Deciding when to start therapy and what treatments to use can leave many people feeling overwhelmed. Taking therapy can greatly slow the course of your HIV disease, extend your life and improve your quality of life. It may also cause side effects. You have time to get informed about your HIV disease as well as about when to start and what to start. This publication can help you do that.

There’s no definitive answer on the best time to start. Some people choose to put off taking meds for as long as safely possible. Others decide to start earlier in the course of their disease. Both strategies have merit and both are supported by some research. Whatever your strategy, your willingness to commit to taking therapy over the long-term as well as getting informed up front on all your options can influence how well you do.

If you look at taking HIV therapy as part of a larger picture, it may be easier to make changes as new information becomes available. Charting out your second and perhaps third regimen ahead of time can be extremely helpful. For instance, you may start one regimen, but then find that the drugs don’t work as well as you hoped. You can then proceed to the second with more confidence rather than being overwhelmed because your first choice didn’t quite work out.
Some questions to answer before starting first line therapy ...

What is your current CD4+ cell count?
› Overall, what is the trend? Increasing? Decreasing? Stable?
› Is it above 350, below 200, or in between?
› Are you aware of the health risks related to a count below 200?

What is your current viral load?
› Overall, what is the trend? Increasing? Decreasing? Stable?
› Is it below 10,000 or even undetectable?
› Is it above 55,000 or steadily climbing on two or more tests?

Are you ready and willing to commit to therapy?
› Have you taken medicine that you had to take on time every day? Was that easy or difficult?
› What situations might make you miss a dose?
› Do you want privacy and in what situations?
› Can you keep your medicine with you throughout the day? Where's best place to store it so you can get to it and not forget to take it?
› Does your doctor's office, clinic or local AIDS organization offer services to help you take your meds as prescribed?

Are you aware of the possible side effects?
› Do you know what side effects may give you the most problems, like nausea or diarrhea?
› Are you aware which may happen only within the first week or so and are likely to get better over time?
› Are you aware of the signs of more dangerous or long-term side effects? Do you have another regimen to switch to?
› Do you know what you can do to help avoid or lessen them? (Read Project Inform's publication, Dealing with Drug Side Effects.)

Do you know which therapies may preserve more options for later?
› Have you considered what your second, and perhaps third, regimen will be if your first doesn't work?
› Have you read about the drugs that are being studied and how they may be used?
› Do you want to start with the most potent combination, or would you rather save those drugs for later?

How do you feel about therapy?
› Do you feel confident that starting now is right for you? What makes you feel this way?
› Are you anxious or worried? Have you talked with your doctor about your concerns?
› How do you feel about specific drugs? What might help address your concerns?

Are you aware of how therapy may impact your life?
› How do you feel about taking pills every day, perhaps for the rest of your life? What support do you have to help you through the difficult times?
› In the first days after you start therapy, what support and flexibility do you have with commitments like work, taking care of children or volunteering?
› Will starting treatment limit you taking part in activities that you enjoy?
› How do you plan to carry your meds with you? If you’re away from home overnight, on vacation or in places that are awkward for taking them?
When to start therapy

It's possible and reasonable to start HIV drugs at any point in the course of your HIV disease. This is true even if you didn't find out you have HIV until you became ill. Although there's no agreement on the best time to start, it's never too late to start and benefit from therapy.

To help guide people with their treatment decisions, a group of researchers, doctors, people living with HIV, and their advocates regularly meet to discuss the results of studies and their experiences treating and living with HIV. This group is called the Federal Guidelines Panel, and every year or so they update the “Federal Guidelines” or more simply “Guidelines.” The excerpts below are for adults and adolescents.

These Guidelines are meant to help guide people through the issues that may arise while using therapy, including when and what to start. They’re not absolute rules. When enough information is known about some aspect of treating HIV disease, the Guidelines will recommend or suggest a preference. When data are less clear, they will state just that.

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basic federal guidelines for when to start therapy

updated january 2008

► HIV treatment should be started in anyone before their CD4 counts fall below 350.

► HIV treatment is recommended regardless of CD4 count for:
  • anyone with a history of an AIDS-defining illness
  • pregnant women
  • people with HIV Associated Nephropathy (HIVAN)
  • people co-infected with hepatitis B virus (HBV) for whom treating HBV is warranted

► The risk of death or serious illness in people with CD4 counts above 350 is low. Any benefit from starting treatment at high CD4 counts is likely to be small.

► However, some data — for example the ATHENA study — show that people who start therapy with CD4 counts above 350 will more likely maintain CD4 counts above 800. A Johns Hopkins study shows that people who started treatment with CD4s below 350 would less likely maintain CD4 counts above 500.

► Starting HIV therapy earlier helps reduce the transmission of HIV.

► Factors weighing against early treatment are:
  • lifelong treatment;
  • lack of long-term data on most HIV drugs;
  • potential for developing drug resistance; and
  • interference with quality of life.
the best starting combination

What is the best combination for people starting therapy?

The question of what combination of HIV drugs a person should use as first line therapy can appear confusing. However, there are a few factors to consider which narrow the range of choices for first line therapy. They include:

- its potency;
- its ease of use: how many pills and how often?; and
- its potential for short- and long-term side effects.

Remember the goals of therapy

Being on effective HIV drugs should lower your HIV level as low as possible (preferably to undetectable) and increase your CD4 count. This should happen without causing debilitating side effects or harming your quality of life. The regimen should be easy enough to take so you can take each dose as prescribed (adhere well).

Adhering to medicines cannot be stressed enough. The most common reason for failed therapy is missed doses. So, adherence must play a significant role in the decisions you make about treatment. Project Inform’s publication, Adherence: Keeping up with Your Meds, can help you prepare for and maintain good adherence.

Five classes of HIV drugs are approved for use in different combinations. They are:

- NRTIs/NtRTIs (nucleoside and nucleotide analog reverse transcriptase inhibitors),
- NNRTIs (non-nucleoside reverse transcriptase inhibitors),
- PIs (protease inhibitors),
- Entry inhibitors, and
- Integrase inhibitors.

Each class works in different ways to stop HIV from making more of itself, called replication. Currently, three or more HIV drugs together forms an effective regimen. For first line therapy this usually includes two NRTIs and either one NNRTI or PI. A list of these drugs can be found in the Drug ID Chart on page 9.

Two common tests for checking immune health

Throughout your HIV disease, you will often use two test results: CD4 count, which is the number of an important type of immune cell, and HIV level (viral load), which is the amount of HIV found in a sample of your blood. Taken together with other blood tests, these results will give you a picture of the health of your immune system as it reacts to the HIV.

It’s important to be specific and reasonable about your goals in terms of lower HIV levels and higher CD4 counts. It can be very helpful to have already decided what you’ll switch to if you don’t reach them. Some consider their first regimen successful if it reduces their HIV levels to undetectable within the first few weeks. Others give their therapy up to six months to lower their levels to undetectable. The higher your HIV level before starting therapy, the longer it may take to suppress your HIV infection.
NRTIs and NtRTIs

NRTIs and NtRTIs are almost always used as part of an HIV regimen. Usually two are taken with another class of drugs. Although there are many drugs in this class, few are considered for first line therapy. This is either because a drug like Zerit (stavudine, d4T) is generally considered inferior, or that two of them, like Zerit + Videx (didanosine, ddI), have high risks for side effects when taken together. Zerit and Retrovir (zidovudine, AZT) also should not be used together.

The Guidelines recommend the combination pills Truvada (emtricitabine/FTC + tenofovir) or Epzicom (abacavir + lamivudine/3TC) be used as part of first line therapy. They list the combination pill Combivir (lamivudine/3TC + zidovudine/AZT) as an alternative. This is mainly because AZT causes more loss of fat in the face than other preferred first line NRTIs.

People choosing between Truvada and Epzicom should consider both carefully. Tenofovir, one of the drugs in Truvada, has been linked with kidney problems and bone loss. Each of these side effects is uncommon but they can be serious when they do occur. People with pre-existing kidney problems or bone loss should weigh the pros and cons.

Abacavir, one of the drugs in Epzicom, can cause a serious allergic reaction called hypersensitivity reaction (HSR). Fortunately, a blood test — called an HLA test — can predict whether a person is at risk for abacavir HSR. Anyone considering Ziagen, Epzicom or Trizivir should get an HLA test done first.

Concerns about the side effects of Zerit should limit its use because it greatly weakens mitochondria, the energy source inside your body’s cells. This can lead to lactic acidosis, a dangerous buildup of lactic acid in your blood and other tissues. It can also lead to the loss of fat in the face, butt, arms and legs. The risk of these problems is greatest for those who take Zerit with Videx EC.

Videx EC is not often used in first line therapy because it must be taken on an empty stomach and cannot be taken at the same time as many other meds. This can make it very difficult to use, especially if it’s used with other drugs, like certain PIs that are taken with food.

Several studies show that taking Viread (tenofovir) and Ziagen together may lead to early failure of an HIV regimen for reasons that are not entirely understood. Also, Viread interacts with the PI, Reyataz (atazanavir). NRTIs that should not be used together in any regimen are: Retrovir + Zerit, Videx EC + Zerit, and Emtriva + Epivir.

NNRTIs

NNRTIs work differently than NRTIs, but they act against HIV at the same place in its replication cycle. In first line therapy, NNRTIs are regularly used with two NRTIs. Regimens with Sustiva (efavirenz) have been compared to several other combinations and have consistently proven both potent and long-lasting. Sustiva is listed in the Guidelines as a preferred first line drug.

Even though the Guidelines recommend Sustiva over Viramune (nevirapine), Viramune may be preferred at times. This is mainly true for people who wish to save PIs for later, but who are concerned about the brain-related (neurological) side effects of Sustiva. These may include vivid and disturbing dreams, difficulty concentrating, insomnia and mood changes. In studies, 14–53% of people who took Sustiva reported these side effects. Most doctors report higher rates of these side effects in their patients.

Viramune is listed as an alternative, mostly due to its risk of serious liver toxicity. This happens mostly in people who start it at higher CD4 counts: over 250 for women and 400 for men. Viramune should not be started in people with CD4 counts higher than this.

The risk for rashes from Viramune appears to be slightly higher in women than men. Among women who develop the rash, it’s more likely to be severe. However, pregnant women and women trying to get pregnant should avoid Sustiva. If their CD4 counts are below 250, they may consider Viramune a better option when starting a regimen without a protease inhibitor.

The most recently approved NNRTI, Intelence (etravirine) has not been studied in people taking HIV drugs for the first time. Therefore, it should not be used in this way.

One important point to keep in mind is that Sustiva, Viramune and Rescriptor (delavirdine) are highly cross resistant. This means that when HIV becomes resistant to one of them, it will likely be resistant to the others, making them less useful. Of the four NNRTIs, Rescriptor is used the least often. This is because it’s taken three times a day and interacts with many other meds. Rescriptor has not been well studied either, especially in people on first line therapy.
Protease inhibitors

This class of drugs contains some of the most potent HIV drugs available. Other factors to consider when using them for first line therapy include their ease of use and possible long-term side effects.

There are a wide range of options. The Guidelines list three as preferred choices: Kaletra (lopinavir + ritonavir) twice a day, Reyataz boosted with Norvir (ritonavir), and boosted Lexiva (fosamprenavir) twice a day. Research shows them all to be potent and well tolerated for people on first line therapy.

The Guidelines also list five alternative PIs: unboosted Reyataz, unboosted Lexiva, boosted Lexiva once daily, Kaletra once daily, and boosted Invirase (saquinavir). In each case, there’s enough research to think that these should work well for most people taking HIV drugs for the first time. However, the research is either not as extensive or as favorable as for those listed as “preferred”.

Most PIs are highly potent. Some doctors prefer to save them if or when other less complicated regimens have failed. Although this may be an excellent strategy, not enough studies have yet been done to prove this is the best choice.

Entry and integrase inhibitors

The other two classes of HIV drugs are not recommended for first line use. The fusion inhibitor Fuzeon (enfuvirtide/T20) hasn’t been studied in this way, and it’s given as a shot twice a day. The CCR5 drug Selzentry (maraviroc) has been studied as part of first line therapy, but it failed to match up to Sustiva’s potency. The integrase inhibitor Isentress (raltegravir) is now being studied, but very little data have been seen from it.

The Guidelines list the following combinations as “preferred” first line regimens. This is because research shows that they are potent, well tolerated and easy to take. They also list alternatives that have less data to support their use as first line treatment, but may work just as well.

### federal recommendations for first line therapy (updated January 2008)

<table>
<thead>
<tr>
<th>class</th>
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<th>alternative</th>
<th>not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Truvada</td>
<td>Combivir</td>
<td>Zerit</td>
</tr>
<tr>
<td></td>
<td>Epzicom</td>
<td>Videx + Epivir or Emtriva</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>Sustiva</td>
<td>Viramune</td>
<td>Rescriptor</td>
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<td></td>
<td></td>
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<td>Protease inhibitor</td>
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<td>Reyataz—unboosted</td>
<td>Invirase—unboosted</td>
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<td>Lexiva—unboosted</td>
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<tr>
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<td>Kaletra (1x/day)</td>
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<tr>
<td></td>
<td>Invirase—boosted</td>
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<td>Crixivan</td>
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</table>
What to start first: NNRTIs or PIs?

No large study has yet been done that definitively shows which drug class is the better to start. So far, we know that when a person’s HIV level remains under 50 for at least one year on therapy, it usually remains that way for at least another two years, assuming good adherence. This is true for almost any combination used.

Less clear is how much the choice of a first regimen impacts how well a second one will work. In most cases if a person starts therapy with a PI, he or she will likely be able to use Sustiva successfully as second line therapy. So far, there are less data on the other way around, but there’s no reason to think there would be a difference.

Perhaps the most limiting factor of all the drugs is cross resistance. When a person’s HIV develops a high level of resistance to one drug in a specific class, it will generally have at least some resistance to the other drugs in that class. When HIV develops even low levels of resistance, it causes the drug to be less potent.

Some people believe that the best first line strategy is to take whatever is the most potent. The most powerful and long-lasting effects come from a person’s first regimen. The longer a person stays on it without major side effects or resistance, the better. The longer it continues working, the more likely that new drugs may be approved in the meantime, giving more options for second and third line regimens. As a rule, boosted PIs like Kaletra are considered the most potent and long-lasting.

Others feel that saving potent and longer lasting medications for second line therapy is the better strategy. They think that starting treatment with an NNRTI is better. This would likely work for most people for some time and it keeps PIs for later. Unlike the PIs, it’s also hoped that the NNRTIs and NRTIs will have fewer long-term effects on cholesterol and triglycerides or fat redistribution (lipodystrophy), though these data are mixed. Again, the theory has some merit, but no studies prove this is the better long-term strategy.

Things that might help to ask your doctor

- What if I’m not ready to start therapy?
- What regimen(s) do you recommend and why? Why is one better than another?
- What are my next regimens if the first one doesn’t work?
- How do my CD4 count and HIV level affect my decision to start?
- What are the possible side effects of the drugs I would take?
- How many pills would I take? How often? Are they taken with or without food?
- When should I let you know if I think something is wrong?
- What do you mean when you say I should adhere to my drug regimen?
- Are there are any other tests that I should take before starting a regimen?
Starting therapy in women

For the most part, the recommendations for when and what to start are the same for women and men. If a woman is not pregnant, not planning to become pregnant and not taking hormonal contraceptives, by and large their treatment recommendations are the same as for men.

While HIV drugs have not been studied as extensively in women, most evidence to date shows that they work as well for both. There are two special considerations for women considering Viramune. See the NNRTI section on page 5 for this information.

The Guidelines recommend that all HIV-positive pregnant women be on HIV therapy, regardless of their CD4 counts or HIV levels. Some doctors recommend that they wait to begin treatment until their second trimesters (13–24 weeks). Since the first trimester is when the baby’s major organs develop, this is when birth defects from taking medicines will most likely occur. Some HIV drugs should NOT be taken during pregnancy, which are discussed in the next section. (For more information, read Project Inform’s publication, Pregnancy and HIV.)

Some HIV drugs interact with oral contraceptives or other female hormone replacement therapies. So it may be necessary to adjust the dose of the oral contraceptive, use other methods of birth control, or change your HIV drugs. You can discuss these interactions with your health provider or pharmacist.

HIV drug resistance testing

Data show that about 1 in 5 of all newly infected people in the US may have drug-resistant strains of HIV. More than 5% of these are resistant to more than one class of drugs. For this reason, it’s recommended that people get resistance testing done before choosing their first regimen. This can help ensure that it has the best chance for working well.

For more information, read Project Inform’s publication, HIV Drug Resistance Tests.

take charge of your health

Project Inform has several publications that can help you create and manage your own personal treatment plan. Along with this publication, we have five others that may be useful to you. They include: Strategies for Maintaining Your General Health; Strategies for Managing Opportunistic Infections; Strategies for Third Line HIV Therapy; Strategies for Switching HIV Therapy; and Structured Treatment Intermittions. These and many other publications are all available free from Project Inform at 1-800-822-7422 or www.projectinform.org.
Project Inform believes that HIV treatment decisions should be driven by a combination of the best available medical data, a person’s unique life situation, medical history, and personal preference. We also recognize that in most diseases earlier treatment usually leads to better treatment outcomes. There’s no evidence to suggest this would not be true for HIV disease.

Your doctor may have strong opinions about when to start therapy or which regimen is best for you. Your opinion and your concerns count too. Share your concerns with your doctor(s) so they can help you build the best strategy for you. Project Inform’s publication, Building a Cooperative Doctor/Patient Relationship, offers tips.

Only you can decide when the best time is for you to start therapy. Because it’s your life and your body, only you can ultimately decide how you wish to balance the need to keep your HIV in control with any risks for disease progression and side effects. With over two dozen HIV drugs on the market today — many of which are simpler to take and seem to have fewer side effects — you can probably find a regimen that works best for you.

In conclusion

Project Inform believes that HIV treatment decisions should be driven by a combination of the best available medical data, a person’s unique life situation, medical history, and personal preference. We also recognize that in most diseases earlier treatment usually leads to better treatment outcomes. There’s no evidence to suggest this would not be true for HIV disease.

In addition to protecting the health and well-being of the person living with HIV, HIV treatment also reduces the risk of transmission. While treatment decisions should be primarily guided by the needs of the person living with HIV, the health and well-being of their partners and the larger community can also benefit. This could be particularly important for mixed status couples or people with multiple sexual partners.
things to think about

If HIV drugs were easy to take, free from side effects and always worked in spite of resistance, then making decisions about when to start would be easy. While none are ideal, HIV medicines have improved over time, making them easier to take and generally more tolerable. The trick is to balance the benefits of reducing your HIV level and increasing your CD4 count along with the risks of side effects and treatment failure. These examples help make dealing with this struggle clearer. Each has its own possible benefits and disadvantages. These pros and cons are explained, but the only "right" answer for your situation comes from carefully considering both sides.

A man knows that he was exposed to HIV several weeks ago. His HIV level is 600,000, but he continues to test negative on antibody tests. This indicates that he’s in the acute or primary stage of HIV infection. His doctor says that he should start treatment immediately and only has days to decide. Should he start now?

the pros

No data prove that starting now results in a longer, healthier life. However, some researchers suggest that early treatment may:

› decrease the severity of the acute syndrome;
› change the initial viral set point, which is shown in some research to affect the rate of disease progression;
› keep HIV from changing (mutating) around the body’s defenses;
› preserve immune health; and
› Prevent HIV from damaging tissues and cells due to inflammation

the cons

These points are less theoretical and include the possibility that a person will:

› have to take therapy indefinitely;
› go through his or her treatment options too quickly; and
› develop long-term side effects.
A woman, who has been HIV-positive for ten years, has watched her CD4 count decline from 550 to 475 to 380 over 6 months. However, her HIV level is relatively stable around 15,000. She’s scared about side effects and hesitant about starting therapy. Should she start now or wait to see what happens with these two markers?

### the pros
- She may reduce her risk of getting sick within the next three years.
- She may have a stronger and more durable response to therapy.
- She’s less likely to face significant side effects if she starts with a higher CD4 count.

### the cons
- Her fears are strong enough:
  - She may find it difficult to stay on her regimen.
  - Starting now may reduce the risk of disease progression in the short-term, but it may not hold up over time. This risk for treatment failure from drug resistance and/or side effects increases with each year on therapy.

---

A man finds out that he’s HIV-positive. He reads a lot of literature on the Internet and gets excited about some of the newer experimental drugs. His CD4 count is 650 and his HIV level has never been above 4,000 on 3 tests over the last 6 months. He wants to fight his HIV aggressively and would like to try therapy. Should he start?

### the pros
- Starting this early may theoretically lead to long-term benefits in his immune health, may protect his organs from damage caused by inflammation and might prevent the development of viral diversity. However, the possible benefits have not been proven when taking treatment in earlier disease.

### the cons
- Treatment started at this point may have to be taken for life and could lead to him running out of options sooner.
- The risks for treatment failure from drug resistance and/or side effects increases with each year on therapy.

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A woman has lived with HIV for more than ten years. She also has had hepatitis C (HCV) for 20 or more years. She recently found out she has significant liver damage. Liver function tests and a biopsy show that the HCV is causing this damage. She has never been on HIV or HCV therapy. Her CD4 count is 400 and HIV level is 80,000. Should she start HIV therapy now or wait until after she has tried to treat the HCV?

### the pros
- Starting HIV therapy now will reduce the risk that her CD4 count will drop and lead to an AIDS-related infection.
- HIV therapy works as well in people with HCV as in those who do not have HCV.
- HIV therapy can be well tolerated by people with HCV.

### the cons
- Treatment started at this point may have to be taken for life and could lead to him running out of options sooner.
- The risks for treatment failure from drug resistance and/or side effects increases with each year on therapy.
Filling this out before your next doctor’s appointment can improve your discussions about starting HIV therapy.

What factors do you consider most important in selecting your first regimen?

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<td>Fewer pills in each dose</td>
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</table>

After looking over the available information on HIV therapies, what are two possible combinations that appear to meet the most of your concerns?

Regimen #1:  
Regimen #2:

My reasons for considering these regimens:

Concerns I have about these regimens:

Side effects to discuss with my doctor and plan for:

Adherence strategies I will use include:

Questions to ask my doctor: