PROJECT inform
Information, Inspiration and Advocacy for People Living with HIV/AIDS

Date: 1/03

Cell Cycles, Anti-HIV Drugs and Treatment

Cell Cycles, Anti-HIV Drugs and Treatment

New research regarding how and when anti-HIV drugs are effective (and ineffective) raise questions about many of the combination treatment regimens in use today. The data seem to provide additional insights into why drugs fail, and consequently suggest new strategies for improving the effectiveness of combination therapy.

Current Reasons for Drug Failures

Two closely connected reasons are commonly used to explain why anti-HIV drugs fail over time. Part of the blame is assigned to the drugs themselves and part is assigned to the person who uses them.

First, let's look at the way the drug itself contributes to failure. At the simplest level, the most common reason for drug failure is because HIV develops resistance to them. How easily and quickly this happens is at least partially determined by the design of the drug. The most effective drugs remain stable in the blood for long periods. As a result, the level of the drug in the blood rarely falls below the amount needed to sustain full suppression of the virus, and thus, there is little opportunity for the growth of resistant forms of HIV. In contrast, some drugs are quickly flushed out of the body. As a result, the level of drug in the blood is constantly rising and falling as people take their daily doses. This often creates periods in which the level of drug in the blood is too low to fully suppress the virus, and this is precisely the condition which encourages the development of resistance, and thus, drug failure.

Next let's look at how the drug's user can contribute to the problem. The key issue here is adherence—how carefully the user follows the instructions on taking the drug. This is particularly critical with drugs that are quickly flushed out of the body. The only way to make such drugs work well is to constantly replenish the drug supply in the bloodstream. For some drugs, this means taking them on a precise time schedule two or three times a day. The worse the drug is at maintaining a high, steady level in the bloodstream, the more important adherence becomes. Yet, we are all human and it's hard to expect people to adhere to their drug regimens' perfectly year after year.

New Research Provides New Reason

In theory, these two issues should explain most incidences of drug failure, assuming that people are using a minimum of three anti-HIV drugs together in a combination. However, any doctor who treats large numbers of people with HIV sees cases where drugs seem to fail despite careful selection and near perfect adherence. What explains this discrepancy?

New research suggests the startling conclusion that not everyone using a 3-drug regimen is actually getting the effect of three drugs. A new study, conducted by Drs. Robert Redfield, Charles Davis and Alonso Heredita, reported in the Journal of Human Virology (Vol. 4: pp113-122), shows that another variable, called *cell-cycle dependency*, is also at work and affecting the outcome of anti-HIV therapy.

Simplistically, there are two basic states for every type of cell, including the cells that are infected by HV. In the ACTIVE state, a cell is engaged in the process of replication, or making copies of itself. In the RESTING state, a cell is quietly awaiting a signal to turn itself on. The cells, however, can produce copies of HIV or become infected in either state. What makes this an issue for anti-HIV therapy is that some drugs only work in ACTIVE cells, some work only in RESTING cells and some work in both cell states. Ideally, a drug should work without regard for the cell cycle. Drugs that work only in one state of the cell are said to be CELL CYCLE *DEPENDENT*. Drugs that work regardless of the state of the cell are said to be CELL CYCLE *INDEPENDENT*. In contrast, HIV can infect cells in either the active or resting state.

The implications of this appear to be highly significant. Unless all three drugs in a combination are CELL CYCLE INDEPENDENT, the person using the combination is not really on a 3-drug combination all the time. If the combination includes one drug that doesn't work in resting cells, the user is for all intents and purposes only on a 2-drug combination in regard to resting cells. Some combinations even use two drugs that have little or no effect in resting cells.

National Hotline 1-800-822-7422
SF Area and International 415-558-9051 - Fax 415-558-0684
Administrative Offices 415-558-8669 - Web Site www.projectinform.org

© 2003 Project Inform, Inc., 205 13th Street #2001, San Francisco, CA 94103-2461

Cell Cycles, Anti-HIV Drugs and Treatment

Drug Name	Drug works in: active cells	resting cells
NRTIs		
3TC (Epivir)	yes	yes
abacavir (Ziagen)	yes	yes
AZT (Retrovir)	yes	no
ddI (Videx)	no	yes
d4T (Zerit)	yes	no
FTC (Coviracil)	yes	yes
tenofovir (Viread)	yes	yes
NNRTIs		
delavirdine (Rescriptor)	yes	yes
efavirenz (Sustiva)	yes	yes
nevirapine (Viramune)	yes	yes
PROTEASE INHIBITORS		
indinavir (Crixivan)	yes	no
ritonavir (Norvir)	yes	no
saquinavir (Fortovase)	yes	no
amprenavir (Agenerase)	yes	no
nelfinavir (Viracept)	yes	no
ritonavir boosted lopinavir (Kaletra)	yes	no
atazanavir	yes	no

Most, but not all, drugs work in active cells. The exception is ddI, which works mostly in resting cells. The biggest differences occur in the effect of drugs on resting cells. Here, two of the most common nucleoside analogue drugs, AZT and d4T, and all protease inhibitors have little effect in resting cells. Fortunately, there are a number of drugs that work well in both cell states. The chart (next page) summarizes the activity of various drugs in the two different activity states.

Limitations

The data suggest that many commonly used 3-drug combinations do not provide full 3-drug coverage all the time. But this is perhaps an oversimplification, as the implications of the new data are not yet clear. The data are based in laboratory findings (*in vitro*). The lab data don't conclude that certain drugs have no activity against one or the other cell state, but only that the drug's effectiveness is sometimes significantly diminished. We also don't know the relative contribution of viral reproduction that is made by active cells and resting cells, and therefore can't yet predict how big an impact these finding will have. Nor is it entirely clear whether full 3-drug combinations are needed for both active and resting cell types.

This data raises many important questions that can only be answered by human trials. On the surface, though, these findings may help explain why some people experience drug failure despite good adherence.

Can any conclusions be drawn while awaiting further research? Possibly. For example, it seems reasonable to want to make sure that every combination include at least two (if not three) drugs that are effective against cells in both the ACTIVE state and the RESTING state. In some cases, this might require using more than three drugs in total, or at least carefully selecting three.

Looking at the chart, it is clearly possible to meet the goals implied by this data. For example, any of the following combinations would provide full coverage in both cell states:

Any two from column A, plus one from column B:

Column A	Column B
abacavir (Ziagen)	*delavirdine (Rescriptor)*
tenofovir (Viread)	*efavirenz (Sustiva)*
3TC (Epivir)	*nevirapine (Viramune)*
FTC (Coviracil)	

Other factors, however, would also have to be considered in a typical situation, such as a person's drug history, any known resistance to individual drugs, relative potency, etc. In most situations, there won't be simple solutions like those implied above. Any protease inhibitor, for example, lacks effectiveness against resting cells. Thus, care should be taken when selecting a regimen based on a protease inhibitor to include at least two drugs that are effective in RESTING cells.

Conclusion

The challenge of this new data will be to determine how to integrate into our thinking about combination therapy. The basic findings seem reasonable and logical, but it is unclear what relative value to place on them in the overall context of factors that are considered in putting a treatment regimen together. Initially, it might make sense for this data to be considered first for people who are having difficulty establishing and maintaining an effective regimen. This provides one more piece of the puzzle in understanding why things happen the way they do. For people already on stable, effective therapy, the new data may be less important, unless they find they are on two drugs that fail to address one or the other cell state.

In the long term, these observations must be factored into the search for new drugs, so that ideally, new therapies that work in both ACTIVE and RESTING cells might be given priority.

© 2003 Project Inform, Inc., 205 13th Street #2001, San Francisco, CA 94103-2461