of polypharmacy and organ failure in ICU are still valid. The toxicities of concern include hypersensitivity reactions, lactic acidosis, severe hepatitis and acute renal failure. The incidence of hypersensitivity reactions which occur commonly with nevirapine and abacavir has been reduced as these drugs are not used as first-line treatment. Lactic acidosis, associated with nucleoside reverse transcriptase inhibitors (NRTIs), occurs less frequently in the new regimens following the phasing out of stavudine and didanosine. Tenofovir remains a valid concern for renal toxicity in the ICU.

To my knowledge, zidovudine and enfuvirtide are the only ART available for parenteral administration. Their use is unsuitable since triple-drug therapy with two NRTIs and a nonnucleoside reverse transcriptase inhibitor or protease inhibitor is recommended to prevent drug resistance. The use of a fixed-drug combination has resulted in ease of use, although the problems of unpredictable absorption in critical illness remain. The WHO's recommended first-line combination of efavirenz, emtricitabine and tenofovir should be taken on an empty stomach for maximum absorption, thus enteral feeds have to be interrupted. Therapeutic drug monitoring is useful in ensuring optimal dosing in critically ill patients, although the costs are restrictive.

In conclusion, initiating ART in the critically ill is controversial, with no clear guidance from the literature. It should be considered in patients admitted with AIDS, with careful screening for opportunistic infections and a minimum of 2-4 weeks given

after the initiation of therapy for the opportunistic infection. It should also be considered in patients with a protracted critical care course and signs of immunosuppression. Therapeutic drug monitoring is advisable in defining the pharmacokinetics of these drugs in the critically ill.

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