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Is Starting Antiretroviral Therapy (ART) in HIV Positive Adults with CD4 Cell Count of <300 Cells>/µl within Four Weeks of Initiating New Tuberculosis (TB) Therapy More Effective in Reducing Mortality Rates than Starting ART Four Weeks or Later after Initiating New TB Therapy?

Janna Erlien
Philadelphia College of Osteopathic Medicine, jannae@pcom.edu

Is starting antiretroviral therapy (ART) in HIV positive adults with CD4 cell count of <300 cells/µl within four weeks of initiating new tuberculosis (TB) therapy more effective in reducing mortality rates than starting ART four weeks or later after initiating new TB therapy?

Janna Erlien, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective:

The objective of this selective EBM review is to determine whether or not starting antiretroviral therapy (ART) in HIV positive adults with CD4 cell count of <300 cells/µl within four weeks of initiating new tuberculosis therapy more effective in reducing mortality rates than starting ART four weeks or later after initiating new tuberculosis therapy.

Study Design:

Systematic review of three English language primary studies published in the New England Journal of Medicine in 2011.

Data Sources:

Three open label, randomized, controlled trials published in 2011, comparing the timing of ART for HIV+ adults with confirmed or suspected new TB infections to reduce mortality rates in reference to initiating TB therapy were obtained using PubMed, Medline and OVID databases.

Outcome Measured:

Outcomes measured include mortality rate, new AIDS defining illness, and immune reconstitution inflammatory syndrome (IRIS).

Results:

Karim et. al. (2011) found in patients with a CD4+ cell count less than 300 cells/µl the incidence rate of death was 7.0% in the earlier ART group compared to 6.9% in the later ART group, with IRIS occurring in 20.0% in the early ART and 8.4% in the late ART group. In groups with CD4+ cell counts of less than 50 cells/µl the mortality rates were 8.1% and 20.0% and incidence rates of IRIS as 37.8% and 11.4% for early and late ART respectively. Blanc et. al. (2011) found in patients with CD4+ cell counts of 200 or less cells/µl a 17.8% mortality rate in the early ART group compared to a 27.4% mortality rate in the late ART group. They also found a significant increase in IRIS in the early ART group, 42.5% compared to just 20.0%. Havlir et. al. (2011) found a 7.7% mortality rate in the early ART group and 9.2% in the late ART group with both groups starting with a CD4+ count of less than 200 cells/µl. For patients with CD4+ T-cell count of less than 50 cells/µl, they found the mortality rate and incidence of new AIDS-defining illnesses was significantly lower in the early ART group 15.5% vs. 26.6% in the later group.

Conclusions:

Karim et al. and Havlir et al. both found that starting ART early in TB therapy showed no significant statistical difference in mortality outcomes in patient with a CD4+ cell count less than 300 cells/µl, but if the group has a CD4+ count of less than 50 cells/µl, new AIDS related illness and death were reduced. Blanc et al. found that survival improved when ART was initiated within 2 weeks of starting TB therapy in HIV + adults with a CD4+ count of 200 or less cells/µl. All three studies showed an increase incidence of IRIS when ART was started within four weeks of initiating TB therapy.

Key Words:

"HIV/AIDS", "Tuberculosis", "TB", "timing of antiretroviral therapy"

Introduction

Tuberculosis (TB) is a contagious infection, mainly bacterial, that is spread via airborne particles. It primarily affects the lungs but can spread to different organs in the body. In healthy populations, most TB infections can be controlled by the body and remain latent. In populations of extreme age or immunocompromise TB is more likely to be active and symptomatic, leading to higher mortality rates. A recent report from WHO noted that in 2011 8.7 million people worldwide became ill with TB and 1.4 million died.[1] In the U.S. in 2011 a total of 10,528 new TB cases were reported and, of those, 82.5% had information on their HIV status and 7.7% were HIV positive.[2] The treatment of TB depends on whether the person has latent or active TB as well as specific sensitivities appropriate for the region. For latent infections, the person has been exposed to the bacteria but does not have symptoms and cannot spread the disease. Treatment generally includes a single drug, Isoniazid, taken daily for 6-9 months which aims at destroying the TB bacteria and preventing active TB. Patients with active TB are symptomatic and able to spread the disease. Drug therapy is more complicated and longer to prevent multidrug-resistant TB. After an intense 8 week induction phase of drug therapy which includes daily Isoniazid, Rifampicin, Pyrazinamide and Ethambutol, the continuation phase follows with four months of daily Isoniazid and Rifampicin. (treatments vary by country and disease susceptibility)[3,4,5]

Acquired Immune Deficiency Syndrome (AIDS) results from the Human Immunodeficiency Virus (HIV), which is transmitted through infected body secretions; primarily blood, semen, breast milk and vaginal fluid. The CD4+ T-cells are the primary site of infection and therefore often used to measure the status of the immune system as well as predict severity of HIV infection. HIV/AIDS is the largest cause of death from an infectious agent worldwide. Although the number of new infections and AIDS related deaths are declining worldwide, in 2011 it was estimated that there were 34.2 million people living with HIV, 2.5 million newly infected

and 1.7 million deaths.[6] In the U.S. there was an estimated 48,100 new HIV cases diagnosed in 2009[7] in addition to the 1.2 million HIV positive people already diagnosed in the U.S.[8] Of those living with HIV worldwide, they accounted for 13% of all new tuberculosis cases and about 360,000 deaths from HIV-related TB.[9] Therapy for HIV/AIDS is based on the CD4+ cell count as well as symptoms or co-infections. ART is multidrug and the treatment selected depends on viral strains, sensitivities and available medications in the region. It aims to completely suppress the viral replication. The treatment of HIV includes combinations of drugs such as: Efavirenz, Lamivudine, Tenofovir, Emtricitabine, Stavudine and Didanosine. (treatments vary by country and disease susceptibility)[3,4,5]

Physician Assistants will inevitably encounter patients with either TB, HIV/AIDS or both, and those specializing in infectious disease will be responsible for the treatment plans of such patients. It is important for Physician Assistants to understand the indications and complications that accompany treating these complex cases.

In 2006 in the U.S. the mean annual cost of HIV treatment was $19,912, but costs ranged from $40,678 in patients with a CD4 cell count of <50 cells/µl to $16,614 in patients with a CD4 cell count of >500 cells/µl.[10] In 2010, the CDC estimated the lifetime cost of HIV treatment to be nearly $380,000.[11] TB treatment involves multiple medications and lengthy treatment and can range from $101, 553 for hospital treatments to $27,490 with less expensive medicines in the US.[12] Data were unavailable as to the combined cost of HIV positive persons co infected with TB.

Both TB and HIV are serious conditions, but when they are co-infecting a patient it can become a lethal combination. The WHO estimates that at least 33% of the 34 million diagnosed HIV positive are infected with TB, and that population is up to 34 times more likely to progress from latent to active TB than an HIV negative population[1]. TB continues to be a significant cause

of death in HIV positive adults, up to 25% according to the WHO. The current 2009 WHO guideline is to start ART as soon as possible after TB therapy is started without regard to the patient's CD4+ T-cell count.[13] It has been proposed that starting ART early (within four weeks) of TB treatment can be beneficial in reducing mortality rates in HIV positive patients with any CD4 cell counts, but more effective in patients with lower CD4 cell counts.

ART is important in HIV patients with active TB infections but there is concern with starting ART during the induction phase which can cause a high pill burden, drug interactions and an increased likelihood of immune reconstitution inflammatory syndrome (IRIS) when both treatments are combined.[3]

Objective

The objective of this selective EBM review is to determine whether or not starting HIV therapy within the first 4 weeks of a positive TB test in adults with a CD4 cell count of <300 cells/µl has a lower mortality rate than waiting to start treatment until after 4 weeks of TB treatment.

Methods

All three studies in this review were open-labeled randomized controlled studies, one being a prospective study (Table 1). The populations selected include: HIV positive, >13 years old, CD4 cell count of <300 cells/µl, suspected or confirmed TB infection, no previous ART or TB treatments. The interventions used in the studies were dependent upon disease susceptibility, countries involved, medications available and their specific protocol. The ART includes: Efavirenz, Lamivudine, Tenofovir, Emtricitabine, Stavudine and Didanosine. TB therapy includes: Isoniazid, Rifampin, Ethambutol and Pyrazinamide. Each study looked at the timing of starting ART in reference to initiating new TB treatment. The earlier start of ART was within four weeks of initiating TB therapy and the later start of ART was four weeks or more after initiating

TB therapy. The outcomes measured qualified as patient oriented evidence that matters (POEM) and encompassed mortality rates, new AIDS defining illness, and IRIS. The commonality between the three studies were mortality rates and IRIS.

A detailed search by the author using PubMed, Medline and OVID was conducted using the key words "HIV/AIDS", "TB", "timing of antiretroviral therapy". All studies were published in English in The New England Journal of Medicine in 2011. Inclusion criteria for the articles included: HIV positive, TB suspected or confirmed, negative pregnancy test, no previous ART or TB therapies and patients over 13 years old, CD4 cell count <500 cells/μl, randomized controlled trials, and mortality measured as an outcome. The exclusion criteria used were: patients under 13 years old, pregnant or breast feeding, previous ART or TB treatment, CD4 >500 cells/μl, outcome not evaluating mortality rate. The summary of statistics reported and/or used include p-values, 95% confidence intervals (CI), hazard ratio and incidence-rate ratio.

Outcomes measured

In the 2011 study by Halvir et al., the primary end point was survival without a new AIDS defining illness over the 48 week study. An independent reviewer unaware of group assignments used standardized definitions of AIDS defining illness to assess the diagnosis. TB-associated IRIS was confirmed by a reviewer unaware of study group assignment. The cause of death was reviewed by study members unaware of the study group assignments. Clinical and laboratory evaluations were completed upon entry into the study, at weeks 4, 8, 12 and 16 and then every 8 weeks until the completion of the study at 48 weeks. At conclusion, the Kaplan-Meier method was used to calculate proportions of test subjects which survived without a new AIDS event. Plasma HIV-1 RNA and CD4+ cell counts were measured at Division of AIDS certified laboratories. Participants were taken from Asia, North America, Africa and South America.

Table 1- Demographics and Characteristics of studies							
Study	Type	# of Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions*
Havlir[3] (2011)	Open Label, RCT	806 total pt from Africa, Asia, N. America and S. America	median age 34y	Age >13 with CD4 count <250 cell/mm3 being treated for TB and naive to ART, negative pregnancy test	Age <13, previous ART, breast-feeding, history of resistant TB	68 (17%) did not complete the early-ART arm. 62 (15%) did not complete the late-ART arm.	ART: **EFV** 600mg qd, **FTC** 200mg qd, **TDF** 300mg qd TB: All patients received **R** or other Rifamycin-based treatment according to WHO and country guidelines
Blanc[4] (2011)	Prospective, Open Label RCT	661 total pt from Cambodia	median age 35.5y	Age >18 with CD4 count <200 cell/mm3 with a positive TB spear and naive to ART, negative pregnancy test	Age <18, negative HIV test or negative TB spear, CD4+ >200 cell/mm3, pregnant or breast-feeding, impaired hepatic function, previous ART	73 (22%) did not complete the early-ART arm. 104 (32%) did not complete the late-ART arm.	ART: **EFV** 600mg qd, **D4T** 30 mg/**3TC** 150 mg, 1 tablet BID TB: 2 months of **E**15-20 mg/kg qd, **H** 4-5 mg/kg qd, **R**10 mg/kg qd, **Z** 20-30 mg/kg qd, followed by 4 months of **H** 10 mg/kg qd, **R** 4-5 mg/kg qd
Karim[5] (2011)	Open Label, RCT	642 total pt from South Africa	median age 34.4 ± 8.4 y	Age >18 with CD4 count <500 cell/mm3 with a positive TB spear and naive to ART, negative pregnancy test	Age <18, negative HIV test or negative TB spear, CD4+ >500 cell/mm3, pregnant or breast-feeding, impaired hepatic function, previous ART	45 (22.7%) did not complete the early-ART arm. 26 (15.9%) did not complete the late-ART arm.	ART: **enteric-coated Didanosine** (250 mg if the pt weight was <60 kg and 400 mg if weight was ≥60 kg), **3TC** 300 mg qd, **EFV** 600 mg qd TB: 2 months of **RHZE** (150,75, 400, 275)mg 30-37 kg 2 tabs, 38-54kg 3 tabs, 55-70kg 4 tabs five times/week, followed by 4 months of **RH** (150, 75)mg 30-37 kg 2 tabs, 38-54kg 3 tabs, or **RH** (300,150)mg 55-70kg 4 tabs five times/week.

*Drug Abbreviations:

Antiretroviral (ART) Medications; **EFV-Efavirenz, FTC-Emtricitabine, TDF-Tenofovir disoproxil fumarate, D4T-Stavudine, 3TC-Lamivudine**

Tuberculosis (TB) Medications; **R-Rifampicin, H-Isoniazid, Z-Pyrazinamide, E-Ethambutol**

Substitutions for ART drugs were permitted if necessary to manage toxic effects. There were no significant demographic differences between study groups.

Blanc et al. collected data from five Cambodian hospitals from 2006 to 2009. The primary end point was survival with secondary end points being IRIS events, CD4+ T-cell count, evolution of drug resistant TB, medication side effects and viral load. The CD4+ T-cell count and plasma HIV RNA viral load were measured at weeks 8, 26, 50 and 78 and then every 6 months. Participants were followed for 50 weeks after the enrollment of the last patient. Comparisons between subject groups were performed using Student's t-test for continuous variables and chi-square test of the Fisher's exact test for categorical variables. Participant survival was analyzed using Kaplan-Meier estimates with the log-rank test comparing between groups. There were no significant differences between the study groups in regards to their baseline demographics.

In the 2011 South African study by Karim et al, the primary outcome was incidence rate of AIDS or death. IRIS was measured as a secondary outcome. Outcomes were analyzed using the Kaplan-Meier curves. Poisson approximations were used to calculate confidence intervals for the incidence-rate ratios. For confounding variables, Cox proportional-hazards regression was used while the Fisher's exact test was used for analyzing categorical data. For continuous data, unpaired t-tests or the Wilcoxon two-sample test was used. At baseline the two sample groups had similar demographics. Duration of the study lasted 18 months after randomization or at the time of death or AIDS-defining illness or withdrawal from the study, whichever occurred first.

Results

Halvir et al. (2011) found that there was no statistical difference between the early ART and later ART groups in the mortality rate or new AIDS-defining illness when the patients had a CD4+ T-cell count of 250 cells/μl or less. In the early ART group they had 26 new AIDS-defining illnesses and 31 (8%) deaths compared to 37 new AIDS-defining illnesses and 37 (9%)

deaths in the later ART group (95% CI, -1.8 to 8.1; P= 0.45) when stratified according to the CD4+ cell count (Table 2). As calculated from the mortality rates the number needed to treat to prevent mortality is 64 patients. Of the deaths during the study, 68% and 57% were attributed to HIV-related disease in the early and late ART groups respectively. When a subgroup analysis was done for patients with CD4+ T-cell count of less than 50 cells/μl, they found the mortality rate and incidence of new AIDS-defining illnesses was significantly lower in the early ART group 15.5% vs. 26.6% (95% CI, 1.5 to 20.5; P=0.02). Medication adverse reactions occurred in 18% of the total sample population with similar numbers between groups (Table 3). Twenty-one of the 783 participants, 14 in the early arm and 7 in the later arm, switched ART therapies due to adverse reactions. A total of 56% of patients completed TB treatment without modification or interruption without significant difference between arms.

The CAMELIA study by Blanc et al. (2011) found in patients with CD4+ T-cell counts of 200 or less cells/μl a mortality rate in the early ART group was 8.28 per 100 person-years, or 17.8%, (95% CI, 6.42 to 10.69) and 13.77 per 100 person-years, or 27.4%, for the late ART group (95% CI, 11.20 to 16.93) (P=0.002); see Table 2. According to these data the number needed to treat to prevent a mortality is 11. When Blanc et al. looked at patients with a CD4+ T-cell count of less than 50 cells/μl, they found the hazard ratio did not significantly differ between the early and late ART treatment groups (P=0.49). They also found a significant increase in IRIS in the early ART group, 42.5% compared to just 20.0% in the later group. The incidence within the first 50 weeks of the study was 3.76 cases per 100 person-months (95% CI, 3.14 to 4.47) with the early ART group, and 1.53 cases per 100 person-months in the later ART group (95% CI, 1.13 to 2.03) ($P < 0.001$). Of the 332 participant in the early ART group, 259 (78.0%) completed the study, and 225 (68.4%) of the 329 participants in the late ART group completed the study. Drug

toxicity was the second most common cause of death following TB. In the early ART group, there were 2.93 per 100 person-month serious drug-related adverse effects noted (95% CI, 2.85 to 3.32) and 3.21 events in the later ART group (95% CI, 2.83 to 3.63; P=0.31); see Table 3.

Table 2. Mortality rates according to study for early vs. late ART.

Study Author	Deaths as % in Early ART group	Deaths as % in Later ART group	Statistical Values
Havlir et al.	7.7	9.2	95% CI, -1.8 to 8.1; P= 0.45*
Blanc et al.	17.8	27.4	Adjusted hazard ratio, 0.62; 95% CI, 0.44 to 0.86; P=0.006
Karim et al.	7	6.9	Incidence-rate ratio 0.96, 95% CI, 0.44-2.10; P=0.91

* Statistical values only given in study for combination of "AIDS or Death"

In the final study by Karim et al (2011), they found in patients with a CD4+ T-cell count less than 300 cells/µl the incidence rate death was 5.7 cases per 100 person-years, or 7.0%, in the earlier ART group compared to 6.0 cases per 100 person-years, or 6.9%, in the later ART group (incidence-rate ratio 0.96; 95% CI, 0.44 to 2.10; P=0.91); see Table 2. Although both study arms had 15 deaths, since the early group started with one less person the number needed to treat to prevent mortality calculated is -76, implying that mortality was higher in the early treated group. When the study analyzed death according to the CD4+ T-cell count they found in patients with a CD4+ T-cell count of less than 50 cells/µl the incidence rate was 6.3 cases per 100 person-years (95% CI, 1.3 to 18.5) in the early ART group, compared to 16.3 per 100 person-years (95% CI, 6.5 to 33.5) in the later ART group (incidence rate ratio, 0.39; 95% CI, 0.06 to 1.70; P=0.17). In groups with CD4+ T-cell counts of less than 50 cells/µl the incidence rate of IRIS was 4.7 times higher in the early ART group (P=0.01). In groups with CD4+ T-cell counts of more than 50 cells/µl the incidence rate of IRIS was only 2.2 times higher in the early ART group (P=0.02). Karmin et al noted that 8.9% of early ART participants and 8.8% of the later ART participants defaulted on their TB therapy. Ten patients in the early ART and one in the later ART group had

to switch ART due to adverse reactions (P=0.006); see Table 3. Change in ART due to virologic failure occurred in 6 patients in the early ART and 9 in the later ART (P=0.18).

Table 3. Adverse events due to treatment regime for early vs. late ART.

Study Author	Percent of patients experiencing adverse events to treatment in early ART	Percent of patients experiencing adverse events to treatment in later ART
Havlir et al.	1.2	0.9
Blanc et al.*	27	28
Karim et al.	4.7	0.5
*Only 21 of the 783 patients (14 in early ART and 7 in later ATR) required a switch in treatments.		

Discussion

Two of the three studies addressed in this review demonstrate that there is no statistical significance in reducing mortality when starting ART in HIV+ adults with CD4+ T-cell counts of less than 300 cells/µl within four weeks of initiating new TB treatment.[3,5] All of the studies found that starting ART earlier resulted in a higher incidence of IRIS.[3,4,5] When the studies analyzed participants by their CD4+ T-cell count, they all found a significant improvement in the AIDS-free survival when ART was started early in patients with a CD4+ cell count of less than 50 cells/µl, despite the increased risk of IRIS. This is perhaps why the CAMELIA study by Blanc et al. found a notable improvement in survival; the median CD4+ cell count of their participants was 25 cells/µl. The CAMELIA study also followed the patients for a longer duration (median follow up of 25 months), had a lower overall average of body mass index than the other two studies and only enrolled patients with a confirmed TB diagnosis.[4]

One limitation in comparing data was in the Havlir et al. study, the 95% CI and P Values were calculated for the combination of AIDS-defining illness *and* death rather than separating each into its own statistical finding. The number of deaths also was inconsistently mentioned in the report; once claiming only 53 deaths and elsewhere in the paper 68 deaths.[3] This study started with only 46% of patients having a confirmed TB infection, the remaining were clinically suspected.

A general limitation of comparing these three studies is that they were conducted in different countries and each study with significant drop out rates. The research groups had different evaluators to diagnose IRIS and in some cases TB infection. Each country also has its own availability of medication, recommendations on its use and guidelines as to when to switch if adverse reactions occur. There are also different susceptibilities to both TB and HIV from country to country. None of the studies used the exact same medication regimes. The only similarities were Efavirenz in ART as suggested by the WHO due to its lower incidence of interaction with Rifampicin compared to other ART medications and the combination of TB treatment (Table 1).

Conclusion

Although the studies differ in their recommendations for patients with higher CD4+ T-cell counts, they all agree that starting ART early in the TB treatment depends more on the immune status of the patient than the presence of co-infection between TB and HIV. With CD4+ T-cell counts of less that 50 cells/μl, survival is greatly improved despite the increased risk of IRIS and high pill burden when ART is started within 4 weeks of the TB therapy. Although the studies were large and generally lengthy, it would be ideal to use the same medication regime to ensure that adverse reactions or IRIS are a result of the medications only. Further evaluation could also be completed using the CD4+ cell count as the dividing factor when all participants start ART early in their TB therapy. The current WHO guideline in the US is to begin ART as soon as possible after TB therapy is started regardless of the patient's CD4+ T-cell count but analysis of these studies indicate that the 2009 guideline may need revision. The most recent Programmatic Update from June 2012 has indicated investigational studies are underway to determine the best recommendations.[14] Further study is warranted to evaluate a more specific guideline for starting ART in regards to the timing of TB treatment and most beneficial CD4+ T-cell count or even viral load counts at which ART should be initiated.

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