# HIV drug resistance

## Fewer people are running out of treatment options but resistant virus is still a threat

by Guinevere Queenie Lee and Dr. Richard Harrigan

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There are now more than 20 antiretrovirals (ARVs) from six drug classes available to combine in highly active antiretroviral therapy (HAART) regimens. As a result, people are much less likely to reach a stage where their virus is resistant to all available drugs, as was relatively common only a few years ago.

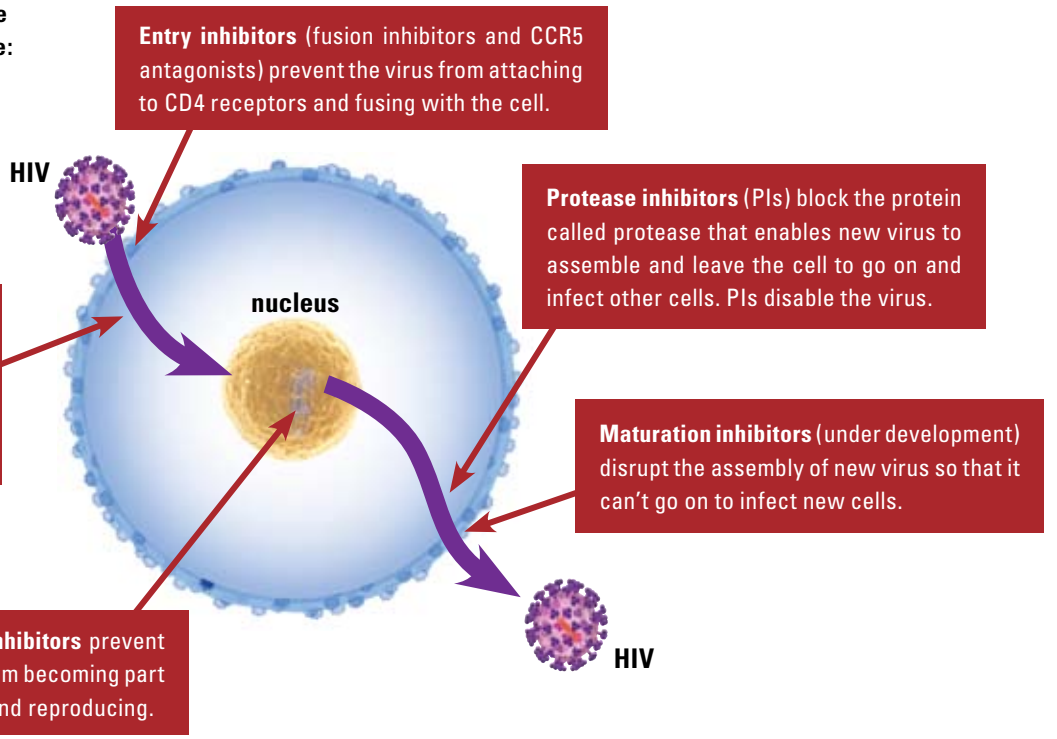
However, the expanded range of options shouldn't make us any less vigilant about preventing resistance. Missed doses of medications can lead to incomplete viral suppression. This enables the virus to start its life cycle again and allows drug-resistant strains to emerge quickly. While there are usually several alternative drug classes available, the choices aren't unlimited. If the cycle of missing doses continues as a person switches from one regimen to another, it's still possible to exhaust currently available options.

### Where do resistant viruses come from?

In a person with untreated HIV infection, the body produces billions of HIV particles every day. However, this production process lacks quality control, and each new virus may be a little different than the others. In fact, the quality control process is so poor

Figure 1
## Drug targets along the HIV life cycle

**HIV has two strands of RNA and three proteins that help the virus reproduce: reverse transcriptase, integrase and protease. ARVs work by blocking these proteins, which are not needed by the healthy cell.**




that every single possible change in the HIV can be produced within one or two days of infection.

Each of these slightly different viruses may respond differently to a given ARV medication. When exposed to an ARV, viruses that are less able to tolerate the drug become extinct. If there are any viruses that are more tolerant (i.e. resistant), they will survive and resist the effect of the drug. These survivors go on to produce more viruses, which inherit this drug tolerance and can reproduce in the presence of the drug. Soon, the resistant virus becomes the predominant strain of HIV in the body and can even spread from person to person. That's why a person can have drug-resistant virus even when they've never taken any HIV medication before.

### Combination therapy

In the early 1990s, only a few drugs were available to treat HIV, and when these drugs were used alone or in pairs, resistant viruses rapidly emerged in most people. Fortunately, by the mid-1990s, more new drugs were available, some of which worked by different mechanisms.

The development of new drugs that target different steps in the HIV life cycle made it less likely for a single HIV virus to evolve and become resistant to all of these drugs at the same time (**Figure 1** above shows where each class of ARV works to disrupt the life cycle of HIV). This marked the beginning of the new era of highly active anti-retroviral therapy (HAART), in which a combination of anti-HIV drugs was prescribed instead of a single drug. HAART has greatly reduced the likelihood of developing drug-resistant HIV.

Unfortunately, HAART isn't perfect. To date, no combination of drugs can completely remove HIV from the body — they can only bring the rate of HIV replication down to an undetectable level. The HIV infection isn't "cured", but rather "controlled." It's always possible for HIV replication to re-start if it's given the opportunity.

### Resistance is forever

It's important to remember that once your virus develops resistance to a particular drug, that drug will never again be an effective option. After you switch to a new drug, the resistant virus may slowly become a minority and lurk in the background behind non-resistant virus. But there's no way to rid the body of this resistant strain completely, since HIV hides in the DNA of our cells

and can hibernate for years. And it hides very well: routine drug resistance testing may not reveal the presence of these resistant viruses.

This means that once viruses have developed resistance at any time during a person's treatment history, they can reappear very quickly if that same drug is given again. It's very important that your physician know about all the drugs you've ever taken, and which drugs your HIV has ever become resistant to. By looking at your treatment history, your physician will be better able to prescribe the most effective combination of drugs for suppressing the virus in your body.

## Current drug options

Routine lab tests are performed to make sure that the ARVs you're taking are working together successfully to suppress the replication of the virus. If, however, the viral load in your blood starts to climb, it may be an indication that the drugs are no longer working. The virus will then be sampled and a drug-resistance test will be performed while you're still on the original therapy.

There's no need to panic if the test shows the presence of resistant virus. There's now a good selection from six different classes of drugs.

Integrase inhibitors and CCR5 antagonists are the newest classes, and have only been in use since 2007. New investigational drugs are being developed in these and other drug classes and may become available in the near future.

## Cross-resistance

Often, when a virus becomes resistant to one drug, the effectiveness of other drugs that belong to the same class can be lost or reduced. This is called "cross-resistance" and means that the number of drugs that can realistically be useful to that person in the future is reduced by more than one when resistance develops. To avoid extensive cross-resistance, it's important that your doctor monitor any change in the virus and switch your therapy as soon as drug-resistant virus is detected.

Finding an effective regimen is more complicated in treatment-experienced people whose virus is resistant to more than one drug. In these cases, the more recently developed drugs, such as the integrase inhibitor raltegravir (Isentress™), the CCR5 antagonist maraviroc (Celsentri™), or the fusion inhibitor enfuvirtide (Fuzeon®), may prove very useful. However, each of them has drawbacks: viruses develop resistance to raltegravir rather quickly; not everyone can take maraviroc because it depends on the type of HIV you have in your body (a blood test can reveal whether it will be useful); and enfuvirtide is given by injection, not in pill form.

To complicate things further, not every drug pairing is possible. For example, some combinations of drugs will reduce the level of other drugs in the blood and compromise the effectiveness of the regimen.

## Resist resistance!

The best way to avoid drug resistance is to prevent HIV from replicating and changing. The best way to do this is to stick as closely as possible to your medication regimen, which is likely to consist of multiple drugs working together to minimize HIV replication at different stages of its life cycle.

If resistant viruses do appear, we're fortunate to have a number of options. Frequent monitoring of the viral load is important so that resistance is detected early to avoid cross-resistance. Your physician should design your next drug regimen based on your treatment history, the types of resistant virus developed, and the effectiveness of various drug combinations.

HIV drug resistance has become less common in recent years. But the problem hasn't gone away. Both you and your physician must take an active role in managing HIV disease to prevent its appearance.