March 2011

Recent Advances Spark Significant Guideline Change: Antiretroviral Therapy (ART) at High CD4+ Counts in the Treatment Naïve Patient

Joshua Ilenin  
*Ohio Northern University*

Kelly Fargo  
*Ohio Northern University*

Lisa Berni  
*Ohio Northern University*

Kristen Thatcher  
*Ohio Northern University*

Caitlin Swann  
*Ohio Northern University*

Follow this and additional works at: [https://digitalcommons.onu.edu/paw_review](https://digitalcommons.onu.edu/paw_review)

Part of the Immune System Diseases Commons, Infectious Disease Commons, Pharmaceutics and Drug Design Commons, and the Therapeutics Commons

**Recommended Citation**

Recent Advances Spark Significant Guideline Change: Antiretroviral Therapy (ART) at High CD4+ Counts in the Treatment Naïve Patient

Authors
Joshua Ilenin, Kelly Fargo, Lisa Berni, Kristen Thatcher, Caitlin Swann, and Andrew Roecker

This article is available in Pharmacy and Wellness Review: https://digitalcommons.onu.edu/paw_review/vol2/iss1/2
Recent Advances Spark Significant Guideline Change: Antiretroviral Therapy (ART) at High CD4+ Counts in the Treatment Naïve Patient

Joshua Ilanin, fourth-year pharmacy student from Mantua, Ohio; Kelly Fargo, fourth-year pharmacy student from Chagrin Falls, Ohio; Lisa Bernt, fifth-year pharmacy student from Dennison, Ohio; Kristen Thatcher, fifth-year pharmacy student from Pittsburgh Pa.; Caitlin Swann, fifth-year pharmacy student from Strongsville, Ohio; Andrew Roecker, PharmD '06, BCPS, associate professor of pharmacy practice

Objectives:

1. Identify the pertinent laboratory values and/or symptomatology required for antiretroviral therapy initiation in treatment-naïve HIV patients.
2. Describe the limitations of early versus deferred treatment for HIV infection.
3. List the factors that limit patient adherence to antiretroviral therapy.
4. Identify the significant changes made to the newest version of the NIH HIV treatment guidelines.

Abstract

Human immunodeficiency virus (HIV) targets CD4+ lymphocytes, a critical component to proper functioning of the human immune system. HIV is a significant public health concern, having resulted in over 27 million deaths since its discovery. Currently, several different treatment options exist, with combination antiretroviral therapy (ART) at the forefront. Despite the success of ART therapy, there are a number of problems, including poor patient compliance. Due to this, the appropriate time to initiate therapy in the treatment naïve patient is under continuous scrutiny. Recently, several trials have demonstrated evidence suggesting that initiating ART at high CD4+ counts in the treatment naïve patient is beneficial in preventing outcomes such as progression to AIDS and death due to complications from HIV. This review will discuss two trials influential in the recent change in The National Institute of Health's guidelines on therapy for treatment naïve patients. The trials reviewed here are the North American AIDS Cohort Collaboration on Research Design (NA-ACCORD) and the Antiretroviral Therapy Cohort Collaboration (ART-CC). Despite the success of therapy, it is associated with many negative side effects and high cost, which may affect patient compliance, lead to possible drug resistance and result in treatment failure. Along with the new evidence presented in clinical trials, these factors also must be considered when initiating therapy in the treatment naïve HIV patient.

Background

Human immunodeficiency virus (HIV) infects cells of the immune system and progressively leads to the destruction or deterioration of immune function. HIV normally infects humans by targeting a type of white blood cell known as CD4+ T lymphocytes, which are involved in cell-mediated immunity. Viral particles bind to specific receptors on the cell surface and fuse with the cell. The virus can then enter the host cell and insert its viral DNA into the normal DNA of the host, forcing the newly infected cell to produce additional copies of HIV. These new copies of HIV can go on to infect other cells, leading to a progressive decline in the number and function of CD4+ T lymphocytes and attenuation of the immune system. As a result of increased patient education on prevention and protection, the spread of HIV has decreased in recent years. However, the total number of infected individuals continues to rise as they are identified earlier and treated with more advanced medication regimens. Antiretroviral therapy (ART) blocks HIV's activity on CD4+ cells by targeting different stages in the HIV lifecycle and decreasing the overall viral load in infected individuals. ART involves various combinations of the four drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), integrase strand transfer inhibitors (INSTIs). ART involves various combinations of the antiviral drug classes. There are three preferred regimens for treatment naïve patients in the current NIH guidelines. The regimens include a 2-NRTI backbone along with either an NNRTI, PI (ritonavir boosted) or INSTI. While the efficacy of antiretroviral therapy in slowing the progression of HIV and maintaining higher CD4+ counts has long been established, there is disagreement about when such therapy should be initiated. Over the past decade, several large-scale clinical trials have studied the risks and benefits of initiating ART at higher CD4+ counts, resulting in changes to the NIH guidelines for antiretroviral therapy in treatment naïve HIV patients.
NA-ACCORD
The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) evaluated the rate of death for treatment naïve patients who initiated ART therapy within different thresholds of CD4+ counts. Patients in two different CD4+ count ranges, either 351-500 cells/mm³ or greater than 500 cells/mm³, were allowed to initiate or defer ART therapy as a part of their HIV treatment when entering the trial. Patients who initiated ART therapy more than six months after the start of the trial were included in the deferred group. A total of 8,092 women, were included in the first analysis, [who contributed 23,977 person-years of follow-up], which looked at patients whose baseline CD4+ counts were between 351-500 cells/mm³. ART therapy was initiated in 25 percent of patients within six months, while the remaining 75 percent deferred therapy. The second analysis included 9,165 patients (who contributed 26,430 person-years of follow-up) whose CD4+ count was greater than 500 cells/mm³ at the beginning of the trial. In this group, 24 percent of patients initiated therapy early, and 76 percent deferred for greater than six months. The results of this study were significant because they assessed HIV patients with CD4+ counts above the guideline recommendation at that time, which did not recommend initiation of ART until CD4+ count decreased to less than 350 cells/mm³. Throughout the study, the CD4+ counts and rate of death for patients in each group were assessed. A statistically significant increase in the risk of death for patients who deferred therapy was seen in both patient groups. The relative risk of death was 59 percent higher (P<0.001) for patients who deferred therapy with a CD4+ count of 351-500 cells/mm³ and 94 percent higher in patients who deferred when their CD4+ count was greater than 500 cells/mm³. The large patient population and significant duration of observation gave this trial strong external validity and allowed death to be used as an endpoint rather than an HIV/AIDS related biomarker. The deferral group in each CD4+ count range essentially served as a control for the study and allowed for an effective analysis of when to initiate ART therapy for patients based on their CD4+ count. No randomization or blinding of study participants was done in this study. However, the use of death as an endpoint limited the risk of bias in the results. Relative risk adjustments for confounding variables such as intravenous drug use and hepatitis C infection were performed, although an analysis sensitivity analysis suggested that due to the size of the trial, confounding would have had to have been unusually large to affect the results. These adjusted relative risk calculations also demonstrated an increased risk of mortality for the deferring group in each of the respective cohorts.

ART-CC
The Antiretroviral Therapy Cohort Collaboration (ART-CC) was an analysis of 12 cohort studies performed in Europe and North America between 1995 and 2003. The study evaluated ART-naïve HIV patients and the progression of their disease once ART was initiated. The trial evaluated five prognostic variables indicative of disease progression, including CD4+ cell count, HIV-1 RNA level, injection drug use (IDU), age, and clinical AIDS. A total of 22,217 patients were included in the cohort database. From the initiation of ART, 20,379 of the patients were analyzed. Due to a lack of CD4+ cell counts between months three and nine during the trial, only 16,167 were included in the analysis from six months after initiation. For each of the variables, a hazard ratio was calculated for patients who progressed to AIDS before death and patients who died prior to the progression to AIDS. After five years, the risk for both endpoints, progression to AIDS followed by death or death alone, ranged from 5.0-77 percent. For example, patients who were less than 30 years old, were infected with HIV via some means other than IDU, had a CD4+ count of less than 350 cells/mm³ at therapy initiation and had an HIV-RNA level below 5 log copies/ml possessed only a 5.6 percent risk of death over a five-year period. Patients who were 50 years old or older, became infected with HIV via IDU, started ART with clinical AIDS and a CD4+ count of less than 25 cells/mm³, had an HIV-1 RNA level equal to or greater than 5 log copies/ml and whose disease had progressed to AIDS had a 77 percent risk of death over the course of the trial. The results of this study demonstrated the significance of CD4+ cell counts as an indicator of overall survival in HIV patients. The hazard ratios (95 percent CI) ranged from 0.18 for patients with a six-month CD4+ count of greater than 350 cells/mm³ to 0.75 for those with a six-month CD4+ count ranging from 25-49 cells/mm³. This study demonstrated strong internal validity due to its size and adjustment in the hazard ratios for confounding variables. A limitation of the study was the study's use of cause-specific mortality data for patients in each of the respective cohorts.

Updated Guidelines
Studies such as the NA-ACCORD analysis and ART-CC trial have contributed to the increasing evidence in support of early ART therapy initiation in HIV patients. As a result of these and other similar trials, a panel from the Department of Health and Human Services made significant changes to the current ART therapy guidelines with the goal of providing health care professionals with recommendations for HIV treatment that reflected the findings of the most recent clinical trials. A full version of the now 2010 NIH guidelines can be viewed online at www.aidsinfo.nih.gov. Among the many modifications to the guidelines, the panel made several suggested changes to the timing of ART therapy initiation in treatment naïve patient. Citing evidence of decreased mortality in the NA-ACCORD and ART-CC clinical trials, the panel now recommends initiating therapy in all patients with CD4+ counts 500 cells/mm³ or less. While the benefits of initiating therapy earlier were clearly demonstrated in the above clinical trials, the panel remained concerned about the long-term impact of side effects on patient adherence and the overall success of treatment. As a result of the NA-ACCORD trial, the panel also made a recommendation for patients with CD4+ counts greater than 500 cells/mm³. However, after the lack of supporting evidence from other cohorts or randomized clinical trials, the panel chose to classify initiation of ART therapy in these patients as optional and not to be considered as a case-by-case basis. In all recommendations made by the panel, they stressed the importance of assessing each individual patient's commitment to lifelong ART therapy and adequately explaining the associated benefits and risks before initiating therapy.

Cost
Patients who choose to begin antiretroviral therapy as a part of their HIV treatment are making a lifelong commitment to expensive medications. One argument against initiating such high-priced medications earlier in the course of HIV progression is that the costs of treatment will be unnecessarily increased. A 2001 study on the cost effectiveness of antiretroviral treatment found that patients who initiated combination therapy at 500 cells/mm³ could expect to live an average of 9.1 years after starting treatment and would incur a lifetime medical cost of $104,100. Patients in the study who chose to defer treatment until their CD4+ counts fell below 200 cells/mm³ were expected to live an additional 8.5 years at a total treatment cost of $79,000. The results also showed an increase in the number of opportunistic infections experienced by HIV patients who deferred antiretroviral therapy. Over the course of many years of treatment, the costs associated with initiating therapy early are relatively
small compared to the demonstrated increase in life expectancy and decrease in the risk for opportunistic infections.

**Patient Adherence and Adverse Events**

Patient adherence to ART therapy was not addressed in earlier studies, but remains a concern for practitioners and patients because it directly correlates with treatment success. Specifically, the most common cause of antiretroviral therapy failure in HIV patients is non-adherence. Pill burden, timing, tolerability, cost and interactions all limit patient adherence. Zidovudine (AZT) was the first antiretroviral medication brought to the market in the 1980s. Patients were required to take AZT five times daily and experienced a number of debilitating side effects. Although newer, more tolerable antiretroviral drug therapies continue to become available, each current class of antiviral medications has general side effects that can affect patient adherence. NRTIs can cause mitochondrial toxicity including lactate acidosis, hepatic steatosis and pancreatitis. NNRTIs can produce rashes and hepatic dysfunction. PIIs cause gastrointestinal disturbance (nausea, vomiting, diarrhea), bleeding problems, hepatotoxicity and metabolic issues including hyperlipidemia, fat malnutrition and insulin resistance. Enfuvirtide, currently the only FI on the market, is administered subcutaneously and can cause injection-site reactions, bacterial pneumonia, insomnia, nausea and diarrhea. Hepatotoxicity, fever, rash and upper respiratory tract infection are common side effects seen in maraviroc, an entry inhibitor. Raltegravir is an INSTI, the newest class of HIV antiretroviral drugs, and has been associated with an increase in total cholesterol. In addition to tolerability, pill burden also affects patient adherence. The availability of combination antiretroviral drugs has helped curb some of these adherence issues. In addition, drug-drug and drug-food interactions exist and are considered in therapy and monitoring. Pharmacists play an important role in screening for drug interactions, educating patients on side effects and the importance of adherence, as well as screening for other health issues and administering appropriate immunizations. Overall, patient adherence must be managed by all clinicians, including pharmacists, in order to prevent progression of the disease and improve quality of life.

**Drug Resistance**

Antiretroviral drug resistance is an important consideration in the treatment of HIV patients because it can have a significant impact on the success of ART therapy and lead to increased mortality. Opponents of early antiretroviral initiation claim that using these drugs early in the course of HIV progression can increase the risk for resistance and limit future treatment options for patients. Resistance to antiretroviral drugs is caused by mutations in the viral particles that result in different forms of HIV within an individual. Some of these variants of HIV are more resistant to antiretroviral drugs and can lead to a decrease in the effectiveness of treatment. One of the most influential factors in developing resistance to antiretroviral drugs is poor adherence to medication regimens. Patients who choose to initiate therapy and are subsequently poorly adherent expose themselves to antiretroviral drugs but do not fully suppress the replication of the virus. The virus then can continue to replicate in the presence of subtherapeutic drug concentrations, and the risk for mutant strains of the virus developing is increased. The risk of developing resistance to three major classes of antiretroviral drugs, NRTIs, NNRTIs and PIs, has been shown to decrease if treatment is initiated at higher CD4+ counts. In order to reduce the risk of drug resistance and maximize the effectiveness of antiretroviral therapy, pharmacists and other clinicians must stress the importance of medication adherence to patients beginning treatment.

**Conclusion**

The benefits of initiating therapy at CD4+ counts above 350 cells/mm³ were clearly demonstrated by the NA-ACCORD and ART-CC trials, and the newly refined guidelines reflect these new findings. However, treating HIV patients with ART therapy does have a number of limitations as well. Antiretroviral drug costs in the United States remain high, and regardless of the CD4+ count at which they are initiated, represent a significant financial burden for patients, insurance companies and government programs. Many classes of antiretroviral drugs also have serious potential side effects that can lead to increased morbidity and decreased patient adherence. A patient's adherence to their medication regimen is vital to slowing the progression of HIV and improving life expectancy. Most types of antiretroviral therapy include multiple different classes of drugs, and the resulting pill burden can lead to lower rates of adherence in patients, especially those with higher CD4+ counts that may not be experiencing an AIDS defining illness. Resistance to antiretroviral drugs, commonly the result of poor patient adherence, can limit treatment options for patients as they progress through the disease as well. However, despite these issues and others, it is important to focus on the consistently improved patient outcomes demonstrated in early initiation groups from the reviewed clinical trials. Across almost all demographic groups, participants who initiated ART therapy earlier in the course of the disease were more likely to live longer and less likely to progress to clinical AIDS. The success of ART in HIV patients is dependent on a variety of different factors, and a careful assessment of the risks and benefits of treatment must be performed for patients considering initiating therapy at any point in the progression of the disease. Pharmacists and other health care professionals must play an active role in discussing the risks and benefits of treatment with patients and assessing the readiness to make a lifelong commitment to antiretroviral therapy. The most recent findings certainly do not signal the end of the debate on ART therapy, and HIV treatment will undoubtedly continue to be the focus of much discussion and research in the future.

**References**

Antiretroviral Therapy (ART) at High CD4+ Counts in the Treatment Naïve Patient

Assessment Questions

1. There are currently __________ people in the United States living with HIV/AIDS:
   a. 500,000
   b. 1 million
   c. 2 million
   d. 5 million

2. All of the following patient populations are at an increased risk of contracting HIV EXCEPT:
   a. Hispanic/Latino Americans
   b. Men who have sex with men (MSM)
   c. African Americans
   d. All of the above

3. Which of the following is NOT considered a preferred antiretroviral treatment regimen for treatment naïve patients:
   a. 2-NRTI + 1 PI (ritonavir boosted)
   b. 2-NRTI + 1 FI
   c. 2-NRTI + 1 NRTI
   d. 2-NRTI + 1 INSTI

4. Which of the following CD4+ count values is the minimum at which an asymptomatic HIV-positive patient would not be classified as an AIDS patient:
   a. 500 cells/mm3
   b. 200 cells/mm3
   c. 100 cells/mm3
   d. 50 cells/mm3

5. The 2010 NIH Guidelines state that antiretroviral therapy should be initiated in patients with each of the following CD4+ counts EXCEPT:
   a. 300 cells/mm3
   b. 350 cells/mm3
   c. 400 cells/mm3
   d. 600 cells/mm3

6. Results of a study conducted by Schackman et al published in 2001 suggested that patients initiating ART therapy at 500 cells/mm3 could expect to live an additional _______ years as a result of treatment:
   a. 9.1 years
   b. 7.5 years
   c. 6.3 years
   d. 10.6 years

7. All of the following are considered to be limitations to patient adherence with antiretroviral therapy EXCEPT:
   a. Pill burden
   b. Cost of treatment
   c. Requires inpatient administration
   d. Side effects

8. Protease Inhibitors are associated with which of the following side effects:
   a. Upper respiratory tract infection
   b. Insulin resistance
   c. Insomnia
   d. Renal failure

9. Which of the following is considered a role of the pharmacist in improving patient adherence and limiting adverse effects with antiretroviral drugs?
   a. Administering appropriate immunizations
   b. Screening for drug-drug and drug-food interactions
   c. Educating patients on common side effects of their medications
   d. All of the above

10. One argument against earlier initiation of ART therapy is that poor patient adherence will lead to a increased risk of:
    a. Side effects from current medications
    b. Clinically significant bleeding episodes
    c. Liver transplantation
    d. Resistance to antiretroviral drugs

To receive continuing education credit for this program, you must answer the above questions and fill out the evaluation form. Please visit www.onu.edu/pharmacy to enter the required information. Please allow two to three weeks for electronic distribution of your continuing education certificate, which will be sent to your valid e-mail address in PDF format.
To receive continuing education credit for this program, visit [www.onu.edu/pharmacy/CE](http://www.onu.edu/pharmacy/CE) OR fill out the form below including your indicated answers to the assessment questions and return to:

Office of Continuing Education at the Raabe College of Pharmacy
Ohio Northern University
525 South Main Street
Ada, Ohio 45810

### Continuing Education Registration & Evaluation Form
Raabe College of Pharmacy Continuing Education Evaluation Form

<table>
<thead>
<tr>
<th>Program Title:</th>
<th>Recent Advances Spark Significant Guideline Change: Antiretroviral Therapy (ART) at high CD4+ Counts in the Treatment Naïve Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAN:</td>
<td>0048-0000-11-002-H01-P</td>
</tr>
<tr>
<td>CEU’s:</td>
<td>0.1</td>
</tr>
</tbody>
</table>

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid Email address.

**Name:**

**Address:**

**City:**

**State:**

**Zip:**

**Phone:**

**E-mail:**

**Pharmacy License #:**

**State:**

**ONU Alumni?**  Y  N

### Program Content:

**Program Content:**

| The program objectives were clear. | 1 2 3 4 5 |
| The program met the stated goals & objectives; | 1 2 3 4 5 |
| Identify the pertinent laboratory values and/or symptomatology required for antiretroviral therapy initiation in treatment-naïve HIV patients. | 1 2 3 4 5 |
| Describe the limitations of early versus deferred treatment for HIV infection. | 1 2 3 4 5 |
| List the factors that limit patient adherence to antiretroviral therapy. | 1 2 3 4 5 |
| Identify the significant changes made to the newest version of the NIH HIV treatment guidelines. | 1 2 3 4 5 |
| The program met your educational needs. | 1 2 3 4 5 |
| Content of the program was interesting. | 1 2 3 4 5 |
| Material presented was relevant to my practice. | 1 2 3 4 5 |

**Comments/Suggestions for future programs:**

---

**Thank You!**

**Answers to Assessment Questions - Please Circle Your Answer**

1. A B C D
2. A B C D
3. A B C D
4. A B C D
5. A B C D
6. A B C D
7. A B C D
8. A B C D
9. A B C D
10. A B C D

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy. This program is eligible for credit until 1/25/2014

Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administration Assistant for the Office of Continuing Education (e-mail: l-bedford@onu.edu, phone 419-772-1871).