

Antiretroviral options for beginners

More choice, fewer pills and better information on side effects make starting treatment easier

by Dr. Alex Klein

If you're just now reaching the point of needing to treat your HIV infection, then your prospects are better than ever. Although needing to start therapy is obviously not desirable, over the past few years the arsenal of available treatments has expanded significantly. As you can see from the sidebars on pages 5 and 6, there are now over 25 different medications to choose from, and two entirely new classes of medication that work in different ways than earlier drugs.

Despite the greater number of drugs and classes, choosing the starting therapy that's best suited to you has gotten simpler. There are fewer recommended or "preferred" choices, all of which involve fewer pills to be taken less often. We also have a better understanding of their potential to cause particular side effects.

The goal of treatment

Treatment aims to suppress levels of the virus, to allow the immune system to recover and to improve overall health and well-being. Although treatment still can't cure HIV, it's now possible to keep it con-



trolled indefinitely. The net result is that life expectancy for those with HIV who stick with their treatment regimen is now almost the same as for the general population. Treatment also significantly reduces the likelihood of transmitting the virus to others — although it doesn't rule it out completely.

Choosing a starting regimen

The choice of medications should be made by you and a doctor with expertise in HIV, and it should be supported by specific treatment guidelines published by expert groups. These guide-

lines recommend preferred and alternative regimens based on the best science of the day, including controlled clinical trial data as well as information from large observational databases. The guidelines include extensive information designed to help doctors and patients make the best choice.

The best starting regimens still consist of three medications (to which your particular virus is sensitive) from two or more of the different classes of antiretroviral (ARV). Your doctor will perform a genotype test, which identifies drugs to which your virus

Dr. Alex Klein is an HIV primary care physician in private practice and a family practitioner at Mount Sinai Hospital in Toronto.

should be susceptible. This test may protect you from possibly failing treatment on your first try if you've been infected with a virus that's resistant to a particular medication. About 10% of new infections are resistant to at least one ARV, so it's very important that you have this screening test.

Current recommendations

A starting regimen typically contains two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Although clinical studies are underway using the new integrase inhibitors as well as the CCR5 entry inhibitors as first treatments, more evidence has to be collected before these drugs are included in the guidelines as recommended starting treatments. If in future these combinations prove superior to the current standard, they'll become the standard. And you can rest assured that your choice of starting regimen now won't limit your potential to switch treatments at a later date if something better becomes available.

Integrase inhibitors and CCR5 entry inhibitors provide a dramatic benefit to those who've developed resistance to other classes of drugs, and are recommended for use in that event. They may be recommended as starting treatment if the genotype test shows that your virus is already resistant to current starting medications.

Combination pill backbones

The treatment backbone of two NRTIs is now available in one fixed-dose combination pill that is considered "preferred" and two combination pills that are considered "alternative." Each has unique side effect issues, which may affect their suitability for a given person, but most people find they can take them without experiencing bothersome effects.

Preferred: Truvada®

Truvada® consists of two NRTIs, tenofovir and emtricitabine (FTC) combined in a single pill. Side effects include a small risk of kidney problems and, infrequently, some mild abdominal discomfort. If you have kidney disease, you should probably use another medication. Both tenofovir and FTC are also active against hepatitis B, so Truvada® is a good choice for HIV/hep B co-infected individuals unless there's a specific reason not to use it.

Alternative: Kivexa®

Kivexa® consists of abacavir plus lamivudine (3TC) combined in a single pill. The major side effect risk here is a possible allergic reaction. There's now a

simple blood test to determine if you're allergic to this drug. Mild rash and mild abdominal discomfort are also possible side effects.

Recently, we've seen evidence of an increased risk of heart attacks with abacavir (see Dr. Marek Smieja's article on page 7) but the risk was relatively small and affected people who were at higher risk for heart attack in the first place. It's currently recommended that people at high risk of heart disease should avoid abacavir.

These NRTI combinations involve taking just one pill daily and neither requires any food restrictions. They don't appear to contribute to lipodystrophy syndrome (though the possibility can't be ruled out) and have less effect on cholesterol levels than earlier NRTIs, which are now used only in salvage situations after multiple-drug resistance develops.

Alternative: Combivir®

Combivir® consists of zidovudine (AZT) plus 3TC. It's been moved from preferred to alternative status

Some cautions with preferred first-line ARVs

NNRTI efavirenz (Sustiva®)

- Can't be used during pregnancy
- Use cautiously with unstable psychiatric disease

NNRTI nevirapine (Viramune®)

- Use cautiously with liver disease
- Don't use if pre-treatment CD4 is > 250 cells/mm³ (women) or > 400 cells/mm³ (men)

PI atazanavir/ritonavir (Reyataz®)

- Use cautiously if you're also taking drugs for gastric reflux or heartburn, such as proton pump inhibitors (PPIs), H2 blockers or antacids
- Don't use if you're taking higher doses of PPIs

PI lopinavir/ritonavir (Kaletra®)

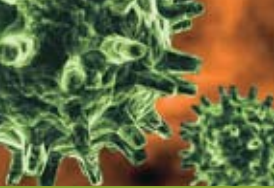
- Don't use once-daily dosing if pregnant
- Don't use once-daily dosing if you've already been on treatment

NRTI tenofovir/emtricitabine (FTC) (Truvada®)

- Use cautiously with unboosted atazanavir
- Can't use with kidney disease

NRTI abacavir/lamivudine (Kivexa®)

- Don't use with high risk of heart disease
- Don't use if testing indicates an allergy to abacavir



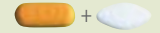
Preferred, alternative and other antiretrovirals

NRTIs

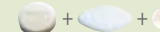
Preferred dual NRTI
tenofovir (Viread®) + emtricitabine (Emtriva®)*



Alternative dual NRTIs
abacavir (Ziagen®) + lamivudine (3TC®)



didanosine (Videx®) + lamivudine (3TC®) or emtricitabine (Emtriva®)*

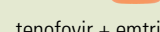


zidovudine (Retrovir®) + lamivudine (3TC®)

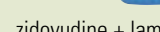


Fixed-dose NRTI formulations

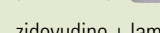
abacavir + lamivudine (Kivexa®)



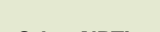
tenofovir + emtricitabine (Truvada®)



zidovudine + lamivudine (Combivir®)

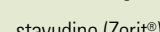


zidovudine + lamivudine + abacavir (Trizivir®)



Other NRTIs

zalcitabine (Hivid®) — no longer available



stavudine (Zerit®)



NNRTIs

Preferred NNRTI
efavirenz (Sustiva®)



Alternative NNRTI
nevirapine (Viramune®)



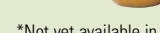
Other NNRTIs
delavirdine (Rescriptor®)



etravirine (Intelence™)



Fixed-dose NRTI + NNRTI formulation
tenofovir + emtricitabine + NNRTI efavirenz (Atripla®)



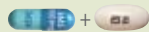
*Not yet available in Canada except as co-formulated in Atripla®



PIs

Preferred PIs

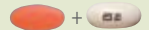
atazanavir (Reyataz®) +
ritonavir once daily



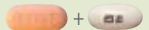
lopinavir/ritonavir
(Kaletra®) once or
twice daily



darunavir (Prezista®) +
ritonavir once daily



fosamprenavir (Telzir®) +
ritonavir twice daily



Alternative PIs

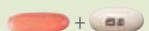
atazanavir unboosted
once daily



fosamprenavir + ritonavir
once daily or fosamprenavir
unboosted twice daily



saquinavir (Invirase®) +
ritonavir twice daily



Other PIs

ritonavir (Norvir®)



indinavir (Crixivan®)



nelfinavir (Viracept®)



amprenavir (Agenerase®)
— no longer available



tipranavir (Aptivus®)



Antiretrovirals for resistant HIV

Entry inhibitors

enfuvirtide (Fuzeon®)



maraviroc (Celsentri™)



Integrase inhibitor

raltegravir (Isentress™)



Recommendations based on U.S.
DHHS guidelines, November 3,
2008.

because it has a greater risk of side effects than the other two combination NRTIs. Anemia occurs in about 5% of people taking Combivir® and it can contribute to lipodystrophy. It must be taken twice daily.

Third drugs: NNRTIs and PIs

The choice of a third drug to complete your regimen will depend mainly on which side-effect profile worries you more and whether you have other health problems that may make certain treatments less appropriate. The two classes to choose from are NNRTIs and PIs.

Preferred: Sustiva®

The most commonly used NNRTI is efavirenz (Sustiva®), which is taken as one pill daily at bedtime. It causes vivid dreams and can disturb sleep, although for most people these effects calm down after the first couple of weeks. Efavirenz can contribute to psychiatric symptoms in people with



prior psychiatric problems. It can cause a rash at the start of treatment, which generally goes away in a few days. It shouldn't be used by women who are currently pregnant or who don't use contraception, as it can cause fetal abnormalities. Liver test abnormalities are a rarer side effect. Efavirenz is included along with Truvada® in the "one pill a day" combination Atripla®.

Alternative: Viramune®

Nevirapine (Viramune®) has a higher reported risk of both liver abnormalities and more serious forms of rash than efavirenz. These are most likely to occur in women and people with higher CD4 levels. In general though, nevirapine is very easy to take and well tolerated. Although it can be taken once daily, it's typically started twice a day with an option to change later.

The most important consideration regarding use of the NNRTI class of drugs is the risk of the virus becoming resistant. Missing these drugs can quickly lead to virologic failure.

Protease inhibitors are another option for the third drug in a regimen. PIs are less vulnerable to the development of resistance than NNRTIs, so they may be a better option if you're less than perfect at taking your pills as they're more forgiving of missed doses. Ritonavir, itself a form of PI, is almost always used alongside another PI to increase blood levels of these medications and allow for fewer pills, fewer daily doses, or both. Unfortunately, ritonavir will often cause some diarrhea and cholesterol abnormalities, as well as interactions with other medications you may need to take.

Preferred: Reyataz®

Atazanavir (Reyataz®) consists of either one or two pills daily. Side effects include infrequent jaundice (yellow skin and eyes). Atazanavir must be taken with food and, because it needs the acid in your stomach to be absorbed, you won't be able to use acid-blocking medications with this regimen. You'll need to take ritonavir tablets alongside atazanavir. For people who are unable to tolerate even low doses of ritonavir, atazanavir can be used alone (unboosted), unless it's being combined with tenofovir (as in Truvada®).

Preferred: Kaletra®

Lopinavir/ritonavir (Kaletra®) is the other preferred PI. It's unique in that the ritonavir is included in the tablets and doesn't have to be taken separately. Kaletra® can be taken once or twice daily for a total of four pills a day. Side effects include varying degrees of stomach upset and diarrhea. It also tends to raise cholesterol levels in many patients.

Preferred: Prezista®

Darunavir (Prezista®), also boosted with ritonavir, was recently approved for use as part of a first-time combination, with a new larger-dose pill to allow for once daily use. It isn't yet approved for coverage in most provinces, but is likely to join the preferred options in the near future. Other PIs are considered alternative options, and may have certain side-effect advantages or disadvantages.

First and lasting choices

Most important in starting treatment is to discuss the options thoroughly and frankly with your care team members to be sure you're making a good choice. If you're able to tolerate your regimen and take the medications consistently, then it's entirely reasonable to expect that not only will the treatment work, but also that your first regimen will be a lasting one. Choose wisely. **R**