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An HIV Information Site & HIV Educational Resource Site

Combining Medications for the Treatment of HIV

Antiretroviral medications must almost always be taken together to work against HIV. One medication is generally not powerful enough to overcome a virus that grows as rapidly as HIV. Through carefully done experiments in the lab, in animals, and in humans, healthcare providers now know which medications to combine together and what doses to use. In some ways its like a menu at a restaurant: take two medications from Column A (usually nucleoside reverse transcriptase inhibitors) and one from Column B (usually one or two protease inhibitors or one nonnucleoside reverse transcriptase inhibitor).

NRTIs Nucleoside RT inhibitors "Nukes"	NNRTIs Non-nucleoside RT inhibitors "Non-Nukes"	PIs - Protease Inhibitors	Fusion Inhibitors Co-Receptor Inhibitors Integrase Inhibitors
Zidovudine (Retrovir, AZT, ZDV) Didanosine (Videx, Videx EC, ddl) Zalcitabine (Hivid, ddC) Abacavir (Ziagen) Stavudine (Zerit, d4T) Lamivudine (Epivir, 3TC) Emtricitabine (Emtriva, FTC) Tenofovir (Viread, TDF) Atripla Trizivir Combivir Epzicom Truvada	Nevirapine (Viramune) Efavirenz (Sustiva) Delavirdine (Rescriptor)	Atazanavir (Reyataz) Darunavir (Prezista) Fosamprenavir (Lexiva) Indinavir (Crixivan) Lopinavir + Ritonavir (Kaletra) Nelfinavir (Viracept) Ritonavir (Norvir) Saquinavir (Invirase) Tipranavir (Aptivus)	Enfuvirtide (Fuzeon) Maraviroc (Selzentry) Raltegravir (Isentress)

When combined in this manner anti-HIV medications often exhibit more than just the sum of their actions. For example if zidovudine is a 1 on the anti-HIV meter, lamivudine is also a 1, and a protease inhibitor is a 2, when all three drugs are combined, they may read a 5 or 6 on the anti-HIV meter (if one existed.) The added effectiveness of these medications when they are combined together is referred to as "synergy." However not all combinations are synergistic or even additive. Some components actually work against each other; **stavudine** and **zidovudine** are such an antagonistic combination. **Lamivudine** and **emtricitabine** do not add to each other, but they do not antagonize each other either; this would be called a neutral effect and would not be recommended due to excessive cost. Some drug combinations are too toxic when they are combined. Some drugs reduce the levels of other drugs excessively

Drugs	Effect of Combining the Drugs
emtricitabine + lamivudine	neutral
stavudine + zidovudine	antagonistic
zalcitabine + stavudine	excess toxicity
zalcitabine + didanosine	excess toxicity
nevirapine + efavirenz	antagonism?
fosamprenavir or amprenavir + lopinavir/ritonavir	excessively decreased levels of lopinavir

indinavir + atazanavir

excess toxicity

If a patient is inconsistent with their medications, the virus may not be inhibited sufficiently to stop its reproduction. Whenever HIV reproduces it makes errors that may hurt the virus or in some cases actually help it. If some drug is present, but not enough to stop reproduction completely (when someone takes their medications inconsistently,) HIV will make errors or mutate during the reproduction cycle that allow it to become resistant to the drugs. This is referred to as drug resistance. If HIV becomes resistant to one drug, often other drugs are affected also. In some cases just one error or mutation can eliminate two drugs (e.g., lamivudine and emtricitabine at the same time) or even an entire class of drugs (e.g., **nevirapine**, **efavirenz**, and **delavirdine** at the same time). For this reason it is actually harmful to take ones medications inconsistently.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs or "nukes")

NRTIs inhibit the formation of HIV genetic material ("RNA") by the drug being mistaken by HIV for a nucleic acid.

The NRTIs are usually considered the backbone of most antiretroviral combinations. In many cases two of these medications will be combined with 1-2 protease inhibitors and/or one nonnucleoside reverse transcriptase inhibitor to form a potent combination. In fact several NRTIs have been combined together into pills or capsules that contain 2 or 3 of the NRTIs. These combination drugs simplify things quite a bit by reducing the number of pills one takes and how often someone has to take pills. The combination drugs also simplify things at the pharmacy so that several prescriptions are eliminated. Simplification is important as that makes it easier to adhere to a medication plan or regimen. The newest combination drug **Atripla** adds the NNRTI **efavirenz** (Sustiva) to **tenofovir** and **emtricitabine** to achieve the first combination medication of its type.

Combination Drug	Components
Combivir	zidovudine 300 mg + lamivudine 130 mg
Trizivir	zidovudine 300 mg + lamivudine 130 mg + abacavir 300 mg
Epzicom	abacavir 300 mg + lamivudine 300 mg
Truvada	tenofovir 300 mg + emtricitabine 200 mg
Atripla	efavirenz 600 mg + tenofovir 300 mg + emtricitabine 200 mg

NRTIs are all well tolerated in general. You can check the [side effects page](#) on this side for more information of possible side effects and how to manage them.

Protease Inhibitors (PIs)

Protease inhibitors work by preventing the correct severance or cleavage of HIV protein production so that the proteins that HIV makes do not function as they should. This effectively prevents reproduction. When reproduction is inhibited then more virus dies than is being produced, and the viral load decreases.

Protease inhibitors are among the most powerful of the HIV medications. In general they are well tolerated, but they can cause problems with the liver, stomach, and bowels in some people. Additionally the number of pills taken every day and the number of times the medication must be taken may be high for some patients.

The latest strategy to make PIs easier to take and most effective is called boosting. Boosting usually refers to combining a PI with another PI. The second PI is usually ritonavir. Ritonavir inhibits the breakdown of most of the other PIs. If the breakdown of a particular PI is slowed down, then that PI will stay in the bloodstream longer and it may not be necessary to take the PI with or without food (depending on the PI.) However, this type of strategy also has its drawbacks: increased cholesterol and triglycerides, possible **redistribution of fat** ("Crixivan belly"), liver problems, and interactions with many other common drugs. These problems do not occur in most persons who take boosted PIs but they are possible. Your healthcare provider will monitor you carefully for these issues.

Boosted PI Combination	Beneficial Effect of Boosting the Drugs	Problems Due to Boosting
indinavir + ritonavir	less pills. less frequent dosing. and no meal dependence	

saquinavir + ritonavir	less capsules, less frequent dosing, and less meal dependence	cholesterol problems, fat redistribution, liver problems, lots of drug interactions
atazanavir + ritonavir	overcomes the negative effect of tenofovir and possibly drug resistance	
lopinavir/ritonavir + ritonavir	overcomes drug resistance better	
amprenavir + ritonavir	less capsules and less frequent dosing	

Two new protease inhibitors (**fosamprenavir**, **atazanavir**) have largely overcome problems with side effects and adherence that have plagued the older PIs. Both may be administered as a single PI or in boosted form. Both of these PIs are very well tolerated and both may be taken once a day in some situations.

Certain herbal products such as milk thistle, St John's wort, and large amounts of garlic lower the amount of protease inhibitors in the bloodstream and this can cause the same problems as missing doses (resistance mutations.)

Resistance mutations to protease inhibitors are relatively slow to develop compared to other drugs.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Like the NRTIs, NNRTIs inhibit the production of HIV's genetic material during reproduction. Therefore, reproduction is inhibited and more virus dies than is being produced. As a result the amount of virus (viral load) decreases.

NNRTIs ("non-nukes") are also very potent antiretrovirals. In contrast to the NRTIs and the PIs, only one NNRTI is used at a time if a NNRTI is used at all. NNRTIs are generally easy to take and pretty well tolerated. However, skin rashes and liver problems are more common with this class of drugs. Also NNRTIs are very subject to just one or two resistance mutations; missing doses or taking NNRTIs inconsistently is very unfortunate in that resistance to one of these drugs eliminates all three drugs in the class (nevirapine, efavirenz, and delavirdine) from ever being used again. Like PIs, NNRTIs tend to interact with many other medications so it is important for your healthcare provider to know all the medications you are taking including over-the-counter drugs and herbal products.

Rashes due to NNRTIs can be very minor or very serious. Every rash you get when you are starting a NNRTI should be reported promptly to your healthcare provider or if that person is not available, you should report to an Emergency Department and be evaluated by someone experienced in HIV care.

Persons with high T-cells may have more trouble with liver problems due to **nevirapine**; therefore, if one starts therapy with high T-cells, you may want to avoid nevirapine.

Some of the most recent scientific information indicates that suddenly stopping **nevirapine** and **efavirenz** can lead to resistance. Therefore, if you need to stop one of these drugs, talk with your healthcare provider first and plan a strategy of exactly how to do this.

Fusion Inhibitors, Integrase Inhibitors, & Co-Receptor Inhibitors

The newest classes of antiretrovirals are the fusion inhibitors, integrase inhibitors, and co-receptor inhibitors.

All three classes of drugs are used in situations where other drugs have not worked either due to resistance or too many side effects.

The co-receptor inhibitors include **maraviroc** which was FDA-approved in September 2007 and vicriviroc which is undergoing study for possible approval (as of October 2007). Candidates for either drug must first be screened with a special blood test to determine whether the strain of HIV that the person has binds to the specific CD4-lymphocyte (T-cell) co-receptor that the drugs inhibit (which is the CCR5 co-receptor.) If that co-receptor is not used exclusively by that person's strain of HIV, then both drugs will not work.

Raltegravir is the only approved integrase inhibitor. Currently it is only approved for patients who do not tolerate or

respond to other antiviral therapies. **Raltegravir** appears to be very well tolerated, very effective, and mixes well with other medications. At some point, **raltegravir** may be used as first-line therapy for HIV.

Unfortunately the only fusion inhibitor that is currently available (**enfuvirtide, Fuzeon**, September 2004) is relatively expensive, only administered by self-injection twice a day, and the frequency of injection site reactions is very high. These factors have shaped recommendations for the use of enfuvirtide such that it is reserved for salvage situations where there are few or no other options. However, there must be at least two other active drugs to use with the enfuvirtide or resistance will develop to the enfuvirtide quickly.

It may seem an extreme step to take injections for HIV, but many patients have adapted easily to this mode. The situation is very similar to some diabetic patients who have to take two injections per day for their entire life or they risk major problems and ultimately death.

Combinations of Antiretrovirals

Most persons especially those that have sensitive ("wild type") or nonmutant strains of HIV will be prescribed combinations of antiviral drugs that can be represented by the following "formulas".

NRTI #1 + NRTI #2 + PI/b or PI

or

NRTI #1 + NRTI #2 + NNRTI

or

NRTI #1 + NNRTI + PI/b

where PI/b is a boosted protease inhibitor and PI is a protease inhibitor without boosting.

Some persons can also be served well by three NRTIs without a PI or NNRTI although this should only be done when other alternatives are not feasible:

NRTI #1 + NRTI #2 + NRTI #3

When a patient has fewer options due to side effects or resistance, then a fusion inhibitor may be used in something like this:

NRTI #1 + NRTI #2 + NRTI #3 + NNRTI + PI/b + FI

where FI is a fusion inhibitor. The exact formula depends on the strain of HIV and how many mutations it has developed to resist medications.

The possible advantages and disadvantages of each type of combination is listed below. Note emphasis on the use of the word "possible." Most patients do not experience the "disadvantages" that are listed.

Combination	Examples	Advantages	Disadvantages
NRTI #1 + NRTI #2 + PI/b	fosamprenavir + ritonavir + tenofovir + didanosine	Probably the most potent form of combination therapy; higher barrier to resistance	Boosting may lead to increased lipid problems, drug interactions
NRTI #1 + NRTI #2 + PI	atazanavir + zidovudine + lamivudine nelfinavir + emtricitabine +	Very potent; high barrier to resistance	Lipid problems, drug interactions, higher pill

	tenofovir		burden
NRTI #1 + NRTI #2 + NNRTI	efavirenz + abacavir + lamivudine	Very potent, possibly less of a pill burden, less problems with lipids	Rash or stimulation from NNRTI, lower "barrier" to resistance than a PI-based regimen
NRTI #1 + NRTI #2 + NRTI #3 +/- NNRTI + PI/b + FI	tenofovir + didanosine + abacavir + lopinavir/ritonavir + enfuvirtide	Very potent; overcomes resistance when other regimens cannot do so	High burden of medication; necessity for self-injection twice a day; possible lipid problems; drug interactions

Drug Combinations to Avoid if Possible:

Combination	Reasons Not To Use This Combination
(nevirapine or efavirenz) + tenofovir + didanosine-EC	combination appears to lose control of the virus more often than it should.
stavudine + didanosine	combination may cause acid build-up, pancreatic inflammation, and nerve damage
zidovudine + stavudine	combination actually works against each other
zalcitabine + lamivudine	combination causes too much nerve damage
zalcitabine + stavudine	combination causes too much nerve damage
zalcitabine + didanosine	combination causes too much nerve damage
lamivudine + emtricitabine	combination is like using one drug and therefore, one of the medications is wasted

Which drugs will be picked for you will be based on a number of different factors including the following:

1. Scientific evidence from studies that compare different drugs and different combinations
2. Your personal medical history especially what drugs you have been on in the past, what side effects you have had, what other medications you are currently taking, and what your other medical problems are besides HIV
3. The resistance that your strain of the virus may have as judged by when you got infected, from whom you got infected, what drugs you have been treated with and your response, and special blood tests that detect resistance (genotype and/or phenotype)
4. Factors that make it easy to take medications such as medications with less pills per day, less frequent dosing, and less side effects
5. Insights that your provider may have into your mental health, personality, work habits, adherence, residential situation, family, and job
6. Your personal preferences about medications such as type of pills or capsules, intolerances, etc.

Using Combinations of Antiretrovirals: The Ten Commandments
1. Never use just one antiretroviral drug by itself. Avoid using just 2 active drugs: 3-4 drugs are usually the best number. Remember that Combivir, Trizivir, Epzicom, and Truvada contain 2-3 drugs in each pill. However lopinavir/ritonavir (Kaletra) only counts as one active drug. In most cases ritonavir (Norvir) does not count as an active drug.
2. Never add a drug to a regimen that is already failing you.
3. Nothing works without at least 95% adherence. If you take 30 doses of medication per month, this means missing less than 2 doses per month. If you are taking 60 doses per month, this means you are missing less than 4 doses per month.
4. Less than 95% adherence may be more harmful than helpful or stated another way, take all of your medications all the time or do not take any until you can take 100%.

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| 5. Report side effects to your healthcare provider promptly. |
| 6. Start new antiretrovirals all at the same time. Avoid starting new drugs if you are out of town or just about to leave town or are going to be out of touch with your healthcare provider. Avoid starting other new medications at the same time as your antiretrovirals so that if side effects develop, it will be simpler to determine which medication is the cause. |
| 7. Avoid stopping your antiretrovirals unless you speak to your healthcare provider first. |
| 8. Never assume you are cured just because you are taking your medications and your viral load is load or undetectable. |
| 9. Never assume that you cannot transmit HIV sexually or through blood contact even if you are taking your medications. |
| 10. Drugs to which your strain of HIV are already resistant do not count toward making an effective combination of medications. |

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