

# ANTI-HIV THERAPY STRATEGIES



## information to consider when deciding to use therapy

A PUBLICATION FROM

PROJECT  
*inform*

Information,  
Inspiration and  
Advocacy for People  
Living With HIV/AIDS

MARCH 2004

HIV (Human Immunodeficiency Virus) is a virus that infects and takes over certain cells of the immune system, which is our body's defense against infections and diseases. These cells are important in fighting disease. Once infected, the virus uses the cells to make new copies of itself (replicates), which then go on to infect other cells. Infected cells function improperly and die prematurely, weakening the immune system and permitting the development of opportunistic infections (infections that take the opportunity to flourish when the immune system is damaged by HIV).



The overall goal of anti-HIV therapy is to slow or stop the ability of HIV to reproduce, and thereby slow or stop the progression of HIV disease and the destruction of the immune system. While other approaches of combating HIV infection have been proposed and tested, thus far only anti-HIV therapy has been proven to slow disease progression and extend life.

While understanding and making decisions about anti-HIV therapy can be an overwhelming process, it isn't insurmountable. With the support

of your doctor and reliable information, it's possible to devise a wise anti-HIV strategy. A balanced approach to such a strategy must include knowledge of the benefits, risks and limitations of existing therapies, and the prospects for improvements offered by combination therapies and newer drugs.

This publication provides information on these decision points. It is intended to be a tool in making the best possible decision about the use of anti-HIV therapies in adults and adolescents.

## the goals of anti-hiv therapy

The goals of anti-HIV therapy should be to:

- **PROLONG** life and improve quality of life for the long-term;
- **SUPPRESS** virus to below the limit of detection on current tests (<50 copies HIV RNA), or as low as possible, for as long as possible;
- **OPTIMIZE** and extend the usefulness of the currently available therapies; and
- **MINIMIZE** drug toxicity and manage side effects and drug interactions.

Once HIV was identified as the cause of acquired immune deficiency syndrome (AIDS), stopping or slowing its replication became a major goal. Significant progress has been made towards reaching this goal, especially with the advent of potent drugs and the use of combination therapy. This has made it possible to develop long-term strategies for managing HIV.

Yet uncertainty remains about when to start and when to switch or how best to combine anti-HIV therapies. Also, the failure of existing drugs to remain completely effective for long periods of time is sometimes misunderstood as meaning that the drugs don't work at all. Making wise decisions about the use of anti-HIV therapies requires understanding the benefits and risks of therapies, good communication with a knowledgeable doctor, and proper use of various lab tests.

It's important to remember that people can live a long time, without symptoms of HIV disease and without using anti-HIV therapy. Thus many, if not most, people don't have to decide about using therapy immediately after learning that they're living with HIV. Assessing your personal risk of HIV disease progression and making decisions that you feel comfortable with and empowered by is part of the key to a successful long-term anti-HIV strategy.

## The challenge of therapy

Many researchers believe that unless HIV replication can be controlled, other efforts at rebuilding immune health will ultimately fail. Although anti-HIV therapies weaken the virus' ability to replicate, they're not a cure since they have not been shown to totally eradicate HIV from the body. Many scientists fear that it will not be possible to fully eradicate it from the body, no matter how good the drugs become or how early treatment is started.

Over time, the virus *mutates* or changes itself enough so that it is no

longer affected by these drugs. This process is called *viral resistance* and is likely to happen with almost all anti-HIV drugs to some degree. It's still clear, however, that suppressing the virus from replicating lengthens a person's survival time and it may be possible, with truly effective therapy, to live out a normal lifespan despite HIV infection. For more information on viral resistance, read Project Inform's publication, *HIV Drug Resistance Tests*.

Even with the limitations of current therapies, however, there's

increasing evidence that using potent anti-HIV therapy has had a dramatic impact on decreasing death rates and increasing life and quality of life of people living with HIV. However, the drugs are not without the risk of side effects, and potential short- and long-term side effects must be weighed against their potential short- and long-term benefits when making decisions about using therapies, particularly when considering when to start.

## Why use anti-HIV therapy?

When a person is first infected with HIV, high virus levels develop that are often accompanied by flu-like symptoms and a decline in the number of CD4+ cells. These are key cells in maintaining and directing immune responses against disease. They are also a common measure of immune health.

Without using anti-HIV therapy, the immune system produces dramatic but incomplete suppression of the virus.

In most cases, CD4+ cell counts return partially toward normal levels and a person usually regains good health for many years. Studies show that even during this time of seemingly good health, there's an aggressive battle waged daily between HIV and the immune system. Over time the immune system is overwhelmed by HIV's rapid and constant activity.

There's a clear relationship among increased levels of HIV found in blood (viral load), more advanced disease states, and increased risk of disease progression. As a general rule, the more virus being produced in the body, the more rapidly disease progresses. Several studies show that when viral load is reduced and CD4+ cell counts increase for six months or longer, disease progression and death are delayed.

Considering these points, it makes sense to attempt to slow down or stop the replication of HIV as much and for as long as possible. A number of drugs have been shown to significantly reduce HIV levels, and these drugs almost always cause some rise in CD4+ cell counts. The reduction in viral load and increase in CD4+ cell counts indicate some improvement in the immune system. Anti-HIV drugs that fail to reduce HIV levels also generally (but not always) fail to improve measures of immune health such as CD4+ cell counts.

It remains unclear when the best time to start therapy is. The "best" time for one person might not be the "best" time for another. Several factors, including HIV levels, CD4+ cell count as well as how you feel about therapy, are important to consider when determining if and when anti-HIV therapy is right for you. For more information, read Project Inform's publication, *Strategies for When to Start Anti-HIV Therapy*, available at 1-800-822-7422 or [www.projectinform.org](http://www.projectinform.org).



### the basic message from project inform

- › Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!
- › If you're positive, don't panic. If you make your health a priority, chances are you will be reasonably healthy for many years.
- › Learn about your healthcare options and local support services.
- › Get a complete physical and blood tests for CD4+ cell count & HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.
- › Work with a doctor to develop a long-term strategy for managing HIV disease.
- › If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.
- › If therapy fails to reduce your HIV level below the "limit of detection" or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.
- › If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven't already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.
- › If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.
- › If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps even monthly. Consider therapies for preventing MAC/MAI and CMV.
- › Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.

## When should I start treatment?

There's much debate about when to start anti-HIV therapy, which drugs to start with, and in what combinations. Should treatment be used immediately when people first learn they're infected, or should it be saved until there are changes in immune health (noted by a decrease in CD4+ cell counts), increases in HIV levels, or until symptoms of HIV develop? These and other questions need to be considered when deciding when and which combinations to use.



In deciding when to start, switch or change anti-HIV regimens, there are generally three medical factors to consider:

- › What's happening with your HIV levels?
- › What's happening with measures of your immune health (particularly CD4+ cell counts)?
- › What's happening with your general health status (such as symptoms of HIV disease or recurrent health conditions despite treatment)?

The decision to begin treatment is not solely a medical matter. Other factors must be considered, including:

- › Your feelings about anti-HIV therapy (if you believe a particular drug or treatment regimen will harm you, then you should consider carefully before deciding to take them);
- › Your readiness and willingness to commit to taking therapy, including your ability to take them as prescribed;
- › The impact therapy will have on your quality of life;
- › The side effects of the therapies;
- › How long therapies can last, and whether or not there will be new and better drugs to replace them if or when they fail; and,
- › Your risk of disease progression in the short-, middle-, and long-term.

## When is the right time to start?

There's no single, right answer to the question of when to start anti-HIV treatment. Some researchers and doctors believe that nearly everyone who is HIV infected—regardless of viral load, symptoms or CD4+ cell counts—should be on treatment. Some believe people should begin therapy only when their CD4+ cell count consistently reads below 300 or their viral load consistently exceeds 30,000–55,000. Others believe that only people with symptoms of HIV disease should consider anti-HIV therapy.

One note of agreement is that most researchers and doctors believe that the decision to start therapy should be guided by looking at overall general health and measures of both CD4+ cell counts and viral load. Increasingly information suggests that CD4+ cell counts, coupled with

viral load tests, provide the most accurate tool to monitor the risk of HIV disease progression.

The most commonly used viral load tests are Roche's RT-PCR (polymerase chain reaction test, called Amplicor HIV Monitor Test), Chiron's bDNA (branch DNA test, called Quantiplex) and Organon Teknika's NASBA (nucleic acid sequence based amplification test, called NucliSens).

It is important to use the same lab and the same test every time as RT-PCR viral load results are consistently higher than those obtained with bDNA. For more information on viral load tests, read Project Inform's publication, *Blood Work: A Useful Tool for Monitoring HIV*, available at 1-800-822-7422 or [www.projectinform.org](http://www.projectinform.org).

## Quality of life issues

The ability to tolerate side effects, drug interactions, and the demands of a particular regimen can be as important as the potency of a drug. If you can't take a drug consistently as prescribed, its potency is irrelevant. Not adhering to a drug regimen will quickly contribute to developing drug resistance, which may include concerns about cross-resistance to many or all other drugs in its class. When choosing a combination, consider the daily pill count (anti-HIV drugs, drugs to prevent and treat other infections, and everything else). Also, consider when they have to be taken, whether they can be taken with other medications, and whether they can be taken with food.

It is easiest to combine drugs that require similar conditions for their use (with or without food, etc.). Otherwise, one's life can become dominated by drug schedules. It is also best to avoid mixing drugs with similar side effects, though sometimes this is impossible. And it is critical to learn about the possible side effects of each drug in a regimen as well as possible drug interactions before mixing any of these drugs together. To help with understanding these issues, Project Inform has materials on each anti-HIV drug as well as the publications, *Drug Side Effects Chart*, *Dealing with Drug Side Effects* and *Drug Interactions*.

While each drug has potential side effects, not everyone who takes a drug will experience them. Learning about possible side effects before taking a drug will allow you to be aware of what types of side effects to check for and to consider approaches to prevent or manage them, proactively. The

more informed you are about the possible side effects and drug interactions of the drugs in a given regimen, the less likely you are to experience severe or life-threatening side effects. Moreover, if someone is prepared for possible side effects, with a plan for managing side effects should they arise, the less likely it is that they'll interfere with adherence.

Information on side effects associated with body composition and the body's ability to process sugars and fats is surfacing. These conditions are called generally called *lipodystrophy*—and include fat accumulation (*lipohypertrophy*) and/or fat loss (*lipoatrophy*) and/or changes in lab values of fats (*dyslipidemia*) or sugars/insulin (*diabetes*). Another condition, impacting the energy source of cells



(*mitochondrial toxicity*) is particularly associated with using NRTIs. Reports of some people experiencing bone weakness have also begun to emerge. All of these conditions might result from long-term use of anti-HIV medications. For more information on these conditions, call Project Inform's toll-free hotline at 1-800-822-7422.

### viral load and women: an additional consideration?

Several studies have suggested that women have lower HIV levels than men at the same CD4+ cell count. Some suggest that these differences decrease or disappear after the first five years of HIV infection.

Current Public Health Service guidelines acknowledge that viral load may be somewhat lower in women, but these differences don't alter the goals of anti-HIV therapy—to lower HIV levels to as low as possible and impact CD4+ cell count and overall general health. They conclude that these data should not affect the approach to therapy for women or for men. More data are needed to confirm the degree and relevance of this noted difference.

The US Department of Health and Human Services released *Guidelines for the Use of Antiretroviral Agents in the Treatment of HIV-Infected Adults and Adolescents*. These are summarized in the table on page 11.

The Federal Guidelines describe the recommendations of researchers, and point out that people with HIV and their doctors must take many other factors into consideration, such as the person's readiness to start treatment and concerns about long-term toxicity and drug resistance.

# Points to think about for people who consider taking anti-HIV therapy

There are many issues to consider and discuss with your doctor before taking anti-HIV therapy. (For more information on specific drugs, call Project Inform's Hotline.) The following issues are offered for consideration for people who are starting therapy for the first time (first line therapy) as well as for those who are switching therapies (second or third line therapy).

1

Reducing viral load as low as possible, preferably below the level of detection, should be an important goal of therapy.

Drug regimens that have a larger, more consistent and longer-lasting effect in reducing HIV levels and increasing CD4+ cell counts are more likely to produce longer-lasting health and survival benefits. People with HIV levels below the limit of detection have a much longer lasting anti-HIV response to a given regimen than people with consistently detectable HIV levels. When therapy fails to reduce HIV levels to below the limit of detection, it's usually a sign that it will fail over the next several months. Studies show, however, that occasional "blips" in viral load (a detectable reading every now and again) does not represent a major concern. Trends over time are more important than any single lab report.

Today, viral load tests measure reliably down to 20 copies. Any number below this is considered *undetectable*. Some researchers believe that people who do not reach undetectable levels after six months on therapy should consider either switching to a new regimen or, if viral levels are detectable but remain very low (like <1,000), adding another drug. Others believe it might be okay for a person with few other options to continue using a regimen if it's controlling viral levels at a low (like <5,000), yet detectable level. While studies show that reaching "undetectable" viral load is optimal, the cost of side effects or the complexity of a regimen necessary to achieve this goal might not be realistic for everyone.

2

There may be some degree of cross-resistance between the drugs in the same class.

Resistance to a drug occurs when HIV changes or modifies itself such that it's no longer crippled in its replication cycle by the effects of a drug. Cross-resistance is when resistance to one drug also causes resistance to other drugs in the same class. (For more information on resistance and resistance testing, read Project Inform's publication, *HIV Drug Resistance Tests*.) Resistance usually occurs when the drugs being used are not potent enough to completely stop HIV replication or when the drugs are not taken as prescribed.

For instance, someone with resistance to one of the NNRTIs\* is almost certainly going to be cross-resistant with the other approved NNRTIs. What this means is that once resistance to one NNRTI develops, the other drugs in this class are less effective, and possible wholly ineffective.

\* Note: NNRTIs are a class of anti-HIV drugs. See the drug chart, page 8.

3

Successful long-term use of therapies is more important than short-term gains.

It's possible to get short-term benefits at the cost of wasting potential long-term benefits. An example of this would be starting a two-drug NRTI\* regimen in a person with high HIV levels (above 100,000). Studies show that resistance can develop within weeks to months after starting a two-drug NRTI regimen. This may impact the usefulness of other similar drugs as well as eliminating options for future therapies.

\* Note: NRTIs are a class of anti-HIV drugs. See the drug chart, page 8.

4

Should I get a resistance test?

Several studies show that people who selected therapies based on resistance testing in addition to considering their history of using anti-HIV drug had longer lasting responses to anti-HIV regimens compared to people who didn't get resistance tests before making decisions. Some researchers are proposing that people get a resistance test before they start anti-HIV therapies for the first time as well as before they switch to a new regimen.

[Note: In order to run a resistance test, a person must have a viral load above 1,000. Resistance testing cannot be done accurately on people with HIV levels below the limit of detection (50). Also, resistance tests are likely most reliable when conducted while someone is taking anti-HIV therapy.]

5

The use of treatment that is only partly effective speeds the development of viral resistance.

If a treatment reduces viral load but still permits a measurable level of viral activity (a measurable viral load), the HIV that's still present is capable of mutating and developing resistance to that treatment. When a three-drug combination doesn't quite succeed in stopping measurable viral activity, many researchers believe it may be wise to either change two of the drugs, or perhaps add a fourth drug.

It makes sense to try and fully suppress viral replication if this can be done with a reasonable quality of life. When this goal cannot be achieved, people should realize they can still benefit from therapy and that longer-term solutions may become apparent when other therapies are available. Again, using resistance testing may help in guiding which therapies are not working or which ones may be useful to add to a regimen.

Learn about drug interactions.

6

With the number of drugs available to treat HIV and prevent or treat opportunistic infections, as well as other conditions, the potential for drug interactions increases. Not only does each therapy have its own possible side effects, it also may increase or decrease the benefit of other drugs. Drug interactions are not always considered when creating a treatment strategy, but they may play a major role in the success of any treatment plan. Make sure your healthcare provider knows about all the therapies you take, including experimental and over-the-counter products. For more information, read Project Inform's publication, *Drug Interactions*.

Using a drug exactly as prescribed is critical to success.

7

Using an inadequate dose, reducing the dose below prescribed levels, or failing to take the drug at regularly spaced intervals will increase the risk of developing resistance. If intolerance or side effects develop, it's often better to try to overcome the side effects than to immediately change the regimen. If side effects aren't manageable, it's better to temporarily stop all the drugs in the regimen rather than reduce doses, and try to solve the problem with a doctor's guidance. The fastest way to develop resistance to anti-HIV drugs is to use them at inadequate or inconsistent dose levels.

8

Stopping and starting a regimen frequently (like on a weekly or even bi-weekly basis) will likely lead to an increased risk of drug resistance.

A Structured Treatment Interruption (STI), as discussed later, may include stopping therapy for a two-week period or longer, then restarting it for some period of time. It's important for people considering an STI to be closely checked for viral load and CD4+ cell counts. Many studies show that some people experience a dramatic increase in HIV levels and decrease in CD4+ cells. For more information, read Project Inform's publication, *Structured Treatment Interruptions*.

9

If you need to interrupt therapy, it's best to stop all drugs at the same time (except nevirapine and efavirenz) rather than just stopping one drug. There are many reasons that people may need to stop taking their meds, including side effects, drug interactions, pregnancy or their drug supply runs out. Stopping anti-HIV drugs, if they're all stopped at the same time, is unlikely to increase drug resistance. Because nevirapine and efavirenz remain in the body longer than any other anti-HIV therapy, they should be stopped at least two or three days and possibly up to two weeks before stopping the others. Otherwise, there's an increased risk of developing resistance to these drugs.

People considering a vacation away from home should wait until they return before starting a new drug regimen.

When side effects occur, they often happen within the first 2–4 weeks after starting a new regimen. Many resolve after a period of time as the body adjusts to being on new meds. Some, but not all, people experience some mild-to-moderate side effects. Usually, only a small percentage of people experience moderate-to-severe side effects. People should avoid starting a new anti-HIV regimen right before going out of town on vacation. In the unlikely event of serious side effects, it's better to be closer to your doctor who is hopefully experienced with your health and with treating HIV or managing side effects from a specific drug.

Not all people have access to the same treatments, and people respond differently to individual drugs. Treatment options include existing approved drugs and combinations, experimental drugs accessed through studies and access programs, and other unapproved drugs.

10

## how will I know if my treatment is working?

The goal of anti-HIV therapy is to reduce HIV levels below the limit of detection (<50 copies) with the current viral load tests. However, not everyone can bring their HIV levels to <50 copies or to <5,000. For these people the minimum change in HIV levels that shows the therapies are active is a three-fold reduction (0.5 logs).

Many doctors believe you need at least ten-fold reduction (1 log) to have a real impact on disease progression. People with lower CD4+ cell counts and high viral load measures may find that HIV levels drop slowly over time, while people who are healthier are likely to see more immediate responses to therapy. Indeed, anecdotal experience suggests that among people in more advanced disease, decreases in HIV levels happen slower (over three to six months).



## Considerations for pregnant women

In general, the guidelines for treating pregnant women are the same as for treating non-pregnant adults. As in other adults, the decisions to start, change or add anti-HIV drugs should be based on HIV levels, CD4+ cell counts and disease stage. The strategies presented in this publication are all valid for pregnant women as well as other adults. The Federal Guidelines recommend that women receive the most effective anti-HIV regimen regardless of pregnancy status.

However, the potential impact of therapy on a pregnant or unborn child is not wholly known. Therefore, deciding use anti-HIV therapy during pregnancy should be made by the woman in consideration of the known and unknown benefits and risks to her and her child. Long-term follow-up is recommended for all infants born to women who have taken anti-HIV therapy during pregnancy.

Women in their first trimester (14 weeks) of pregnancy not taking anti-HIV therapy may decide to delay therapy until after 10–12 weeks because of the possible risks to the developing fetus during this time.

However, if the woman's own health status warrants starting therapy sooner, most would recommend starting it regardless of how far along a woman is in her pregnancy.

Some women already on therapy may consider temporarily stopping it until after her first trimester. While there are no clear data on the effects of anti-HIV drugs on the developing fetus, most doctors would recommend continuing a highly active anti-HIV regimen regardless of how far along the woman is in her pregnancy. Stopping or delaying therapy may increase HIV levels—possibly increasing her own risk of disease progression as

drug i.d. chart	
GENERIC NAME	TRADE NAME
Protease inhibitor	
amprenavir	Agenerase
atazanavir	Reyataz
fosamprenavir	Lexiva
indinavir	Crixivan
lopinavir/ritonavir	Kaletra
nelfinavir	Viracept
ritonavir	Norvir
saquinavir sgc	Fortovase
saquinavir hgc	Invirase
Nucleoside (NRTI) and nucleotide (NtRTI) analog reverse transcriptase inhibitor	
3TC (lamivudine)	Epivir
abacavir	Ziagen
AZT (zidovudine)	Retrovir
AZT/3TC	Combivir
AZT/3TC/abacavir	Trizivir
d4T (stavudine)	Zerit
d4T XR (stavudine)	Zerit XR
ddC (zalcitabine)	Hivid
ddI (didanosine)	Videx
ddI EC (didanosine)	Videx EC
FTC (emtricitabine)	Emtriva
tenofovir	Viread
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	
delavirdine	Rescriptor
efavirenz	Sustiva
nevirapine	Viramune
Fusion inhibitor	
T20 (enfuvirtide)	Fuzeon

well as the risk of transmitting HIV from her to her child.

Nevertheless, if a woman decides to stop her therapy, all drugs (with the exception of nevirapine) should be stopped at the same time to prevent the development of drug resistance. Similarly, once they're resumed, they should be started at the same time. The use of efavirenz is strongly discouraged in pregnant women due possible harmful effects on the developing child. For more information, read Project Inform's publication, *Pregnancy and HIV*, available at 1-800-822-7422 or at [www.projectinform.org](http://www.projectinform.org).

## When is it time to change therapies?

The Federal Guidelines recommend that people switch therapies when:

- › Detectable HIV levels after being undetectable;
- › HIV levels remain detectable after 4–6 months of starting anti-HIV therapy;
- › Persistent decreases in CD4+ cell counts;
- › Intolerable side effects occur;
- › Adherence is poor;
- › There is less than a 0.5-0.75 log (3- to 6-fold) reduction in HIV levels after four weeks or less than one log after eight weeks of starting anti-HIV therapy (As noted above, however, people who start anti-HIV therapy when CD4+ cell counts are low and HIV levels are high, it may take a longer time to appreciate the capabilities of a regimen.);
- › Symptoms of HIV disease occur; and/or
- › A three-fold or greater increase in HIV levels from their lowest levels.



A common infection such as the flu, or even a vaccine shot, can increase HIV levels temporarily. (A flu vaccine can increase HIV levels for up to two months, but they usually fall back to pre-vaccination levels without changes in anti-HIV therapy.) Before making dramatic adjustments in regimens, factor in how other health considerations may be affecting the viral load test results. If necessary, wait and get another test before making decisions. The decision to switch or add therapies should be based on at least two viral load tests and/or two CD4+ cell counts spaced at least two weeks apart, as well as other factors like the readiness to switch and commit to a new regimen.

**Write down a list of questions and concerns that you may have for your doctor. It is also helpful to discuss your feelings about taking anti-HIV therapies, especially for the first time. Some of those questions may include:**

- › How do I know whether I'm ready to start anti-HIV therapy?
- › What I think will happen to me after I start therapy is ...
- › What will happen if I don't start therapy?
- › Is it possible for me to wait?
- › How I feel about starting therapy is ...

**It's probably helpful to keep a list of other questions you may have. Some of these may include:**

- › What is the potency of this regimen?
- › What are the side effects of the various drugs and how often do they occur?
- › Is there anything I need to do if these side effects occur?
- › How do I monitor for these side effects? Are there things I can do to reduce the risk of getting them?
- › How often do I need to come in to check and see if the therapies are working?
- › How often should I take these drugs?
- › What doses should I take?
- › Do any of these drugs require a dose change based on my weight or liver or kidney functions?
- › Are there any interactions between these drugs and other drugs, herbs, vitamins or supplements that I take?

**Other questions for people who may be co-infected with hepatitis B or C may include:**

- › Will these drugs affect my liver?
- › Do any of these drugs have activity against my hepatitis?
- › Should I treat the hepatitis as well as the HIV?
- › Will these drugs interact with my therapies for hepatitis?

## Commentary

In addition to overall general health and quality of life factors, both CD4+ cell counts and viral load must be considered when making decisions about starting anti-HIV therapy or when considering switching therapies. In most studies, as would be expected, there is a direct inverse correlation (when one goes down the other goes up) between viral load and CD4+ cell counts as more virus means more CD4+ cells being infected and destroyed.

There are some people, who despite substantial decreases in HIV levels continue to experience a decline in CD4+ cell counts. In these cases, it is important for doctors to conduct a more extensive diagnosis to see if some other condition is affecting CD4+ cell counts, such as common or even not so common infections.

Ideal combination strategies call for the use of drugs to be started at the same time. This is readily achievable for people beginning therapy for the first time but far more difficult for those who have used many therapies. Existing therapies can sometimes be juggled to achieve the desired effect. At other times, this may be impossible.

For some people, the best choice may sometimes be to delay using protease inhibitors or other new therapies

until there are enough new drugs available to start an ideal combination (e.g. at least two drugs never used before by the person). For most people, this will seldom be more than a year away as several new therapies are on the horizon. But getting there will require some people to resist the urge to jump to each new drug as soon as it is available.

This shift toward long-term thinking is the true hallmark of the second decade of anti-HIV therapy. It must become a part of everyone's thinking. The alternative is the perpetuation of the short-term benefits and long-term failures characteristic of the last decade's approach.

All of this emphasizes the importance of a recent study which showed that people who received medical care from doctors with a great deal of experience in treating HIV infection actually lived longer than those with less experienced ones. The complexity of treating HIV has changed dramatically in the last year and the demands on the knowledge of doctors have increased proportionally.

Whatever medical strategy a person chooses, it should begin with finding a doctor who is experienced in treating HIV and who is wise enough to continue studying and learning from new developments in HIV research.

### federal recommendations for first line anti-hiv therapy

nrti-based regimens		pills/day
Preferred regimens	efavirenz + 3TC + (AZT or tenofovir or d4T); except for pregnant women or women who wish to become pregnant	3–5
Alternative regimens	efavirenz + (3TC or FTC) + ddi; except for pregnant women or women who wish to become pregnant	3–5
	nevirapine + (3TC or FTC) + (AZT or tenofovir or d4T)	4–6
pi-based regimens		pills/day
Preferred regimens	Kaletra + 3TC + (AZT or d4T)	8–10
Alternative regimens	amprenavir + low dose ritonavir + (3TC or FTC) + (AZT or d4T)	12–14
	atazanavir + (3TC or FTC) + (AZT or d4T)	5–10
	indinavir + (3TC or FTC) + (AZT or d4T)	8–10
	indinavir + low dose ritonavir + (3TC or FTC) + (AZT or d4T)	8–12
	nelfinavir + (3TC or FTC) + (AZT or d4T)	6–14
	saquinavir (soft or hard capsule) + low dose ritonavir + (3TC or FTC) + (AZT or d4T)	14–16
nrti regimens (only when an nrti or pi can't be used)		pills/day
Alternative regimens	Trizivir (abacavir + 3TC + AZT)	2
	abacavir + 3TC + stavudine	4–6

## federal recommendations for when to start therapy

- ▶ **Advanced stage disease (severe symptoms of AIDS, with any CD4+ cell count or viral load)**  
All people with severe symptoms of AIDS should be treated with anti-HIV therapy. In this case, anti-HIV therapy is shown to prolong life and is associated with improvements of symptoms. When starting therapy for opportunistic infections at the same time as starting anti-HIV therapy, special care should be taken to avoid drug interactions. A person experiencing an opportunistic infection is generally encouraged to continue anti-HIV therapy.
- ▶ **No symptoms of HIV disease, with CD4+ cell counts below 200 and any viral load**  
Treatment should be initiated after consideration of the issues affecting treatment decision-making, as the risk for disease progression is very high.
- ▶ **No symptoms of HIV disease, with CD4+ cell counts of 200-350 and any viral load**  
Treatment should generally be offered, though controversy exists. Some experts believe it's often safe to wait until the CD4+ count falls to 200. Others believe this offers too little room to accommodate individual differences and feel it's safer to start therapy at 350 CD4+ cells.
- ▶ **No symptoms of HIV disease, with CD4+ cell counts above 350 and viral load above 30,000 copies by bDNA or 55,000 by RT-PCR**  
There are two unproven approaches to treatment in early HIV infection when people do not have symptoms: aggressive and conservative. For people with CD4+ cell counts above 350 and viral load above 30,000 (by bDNA) or 55,000 (by RT-PCR), there are no available data to suggest which approach results in longer survival. Very early, aggressive treatment might lead to longer life. Or it might lead to using up the limited supply of therapies too early in the course of disease. Moreover, it also risks early exposure to possible long-term side effects associated with therapies. As a result many experts would delay starting therapy and continue to check CD4+ cell counts and viral load. On the other hand, the risk of disease progression over the next three years is somewhat high (over 30%) in people who meet this definition and other experts prefer to start treatment without further delay.
- ▶ **No symptoms of HIV disease, with CD4+ cell counts above 350 and viral load below 30,000 by bDNA or 55,000 by RT-PCR**  
Many experts would defer therapy and continue to check CD4+ cell counts and viral load; the risk of disease progression over the next three years in this group is low (below 15%).
- ▶ **Acute Infection (very early, typically within first weeks after infection)**  
If infection is suspected, test for HIV using sensitive and sophisticated techniques. (Note: technologies that measure viral load are not approved and are discouraged for use in diagnosing HIV infection.) Experts agree that if treatment is offered in this very early setting, it should only be done in the context of a study. People interested in exploring very early treatment should be made aware of all of its possible risks. The true long-term effect of very early treatment is unclear because current studies are not yet complete, but the hope is that early treatment may alter the course of disease. Whether or not this is the "right" approach remains uncertain.

## Chart of the risk of progression to AIDS-defining illness

Recent reports show that women progress to HIV disease at a lower viral level than men. While these new data do not currently warrant a new standard of care for women with HIV, women and their doctors should be aware of these reports as they may support starting or switching therapy at lower viral levels than what is currently

recommended. CD4+ cell counts, that provide useful measures for the risk of HIV disease progression, are not influenced by sex. For more information on this issue, call Project Inform's toll-free hotline at 1-800-822-7422.

This chart presents information on viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection.

The table is shown here for ease of use and can also be found as Table 5 on page 45 of the November 10, 2003 issue of the federal *Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents*, or online at [www.aidsinfo.nih.gov/guidelines](http://www.aidsinfo.nih.gov/guidelines).

Risk of progression to AIDS-defining illness in a cohort of gay men predicted by baseline cd4+ cell count and viral load\*

CD4+ cell count ≤ 200 and HIV levels <sup>†</sup> of ...		Percent of AIDS-defining illness <sup>‡</sup>			
bDNA	RT-PCR	n	3 years	6 years	9 years
≤ 500	≤ 1,500	0 <sup>§</sup>	—	—	—
501 – 3,000	1,501 – 7,000	3 <sup>§</sup>	—	—	—
3,001 – 10,000	7,001 – 20,000	7	14.3	28.6	64.3
10,001 – 30,000	20,001 – 55,000	20	50.0	75.0	90.0
> 30,000	> 55,000	70	85.5	97.9	100.0

  

CD4+ cell count 200–350** and HIV levels <sup>†</sup> of ...		Percent of AIDS-defining illness <sup>‡</sup>			
bDNA	RT-PCR	n	3 years	6 years	9 years
≤ 500	≤ 1,500	3 <sup>§</sup>	—	—	—
501 – 3,000	1,501 – 7,000	27	0.0	20.0	32.2
3,001 – 10,000	7,001 – 20,000	44	6.9	44.4	66.2
10,001 – 30,000	20,001 – 55,000	53	36.4	72.2	84.5
> 30,000	> 55,000	104	64.4	89.3	92.9

  

CD4+ cell count > 350 and HIV levels <sup>†</sup> of ...		Percent of AIDS-defining illness <sup>‡</sup>			
bDNA	RT-PCR	n	3 years	6 years	9 years
≤ 500	≤ 1,500	119	1.7	5.5	12.7
501 – 3,000	1,501 – 7,000	227	2.2	16.4	30.0
3,001 – 10,000	7,001 – 20,000	342	6.8	30.1	53.5
10,001 – 30,000	20,001 – 55,000	323	14.8	51.2	73.5
> 30,000	> 55,000	262	39.6	71.8	85.0

### FOOTNOTES FOR MELLORS' CHART

- \* Data from the Multi-Center AIDS Cohort Study (MACS) (Source: JMellors JW, Rinaldo CR Jr, Gupta P, et. al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma, *Science* 1996; adapted by Alvaro Muñoz, PhD, John Hopkins University, 2001)
- † MACS numbers reflect viral load values obtained by 2.0 bDNA testing. RT-PCR values are consistently 2–2.5 fold higher than bDNA values, as indicated.
- ‡ In the reference study, AIDS was defined according to the 1987 CDC definition, which did not include asymptomatic persons with CD4+ cells <200.
- § Too few subjects were in the category to provide a reliable estimate of AIDS risk.
- \*\* A recent evaluation of data from the MACS cohort of 231 persons with CD4+ cell counts >200 and <350 cells demonstrated that of 40 (17%) persons with HIV levels below 10,000, none progressed to AIDS by 3 years (Source: Phair JP, Mellors JW, Detels R, Margolick JB, Muñoz A. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. *AIDS* 2002; 16(18): 2455-9.). Of 28 persons (29%) with HIV levels of 10,000–20,000, 4% and 11% progressed to AIDS at 2 and 3 years, respectively. Viral load was calculated as RT-PCR values from measured bDNA values.