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

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Third Line Therapy Strategies

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One area of anti-HIV therapy research that has been inadequately addressed is strategies around third line therapy regimens. As a result, there is only a modest amount of data to guide physicians and patients in making treatment decisions in this setting.

Third line therapy is usually defined as a regimen for an individual who has developed resistance to at least one drug in all three classes of anti-HIV therapies [nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors] or has failed two treatment regimens. In general, the nucleo*tide* analogue drug, tenofovir (Viread) can be considered an NRTI as it shares some of the same resistance patterns. However, just because someone has developed resistance to some drugs in all three classes of anti-HIV drugs does not mean that they have no further treatment options. This paper will review some of the options available to people exploring third line regimen choices.

New Drugs and Expanded Access Programs

The most obvious option includes new drugs that are active against HIV that is resistant to most or all of the currently available anti-HIV therapies. There are several new drugs that may be active against multi-drug resistant HIV that are FDA approved or are still in early development. These include:

- Fusion inhibitors T-20 (pentafuside) and T-1249;
- Nucleotide analogue tenofovir;
- New protease inhibitors including atazanavir (Zrivada), tipranavir and TMC 114;
- Existing protease inhibitors enhanced by the addition of small doses of ritonavir, which increases their ability to overcome partially resistant virus;
- New NRTIs including DAPD, alovudine and ACH-126,443;
- New NNRTIs including capravirine, TMC125 and DPC 961;
- CCR5 inhibitors including Schering C (SCH 351125) and UK-427,857;
- Entry inhibitors including PRO 367;
- Attachment inhibitors including PRO 542; and
- Integrase inhibitors including S1360.

For most of these drugs, the only method of access is by participating in clinical trials, while some provide drug to people through expanded access programs. Currently there is a very limited expanded access program for T-20 and one planned for atazanavir by the end of the first quarter 2002. The Project Inform hotline will have information about these and other expanded access programs as they become available.

Mega-drug Regimens

Most third line regimens consist of four or more drugs. More traditional anti-HIV therapy regimens typically include only three drugs, or four anti-HIV drugs at the most. A third line regimen, however, often includes a minimum of four drugs and it's not uncommon to see five, six, seven or more drugs used. Different groups have used different terms for these third line multi-drug regimens including megaHAART, gigaHAART, salvage therapy and multi-drug rescue therapy. The theory behind using a larger number of drugs is that not all of the virus in a person's body is going to be resistant to all of the drugs. By using many drugs with different mechanisms of blocking HIV from reproducing, it may still be possible to achieve a potent anti-HIV effect.

The use of several drugs of multiple types, however, also increases the risk of side effects and makes it much more difficult to manage drug interactions. Another approach, the use of therapeutic drug monitoring (see below) may help to reduce side effects while ensuring optimal drug levels are maintained.

Structured Treatment Interruptions (STI)

There is still considerable debate and much research that needs to be done about the role of STIs as part of a third line regimen. The goal of an STI here is focused on the potential for at least partial reversal of drug resistance when all anti-HIV therapies are stopped for some period of time.

Several studies have shown that the majority of people in a third line situation who utilize an STI strategy do in fact see a reversion back to wild type virus (a reversal of resistance), when using the

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standard resistance tests, but when using a more sensitive test, drug resistant HIV can be detected. Still, there is often a period of renewed activity from drugs that had previously failed. It remains unclear how long the anti-HIV benefits will last once therapy is restarted after an STI.

One major concern with STIs in this scenario is that there is often a rapid drop in CD4+ cell counts and an increase in viral load, both of which can be very significant after stopping anti-HIV therapy. Furthermore, after restarting anti-HIV therapy there is a slow increase in CD4+ cells with some people never returning to their pre-STI CD4+ cell counts. On a more positive note, a small French third line study involving a STI shows promising results.

Immune-Based Therapies

The use of immune-based therapies has not been adequately studied as part of third line regimens. There are some data suggesting that the use of GM-CSF (granulocyte colony stimulating factor, Leukine) may have some benefit. It remains to be seen what the role of immune-based therapies may be in third line regimens.

Participate in a Study

There have only been a few studies of third line regimen strategies. One reason is third line regimens require the use of different drugs from the various pharmaceutical companies. Historically, there has been difficulty in getting them to collaborate in these types of studies. However, if a study is available it should be considered as an option.

Resistance Testing

It is probably advisable for people considering a third line regimen to get a resistance test. A phenotypic resistance test may be more useful in this situation than the genotypic test. Results from the resistance test will be useful in putting together a treatment regimen. For more information on HIV resistance tests, call Project Inform's hotline.

Therapeutic Drug Monitoring (TDM)

This is a new experimental diagnostic test that measures the amount of drug in blood. Given that most third line regimens involve many anti-HIV drugs, there are many potential drug interactions. Drug levels that are too low are associated with drug resistance while high drug levels are associated with excess side effects. Several studies have now shown that adequate drug levels are essential to achieve a potent and sustained anti-HIV response. Information from the TDM test can be used to change the dose of a particular drug to ensure that adequate drug levels are achieved. For more information on TDM, call the Project Inform hotline and ask for the publication *Pharmacology: Drug Level Monitoring and Beyond*.

Continued Benefit from "Failing" Drugs

Several studies have reported that even after drug regimens appear to "fail"—defined as a return of measurable viral load despite treatment—there is usually still a lasting benefit for people who stay on treatment. It seems likely that simple viral load tests do not tell the whole story of how the body responds to anti-HIV drugs.

There is much research in this area looking at the "fitness" of the virus. Early results suggest that HIV is not able to replicate as well after it becomes resistant to certain drugs. Thus, for some people who might seem to lack options, one reasonable choice might simply be to stay on whatever regimen they have been using. As long as they stay clinically well and don't suffer a rapid further decline of CD4+ cells, it might not be wise to worry excessively about drug "failure."

Commentary

We are seeing increasing numbers of people in need of third line regimens or at least better therapy. There is a definite need to evaluate the optimal strategy in putting together a third line regimen and the various clinical trial networks and pharmaceutical companies need to make this issue a priority.

The Basic Message

- *Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!*
- *If you're positive, don't panic. If you make your health a priority, chances are you will be reasonably healthy for many years.*
- *Learn about your healthcare options and local support services.*
- *Get a complete physical and blood tests for CD4+ cell count and HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.*
- *Work with a doctor to develop a long-term strategy for managing HIV disease.*
- *If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.*
- *If anti-HIV therapy fails to reduce your HIV level below the "limit of detection" or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.*
- *If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven't already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.*
- *If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.*
- *If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps monthly. Consider therapies for preventing MAC/MAI and CMV.*
- *Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.*