

Why CCR5 inhibitors won't work for everyone

Dr. Cécile Tremblay

CCR5 inhibitors are an exciting new class of drug available to treat HIV-1 infection in treatment-experienced individuals. One member of the class, maraviroc, is now available in Canada as part of an Expanded Access program.

In order to infect a human cell, the HIV virus must first bind to a molecule on the surface of the cell called the CD4 receptor. That's not enough for it to get inside, though. Once the virus has attached to the CD4 receptor, it must then bind to another molecule, called a co-receptor. There are two types of co-receptor used by HIV: CCR5 and CXCR4. Once this second connection is made, the virus can get close enough to the cell so that the viral and cellular membranes can fuse together and the virus can get inside. CCR5 inhibitors are small molecules that bind to a pocket inside the CCR5 co-receptor and interfere with the virus' ability to attach to it. They are the first class of antiretrovirals (ARVs) to target a molecule on the surface of the human cell, rather than on the virus itself.

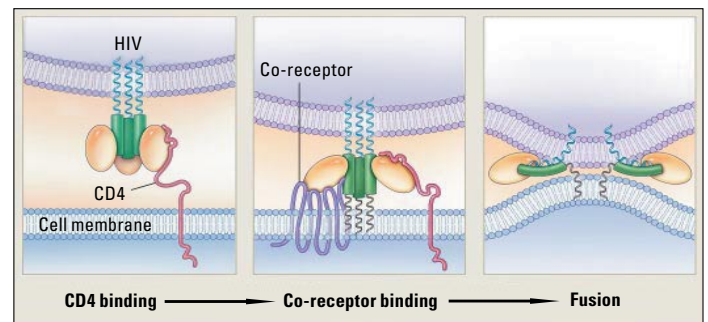
Are CCR5s the key to your cells?

Most strains of HIV use the CCR5 co-receptor to enter the cell. However some strains use CXCR4 instead, and others may use both. This is why CCR5 inhibitors may not be useful for all people with HIV. During primary HIV-1 infection (in the first year of infection), HIV almost always uses CCR5. As the infection progresses and the virus replicates inside the body, some new viruses may also start using CXCR4. Approximately 50% of HIV-infected individuals will eventually develop viruses that use both co-receptors and 50% will remain with CCR5-using viruses. CCR5 inhibitors will not be useful in people infected by a virus that uses CXCR4. It's important to find out what type of receptor your virus uses to know if these drugs can be useful to you.

Take the test

You can find out which receptor your virus is using through a blood test called a tropism assay. It tests the virus for its capacity to use one or the other co-receptor: CCR5 or CXCR4. ("Tropism" is the word used to describe the virus' co-receptor preference). If the virus uses CCR5 exclusively, it means that it's an R5 virus and that CCR5 inhibitors may

be useful. If the virus uses exclusively CXCR4 (X4 virus) or both co-receptors (dual-tropic virus), then it's unlikely that these drugs will be useful.



You're better off having the test done before using a CCR5 inhibitor to avoid the cost and/or potential side effects of a drug that won't benefit you. In a trial studying the efficacy of maraviroc in patients infected with dual-tropic viruses, no benefit in terms of decreasing viral load was found. However, no major toxicities were observed either and CD4 counts were maintained. Maraviroc appears to be well tolerated, but we'll need more data to establish the long-term safety of this new class of drug. **R**

If your doctor has suggested you take maraviroc through the Expanded Access program, you can probably have the test done at your clinic. It will be sent to a California-based company called Monogram that will perform the test, and you should have the results within a month.

Since the assay is necessary in order to prescribe maraviroc, the drug manufacturer will cover the cost. However, when other drugs in this class become clinically available, it will raise the question of who will be paying for these tests and whether it would be useful to have an alternative assay performed locally.

Other CCR5 antagonists are currently under development, but some have run into difficulties. Clinical trials of vicriviroc were halted when several volunteers with advanced HIV disease who had not taken ARVs before were found to have cancer, (though this was not proven to be related to the drug) but trials in treatment-experienced people are ongoing. Development of a third drug, aplaviroc, was also halted after severe liver toxicity was discovered.

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