Appendix C: Building a Treatment Combination

In this section we will provide some background on how treatment combinations are built. We will also look at the characteristics of the different classes of antiretroviral drugs. Our goal is to provide you with enough information so that you can play an active role in choosing a combination with your doctor.

As mentioned, treatment combinations are usually composed of three antiretroviral drugs from two different classes. Generally, two of the drugs are nukes (also called nucleoside analogues or NRTIs). These two drugs form the "backbone" of the combination, which is completed by a third drug from a different class.

For HIV-positive people **choosing their first combination**, the group of possible combinations is fairly well defined. See "First combinations" on page 51 for an overview of recommended first combinations. Then check out Appendix D to learn why you might choose one combination over another.

For people who have already been on treatment and are **changing their drug combination**, choosing the best combination is a more individualized matter. Sometimes—especially early on, when fewer medications have been tried—the most appropriate combinations may be similar to those for first-time treatment.

For more **treatment-experienced people with more drug resistance** (see Appendix E), combination choices will depend on which drugs are most likely to be effective. Later combinations may need to contain more drugs; the goal is to have the equivalent of three "active" antiretroviral drugs. This often involves three drugs, but sometimes it involves combining several drugs that are only partially effective with the hope that together they will suppress the virus.

The "backbone": two nukes …

The base or "backbone" of a drug combination is two nukes. Nukes have a long clinical history—AZT was the first antiretroviral drug to be brought to market, in 1987. The nukes currently available are effective and well tolerated by most people.

There are currently seven nukes approved in Canada. Newer nukes and 3TC are usually preferred because they have fewer side effects. Tenofovir, FTC, abacavir and 3TC are all commonly used. Older nukes, such as d4T and ddI, are seldom used, as they have been linked to side effects, such as lipodystrophy and peripheral neuropathy. Our knowledge of the side effects and toxicities of each of the drugs is constantly evolving, so it is best to talk to your doctor for the latest information.

Because two different nukes are usually taken at the same time, drug manufacturers have produced several co-formulations, where two or more drugs are put into a single pill. Common nuke co-formulations are Truvada (tenofovir and FTC), Kivexa (abacavir and 3TC) and Combivir (AZT and 3TC). Trizivir is one pill that contains three nukes: AZT, 3TC and abacavir (even though Trizivir contains three medications, it is not a preferred combination). One advantage of having several co-formulations is that when it comes time to switch medications, it might be possible to switch to a different co-formulation and thereby continue taking few pills.

Some people have an allergic reaction (or *hypersensitivity reaction*) to abacavir. A simple blood test, done before starting any medications, can tell whether you are one of the people at risk of having this reaction: if so, you should choose a different nuke.

… plus one more drug

When choosing this third drug, consider the known drug interactions, potential side effects and pill-taking schedule of each possibility. Although drugs within each class often share some common characteristics, they can also be significantly different. As with the nukes, there are also recommended drugs within the other classes.

If you are switching to a new anti-HIV drug, you and your doctor will decide whether to switch to a drug of the same class or to a drug from a different class. This decision will be guided by the resistance profile of your virus and the side effects of the individual drug.

Non-nukes

Non-nukes are a class of antiretroviral medications known for their ability to quickly and effectively reduce a person's viral load when taken as part of a drug combination. However, resistance to a non-nuke sometimes develops more easily than to drugs from other classes, and HIV that is resistant to one non-nuke is often resistant to nearly all members of this class. (Etravirine, the newest non-nuke, may still work in people who are resistant to the other non-nukes.)

There are currently four non-nukes approved in Canada:

- Efavirenz (Sustiva, also a component of Atripla) is the most commonly used non-nuke and is a preferred option for first combinations, except for women who are pregnant or planning to become pregnant because it poses a risk to the fetus.
- Nevirapine (Viramune) is an alternative non-nuke but should not be started in people with higher CD4 counts (more than 250 cells in women or more than 400 cells in men) because of a high risk of liver toxicity.
- Delavirdine (Rescriptor) is rarely used because it is not as powerful as newer drugs and needs to be taken three times daily.
- Etravirine (Intelence), the newest non-nuke, is currently used in people infected with strains of HIV that are resistant to efavirenz and nevirapine.

Protease inhibitors (PIs)

PI-based combinations tend to involve more pills than combinations that contain non-nukes, and many have to be taken with food. Many PIs can also cause metabolic problems, such as high levels of cholesterol. Some are associated with an increased risk of cardiovascular disease, and a few are associated with increased blood sugar levels. One advantage of PIs is that if HIV develops resistance to one PI, other PIs can remain effective, providing future treatment options.

A small dose of ritonavir (Norvir) is almost always added to PIs. This dose may be co-formulated in one pill or you may need to take ritonavir in addition to the PI. Adding ritonavir to PI regimens (which is called "boosting") has the following advantages:

- Ritonavir boosts the levels of the other PIs in the blood, resulting in more powerful anti-HIV activity.
- This allows a person to take a smaller dose of the PI, which usually means fewer pills.
- Ritonavir also prolongs the time that the PI remains in the blood, so that the PIs can be taken less frequently. Most PIs are taken once or twice a day.

However, PIs boosted with ritonavir are prone to many possible drug interactions.

Integrase inhibitor

Raltegravir (Isentress) is the only integrase inhibitor currently approved. It was originally studied in HIV-positive people who had previously taken non-nukes and PIs, and it was very effective in that group. More recently, raltegravir has been approved for use as a first-line option and has shown good results so far. It appears to be very effective at inhibiting HIV, with mostly minor side effects.

Other classes

Currently, non-nukes, PIs and integrase inhibitors are the only classes recommended as the "third drug" in a first-time combination. Drugs in other classes are currently reserved for people who have already been on one or more standard HIV drug combinations.

The only *fusion inhibitor* currently available is enfuvirtide (T-20, Fuzeon), which has powerful anti-HIV activity but has to be taken twice a day by injection. Although this is obviously far from desirable, T-20 is still an important option for people who are resistant to many different antiretrovirals.

CCR5 inhibitors (a kind of co-receptor inhibitor) are yet another newer class of drugs. Like the fusion inhibitors and integrase inhibitors, CCR5 inhibitors have been studied mostly in people who have previously tried other treatment combinations. These drugs have generally proven to be quite effective, but only against a strain of HIV called *R5-tropic*. CCR5 inhibitors are not of any use in fighting X4-tropic virus, the other major strain of HIV, which tends to develop in people who have been infected longer. A simple screening test is able to determine whether you have the R5-tropic strain; if so, CCR5 inhibitors are a viable option. Maraviroc (Celsentri) is the first, and currently only, CCR5 inhibitor approved for use.