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I ANTI-HIV AGENTS

A. Massive change in U.S. treatment guidelines

For many years the United States Department of Health and Human Services (DHHS) has been producing guidelines to help physicians when they are considering options for the treatment of their HIV-positive patients. The DHHS guidelines are closely watched because they often set the standard to which guidelines in other countries aspire.

For help writing the guidelines, the DHHS crafted a panel of leading infectious disease and other specialists who have experience in the research and treatment of HIV infection.

On December 1, 2009, the DHHS released the latest version of the guidelines for the treatment of adults and adolescents with HIV. There have been major revisions to the guidelines, resulting in a shift toward much earlier treatment.

Usually the guidelines inform physicians which groups of drugs are best used. In another major departure from recent practice, the guidelines now recommend specific regimens of anti-HIV drugs. This may simplify physician decision-making—after all, more than 20 drugs for the treatment of HIV are available in a confusing array of possible combinations. However, in privileging just a few regimens over others, the panel courts controversy.

The DHHS also makes additional guidelines on these topics:

- the treatment of life-threatening infections
- prevention of mother-to-child transmission of HIV
- caring for HIV-positive children

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www.aidsinfo.nih.gov/Guidelines/Default.aspx?MenuItem=Guidelines&Search=On

In this issue of *TreatmentUpdate*, we highlight key changes in the guidelines, particularly in the area of starting treatment.

B. Earlier initiation of therapy recommended

According to the DHHS, the goals of anti-HIV therapy are supposed to be:

- to maximally and durably suppress HIV in the blood
- to reduce HIV-associated illness and prolong survival
- to improve quality of life
- to restore and preserve the immune system
- to prevent HIV transmission

Readers should note that the effectiveness of treatment in preventing the sexual transmission of HIV is controversial and is still being studied.

Additionally, the authors of the guidelines hope that HIV suppression with anti-HIV therapy may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other health conditions that affect HIV-positive people.

Perhaps the most controversial changes to the DHHS guidelines are in the section on when to start anti-HIV therapy. Over most of the past decade, the DHHS has encouraged doctors to delay starting therapy until later in the course of HIV disease. This was mostly because regimens were cumbersome and had side effects.

However, in the past several years, newer treatments have become more commonly available and co-formulations—putting two or more drugs into one pill—have become standard. This means that the number of pills a person has to take each day, at least when starting therapy, is reduced. Indeed, there is even one pill containing three potent anti-HIV drugs that only has to be taken once daily. Also, medicines used today are generally better tolerated than those a decade ago. So doctors and their patients have more options.

Deep divisions

The usual procedure for the creation and revision of the guidelines is for the guidelines committee or panel to make recommendations and there is usually consensus for these recommendations. However, when revising the recent guidelines, the panel members found that there was no consensus about several major issues. For the first time, decisions of the panel are accompanied by a breakdown in the vote. We will explain these as we cover key issues in the guidelines.

When to start?

For the past several years, major HIV treatment guidelines in the United States and Europe have generally recommended that therapy begin when a key marker of the immune system—the level of CD4+ cells in the blood—has fallen below a threshold of 350 cells. Certainly the panel continues to recommend this. However, they now go beyond this.

Recent results from large observational studies were considered when formulating the new guidelines. These results suggest that the risk of major disease-related events were greatly reduced when HIV-positive people began therapy when their CD4+ counts were between 350 and 500 cells. The events that were avoided were as follows:

- death
- AIDS-related illness
- illness from causes unrelated to AIDS

Based on these results the panel now recommends that HIV-positive people begin therapy when their CD4+ count falls below the 500-cell mark.

However, it is important to note that the panel was deeply divided on this issue: 55% of members voted to strongly recommend this change while 45% felt that starting early deserved only a moderate recommendation.

Should all HIV-positive people be on therapy?

One question the panel dealt with was: What about starting therapy when the CD4+ count is above 500 cells (essentially this would recommend immediate therapy for *all* HIV-positive people)? On this issue the panel was again divided. Half of the panel was in favour of starting therapy at this stage, while the other 50% felt that therapy at high cell counts should be "optional."

There are several reasons why therapy might start very early, such as the following arguments made by some panel members:

- Results from one large observational study show improved health with early therapy.
- In the present era, emerging data suggest that untreated HIV infection is associated with an increased risk for diseases not usually considered AIDS-related, such as cardiovascular, kidney and liver diseases, as well as certain cancers including liver, lung and skin tumours.
- Currently available therapies are better tolerated, more effective and more convenient than older therapies.
- There are hints that some people who take anti-HIV therapy may be less infectious, although the evidence is not conclusive.

The other half of the panel made the following arguments against early therapy:

- There is no conclusive evidence that early anti-HIV therapy will benefit every person whose CD4+ count is more than 500 cells.
- Though treatments are more tolerable today than they were 15 years ago, these drugs still carry both short-term and long-term risk for side effects.
- As anti-HIV therapy has to be taken for the rest of a person's life, there may be problems maintaining adherence over the long-term in people who begin therapy when they are largely symptom-free, as are most people who have CD4+ counts above 500 cells. Difficulty maintaining adherence may give rise to drug-resistant and therefore hard-to-treat strains of HIV, reducing future treatment options.

The psychology of shock

One issue apparently not considered by the panel members is the psychological shock many otherwise healthy and symptom-free HIV-positive people would have if the panel, however divided, had indeed recommended that *all* HIV-positive people start therapy regardless of CD4+ count or other factors.

At best, receiving a diagnosis of HIV infection is a traumatizing event; people, their friends and family need time to adjust to this. For some HIV-positive people such adjustment can take years. Even with acceptance of a changed health status, the additional shock of the news about having to take a complex drug regimen for the rest of one's life may cause additional distress.

Also, today in high-income countries, many people who are HIV-positive may have other unrecognized, undiagnosed or unacknowledged pre-existing health issues that they may also need support to manage, such as:

- depression
- hepatitis B and C virus co-infection
- addiction

The news of their HIV status and the fact that they have to start medication very soon and deal with other health issues could overwhelm some people.

A note on study design

Data from observational studies suggest that there is a benefit from the early initiation of therapy. However, observational studies, by their nature, can only find associations; they **cannot** prove that taking therapy at high CD4+ counts will ultimately benefit people. What's more, because of confounding or channeling bias—a problem with observational studies that makes drawing firm and accurate conclusions when interpreting the data difficult. Such confounding may explain why different research teams have reached different conclusions about abacavir and its possible relation to cardiovascular disease.

Observational studies can produce interesting results and be very useful. These results can then be used to inform studies of a more robust design, such as randomized, controlled clinical trials. We will now take a brief look at a couple of the large observational studies that underpin recent decisions by the guidelines' panel. This exercise will highlight some of the issues of relying on these trials and may explain some of the panel's voting patterns.

The NA-ACCORD

A large Canada-U.S. study called the NA-ACCORD found that among 2,200 HIV-positive participants who began therapy when their CD4+ count was greater than 500 cells, the risk of death was significantly lower than seen in 6,935 HIV-positive participants who began therapy when their counts fell below 500 cells. The panel notes that although the difference in death rates was statistically significant, the number of deaths that occurred was relatively small.

ART-CC

Another large observational study, the ART-CC has a database with health-related information on more than 60,000 HIV-positive people. In analysing its data, the ART-CC research team

found that there was no benefit to starting therapy when the CD4+ count was greater than 450 cells. This analysis also found that the number of people who entered the study with a cell count between 451 and 550 cells and who later developed AIDS or died before their CD4+ count slipped below the 450-cell mark was low.

As previously mentioned, observational studies cannot produce definitive results. And despite the lack of definitive results, 50% of the panel felt that therapy should be started when the CD4+ count is more than 500 cells. In effect, half the panel thinks that all HIV-positive people should be on therapy.

What to do?

When discussing the possibility of starting therapy at high CD4+ counts (more than 500 cells), the panel stated this:

> "Clinicians should inform patients that data on the clinical benefit of starting treatment at such [CD4+ cell] levels is not conclusive. There is a need for further ongoing research (both with randomized clinical trials and cohort studies) to assess the short- and long-term clinical and public health benefits and cost-effectiveness of starting therapy at higher CD4+ counts."

Special considerations for early treatment

The American panel, like similar committees in the European Union, recommends that anti-HIV therapy begin regardless of CD4+ count in HIV-positive people with the following circumstances or conditions:

- pregnancy – to prevent mother-to-child transmission
- HIV-related kidney damage
- hepatitis B virus (HBV) co-infection when there is a need to begin anti-HBV therapy – because several drugs that are used to treat HIV infection also have activity against HBV

Other conditions

The panel stated that in some cases the initiation of therapy may take on added urgency because of special circumstances, including these:

- the diagnosis of a life-threatening infection
- having low CD4+ counts (less than 200 cells)
- having CD4+ counts that decline rapidly from year to year, in other words, losing more than 100 CD4+ cells per year
- having a high viral load (more than 100,000 copies).

REFERENCE:

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* Department of Health and Human Services. December 1, 2009; 1-161.
Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. [Accessed 10 December 2009].

C. Considering delaying the start of therapy

Rushing the initiation of therapy is rarely a good idea and the panel writes that "some patients and their clinicians may decide to defer therapy for a period of time based on clinical or personal circumstances." Although deferring therapy might be reasonable for patients with high CD4+ cell counts, the panel states that "deferral for patients with much lower CD4+ counts (less than 200 cells) should be considered only in rare situations and should only be undertaken with close clinical follow-up. A brief delay in initiating therapy may be considered to allow a patient more time to prepare for lifelong treatment."

Next are some issues that doctors and patients may encounter that might affect the decision to initiate or delay therapy.

Adherence

A high level of adherence to HIV treatment is vital to minimize the risk of developing drug resistance and reducing future treatment options. The panel notes that in cases where patients may be at risk of poor adherence, it may be "prudent" to defer treatment while the barriers to adherence are being addressed. However, in cases where the initiation of anti-HIV therapy is considered urgent, physicians may override their concerns about adherence. When might therapy be needed urgently? See "Other conditions" listed toward the end of section B in this newsletter.

Severe co-existing health issues

The guidelines state that delaying the initiation of anti-HIV therapy may be considered when "either the treatment or manifestations of other medical conditions could complicate the treatment of HIV infection or vice versa." The panel provides these examples to highlight this point:

- the need for surgery that could result in a significantly prolonged interruption of therapy
- taking medicines that have clinically significant drug interactions with anti-HIV therapy

The panel assumes that both of the conditions or situations mentioned above are temporary and that anti-HIV therapy will swiftly begin after these problems have been resolved.

There are certain rare situations in which physicians may choose to not prescribe anti-HIV therapy. Usually these are cases where patients have other conditions that considerably shorten their life span or cause very poor quality of life, such as these:

- the presence of incurable cancers unrelated to HIV infection
- the final stage of liver disease where extremely ill health precludes transplantation

Elite controllers

Researchers have coined the term "elite controllers" to describe an unusual group of HIV-positive people (less than 1%) who can have suppressed viral loads and high CD4+ cell counts for many years without using treatment. It is possible that elite controllers may somehow benefit from the early use of anti-HIV therapy. However, there is no data to support such an idea. So the panel did not recommend treatment for this group of people.

D. What to use for initial therapy

In previous versions of the guidelines, the panel presented readers with recommendations for the use of individual drugs. Now the panel has taken the bold step of recommending specific regimens for the initial treatment of HIV.

The panel asks physicians to consider the following factors so that treatment can be individualized for each patient:

- co-existing health conditions – such as cardiovascular, kidney, liver and psychiatric diseases, addiction and tuberculosis (TB)
- potential drug side effects
- results of HIV drug resistance testing
- if considering nevirapine (Viramune), take into account the person's gender and CD4+ count (this is explained later)
- if considering maraviroc (Celsentri), consider the use of tropism testing
- adherence
- convenience

Here are some medicines that are mentioned throughout this issue of *TreatmentUpdate*:

Nukes

- AZT (zidovudine, Retrovir)
- 3TC (lamivudine)
- AZT + 3TC in one pill (Combivir)
- abacavir (Ziagen)
- abacavir + 3TC in one pill (Kivexa)
- FTC (emtricitabine, Emtriva)
- tenofovir (Viread)
- tenofovir + FTC in one pill (Truvada)

Non-nukes

- efavirenz (Sustiva)
- efavirenz + tenofovir + FTC in one pill (Atripla)
- nevirapine (Viramune)
- etravirine (Intelence)

Protease inhibitors

- atazanavir (Reyataz)
- darunavir (Prezista)
- fosamprenavir (Telzir)
- lopinavir + ritonavir in one pill (Kaletra)
- ritonavir (Norvir)
- saquinavir (Invirase)

Integrase inhibitors

- raltegravir (Isentress)

Preferred regimens

The panel recommends any one of these three specific regimens for the initial treatment of HIV infection:

- Atripla
- atazanavir-ritonavir + Truvada
- raltegravir + Truvada

For pregnant women, the panel recommends this combination:

- Kaletra + Combivir, where Kaletra is dosed twice daily

Caution

Here are some concerns noted by the panel:

- Because efavirenz (found in Sustiva and Atripla) can cause birth defects when given during the first three months of pregnancy, the panel warns

that this drug should not be used during that time or by women who want to become pregnant.
- Atazanavir-ritonavir should not be used in patients taking more than 20 mg/day of the acid-reducing agent omeprazole (Losec) or similar drugs.

Alternative regimens

The panel defines alternative regimens as ones that are tolerable and effective but have potential disadvantages compared to preferred regimens.

Here are the alternative regimens proposed by the panel:

- efavirenz + Combivir
- efavirenz + Kivexa
- nevirapine + Combivir
- atazanavir-ritonavir + Combivir
- atazanavir-ritonavir + Kivexa
- fosamprenavir-ritonavir + one of these: Combivir or Kivexa or Truvada
- Kaletra + one of these: Combivir or Kivexa or Truvada
- saquinavir (Invirase) + Truvada
- tipranvir (Aptivus)

Caution

The panel warns that nevirapine should not be used in people with moderate or severe liver damage. It should not be used in women who have more than 250 CD4+ cells or in men who have more than 400 CD4+ cells because of the risk for severe or life-threatening side effects.

Abacavir should not be used in people who test positive for abacavir hypersensitivity. The panel also warns that it should be used cautiously in patients at high risk for cardiovascular disease or in those who have high pre-therapy viral loads (more than 100,000 copies).

Issues to consider—protease inhibitors

A large European database called DAD has found that the use of lopinavir-ritonavir (Kaletra) or indinavir (Crixivan) was associated with an increased risk of heart attack, heart disease and stroke.

Another large database, the French Hospital Database (FHDB), has found that the use of fosamprenavir (Telzir) or Kaletra was linked to an increased risk of heart attack.

Issues to consider—abacavir

The DAD study has found an association between the recent use (within the first six months) of abacavir and an increased risk of heart attack, particularly among people with pre-existing cardiovascular disease. Some clinical trials have also found this association, while others have not. The FHDB's most recent analysis linked heart attacks in people taking abacavir to the use of cocaine and other illicit substances.

Because of these different findings in different databases and studies, the panel notes that "no consensus has been reached yet on the association or possible mechanism to explain why abacavir might be associated with a heart attack."

What's more, the panel also underscored the issue of confounding or "channeling bias"—a problem with observational studies that makes drawing firm and accurate conclusions when interpreting the data difficult. Such confounding may explain why different research teams have reached different conclusions about abacavir and its possible relation to cardiovascular disease.

E. Simplifying therapy

The panel provides several scenarios for doctors to consider when thinking about simplifying a patient's regimen. The panel takes a broad view of simplification—this can mean anything from taking fewer doses to enhancing tolerability to reducing food and water requirements needed by some regimens. Simplifying therapy can help to improve the quality of life of some patients. Studies have found that simpler regimens are associated with better adherence.

According to the panel, patients who are taking their first regimen and who do not have a history of treatment failure are ideal candidates for regimen simplification.

In selected cases, the panel notes that even people with previous documented or suspected drug resistance may be appropriate candidates for simplification provided that their current regimens are fully suppressive.

The panel provides detailed scenarios in which simplification may occur. It also offers tips for helping to make a smooth transition in order to ensure that the new regimen is working. One of the most important points made by the panel is

that close monitoring for the first two to six weeks after simplifying a regimen is needed to ensure tolerability of the new regimen as well as to ensure viral and immunologic response to therapy.

F. What not to use

As with previous guidelines, the panel added to a growing list of drugs or combinations of drugs that should not be used for the initial therapy of HIV infection. In general, specific combinations are not recommended because of insufficient efficacy, drug interactions or insufficient information on how they work in people who have not previously used these medicines.

Modern monotherapy

In recent years, there have been several studies of just one active drug (such as the use of a ritonavir-boosted protease inhibitor) in a regimen for maintenance therapy. That is, in clinical trials, a conventional triple-drug regimen is used to suppress viral load and raise CD4+ counts for one year, then participants are switched to one of these simple regimens for maintenance:

- atazanavir-ritonavir
- darunavir-ritonavir
- lopinavir-ritonavir

These regimens are being studied in clinical trials and are considered investigational and therefore **not** recommended by the panel.

Other combinations that are not recommended by the panel include the following:

- atazanavir + indinavir; increased toxicity
- ddI + d4T; increased toxicity
- d4T + AZT; reduced anti-HIV activity
- any two non-nukes; increased toxicity
- FTC + 3TC; may interfere with each other
- etravirine and unboosted protease inhibitors; inadequate levels of the protease inhibitors may occur
- etravirine and ritonavir-boosted atazanavir or fosamprenavir; inadequate drug concentrations may occur
- etravirine and ritonavir-boosted tipranavir; inadequate etravirine levels may result
- nevirapine – initiating therapy with this drug in women whose CD4+ counts are greater than 250 cells or in men whose CD4+ counts are greater than 400 cells should not be done (because of a risk of life-threatening side effects) unless "the benefit clearly outweighs the risk"
- unboosted darunavir, saquinavir or tipranavir; inadequate drug levels will occur

G. Acute HIV infection—should it be treated?

There is very limited data on the use of anti-HIV therapy in people with acute HIV infection. The panel writes:

> "The health care provider and the patient should be fully aware that the rationale for therapy of acute HIV infection is based on theoretical considerations, and the potential benefit should be weighed against the potential risks."

At this time the panel considers treatment of acute HIV infection to be "optional."

H. Reducing the risk of HIV transmission

The panel is aware of research from high-income countries that suggests an increase in unprotected sex that began after the introduction of potent anti-HIV therapy. Indeed, in some studies, rates of unprotected intercourse have doubled since that time.

An analysis of several risk-behaviour studies—a meta-analysis—has found that people who believed that taking anti-HIV treatment or having an undetectable viral load in the blood prevented HIV transmission were more likely to engage in unprotected intercourse.

Data from observational studies suggest that anti-HIV therapy may reduce the risk of HIV transmission among heterosexual couples. Observational or cohort studies are good at finding associations but they cannot prove that taking anti-HIV medicines will prevent the transmission of HIV.

In 2008, a trio of Swiss researchers issued an opinion stating that HIV-positive people were sexually non-infectious under the following conditions:

- they were taking anti-HIV therapy and their viral load was consistently undetectable; that is,

less than 40 or 50 copies, depending on the assay used
- there was complete adherence to therapy
- they were in a stable relationship
- they had no sexually transmitted infections (STIs)

Although under these conditions viral load in the genital fluids may sometimes be reduced, the panel wrote:

> "There is not yet published evidence from randomized clinical trials that confirms the reduction or elimination of risk of HIV transmission [with anti-HIV therapy]."

Moreover, the panel highlighted recent findings that showed that HIV has been detected in the semen of men and genital secretions of women despite suppressed HIV in the blood because of therapy. Obviously this poses a risk for transmission.

The panel reminds health care providers that they have a role to play when it comes to initiating discussion about safer sex. The panel goes on to say that an undetectable viral load in the blood does not mean that there is also an undetectable viral load in genital fluids. Furthermore, despite the use of anti-HIV therapy, HIV infection can occur during unprotected sex.

Since STIs help increase the risk of transmitting HIV—by inflaming tissue, causing sores and lesions—doctors should regularly question their patients about symptoms possibly caused by STIs and regular lab testing for these germs is necessary.

I. Hepatitis C virus co-infection

Long-term studies have found that about 33% of people with HCV mono-infection develop severe liver damage in about 20 years after infection. However, the following factors can accelerate the course of liver disease:

- older age
- alcohol abuse
- being male
- having HIV infection

Analysis of several studies in people co-infected with HCV and HIV suggest that the speed at which severe liver damage occurs is about three times greater in cases of co-infection, particularly when CD4+ counts are low.

Before beginning HIV therapy, the panel encourages doctors to test their HIV-positive patients for HCV infection.

Here are some critical points about care that the panel mentions:

- "Co-infected patients should be advised to avoid alcohol consumption, use appropriate precautions to prevent the transmission of both viruses to others, and should be given hepatitis A and B vaccines if [they do not have immunity to these germs]."
- All co-infected patients should be evaluated for HCV therapy.
- The panel recommends treatment for co-infected patients, particularly those with high CD4+ cell counts, according to standard HCV guidelines.
- In patients with less than 200 CD4+ cells, the panel suggests initiating anti-HIV therapy and waiting until cell counts increase before starting HCV therapy.
- Bone marrow stimulants may be needed to reduce the impact of side effects from HCV medicines.

HIV treatment considerations for people with HCV co-infection:

- ddI should not be used with the antiviral drug ribavirin because of the potential for severe toxicity.
- AZT should not be used by people taking ribavirin because of the potential for increased toxicity.
- Although some retrospective studies suggest that the drug abacavir (Ziagen and in Kivexa) may not work well in people taking HCV therapy, there is no robust data from well-designed trials to confirm this. Therefore, the panel does not discourage the use of abacavir in cases of co-infection.

Liver injury

Exposure to anti-HIV drugs may cause liver injury, particularly in people co-infected with HCV and HIV. The greatest risk for this toxicity occurs in people with severe liver damage, cirrhosis or end-stage liver disease. Successful treatment of HCV infection may decrease the chance of liver injury caused by anti-HIV therapy.

Starting anti-HIV therapy

The panel recommends that co-infected people begin therapy once CD4+ counts fall below the 500-cell mark. It recommends the same combinations for co-infected people as for HIV-mono-infected people.

Anti-HIV drugs to avoid

The panel recommends that patients considering or receiving ribavirin should avoid the use of these anti-HIV drugs:

- AZT (zidovudine, Retrovir and in Combivir)
- d4T (stavudine, Zerit)
- ddI (Videx EC)

J. Treatment-experienced patients

According to results from clinical trials, the majority of HIV-positive people benefit from anti-HIV therapy. What's more, in some studies participants are able to prolong their suppression of HIV for three to seven years, depending on the study. However, sometimes anti-HIV therapy can fail. The panel recommends that the reasons for treatment failure be investigated and that treatment failure should be treated "aggressively."

Treatment failure can occur for many reasons. There are some issues that may predispose people to an increased risk for treatment failure even before they start therapy, such as:

- being infected with a strain of drug-resistant HIV
- having a high viral load before starting therapy
- having a very low CD4+ cell count prior to starting therapy
- having had a diagnosis of AIDS
- co-existing health problems, such as depression and/or active substance use

There are further issues that may play a role in treatment failure after people start therapy, such as:

- incomplete adherence and missing clinic appointments
- experiencing drug side effects
- the presence of less-than-normal concentrations of anti-HIV drugs in the blood, caused by poor absorption or drug interactions
- the use of weak regimens
- insufficient physician experience treating HIV infection
- other, unknown reasons

When making decisions about therapy for treatment-experienced patients, the panel emphasizes the importance of resistance testing, reviewing treatment history and using *active* anti-HIV drugs in a new regimen. The panel provides extensive and helpful tips for doctors who care for treatment-experienced patients.

Disclaimer

Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

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