

WHEN HIV COMES KNOCKING

Here's how anti-HIV meds make the virus feel unwelcome.

News from AIDS 2006 expanded our list of potential antiretroviral drug classes by three, with the addition of entry inhibitors, integrase inhibitors and maturation inhibitors. Here's a summary of the different drug classes, where they work in the viral life cycle and the key messages about the new players. A version of this material is available in workshop form. Contact CATIE for more information. Also, check out our *Practical Guide to HAART*.

1 Entry inhibitors Sorry, door's locked; nobody's home

HOW THEY WORK: By making it hard for HIV to grab on to a cell and get inside

THE ONES YOU KNOW: T-20

NEW PLAYERS: maraviroc, vicriviroc, TNX-355

THE LOW-DOWN:

- The CCR5 antagonist **vicriviroc** (Schering-Plough) failed initial tests in treatment-naïve PHAs but is showing some success in treatment-experienced PHAs; however, five cases of cancer among 83 people taking the drug has led to concerns about safety
- **Maraviroc** (Pfizer) is being tested in treatment-experienced patients; this CCR5 antagonist helps improve the immune system but is no better than rivals at beating down viral load; it is also being tested in treatment-naïve patients
- **TNX-355** (Tanox) is an antibody that sticks to the CD4 receptor so that HIV can't; Advantage—drug stays in the blood a long time and can be given every two weeks; Disadvantage—given by 30-minute intravenous infusion

2 Reverse transcriptase inhibitors We don't speak HIV

HOW THEY WORK: Jamming viral reverse transcriptase and stopping the conversion of the virus's RNA (ribonucleic acid) into DNA. Think of reverse transcriptase as an interpreter—without it, RNA language isn't translated into DNA language and so the CD4+ cell can't be hijacked into doing the virus' work. There are two classes: NRTIs and NNRTIs

THE ONES YOU KNOW:

NRTIs – AZT, ddI, 3TC, d4T, FTC, abacavir, tenofovir

NNRTIs – nevirapine, delavirdine, efavirenz

NEW PLAYERS: Atripla, TMC125

THE LOW-DOWN:

- **Atripla** is the long-sought dream of HIV treatment; one pill once a day; it combines three drugs—the two NRTIs tenofovir and FTC and the NNRTI efavirenz; not yet available in Canada
- **TMC125** (Tibotec) is a new NNRTI that works against HIV that is resistant to other NNRTIs; its most common side effects include diarrhea and rash

3 Integrase inhibitors Please, do NOT make yourself at home

HOW THEY WORK: By blocking integrase, so the virus cannot insert (integrate) its genetic material permanently into the DNA of the cell; no integration means no replication

THE ONES YOU KNOW: none approved for sale in Canada or elsewhere

NEW PLAYERS: MK-0518

THE LOW-DOWN:

- Arguably the belle of the AIDS 2006 ball, **MK-0518** (Merck-Frosst) made a splash with news of good results in treatment-naïve patients, which means that one day it might be used as a first-line treatment

4 Protease inhibitors Splitting is not an option

HOW THEY WORK: By gumming up protease, the enzyme that cuts up a long protein into smaller blocks that will eventually be put together to form another HIV particle; think of protease as scissors cutting the string into several pieces before they are tied together to make a net

THE ONES YOU KNOW: amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir

NEW PLAYERS: darunavir, brecanavir

THE LOW-DOWN:

- **Darunavir** (Tibotec) was approved in Canada just days before the conference and is available through an expanded-access program; in trials it worked well against virus resistant to other protease inhibitors
- **Brecanavir** (GlaxoSmithKline) was considered the most promising of the PIs in development; phase II trials showed powerful activity to beat down both wild-type and multi-drug-resistant virus, however, in mid-December 2006, the drug's maker pulled the plug on development because they couldn't make a pill that gave consistent levels of drug in the body

5 Maturation inhibitors Here's your hat, what's your hurry?

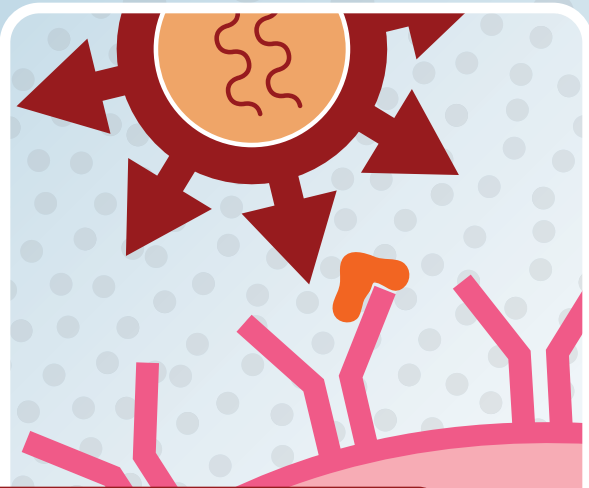
HOW THEY WORK: During virus maturation, the final step of HIV replication, all the building blocks of a new virus are collected and assembled. Maturation inhibitors mess with this assembly and the jumbled virus cannot go on to infect other cells

THE ONES YOU KNOW: none approved for sale in Canada or elsewhere

NEW PLAYERS: bevirimat

THE LOW-DOWN:

- **Bevirimat** (Panacos) is in phase II trials and requires further study; investigators are determining the best dose of the drug



A closer look at CCR5 inhibitors

The CCR5 antagonists maraviroc and vicriviroc garnered much attention at AIDS 2006. CCR5 is one of the proteins on the outside of CD4+ cells. To get into the cell, HIV must first attach to handles, called co-receptors, on the cell surface. One of these co-receptors is CCR5. As antagonists, vicriviroc and maraviroc stop (or antagonize) the interaction between HIV and CCR5, meaning HIV can't grab hold of the cell and work its way in.

CCR5 antagonists target a part of the CD4+ cell, not a part of HIV like most other antiretrovirals. This could lead to some unexpected side effects since CCR5 (the protein on the outside of the CD4+ cells) may also be used by the CD4+ cell in its role as a player in the immune system.

