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For Adult HIV Patients on Highly Active Antiretroviral Therapy, Will Continuation or Initiation of Therapy in Intensive Care Units Improve Patient Outcome During Hospitalization When Compared to Patients Not Receiving Therapy

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For Adult HIV Patients on Highly Active Antiretroviral Therapy, Will Continuation or Initiation of Therapy in Intensive Care Units Improve Patient Outcome During Hospitalization When Compared to Patients Not Receiving Therapy

Abstract

Background: Patients with HIV are living longer due to the advent of highly active antiretroviral therapy (HAART). Before this therapy, admission to the intensive care unit (ICU) was perceived by some patients and providers to be an effort in futility. Now, outcomes appear to be improving for HIV infected patients living in the HAART era. There is no set standard among providers of whether or not to continue or begin this therapy in the intensive care unit. This medication has both benefits, such as bolstering patient's immune system, and drawbacks, such as problems with adverse effect and drug to drug interactions. Currently, there is an unanswered question on whether or not continuing or starting this medication will improve mortality in the ICU for HIV patients.

Clinical Question: Does the use of highly active antiretroviral medications reduce the mortality of patients in the ICU. Study Design: Exhaustive search of available medical literature.

Methods: The focus of this study was to review current literature pertaining to highly active antiretroviral medication in HIV infected patients in the intensive care unit which looked at mortality rate of patients continuing, starting, or not using highly active antiretroviral therapy in the ICU.

Results: An exhaustive literature search yielded two retrospective cohort studies specific for the clinical question. There were no randomized clinical trials on the topic. Both studies determined that patients on highly active antiretroviral therapy had decreased mortality rates in the intensive care unit. Patients with previous HAART use had the lowest mortality rate, followed by patients started on HAART. Finally patients receiving no HAART did the worst.

Conclusion: This is an understudied evolving topic. More studies need to be implemented.

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HIV, HAART, antiretroviral therapy, intensive care unit, critical care

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For Adult HIV Patients on Highly Active Antiretroviral Therapy, Will Continuation or
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Donna Anderson



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

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For the Masters of Science Degree, August 15, 2008

Faculty Advisor: Latha Reddy

Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette
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Biography

Donna Anderson is an Asheville, North Carolina native who has been living in Portland, Oregon since October 2001. She received her Bachelor of Science in Zoology from North Carolina State University in August 1998. She then went back to school in 1999. She graduated in May 2001 with an Associates Degree in Emergency Medical Services and her paramedic certification from Asheville Buncombe Community College. She then briefly worked as a paramedic in North Carolina before moving to Portland, where she worked with the local 911 service for 7 years. Currently she is pursuing her dream of becoming a Physician Assistant at Pacific University of Oregon and intends to graduate August 2008.

Abstract

Background: Patients with HIV are living longer due to the advent of highly active antiretroviral therapy (HAART). Before this therapy, admission to the intensive care unit (ICU) was perceived by some patients and providers to be an effort in futility. Now, outcomes appear to be improving for HIV infected patients living in the HAART era. There is no set standard among providers of whether or not to continue or begin this therapy in the intensive care unit. This medication has both benefits, such as bolstering patient's immune system, and drawbacks, such as problems with adverse effect and drug to drug interactions. Currently, there is an unanswered question on whether or not continuing or starting this medication will improve mortality in the ICU for HIV patients. **Clinical Question:** Does the use of highly active antiretroviral medications reduce the mortality of patients in the ICU. **Study Design:** Exhaustive search of available medical literature. **Methods:** The focus of this study was to review current literature pertaining to highly active antiretroviral medication in HIV infected patients in the intensive care unit which looked at mortality rate of patients continuing, starting, or not using highly active antiretroviral therapy in the ICU. **Results:** An exhaustive literature search yielded two retrospective cohort studies specific for the clinical question. There were no randomized clinical trials on the topic. Both studies determined that patients on highly active antiretroviral therapy had decreased mortality rates in the intensive care unit. Patients with previous HAART use had the lowest mortality rate, followed by patients started on HAART. Finally patients receiving no HAART did the worst. **Conclusion:** This is an understudied evolving topic. More studies need to be implemented.

Keywords: HIV, HAART, antiretroviral therapy, intensive care unit, and critical care

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List of Abbreviations

| | |
|------------|---|
| AIDS..... | Acquired Immunodeficiency Syndrome |
| ART..... | Antiretroviral Therapy |
| CDC..... | Center for Disease Control |
| CMV..... | Cytomegalovirus |
| HAART..... | Highly Active Antiretroviral Therapy |
| HIV..... | Human Immunodeficiency Virus |
| IRIS..... | Immune Reconstitution Inflammatory Syndrome |
| ICU..... | Intensive Care Unit |
| KS..... | Kaposi Sarcoma |
| MAC..... | Mycobacterium Avium Complex |
| NNRTI..... | Nonnucleoside Reverse Transcriptase Inhibitor |
| NRTI..... | Nucleoside/tide Reverse Transcriptase Inhibitor |
| PCP..... | Pneumocystis Carinii Pneumonia |
| PI..... | Protease Inhibitor |
| PPI..... | Proton Pump Inhibitor |
| SFGH..... | San Francisco General Hospital |
| TB..... | Tuberculosis |

For Adult HIV Patients on Highly Active Antiretroviral Therapy, Will Continuation or Initiation of Therapy in Intensive Care Units Improve Patient Outcome During Hospitalization When Compared to Patients Not Receiving Therapy

Introduction

Highly active antiretroviral therapy (HAART) is changing the course of HIV infection from a death sentence to a chronic illness¹⁻³. This is especially true in developed countries, where the medications are more readily available. Studies have shown, that HIV infected people in the HAART era have a decline in rates of AIDS infections and a “significant decrease in mortality and increase in life expectancy”⁴⁻⁶ While improving patient’s life expectancy, HAART is also changing the face of intensive care unit (ICU) admission for HIV infected patients. Providers are now presented with more questions than just a decision whether to admit an HIV patient to the ICU. They are faced with whether to stop, start, or continue HAART during the patient’s hospital course.

According to the center for disease control (CDC) patients with AIDS have “laboratory-confirmed evidence of HIV infection in addition to a CD4+ T-lymphocyte count of <200 cells/ μ L, a CD4+ T-lymphocyte percentage of total lymphocytes of <14, or diagnosis of an AIDS-defining condition”⁷. An opportunistic infection (OI) is an infection that occurs as a result of compromised immune system. OI’s do not typically occur in people with healthy immune systems. HIV was first described in 1981 when cases of OI’s such as Kaposi Sarcoma (KS) and Pneumocystic Carini Pneumonia (PCP) began appearing in young, seemingly healthy homosexual men in Los Angeles, New York, and San Francisco. Intravenous drug users, heterosexual partners of affected

patients and some blood transfusion recipients also began developing similar OI's. This fueled the search for a serologic cause and thus, HIV was discovered in 1984 to be the transmissible agent ⁸.

Medical providers began to use HAART to treat HIV/AIDS patients in the mid 1990's. It is defined as having three antiretroviral medications from at least two of the different groups (Table 1). Studies divide the HIV/AIDS timeline into the pre HAART era and the HAART era ⁹⁻¹¹. Pre HAART is defined as the time when AIDS was first diagnosed in 1981 through 1996 when few antiviral medications were available. HAART is the period from 1996 to present. Although some antiretroviral medications were being utilized, the official HAART era did not begin until protease inhibitors were introduced and made publicly available ¹²⁻¹⁴. Currently, there are more than 20 antiretroviral medications on the market. The three major classes of medications are:

- Nucleoside (and nucleotide reverse transcriptase inhibitors (NRTIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs).¹²

The goals of antiretroviral therapy, according to the department of health and human services, are:

- To reduce morbidity and mortality and prolong survival.
- To improve quality of life
- To Restore and preserve immunologic function
- To maximally and durably suppress viral load
- To prevent vertical HIV transmission ¹⁵.

NRTIs interfere with the reverse transcriptase enzyme suppressing replication of retroviruses. They cause premature termination of the viral precursor chain. With the exception of lamivudine and abacavir, this class of medication is associated with potentially fatal liver toxicities such as lactic acidosis and hepatotoxicities ¹².

NNRTIs bind to HIV reverse transcriptase, inducing a conformational change which results in enzyme inhibition. The drugs commonly have drug to drug interactions and a high incidence of hypersensitivity reactions, including rash. Some NNRTIs can inhibit Cytochrome P34A isoenzyme of cytochrome P450, resulting in possible toxic accumulations of drugs that rely on cytochrome P450 metabolism for their termination of action ¹²

PI's work by inhibiting the HIV aspartyl protease, which is an enzyme used in the production of new viruses. Common adverse effects are paresthesias, nausea, vomiting and diarrhea. They can also cause disturbances in glucose and lipid metabolism resulting in hypercholesterolemia and diabetic complications. PI's are also inhibitors of the CYP34A isoenzyme of cytochrome P450 ¹².

A study performed by Mok et al, to evaluate drug interactions that commonly occur in hospitalized patients on HAART, found that 86% of their patients had at least one drug related problem ¹⁶. They also found Atazanavir, a protease inhibitor, to be the most commonly implicated medication. Furthermore, they reported that of the twenty three drug to drug interactions involving atazanavir, 11 occurred with proton pump inhibitors or histamine-2 blockers. Therefore, while the CDC shows a decrease in morbidity and mortality since the formal introduction of the medication ¹⁷, the medications are not without complications.

The possible side effects and adverse reactions of HAART are numerous. Lactic acidosis, Hypersensitivity syndromes, hepatitis and immune reconstitution inflammatory syndrome (IRIS) manifest during therapy (Table 2). These issues can be difficult to distinguish from other non HAART related medical illnesses in hospitalized patients¹⁸. These, in addition to dosing complications, give rise to the question of whether or not to utilize the medications in critically ill patients during their ICU course.^{18, 19}

In the pre HAART era providers were faced with the difficult task of whether or not to admit a patient to the ICU with an AIDS related opportunistic infection (OI). Providers often viewed admission as an effort in futility.^{1, 2, 18}. In this era, the prognosis of OI's was typically grim^{1, 2}. The HAART era has seen a decrease in the admission of patients with OIs, while the ICU admission rates have remained relatively stable according to one study¹¹, and shown slight increase in others^{1, 18, 20}. There has been speculation that admissions have remained stable or increased because in the pre HAART era patients with OIs were not referred to ICU, while currently with the use of HAART, patients have an improved outcomes with ICU admissions, leading to more aggressive treatments¹⁸. Typical ICU admissions in the pre HAART era were Pneumocystis Carini pneumonia (recently renamed pneumocystis jiroveci pneumonia), Mycobacterium avium complex (MAC), cytomegalovirus (CMV) toxoplasmosis, and tuberculosis (TB)²¹. Currently, while studies indicate respiratory failure is still the number one reason for admission, the rate of PCP is decreasing and non HIV related reasons for admissions are increasing^{1, 11, 20}. Although some studies indicate there is no improvement for outcome of patients receiving HAART prior to hospital admission^{3, 9}, other studies have shown HAART to be beneficial to ICU outcomes, as well as to long term outcomes for patients already on

therapy^{1, 4, 10, 11, 13, 22, 23}. One particular study at San Francisco General Hospital (SFGH) published in 2003, showed a resulting decrease in mortality and as a reason to start HAART for patients with PCP in the ICU²².

Whether or not to continue HAART in the ICU is a current debate among many providers. There are few studies relating to the use of HAART in ICU patients and there have been no randomized clinical trials. The complications of administration, the cost of HAART, the possible side effects and drug interactions of HAART initially lead to the decision to discontinue therapy for patients in the ICU. Now, however, with more studies showing improved outcomes for patients having previously received HAART, because they are healthier at the time of admission and two published studies showing positive effects of therapy in ICU patients, whether or not to continue or initiate therapy is worthy of further study.

Methods

An exhaustive literature search was performed using Medline, CINAHL, Pubmed, MD Consult, StatRef and web of science in the Pacific University library server. The search terms HIV, HAART, antiretroviral therapy, ICU and critical care were employed in various combinations. A very low inclusion criteria on study endpoints was utilized due to lack of studies available on an evolving topic. Any study done after 1996, specifically involving HAART administration in HIV patients in the ICU, whether beginning treatment or continuing was included. Exclusion criteria were studies which did not specify whether or not patients continued or received therapy in ICU and studies printed in foreign languages. Numerous studies were found involving HAART and HIV ICU patients. Of the twenty, two met the inclusion and exclusion criteria for the paper.

RESULTS

A retrospective cohort study done by Morris et al at San Francisco General Hospital in San Francisco, evaluated 58 HIV infected adults admitted to the ICU. The study was a standardized chart review for the years 1996-2001 that assessed mortality while in the ICU or hospital for HIV infected patients admitted with *Pneumocystis carinii* pneumonia (PCP). The patients were divided into three subgroups, those receiving HAART prior to admission and continued, patients started on HAART in ICU, and patients not receiving HAART. The study found a mortality rate of 16.7% (on HAART), 33.3% (starting HAART) and 63.0% (no HAART) respectively. Overall the mortality rate between patients receiving HAART in ICU versus patients not receiving HAART was 25.0% to 63.0%.

A 2009 study found was done at a tertiary care teaching hospital in Sao Paulo, Brazil. Croda et al. performed a retrospective cohort study measuring in ICU mortality and 6 month mortality in HIV infected patients on, off, or started on HAART therapy. The study evaluated a total of 278 HIV infected patients admitted to the ICU. The study found that the use of antiretroviral therapy (ART; Croda et al uses ART interchangeably with HAART) “was more beneficial to patients with a history of previous ART use (HR=0.46 [95%CI 0.25-0.84].” While patients without use of ART have a HR=0.92 [95%CI 0.58-1.46]. It was also found that patients who received ART and discontinued therapy during ICU admission had a higher mortality risk with HR=2.00 [95%CI 0.30-1.53] when compared with patients who continued ART in ICU; HR=1.00 [95%CI 0.30-0.98]. The study found in a subgroup analysis that, “ART remained a significant negative risk factor of mortality” comparing patients started on ART during the ICU stay, with patients who

did not receive ART resulting in HR=.55 [95%CI 0.31-0.98]. Of the patients started on ART, 18.1% were found to have adverse reactions, which resulted in either a switch or discontinuation of ART therapy. Mortality did not appear to be different among patients with continuous ART versus patients who interrupted or modified ART during the hospital course.

DISCUSSION

With the advent of HAART, life expectancy among HIV patients has increased⁴⁻⁶. An increasing number of studies are showing an improvement in the outcome of patients presenting to the ICU with HIV and a wider variety in reasons for admission^{4,11,23}. The number one diagnosis for HIV patients presenting to the ICU is still respiratory failure but other conditions such as liver failure, gastrointestinal bleeds, and cardiac issues are increasing^{1,6,11,20,22}. In the Pre HAART era, many physicians wrestled with the idea of admitting patients with OI's due to perceived futility of doing so²². Now admissions are extremely common as outcomes improve²². One of the biggest controversies around HIV patients in the ICU is HAART. The decision whether or not to continue HAART in a patient admitted to the ICU remains a difficult one. There is the additional question of the appropriateness of beginning HAART under these circumstances. There are arguments for and against each of these options (Table 3).

HAART reduces viral load and increases CD4 counts in patients. This has a positive effect on the function of the immune system, making the patients less susceptible to opportunistic infections^{5,21,24}. This is favorable in any hospital setting, but especially in the ICU. The incidence of pneumonia, both community acquired and hospital acquired has been shown to be greatly reduced in patients on HAART²⁵. Also, if HAART is

discontinued in patients, there is risk for a rebound effect of stopping the medication, with an immediate decrease in CD4 count and increase in viral load¹⁴. This can make patients more susceptible to secondary infections, or to worsening of their presenting illness¹⁴. Discontinuation may also result in viral resistance to HAART^{6, 14, 16, 18}. NNRTIs have a longer half life than other antiretroviral medications. Abruptly discontinuing medication in HAART without accounting for the long half life of the NNRTI can result in monotherapy which can lead to a viral strain resistance to the medication regimen^{6, 16, 18, 19}. Finally, starting HAART in PCP has shown a positive effect on CD4 counts and decreased viral load while reducing mortality according to Morris et al.

Continuing HAART, however, is not without problems. The regimen is extremely difficult to maintain in ICU patients, who are typically unable to eat. Some of the medications require food for absorption, while others need to be taken on an empty stomach. This presents problems in the ICU for patients on continuous tube feedings. Medications such as saquinavir, a protease inhibitor, require high fat meals for absorption. This is in direct contrast to amprenavir, a protease inhibitor, where high fat meals should be avoided^{18, 19}. Administration of medications can also cause issues. Only Zidovudine, an NRTI, can be given intravenously⁶. Some medications come in oral suspension, while others can be crushed and both can be given via gastric tube. Still, others have to be taken whole for appropriate absorption due to their enteric coatings. Patients in ICU are also typically on proton pump inhibitors (PPI) for stress ulcer prophylaxis. Many HAART medications need stomach acids for absorption, which conflicts with the PPI regimen, making continuing appropriate medication dosages difficult^{6, 18, 19}. Due to their side effects, HAART medications can also cause new problems in ICU patients. This can

make it difficult for clinicians to distinguish between worsening of a patient's conditions due to progression in the presenting illnesses, or a compounding complication due to HAART¹⁸, Some HAART medications also interfere with the cytochrome P45A, an isoenzyme of cytochrome P450, which results in problems of metabolizing other drugs, particularly medications used in the ICU (table 4). Finally, when starting patients on HAART, there is a chance of immune reconstitution inflammatory syndrome development (IRIS).

IRIS is a syndrome that can develop when a person is started on HAART, and is a “paradoxical worsening of preexisting, untreated, or partially treated opportunistic infections”²⁶. It is an inflammatory response resulting from an improvement in a patients immune system due to antiretroviral medications and is most commonly seen in patients with mycobacterium tuberculosis, mycobacterium avium, PCP and endemic fungi¹⁹. The symptoms can present anywhere from weeks to years after initiating therapy. Symptoms of IRIS are dyspnea, hypoxemia, fever and cough with new or worsened chest x ray findings^{18,27}. In the 2009 study published by Croda et al, three patients developed IRIS following initiation of HAART. According to the study however, it was not necessary to discontinue their therapy¹³.

There are still no set standards for how HAART should be applied in the ICU setting. Numerous complications including medication interactions, absorption, administration, and adverse reactions including IRIS, all tend to lead providers to reject the use for HAART in the ICU. Two recent studies however, have shown improved clinical outcomes for patients with the use of HAART in the ICU. Croda et al found a decrease in mortality among patients continuing, and starting on HAART while in the ICU. Morris et

al also found a decrease in mortality among patients with PCP continuing or starting HAART in the ICU. Both had similar patient characteristic information. Median age for Morris et al was 36.6 in HAART users and 41.6 for non HAART. Croda et al reported a median age of 39.4 and the majority of patients in both studies were male (greater than 70%). Both studies utilized multivariate regression analysis to determine variables of predictive in hospital analysis. Both studies also reported mechanical ventilation within the first twenty-four hours to be an independent predictor of patient mortality. The limitations of these studies were similar in that they were not broad in their patient spectrum. Both studies were retrospective cohort studies obtained at specific institutions. Morris et al only surveyed 58 patients over the course of the 5 year study and there was no follow up. Croda et al included 278 patients with a 6 month follow up. Both studies similarly acknowledge, due to the retrospective cohort nature of their studies, unmeasured factors may have contributed to the difference in survival. Both studies also acknowledge that hospital policies, admission, discharge practices and practice patterns of staff may result in differing outcomes with other institutions. Variations in patient populations and adherence to prior HAART as well as post HAART adherence can have an effect of patient outcome which is difficult for retrospective cohort studies to take into consideration.

Limitations of Review

An exhaustive literature search yielded only 2 specific articles pertaining to actual HAART use in ICU patients. There have been no randomized clinical trials. This is an understudied area.

Conclusion

The argument as to whether or not to continue HAART in ICU patients is far from resolved. There is no set standard of care and the decision on whether to start or continue therapy is left to specific institutions and providers. The newest study from Croda et al shows improved mortality in ICU patients continuing or starting HAART. It is evidence that more studies need to be performed in this area with broader patient populations to reach a consensus on providing the best possible outcome for patients.

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Tables

Table 1. Highly Active Antiretroviral Therapy

| HAART |
|--|
| Two nucleoside/tide reverse transcriptase inhibitors Plus One protease inhibitor |
| OR |
| Two nucleoside/tide reverse transcriptase inhibitors Plus One non-nucleoside reverse transcriptase inhibitor |

Table 2 .Antiretroviral Medication Side Effects*

| Side Effect | Drugs |
|------------------------------|--|
| Lactic acidosis | Nucleoside reverse transcriptase inhibitors, especially didanosine and stavudine |
| Hypersensitivity reactions | Abacavir, nevirapine |
| Liver toxicity | Saquinavir, ritonavir, nelfinavir, tenofovir, efavirenz, atazanavir |
| Pancreatitis | Didanosine, stavudine, zalcitabine, lopinavir/ritonavir |
| Nephrolithiasis | Indinavir |
| Acute tubular necrosis | Tenofovir |
| Acute interstitial nephritis | Indinavir, ritonavir |
| Myelosuppression | Zidovudine |
| Myopathy | Zidovudine |
| Neuropathy | Stavudine, didanosine, zalcitabine |

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Table 3. Potential Problems and Benefits of Antiretroviral Therapy in the Intensive Care Unit.*

| Potential Problems | Potential Benefits |
|--|---|
| <p>Limited availability of intravenous or liquid medications. Erratic gastrointestinal absorption leading to sub therapeutic drug levels. Potential HIV resistance.</p> <p>Possibility of immune reconstitution inflammatory syndrome. Possible non compliance after discharge. Multiple drug interactions, side effects and overlapping toxicities.</p> | <p>Immune reconstitution may improve prognosis. Beneficial effects of viral suppression during acute illness. Decreased risk for subsequent opportunistic infections.</p> |

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Table 4. Common Antiretroviral Medication Interactions with Commonly Used Intensive Care Unit Medications.

| Drugs | Antiretrovirals | Interactions |
|---------------------|---|------------------------------|
| Midazolam/triazolam | Most PIs, NNRTIs | Increased sedative effects |
| Methadone | Most PIs, NNRTIs, NRTIs | Narcotic withdrawal |
| Meperidine | Ritonavir | Increased normeperidine |
| Ergotamine | Amprenavir, delavirdine, efavirenz, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir | Ergotamine toxicity |
| Metronidazole | Amprenavir, Lopinavir/ritonavir, ritonavir | Disulfiram-like reaction |
| Amiodarone | Ritonavir | Increased cardiac effects |
| Diltiazem | Amprenavir, atazanavir | Increased cardiac effects |
| Nifedipine | Amprenavir, delavirdine, Lopinavir/ritonavir | Increased cardiac effects |
| Sildenafil | PIs | Increased sildenafil effects |

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